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- (54) **Title:** ASYMMETRIC SYNTHESIS OF CHIRAL COMPOUNDS

(57) **Abstract:** The present invention provides processes for the production of chiral compounds in a stereoisomeric excess, the processes comprising: (i) contacting a first compound comprising an alkene or alkyne bond with a hydrometallating agent, wherein the first compound and the hydrometallating agent are contacted under conditions such that the first compound is hydrometallated by said hydrometallating agent; and (ii) contacting the hydrometallated first compound with a second compound comprising an allylic group, wherein the hydrometallated first compound and the second compound are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction in which a carbon atom of the hydrometallated first compound binds to a carbon atom of said allylic group, forming a stereoisomeric excess of a compound having a chiral centre in an allylic position, said chiral centre being located at the carbon atom bound by said first compound, wherein said asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand. In particular, the present invention provides processes for the production of a stereoisomeric excess of a compound of the formula (IA), (IB), (IA') or (IB') as defined herein.



ASYMMETRIC SYNTHESIS OF CHIRAL COMPOUNDS

Field of the Invention

5 This invention relates to processes for the production of organic compounds. More particularly, the present invention relates to processes for the asymmetric synthesis of chiral compounds.

Background to the Invention

10

The development of catalytic methods for asymmetric synthesis is one of the foremost achievements in recent chemistry. At present, many broadly useful methods for catalytic asymmetric oxidation and reduction exist; however, far fewer catalytic asymmetric methods for forming carbon-carbon bonds have been devised. This is not only
15 remarkable in view of the importance of carbon-carbon bond formation in synthesis, but also reflects the major difficulties and challenges associated with enantioselective versions of these transformations. The development of asymmetric carbon-carbon bond forming reactions that are new, powerful and practical is of great importance.

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Asymmetric allylic alkylation reactions are particularly useful for the asymmetric synthesis of chiral compounds (for a review, see *e.g.* Langlois *et al*, Top Organomet. Chem., 2012, 38, 235-268). The use of organozincs and Grignard reagents, readily available from alkylhalides, has made asymmetric allylic alkylation reactions based on organometallic reagents practical. However, these reagents are far from ideal. For
25 instance, in the synthesis of complex molecules, functional groups may be present which are incompatible with organometallic reagents. Even the use of a protecting group strategy, which blocks incompatible reaction sites, is often ineffective, due to the reactivity of organometallic reagents and the extreme sensitivity of many asymmetric procedures. The sophistication of the organometallic reagents used in these methods is
30 also quite limited; often only simple substrates and nucleophiles can be used. Moreover, the reactivity of organometallic reagents is associated with serious safety issues. A still further limitation of presently available procedures is that they must generally be performed at cryogenic temperatures (*e.g.* less than -30 °C) for high levels of selectivity

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to be obtained. This is not usually possible in industry and so represents a serious limitation of these methods. The aforementioned methods are generally too reactive, too expensive and/or of limited availability.

5 Summary of the Invention

According to a first aspect of the present invention, there is provided a process for producing a chiral compound in a stereoisomeric excess, the process comprising:

10 (i) contacting a first compound comprising an alkene bond with a hydrometallating agent, wherein the first compound and the hydrometallating agent are contacted under conditions such that the first compound is hydrometallated by said hydrometallating agent; and

15 (ii) contacting the hydrometallated first compound with a second compound comprising an allylic group, wherein the hydrometallated first compound and the second compound are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction in which a carbon atom of the hydrometallated first compound binds to a carbon atom of said allylic group, forming a stereoisomeric excess of a compound having a chiral centre in an allylic position, said chiral centre being located at the carbon atom bound by said first compound, wherein said asymmetric allylic alkylation reaction is
20 performed in the presence of a metal catalyst comprising a chiral ligand.

In particular, the present invention provides a process for producing a stereoisomeric excess of a chiral compound of the formula (IA) or (IB) as defined herein.

25 According to a second aspect of the present invention, there is provided a process for producing a chiral compound in a stereoisomeric excess, the process comprising:

(i) contacting a first compound comprising an alkyne bond with a hydrometallating agent, wherein the first compound and the hydrometallating agent are contacted under conditions such that the first compound is hydrometallated by said
30 hydrometallating agent; and

(ii) contacting the hydrometallated first compound with a second compound comprising an allylic group, wherein the hydrometallated first compound and the second compound are contacted under conditions such that they undergo an asymmetric allylic

alkylation reaction in which a carbon atom of the hydrometallated first compound binds to a carbon atom of said allylic group, forming a stereoisomeric excess of a compound having a chiral centre in an allylic position, said chiral centre being located at the carbon atom bound by said first compound, wherein said asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

In particular, the present invention provides a process for producing a stereoisomeric excess of a chiral compound of the formula (IA') or (IB') as defined herein.

The present processes offer various advantages compared with conventional asymmetric carbon-carbon bond formation syntheses. In particular, unactivated alkene substrates may be used as nucleophiles in catalytic asymmetric carbon-carbon bond formation. Alkenes are readily available and have a number of favourable properties as compared to other substrates, such as premade organometallics. The use of simple and readily available materials is highly practical and, through exploitation of the starting materials, may allow rapid access to valuable classes of molecules. In addition, desirable stereoselectivity may be attained, particularly as chiral compounds may be formed via a dynamic kinetic resolution or dynamic kinetic asymmetric transformation process. Unactivated alkyne substrates afford similar advantages.

Description of Various Embodiments

For the purposes of the present invention, the following terms as used herein shall, unless otherwise indicated, be understood to have the following meanings.

The term "hydrocarbyl" as used herein refers to a group consisting exclusively of hydrogen and carbon atoms, the group having from 1 to 30 carbon atoms. For instance, a hydrocarbyl group may have from 1 to 20 carbon atoms, *e.g.* from 1 to 12 carbon atoms, *e.g.* from 1 to 10 carbon atoms. A hydrocarbyl group may be an acyclic group, a cyclic group, or may comprise both an acyclic portion and a cyclic portion. Examples of hydrocarbyl groups include alkyl, alkenyl, alkynyl, carbocyclyl (*e.g.* cycloalkyl, cycloalkenyl or aryl) and aralkyl.

The term "alkyl" as used herein refers to a straight or branched chain alkyl moiety having from 1 to 30 carbon atoms. For instance, an alkyl group may have from 1 to 20 carbon atoms, *e.g.* from 1 to 12 carbon atoms, *e.g.* from 1 to 10 carbon atoms. In particular, an alkyl group may have 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, sec-butyl or tert-butyl), pentyl, hexyl and the like.

The term "alkenyl" as used herein refers to a straight or branched chain alkyl group having from 2 to 30 carbon atoms and having, in addition, at least one carbon-carbon double bond, of either E or Z stereochemistry where applicable. For instance, an alkenyl group may have from 2 to 20 carbon atoms, *e.g.* from 2 to 12 carbon atoms, *e.g.* from 2 to 10 carbon atoms. In particular, an alkenyl group may have 2, 3, 4, 5 or 6 carbon atoms. Examples of alkenyl groups include ethenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl and the like.

The term "alkynyl" as used herein refers to a straight or branched chain alkyl group having from 2 to 30 carbon atoms and having, in addition, at least one carbon-carbon triple bond. For instance, an alkynyl group may have from 2 to 20 carbon atoms, *e.g.* from 2 to 12 carbon atoms, *e.g.* from 2 to 10 carbon atoms. In particular, an alkynyl group may have 2, 3, 4, 5 or 6 carbon atoms. Examples of alkynyl groups include ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl and the like.

The term "alkoxy" as used herein refers to -O-alkyl, wherein alkyl is as defined above. In some instances, an alkoxy group may have from 1 to 20 carbon atoms, *e.g.* from 1 to 12 carbon atoms, *e.g.* from 1 to 10 carbon atoms. In particular, an alkoxy group may have 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, hexoxy and the like.

The term "carbocyclyl" as used herein refers to a saturated (*e.g.* cycloalkyl) or unsaturated (*e.g.* cycloalkenyl or aryl) carbocyclic ring moiety having from 3 to 30 carbon atoms. For instance, a carbocyclyl group may have from 3 to 20 carbon atoms, *e.g.* from 3 to 16 carbon atoms, *e.g.* from 3 to 10 carbon atoms. In particular, a carbocyclyl group

may be a 5- or 6-membered ring system, which may be saturated or unsaturated. Examples of carbocyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, fluorenyl, azulenyl, indenyl, anthryl and the like.

- 5 The term "cycloalkyl" as used herein refers to an aliphatic carbocyclic moiety having from 3 to 20 ring carbon atoms. For instance, a cycloalkyl group may have from 3 to 16 carbon atoms, *e.g.* from 3 to 10 carbon atoms. In particular, a cycloalkyl group may have 3, 4, 5 or 6 ring carbon atoms. A cycloalkyl group may be a monocyclic, polycyclic (*e.g.* bicyclic) or bridged ring system. Examples of cycloalkyl groups include cyclopropyl,
10 cyclobutyl, cyclopentyl, cyclohexyl, norbornyl and the like.

The term "cycloalkenyl" as used herein refers to an aliphatic carbocyclic moiety having from 5 to 20 ring carbon atoms and having, in addition, at least one carbon-carbon double bond in the ring. For instance, a cycloalkenyl group may have from 5 to 16
15 carbon atoms, *e.g.* from 5 to 10 carbon atoms. In particular, a cycloalkenyl group may have 5 or 6 ring carbon atoms. A cycloalkenyl group may be a monocyclic, polycyclic (*e.g.* bicyclic) or bridged ring system. Examples of cycloalkenyl groups include cyclopentenyl, cyclohexenyl and the like.

- 20 The term "aryl" as used herein refers to an aromatic carbocyclic ring system having from 6 to 30 ring carbon atoms. For instance, an aryl group may have from 6 to 16 ring carbon atoms, *e.g.* from 6 to 10 ring carbon atoms. An aryl group may be a monocyclic aromatic ring system or a polycyclic ring system having two or more rings, at least one of which is aromatic. Examples of aryl groups include phenyl, naphthyl, fluorenyl, azulenyl,
25 indenyl, anthryl and the like.

The term "aralkyl" as used herein refers to an alkyl group substituted with an aryl group, wherein the alkyl and aryl groups are as defined herein. An example of an aralkyl group is benzyl.

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The term "heterocyclyl" as used herein refers to a saturated (*e.g.* heterocycloalkyl) or unsaturated (*e.g.* heterocycloalkenyl or heteroaryl) heterocyclic ring moiety having from 3 to 30 ring atoms, wherein said ring atoms include at least one ring carbon atom and at

least one ring heteroatom selected from nitrogen, oxygen, phosphorus, silicon and sulphur. For instance, a heterocyclyl group may have from 3 to 20 ring atoms, *e.g.* from 3 to 16 ring atoms, *e.g.* from 3 to 10 ring atoms. In particular, a heterocyclyl group may have 5 or 6 ring atoms, and may be saturated or unsaturated. Examples of heterocyclic groups include imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, chromenyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, indoliziny, indolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl, oxiranyl, azirinyl, 1,2-oxathiolanyl, chromanyl and the like.

The term "heterocycloalkyl" as used herein refers to a saturated heterocyclic moiety having from 3 to 10 ring carbon atoms and 1, 2, 3, 4 or 5 ring heteroatoms selected from nitrogen, oxygen, phosphorus and sulphur. The group may be a monocyclic or polycyclic ring system. Examples of heterocycloalkyl groups include azetidiny, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxiranyl, pyrazolidinyl, imidazolyl, indolizidinyl, piperazinyl, thiazolidinyl, morpholinyl, thiomorpholinyl, quinolizidinyl, tetrahydropyranyl, and the like.

The term "heterocycloalkenyl" as used herein refers to a saturated heterocyclic moiety having from 3 to 10 ring carbon atoms and 1, 2, 3, 4 or 5 ring heteroatoms selected from nitrogen, oxygen, phosphorus and sulphur, and having, in addition, at least one carbon-carbon double bond in the ring. The group may be a monocyclic or polycyclic ring system. An example of a heterocycloalkenyl group is pyranyl.

The term "heteroaryl" as used herein refers to an aromatic heterocyclic ring system having from 5 to 30 ring atoms, wherein said ring atoms include at least one ring carbon atom and at least one ring heteroatom selected from nitrogen, oxygen and sulphur. The

group may be a monocyclic ring system or a polycyclic (*e.g.* bicyclic) ring system having two or more rings, at least one of which is aromatic. Examples of heteroaryl groups include pyridazinyl, pyrimidinyl, furanyl, benzo[b]thiophenyl, thiophenyl, pyrrolyl, imidazolyl, pyrrolidinyl, pyridinyl, benzo[b]furanyl, pyrazinyl, purinyl, indolyl, benzimidazolyl, quinoliny, phenothiazinyl, triazinyl, phthalazinyl, 2H-chromenyl, oxazolyl, isoxazolyl, thiazolyl, isoindolyl, indazolyl, isoquinoliny, quinazoliny and the like.

The terms "halogen" and "halo" as used herein refer to F, Cl, Br or I.

10 The term "alkene bond" as used herein refers to an aliphatic carbon-carbon double (C=C) bond.

The term "alkyne bond" as used herein refers to an aliphatic carbon-carbon triple (C≡C) bond.

15 The term "allylic group" as used herein refers to an allyl group ($-\text{CH}_2\text{CH}=\text{CH}_2$) and derivatives thereof formed by substitution. The term includes, without limitation, monovalent allylic groups (*e.g.* $-\text{CH}_2-\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}=\text{CH}(\text{CH}_3)$, $-\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}(\text{CH}_3)$ and $-\text{CH}_2\text{CH}=\text{CH}(\text{C}_6\text{H}_5)$) and divalent allylic groups (*e.g.* $-\text{CH}_2\text{CH}=\text{CH}-$ and $-\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}-$). Thus, an allylic group may be or may form part of a pendant group attached to a parent moiety, it may form part of a straight or branched chain (*e.g.* a hydrocarbyl chain containing at least one alkene bond), or it may form part of a ring or ring system (*e.g.* a ring or ring system comprising a cycloalkene ring). In some instances, an allylic group is an allyl group which is substituted by one or more substituents, *e.g.* an allyl group substituted by 1, 2, 3, 4 or 5 R^a . The term "allylic position" as used herein refers to the saturated carbon atom of an allylic group, *i.e.* to a saturated carbon atom which is adjacent to a carbon atom forming part of the alkene bond of the allylic group.

30 The term "optionally substituted" as used herein means unsubstituted or substituted.

The term "substituted" as used herein in connection with a chemical group means that one or more (*e.g.* 1, 2, 3, 4 or 5) of the hydrogen atoms in that group are replaced

independently of each other by a corresponding number of substituents. It will, of course, be understood that the one or more substituents may only be at positions where they are chemically possible, *i.e.* that any substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound. The term is contemplated to include all permissible substituents of a chemical group or compound. It will be understood by those skilled in the art that one or more hydrogen atoms on a given substituent can themselves be substituted, if appropriate.

Where two or more moieties are described as being "each independently" selected from a list of moieties, this means that the moieties may be the same or different. The identity of each moiety is therefore independent of the identities of the one or more other moieties. Where multiple substituents are indicated as being attached to a structure, it will be understood that the substituents can be the same or different.

The present invention provides processes for the asymmetric synthesis of chiral compounds, wherein the processes involve an asymmetric allylic alkylation reaction. The present processes involve the use of a first compound comprising an alkene or alkyne bond, which compound is hydrometallated using a hydrometallating agent.

Processes involving a first compound comprising an alkene bond

In a first aspect, the present invention provides a process for producing a chiral compound in a stereoisomeric excess, the process comprising:

(i) contacting a first compound comprising an alkene bond with a hydrometallating agent, wherein the first compound and the hydrometallating agent are contacted under conditions such that the first compound is hydrometallated by said hydrometallating agent; and

(ii) contacting the hydrometallated first compound with a second compound comprising an allylic group, wherein the hydrometallated first compound and the second compound are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction in which a carbon atom of the hydrometallated first compound binds to a carbon atom of said allylic group, forming a stereoisomeric excess of a compound

having a chiral centre in an allylic position, said chiral centre being located at the carbon atom bound by said first compound, wherein said asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

- 5 The first compound comprises at least one alkene bond, *i.e.* at least one aliphatic carbon-carbon double (C=C) bond. The first compound may be an acyclic compound, a cyclic compound, or may comprise an acyclic portion and a cyclic portion. The compound may consist exclusively of carbon and hydrogen atoms, or may comprise one or more other atoms in addition. In an embodiment, the first compound is a straight or
10 branched alkene compound having from 2 to 30 carbon atoms, *e.g.* from 2 to 20 carbon atoms, *e.g.* from 2 to 12 carbon atoms, *e.g.* from 2 to 10 carbon atoms, *e.g.* 2, 3, 4, 5 or 6 carbon atoms. The alkene compound may be unsubstituted or substituted with one or more substituents, *e.g.* with 1, 2, 3, 4 or 5 substituents selected from R^a; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a; and -(CH₂)_j-heterocyclyl optionally
15 substituted with 1, 2, 3, 4 or 5 R^a; wherein R^a and j are as defined elsewhere herein.

Preferably, the first compound is a terminal alkene. Terminal alkenes are typically produced annually on the megaton scale, and are among the most readily available organic molecules. These inexpensive raw materials are feedstocks for the preparation
20 of many classes of organic compounds. Catalytic intermolecular reactions using these alkenes may have a tremendous value-added component because they convert inexpensive raw materials into highly functionalised compounds. Alternatively, the first compound may be an internal alkene; such compounds are also readily available and commonly used in chemistry.

25 The first compound is reacted with a hydrometallating agent under conditions such that the first compound is hydrometallated. Hydrometallation of the first compound will typically result in the addition of a metal atom to one carbon atom of the alkene bond and a hydride ligand to the other. In certain instances, the first compound may undergo one or more intramolecular rearrangements (*e.g.* beta hydride elimination followed by further hydrometallation) in which the alkene bond relocates to a different position within the first compound, prior to or during reaction with the hydrometallating agent. Thus, for
30 instance, the hydrometallation reaction may result in the attachment of the metal at the

sterically less hindered position of the alkene chain. In this case, hydrometallation may occur either by regiospecific addition of the agent to a terminal alkene bond or by addition of the agent to an internal alkene bond followed by rearrangement via metal hydride elimination and readdition to place the metal at a less hindered position of the alkene chain (see *e.g.* Schwartz *et al*, Angew. Chem. Int. Ed., 1976, 6, 333). All such hydrometallation reactions fall within the scope of the present invention.

Various hydrometallating agents are known in the art. The hydrometallating agent may comprise a metal and at least one hydride group. By way of illustration, the hydrometallating agent may comprise at least one metal selected from zirconium, titanium, hafnium, niobium, tantalum, aluminium, tin, magnesium, zinc, palladium, iridium, copper, rhodium, ruthenium, platinum, rhenium, nickel and the like. The term "metal" as used herein in connection with the hydrometallating agent does not include metalloids such as boron, silicon and germanium. Preferably, the hydrometallating agent comprises a transition metal. More preferably, the hydrometallating agent comprises zirconium. The hydrometallating agent may be in the form of a metal complex comprising a metal (*e.g.* a transition metal) bound to one or more ligands, at least one of which is a hydride ligand.

In a preferred embodiment, the hydrometallating agent is a zirconium complex, *e.g.* a zirconium halohydride complex. In an embodiment, the hydrometallating agent is a zirconium complex of the formula HZrR_2X , wherein each R is independently an optionally substituted 6π electron donating ligand (*e.g.* having 5 carbon atoms, *e.g.* a π -cyclopentadienyl ligand) and X is another ligand, *e.g.* selected from halogen, triflates, alcohols and nitrogen-containing compounds. In a preferred embodiment, the hydrometallating agent is a zirconium complex of the formula HZrCp_2X , wherein each Cp is an optionally substituted π -cyclopentadienyl ligand and X is a ligand selected from halogen, triflates, alcohols and nitrogen-containing compounds. Preferably, X is halogen. Particularly preferred is a zirconium complex of the formula HZrCp_2Cl , which is commonly known in the art as the "Schwartz reagent" (see Schwartz *et al*, J. Am. Chem. Soc., 96, 8115-8116, 1974).

The hydrometallating agent may be prepared according to procedures known in the art

(see *e.g.* Org. Syn., coll. Col. 9, p. 162 (1998), vol. 71, p 77 (1993); Negishi, Tet. Lett. 1984, 25, 3407; Buchwald, Tet. Lett. 1987, 28, 3895; Lipshutz, Tet. Lett., 1990, 31, 7257; Negishi, J. Org. Chem. 1991, 56, 2590; and Negishi, Eur. J. Org. Chem. 1999, 969).

- 5 The hydrometallated first compound is reacted with a second compound, the second compound comprising an allylic group. The second compound may be an acyclic compound, a cyclic compound, or may comprise an acyclic portion and a cyclic portion. The second compound will typically comprise a leaving group at an allylic position, wherein the leaving group is displaced from said position during the asymmetric
- 10 alkylation reaction. By way of illustration, and without limitation, the leaving group may be any leaving group as described in relation to the moiety R¹⁰ herein. In an embodiment, the leaving group is a halogen, *e.g.* Cl, Br or I. Preferably, the leaving group is Cl. In some instances, the leaving group forms a ring within the second compound, and displacement of the leaving group from the allylic position results in ring-
- 15 opening. Thus, by way of illustration, the leaving group may be an oxygen atom which forms an epoxide ring within the second compound, and the binding of the hydrometallated first compound to the second compound results in the epoxide ring undergoing ring-opening, forming a hydroxy group in the resulting chiral compound. In an embodiment, the second compound consists exclusively of carbon and hydrogen
- 20 atoms and a leaving group at an allylic position.

The hydrometallated first compound and the second compound are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a chiral compound. Thus, the carbon atom of the hydrometallated first compound to which

25 the metal is attached binds to a carbon atom of the allylic group, forming a stereoisomeric excess (*e.g.* an enantiomeric or diastereomeric excess) of a compound having a chiral centre at an allylic position, said chiral centre being located at the carbon atom bound by the hydrometallated first compound. The asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

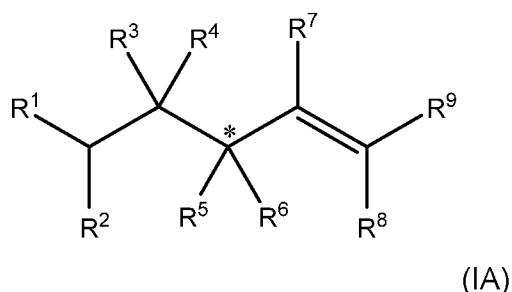
30 Preferably, the chiral ligand is a non-racemic chiral ligand.

Asymmetric allylic alkylation reactions may proceed via different pathways, each of which typically involves displacement of a leaving group located in an allylic position (see

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e.g. Langlois *et al*, *supra*). The present processes may therefore be used to form a variety of chiral compounds. Thus, for example, in cases where the allylic group forms part of a linear substrate, a chiral compound may be obtained via a pathway in which the carbon atom of the hydrometallated first compound binds to the terminal (outer) unsaturated carbon atom of the allylic group, resulting in rearrangement of the alkene bond and subsequent displacement of the leaving group. As a consequence, the carbon atom that was previously the terminal unsaturated carbon atom of the allylic group is transformed into a chiral centre. In other cases, for example where the allylic group forms part of a cyclic and/or substantially symmetrical substrate, the carbon atom of the hydrometallated first compound may bind to the carbon atom at the allylic position of the second compound, displacing the leaving group from said allylic position without rearrangement of the alkene bond. As will be apparent to those skilled in the art, parameters such as the starting materials, catalysts and reaction conditions may be varied so as to favour a certain reaction mechanism and thus a particular chiral product.

In particular, the present invention provides a process for producing a chiral compound of the formula (IA) in a stereoisomeric excess:



wherein

R^1 , R^2 , R^3 and R^4 are each independently selected from hydrogen, R^a , hydrocarbonyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^1 and R^3 taken together with the carbon atoms to which they are attached may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

R^5 , R^6 , R^7 , R^8 and R^9 are each independently selected from hydrogen, R^a ,

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hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^5 and one of R^6 and R^8 , or R^6 and R^7 , or R^7 and R^9 , taken together with the carbon atoms to which they are attached, may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

each R^a is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^b$, $-OR^b$, $-C(O)R^b$, $-C(O)N(R^b)R^c$, $-C(O)OR^b$, $-C(O)SR^b$, $-C(O)SeR^b$, $-OC(O)R^b$, $-S(O)_kR^b$, $-S(O)_kN(R^b)R^c$, $-N(R^b)R^c$, $-N(R^b)N(R^b)R^c$, $-N(R^b)C(O)R^c$ and $-N(R^b)S(O)_kR^b$;

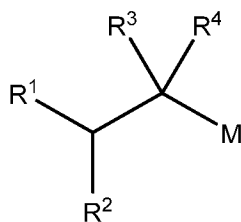
R^b and R^c are each independently hydrogen or selected from hydrocarbyl and $-(CH_2)_j$ -heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, oxo, cyano, amino, hydroxy, alkyl and alkoxy;

j is 0, 1, 2, 3, 4, 5 or 6;

k is 0, 1 or 2; and

the asterisk * designates a chiral centre of (*R*) or (*S*) configuration.

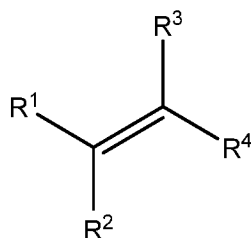
The compound of formula (IA) may be obtained by first contacting a compound comprising an alkene bond with a hydrometallating agent of the formula HM, wherein M comprises a metal (*e.g.* a transition metal), wherein said compound and the hydrometallating agent are contacted under conditions such that they react to form a compound of the formula (II):



(II).

Thus, for instance, the process may comprise contacting an alkene compound of the formula (IV):

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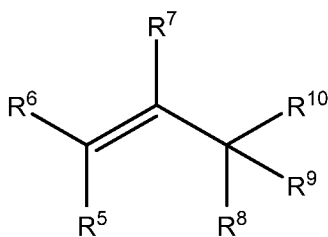


(IV)

with a hydrometallating agent of the formula HM under conditions such that the compounds react to form the compound of formula (II).

5

The compound of formula (II) is then contacted with a compound of the formula (IIIA):



(IIIA)

10

wherein R^{10} is a leaving group.

In the compound of formula (IIIA), the radicals R^5 and R^6 are different, and they are also each different to the moiety $\text{CH}(\text{R}^1)(\text{R}^2)\text{C}(\text{R}^3)(\text{R}^4)-$, such that a chiral centre is formed at the position denoted by the asterisk in formula (IA).

15

The compound of formula (II) and the compound of formula (IIIA) are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a stereoisomeric excess of a compound of formula (IA). The asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

20

In embodiments, one or more of the following apply: (i) R^1 is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; (ii) R^1 is alkyl, cycloalkyl or aralkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a ; (iii) R^3 is hydrogen or hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; (iv) R^3 is hydrogen or alkyl optionally substituted with

25

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1, 2, 3, 4 or 5 R^a ; (v) R^1 and R^3 taken together with the carbon atoms to which they are attached form, in the compounds of formulae (II) and (IV), cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and (vi) R^2 and R^4 are each hydrogen.

- 5 In an embodiment, M comprises a metal selected from zirconium, titanium, hafnium, niobium, tantalum, aluminium, tin, magnesium, zinc, palladium, iridium, copper, rhodium, ruthenium, platinum, rhenium and nickel. Preferably, M comprises a transition metal.

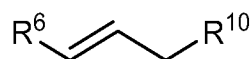
More preferably, the compound of formula (II) is obtained by hydrozirconation of the
 10 compound comprising said alkene bond, *e.g.* by hydrozirconation of a compound of the formula (IV). Thus, in a preferred embodiment, the hydrometallating agent HM comprises zirconium. Preferably, the hydrometallating agent is a zirconium complex of the formula $HZrR_2X$ as defined above. In a preferred embodiment, the hydrometallating agent is a zirconium complex of the formula $HZrCp_2X$ as defined above. Particularly
 15 preferred is a zirconium complex of the formula $HZrCp_2Cl$ (the Schwartz reagent).

In an embodiment, R^7 is hydrogen.

R^8 and R^9 will typically be different to R^{10} . In an embodiment, R^8 and R^9 are each
 20 independently selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, R^8 and R^9 are each independently selected from hydrogen and alkyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

25 In an embodiment, the compound of formula (IIIA) is a compound of the formula (IIIA.1):



(IIIA.1).

30 In an embodiment, R^6 is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a . In an embodiment, R^6 is selected from alkyl, aryl, aralkyl and cycloalkyl, each of which is

optionally substituted with 1, 2, 3, 4 or 5 R^a . In an embodiment, R^b is aryl or aralkyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, R^{10} is a leaving group selected from halogen, cyano, cyanate, thiocyanate, $-OR^{11}$, $-C(O)R^{11}$, $-C(S)R^{11}$, $-C(O)N(R^{11})R^{12}$, $-C(O)OR^{11}$, $-C(O)SR^{11}$, $-C(O)SeR^{11}$, $-OC(O)R^{11}$, $-S(O)_mR^{11}$, $-SeR^{11}$, $-S(O)_mN(R^{11})R^{12}$, $-N(R^{11})R^{12}$, $-N(R^{11})N(R^{11})R^{12}$, $-N(R^{11})C(O)R^{12}$, $-N(R^{11})S(O)_mR^{12}$ and $-P(O)(OR^{12})_2$, wherein R^{11} and R^{12} are each independently selected from hydrogen, alkyl, aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a ; and m is 0, 1 or 2. In an embodiment, R^{10} is a halogen. Preferably, R^{10} is Cl.

In an embodiment, R^{10} is an oxygen atom which forms an epoxide ring within the second compound, and the binding of the hydrometallated first compound to the second compound results in the epoxide ring undergoing ring-opening, forming a hydroxy group in the resulting chiral compound.

In an embodiment, R^{10} is $-OP(O)(OR^{12})_2$, wherein each R^{12} is as defined above. In an embodiment, each R^{12} is alkyl, *e.g.* methyl or ethyl.

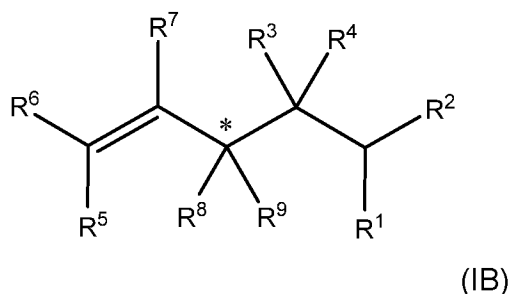
In an embodiment, each R^a is independently selected from acyl, alkoxy, alkoxycarbonyl, alkylamino, alkylsulfinyl, alkylsulfonyl, alkylthio, amino, aminoalkyl, aralkyl, cyano, dialkylamino, halo, haloalkoxy, haloalkyl, hydroxy, formyl, nitro, alkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen or haloalkyl), aryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heterocycloalkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), aminoacyl, aminosulfonyl, acylamino, sulfonylamino, heteroarylalkyl, aryloxy, heteroaryloxy, arylalkyloxy and heteroarylalkyloxy.

In an embodiment, each R^a is independently selected from aralkyl, alkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen or haloalkyl), aryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl),

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and heterocycloalkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl).

The present invention also provides a process for producing a chiral compound of the
5 formula (IB) in a stereoisomeric excess:



10 wherein

R^1 , R^2 , R^3 and R^4 are each independently selected from hydrogen, R^a , hydrocarbonyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^1 and R^3 taken together with the carbon atoms to which they are
15 attached may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

R^5 , R^6 , R^7 , R^8 and R^9 are each independently selected from hydrogen, R^a , hydrocarbonyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^5 and one of R^6 and R^8 , or R^6 and R^7 , or R^7 and R^9 , taken together
20 with the carbon atoms to which they are attached, may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

each R^a is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^b$, $-OR^b$, $-C(O)R^b$, $-C(O)N(R^b)R^c$, $-C(O)OR^b$, $-C(O)SR^b$, $-C(O)SeR^b$,
25 $-OC(O)R^b$, $-S(O)_kR^b$, $-S(O)_kN(R^b)R^c$, $-N(R^b)R^c$, $-N(R^b)N(R^b)R^c$, $-N(R^b)C(O)R^c$ and $-N(R^b)S(O)_kR^b$;

R^b and R^c are each independently hydrogen or selected from hydrocarbonyl and $-(CH_2)_j$ -heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, oxo, cyano, amino, hydroxy,

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alkyl and alkoxy;

j is 0, 1, 2, 3, 4, 5 or 6;

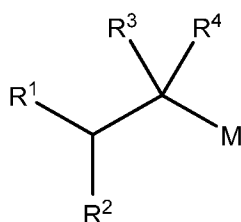
k is 0, 1 or 2; and

the asterisk * designates a chiral centre of (*R*) or (*S*) configuration.

5

The compound of formula (IB) may be obtained by first contacting a compound comprising an alkene bond with a hydrometallating agent of the formula HM, wherein M comprises a metal (*e.g.* a transition metal), wherein said compound and the hydrometallating agent are contacted under conditions such that they react to form a compound of the formula (II):

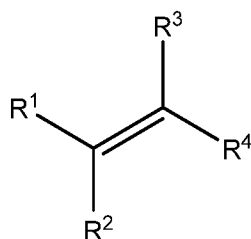
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(II).

Thus, for instance, the process may comprise contacting an alkene compound of the formula (IV):

15



(IV)

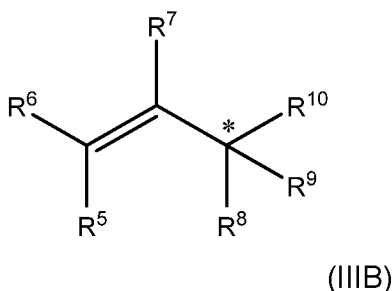
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with a hydrometallating agent of the formula HM under conditions such that the compounds react to form the compound of formula (II).

The compound of formula (II) is then contacted with a compound of the formula (IIIB):

25

- 19 -



wherein

R^{10} is a leaving group; and

5 the asterisk * designates a chiral centre of (*R*) or (*S*) configuration.

In the compound of formula (IIIB), the radicals R^8 , R^9 and R^{10} are each different, and they are also each different to the moiety $CH(R^1)(R^2)-C(R^3)(R^4)-$, such that a chiral centre is formed at the position denoted by the asterisk in formula (IB).

10

The compound of formula (II) and the compound of formula (IIIB) are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a stereoisomeric excess of a compound of formula (IB). The asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

15

In embodiments, one or more of the following apply: (i) R^1 is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; (ii) R^1 is alkyl, cycloalkyl or aralkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a ; (iii) R^3 is hydrogen or hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; (iv) R^3 is hydrogen or alkyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; (v) R^1 and R^3 taken together with the carbon atoms to which they are attached form, in the compounds of formulae (I) and (IV), cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and (vi) R^2 and R^4 are each hydrogen.

20

In an embodiment, M comprises a metal selected from zirconium, titanium, hafnium, niobium, tantalum, aluminium, tin, magnesium, zinc, palladium, iridium, copper, rhodium, ruthenium, platinum, rhenium and nickel. Preferably, M comprises a transition metal.

25

More preferably, the compound of formula (II) is obtained by hydrozirconation of the compound comprising said alkene bond, e.g. by hydrozirconation of a compound of the

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formula (IV). Thus, in a preferred embodiment, the hydrometallating agent HM comprises zirconium. Preferably, the hydrometallating agent is a zirconium complex of the formula HZrR_2X as defined above. In a preferred embodiment, the hydrometallating agent is a zirconium complex of the formula HZrCp_2X as defined above. Particularly preferred is a zirconium complex of the formula HZrCp_2Cl (the Schwartz reagent).

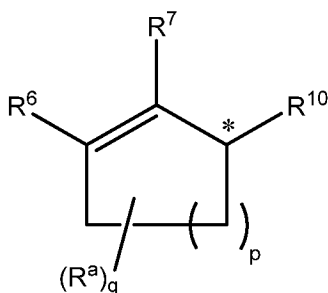
In an embodiment, R^8 and R^9 are each independently selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(\text{CH}_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, R^5 and R^8 , taken together with the carbon atoms to which they are attached, form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, R^5 and R^8 , taken together with the carbon atoms to which they are attached, form a 5-, 6-, 7- or 8-membered carbocyclic or heterocyclic group which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, R^9 is hydrogen.

In an embodiment, the compound of formula (IIIB) is a compound of formula (IIIB.1):



(IIIB.1)

wherein

p is 1, 2, 3 or 4; and

q is 0, 1, 2, 3, 4 or 5.

In an embodiment, p is 2. In an embodiment, q is 0.

In an embodiment, R⁶ is selected from hydrogen and alkyl, *e.g.* hydrogen and methyl.

5 In an embodiment, R⁷ is hydrogen.

In an embodiment, R¹⁰ is a leaving group selected from halogen, cyano, cyanate, thiocyanate, -OR¹¹, -C(O)R¹¹, -C(S)R¹¹, -C(O)N(R¹¹)R¹², -C(O)OR¹¹, -C(O)SR¹¹, -C(O)SeR¹¹, -OC(O)R¹¹, -S(O)_mR¹¹, -SeR¹¹, -S(O)_mN(R¹¹)R¹², -N(R¹¹)R¹²,
 10 -N(R¹¹)N(R¹¹)R¹², -N(R¹¹)C(O)R¹², -N(R¹¹)S(O)_mR¹² and -P(O)(OR¹²)₂, wherein R¹¹ and R¹² are each independently selected from hydrogen, alkyl, aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a; and m is 0, 1 or 2. In an embodiment, R¹⁰ is a halogen. Preferably, R¹⁰ is Cl.

15 In an embodiment, R¹⁰ is an oxygen atom which forms an epoxide ring within the second compound, and the binding of the hydrometallated first compound to the second compound results in the epoxide ring undergoing ring-opening, forming a hydroxy group in the resulting chiral compound.

20 In an embodiment, each R^a is independently selected from acyl, alkoxy, alkoxycarbonyl, alkylamino, alkylsulfinyl, alkylsulfonyl, alkylthio, amino, aminoalkyl, aralkyl, cyano, dialkylamino, halo, haloalkoxy, haloalkyl, hydroxy, formyl, nitro, alkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen or haloalkyl), aryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl
 25 (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heterocycloalkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), aminoacyl, aminosulfonyl, acylamino, sulfonylamino, heteroarylalkyl, aryloxy, heteroaryloxy, arylalkyloxy and heteroarylalkyloxy.

30 In an embodiment, each R^a is independently selected from aralkyl, alkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen or haloalkyl), aryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl),

and heterocycloalkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl).

Preferably, the compound of formula (IIIB) is formed via a dynamic kinetic resolution
5 process or a dynamic kinetic asymmetric transformation process. Such processes are known in the art to be highly enantioselective and may allow for the conversion of both enantiomers of a racemic compound into a single enantiomerically enriched compound (see *e.g.* Trost *et al*, 1994, J. Am Chem. Soc. 116, 4089-4090; and Langlois *et al*, *supra*). Thus, for example, either or both enantiomers of a compound of formula (IIIB) may be
10 converted into a single enantiomer of a compound of formula (IB). The resulting chiral compound may have an enantiomeric excess greater than 80%, *e.g.* greater than 90% *e.g.* greater than 95%, *e.g.* greater than 99%. In particular, when starting from a second compound which is racemic, a chiral compound may be formed in a 100% enantiomeric excess. Preferably, the second compound is in racemic form, *e.g.* the second compound
15 is a racemic compound of the formula (IIIB). Preferably, the second compound is a cyclic and/or substantially symmetrical compound. Thus, for example, a process of the invention may involve the use of a compound of formula (IIIB) which is cyclic and/or substantially symmetrical.

20 In an embodiment, the chiral compound is formed via desymmetrisation of a meso compound containing an allyl group.

The asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising at least one chiral ligand. In an embodiment, the metal catalyst
25 comprises a metal, one or more chiral ligands and one or more counterions.

In an embodiment, the metal catalyst comprises a transition metal, *e.g.* selected from copper, cobalt, iridium, rhodium, ruthenium, nickel, iron, palladium, gold, silver and platinum.

30

In a preferred embodiment, the metal catalyst comprises copper. In this regard, it has been found that copper can catalyse asymmetric allylic addition reactions with high overall yield. The reaction tolerates various functionalities; indeed, functional groups that

are not compatible with Grignard reagents and organozincs may be compatible with the processes described herein.

5 The metal catalyst may comprise any catalytic metal and/or catalyst precursor as it is introduced into the reaction vessel and which may be, if needed, converted *in situ* into the active form, as well as the active form of the catalyst which participates in the reaction. In embodiments, the metal catalyst is provided in the reaction mixture in an amount ranging from about 5% to about 10% by weight. The catalyst may be prepared *in situ* by stirring the metal, chiral ligand and any other components (*e.g.* one or more
10 other ligands) together at *e.g.* room temperature.

Preferably, the metal catalyst comprises copper(I). In a particular embodiment, the metal catalyst is formed from a copper (I) salt comprising a non-coordinating counterion. Preferably, the metal catalyst is formed using a copper halide salt, wherein the halide is
15 preferably Cl, Br or I. More preferably the metal catalyst is formed using a copper iodide salt. Using a copper iodide salt in accordance with the process of the present invention has been shown to give high enantioselectivity.

The metal catalyst comprises at least one chiral ligand. Preferably, the chiral ligand is a
20 non-racemic chiral ligand. The chiral ligand may be a chelating ligand or a non-chelating ligand. Examples of suitable ligands include phosphines, bisphosphines, amines, diamines, imines, arsines, sulfides, sulfoxides, carbenes (*e.g.* N-heterocyclic carbenes), peptides and hybrids thereof, including hybrids of phosphines with amines, hybrids of phosphines with peptides, and hybrids of phosphines with sulfides.

25 In a more preferred embodiment, the non-racemic chiral ligand is a phosphoramidite ligand. Particularly preferred for use in the present processes are the phosphoramidite ligands A and G as described in the Examples herein.

30 The chiral ligand may be used in the form of a purified stereoisomer. The metal catalyst may comprise one or more other ligands, in addition to the at least one chiral ligand. In particular, the metal catalyst may include one or more additional ligands as is necessary to obtain a stable complex. The or each ligand can be added to the reaction mixture in

the form of a metal complex, or added as a separate reagent relative to the addition of the metal.

5 The various synthetic steps described herein may be performed in separate reaction vessels or in the same reaction vessel (*i.e.* as a “one-pot” reaction). The process may comprise isolating and/or characterising one or more intermediates, *e.g.* the hydrometallated alkene, of the process.

10 A process of the present invention may be conducted at a temperature of from 0 °C to 60 °C. In particular, the present processes may be conducted at a temperature of from 10 °C to 30 °C, *e.g.* from 20 °C to 25 °C. More preferably, the present processes are conducted at room temperature.

15 A process of the present invention will generally be conducted in the presence of one or more solvents. Examples of suitable solvents include dichloromethane, 1,2-dichloroethane, chloroform, Et₂O, t-BuOMe, i-Pr₂O, 2,2-dimethoxypropane, tetrahydrofuran, 2-methyltetrahydrofuran, diglyme, 1,4-dioxane, toluene, m-xylene and hexane. A preferred solvent is chloroform.

20 *Processes involving a first compound comprising an alkyne bond*

In a second aspect, the present invention provides a process for producing a chiral compound in a stereoisomeric excess, the process comprising:

25 (i) contacting a first compound comprising an alkyne bond with a hydrometallating agent, wherein the first compound and the hydrometallating agent are contacted under conditions such that the first compound is hydrometallated by said hydrometallating agent; and

30 (ii) contacting the hydrometallated first compound with a second compound comprising an allylic group, wherein the hydrometallated first compound and the second compound are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction in which a carbon atom of the hydrometallated first compound binds to a carbon atom of said allylic group, forming a stereoisomeric excess of a compound having a chiral centre in an allylic position, said chiral centre being located at the carbon

atom bound by said first compound, wherein said asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

5 The first compound comprises at least one alkyne bond, *i.e.* at least one aliphatic carbon-carbon triple ($C\equiv C$) bond. The first compound may be an acyclic compound or may comprise an acyclic portion and a cyclic portion. The compound may consist exclusively of carbon and hydrogen atoms, or may comprise one or more other atoms in addition. In an embodiment, the first compound is a straight or branched alkyne compound having from 2 to 30 carbon atoms, *e.g.* from 2 to 20 carbon atoms, *e.g.* from 2
10 to 12 carbon atoms, *e.g.* from 2 to 10 carbon atoms, *e.g.* 2, 3, 4, 5 or 6 carbon atoms. The alkyne compound may be unsubstituted or substituted with one or more substituents, *e.g.* with 1, 2, 3, 4 or 5 substituents selected from R^a ; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; wherein R^a and j are as defined elsewhere herein.

15 Preferably, the first compound is a terminal alkyne. Alternatively, the first compound may be an internal alkyne.

20 The first compound is reacted with a hydrometallating agent under conditions such that the first compound is hydrometallated. Hydrometallation of the first compound will typically result in the addition of a metal atom to one carbon atom of the alkyne bond and a hydride ligand to the other thereby forming an alkene bond in place of the alkyne bond.

25 Various hydrometallating agents are known in the art. The hydrometallating agent may comprise a metal and at least one hydride group. By way of illustration, the hydrometallating agent may comprise at least one metal selected from zirconium, titanium, hafnium, niobium, tantalum, aluminium, tin, magnesium, zinc, palladium, iridium, copper, rhodium, ruthenium, platinum, rhenium, nickel and the like. The term "metal" as used herein in connection with the hydrometallating agent does not include
30 metalloids such as boron, silicon and germanium. Preferably, the hydrometallating agent comprises a transition metal. More preferably, the hydrometallating agent comprises zirconium. The hydrometallating agent may be in the form of a metal complex comprising a metal (*e.g.* a transition metal) bound to one or more ligands, at least one of

which is a hydride ligand.

- In a preferred embodiment, the hydrometallating agent is a zirconium complex, *e.g.* a zirconium halohydride complex. In an embodiment, the hydrometallating agent is a zirconium complex of the formula HZrR_2X , wherein each R is independently an optionally substituted 6π electron donating ligand (*e.g.* having 5 carbon atoms, *e.g.* a π -cyclopentadienyl ligand) and X is another ligand, *e.g.* selected from halogen, triflates, alcohols and nitrogen-containing compounds. In a preferred embodiment, the hydrometallating agent is a zirconium complex of the formula HZrCp_2X , wherein each Cp is an optionally substituted π -cyclopentadienyl ligand and X is a ligand selected from halogen, triflates, alcohols and nitrogen-containing compounds. Preferably, X is halogen. Particularly preferred is a zirconium complex of the formula HZrCp_2Cl , *i.e.* the Schwartz reagent.
- 15 The hydrometallating agent may be prepared according to procedures known in the art (see *e.g.* Org. Syn., coll. Col. 9, p. 162 (1998), vol. 71, p 77 (1993); Negishi, Tet. Lett. 1984, 25, 3407; Buchwald, Tet. Lett. 1987, 28, 3895; Lipshutz, Tet. Lett., 1990, 31, 7257; Negishi, J. Org. Chem. 1991, 56, 2590; and Negishi, Eur. J. Org. Chem. 1999, 969).
- 20 The hydrometallated first compound is reacted with a second compound, the second compound comprising an allylic group. The second compound may be an acyclic compound, a cyclic compound, or may comprise an acyclic portion and a cyclic portion. The second compound will typically comprise a leaving group at an allylic position, wherein the leaving group is displaced from said position during the asymmetric alkylation reaction. By way of illustration, and without limitation, the leaving group may be any leaving group as described in relation to the moiety R^{10} herein. In an embodiment, the leaving group is a halogen, *e.g.* Cl, Br or I. Preferably, the leaving group is Cl. In some instances, the leaving group forms a ring within the second compound, and displacement of the leaving group from the allylic position results in ring-
- 25 alkylation reaction. By way of illustration, and without limitation, the leaving group may be any leaving group as described in relation to the moiety R^{10} herein. In an embodiment, the leaving group is a halogen, *e.g.* Cl, Br or I. Preferably, the leaving group is Cl. In some instances, the leaving group forms a ring within the second compound, and displacement of the leaving group from the allylic position results in ring-
- 30 opening. Thus, by way of illustration, the leaving group may be an oxygen atom which forms an epoxide ring within the second compound, and the binding of the hydrometallated first compound to the second compound results in the epoxide ring undergoing ring-opening, forming a hydroxy group in the resulting chiral compound. In

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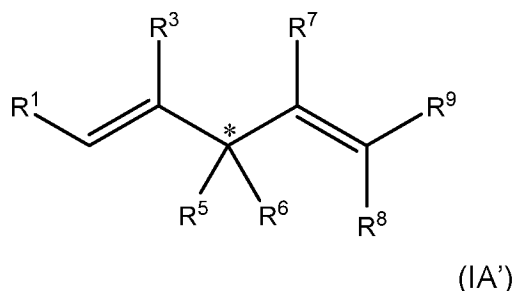
an embodiment, the second compound consists exclusively of carbon and hydrogen atoms and a leaving group at an allylic position.

The hydrometallated first compound and the second compound are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a chiral compound. Thus, the carbon atom of the hydrometallated first compound to which the metal is attached binds to a carbon atom of the allylic group, forming a stereoisomeric excess (*e.g.* an enantiomeric or diastereomeric excess) of a compound having a chiral centre at an allylic position, said chiral centre being located at the carbon atom bound by the hydrometallated first compound. The asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand. Preferably, the chiral ligand is a non-racemic chiral ligand.

Asymmetric allylic alkylation reactions may proceed via different pathways, each of which typically involves displacement of a leaving group located in an allylic position (see *e.g.* Langlois *et al, supra*). The present processes may therefore be used to form a variety of chiral compounds. Thus, for example, in cases where the allylic group forms part of a linear substrate, a chiral compound may be obtained via a pathway in which the carbon atom of the hydrometallated first compound binds to the terminal (outer) unsaturated carbon atom of the allylic group, resulting in rearrangement of the alkene bond and subsequent displacement of the leaving group. As a consequence, the carbon atom that was previously the terminal unsaturated carbon atom of the allylic group is transformed into a chiral centre. In other cases, for example where the allylic group forms part of a cyclic and/or substantially symmetrical substrate, the carbon atom of the hydrometallated first compound may bind to the carbon atom at the allylic position of the second compound, displacing the leaving group from said allylic position without rearrangement of the alkene bond. As will be apparent to those skilled in the art, parameters such as the starting materials, catalysts and reaction conditions may be varied so as to favour a certain reaction mechanism and thus a particular chiral product.

In particular, the present invention provides a process for producing a chiral compound of the formula (IA') in a stereoisomeric excess:

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wherein

5 R^1 and R^3 are each independently selected from hydrogen, R^a , hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

R^5 , R^6 , R^7 , R^8 and R^9 are each independently selected from hydrogen, R^a , hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl
10 optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^5 and one of R^6 and R^8 , or R^6 and R^7 , or R^7 and R^9 , taken together with the carbon atoms to which they are attached, may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

each R^a is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^b$, $-OR^b$, $-C(O)R^b$, $-C(O)N(R^b)R^c$, $-C(O)OR^b$, $-C(O)SR^b$, $-C(O)SeR^b$,
15 $-OC(O)R^b$, $-S(O)_kR^b$, $-S(O)_kN(R^b)R^c$, $-N(R^b)R^c$, $-N(R^b)N(R^b)R^c$, $-N(R^b)C(O)R^c$ and $-N(R^b)S(O)_kR^b$;

R^b and R^c are each independently hydrogen or selected from hydrocarbyl and $-(CH_2)_j$ -heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or
20 5 substituents independently selected from halogen, oxo, cyano, amino, hydroxy, alkyl and alkoxy;

j is 0, 1, 2, 3, 4, 5 or 6;

k is 0, 1 or 2; and

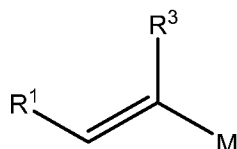
the asterisk * designates a chiral centre of (*R*) or (*S*) configuration.

25

The compound of formula (IA') may be obtained by first contacting a compound comprising an alkyne bond with a hydrometallating agent of the formula HM, wherein M comprises a metal (*e.g.* a transition metal), wherein said compound and the hydrometallating agent are contacted under conditions such that they react to form a

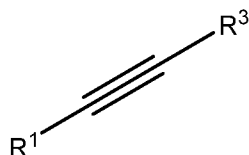
- 29 -

compound of the formula (II'):



(II').

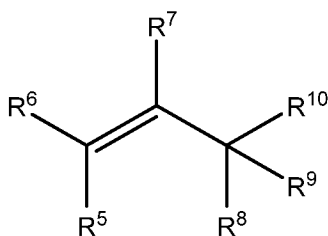
- 5 Thus, for instance, the process may comprise contacting an alkyne compound of the formula (IV'):



(IV')

- 10 with a hydrometallating agent of the formula HM under conditions such that the compounds react to form the compound of formula (II').

The compound of formula (II') is then contacted with a compound of the formula (IIIA'):



(IIIA')

15 wherein R¹⁰ is a leaving group.

- 20 In the compound of formula (IIIA'), the radicals R⁵ and R⁶ are different, and they are also each different to the moiety CH(R¹)(R²)C(R³)(R⁴)-, such that a chiral centre is formed at the position denoted by the asterisk in formula (IA').

The compound of formula (II') and the compound of formula (IIIA') are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a

stereoisomeric excess of a compound of formula (IA'). The asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

In embodiments, one or more of the following apply: (i) R^1 is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; (ii) R^1 is alkyl, cycloalkyl or aralkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a ; (iii) R^3 is hydrogen or hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and (iv) R^3 is hydrogen or alkyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

10 In an embodiment, M comprises a metal selected from zirconium, titanium, hafnium, niobium, tantalum, aluminium, tin, magnesium, zinc, palladium, iridium, copper, rhodium, ruthenium, platinum, rhenium and nickel. Preferably, M comprises a transition metal.

More preferably, the compound of formula (II') is obtained by hydrozirconation of the compound comprising said alkyne bond, e.g. by hydrozirconation of a compound of the formula (IV'). Thus, in a preferred embodiment, the hydrometallating agent HM comprises zirconium. Preferably, the hydrometallating agent is a zirconium complex of the formula $HZrR_2X$ as defined above. In a preferred embodiment, the hydrometallating agent is a zirconium complex of the formula $HZrCp_2X$ as defined above. Particularly preferred is a zirconium complex of the formula $HZrCp_2Cl$ (the Schwartz reagent).

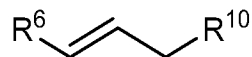
In an embodiment, R^7 is hydrogen.

R^8 and R^9 will typically be different to R^{10} . In an embodiment, R^8 and R^9 are each independently selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, R^8 and R^9 are each independently selected from hydrogen and alkyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, the compound of formula (IIIA') is a compound of the formula (IIIA.1'):

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(IIIA.1').

In an embodiment, R^6 is hydrocarbonyl optionally substituted with 1, 2, 3, 4 or 5 R^a . In an embodiment, R^6 is selected from alkyl, aryl, aralkyl and cycloalkyl, each of which is optionally substituted with 1, 2, 3, 4 or 5 R^a . In an embodiment, R^6 is aryl or aralkyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, R^{10} is a leaving group selected from halogen, cyano, cyanate, thiocyanate, $-\text{OR}^{11}$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{S})\text{R}^{11}$, $-\text{C}(\text{O})\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{C}(\text{O})\text{SR}^{11}$, $-\text{C}(\text{O})\text{SeR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_m\text{R}^{11}$, $-\text{SeR}^{11}$, $-\text{S}(\text{O})_m\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{N}(\text{R}^{11})\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{N}(\text{R}^{11})\text{C}(\text{O})\text{R}^{12}$, $-\text{N}(\text{R}^{11})\text{S}(\text{O})_m\text{R}^{12}$ and $-\text{P}(\text{O})(\text{OR}^{12})_2$, wherein R^{11} and R^{12} are each independently selected from hydrogen, alkyl, aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a ; and m is 0, 1 or 2. In an embodiment, R^{10} is a halogen. Preferably, R^{10} is Cl.

In an embodiment, R^{10} is an oxygen atom which forms an epoxide ring within the second compound, and the binding of the hydrometallated first compound to the second compound results in the epoxide ring undergoing ring-opening, forming a hydroxy group in the resulting chiral compound.

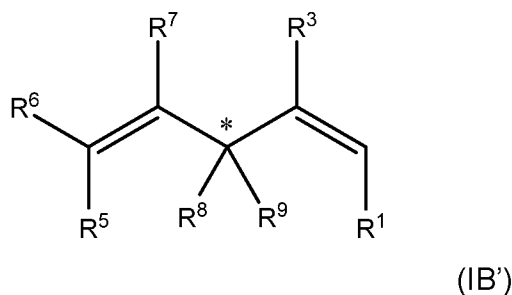
In an embodiment, R^{10} is $-\text{OP}(\text{O})(\text{OR}^{12})_2$, wherein each R^{12} is as defined above. In an embodiment, each R^{12} is alkyl, *e.g.* methyl or ethyl.

In an embodiment, each R^a is independently selected from acyl, alkoxy, alkoxycarbonyl, alkylamino, alkylsulfinyl, alkylsulfonyl, alkylthio, amino, aminoalkyl, aralkyl, cyano, dialkylamino, halo, haloalkoxy, haloalkyl, hydroxy, formyl, nitro, alkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen or haloalkyl), aryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heterocycloalkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), aminoacyl, aminosulfonyl, acylamino, sulfonylamino, heteroarylalkyl,

aryloxy, heteroaryloxy, arylalkyloxy and heteroarylalkyloxy.

In an embodiment, each R^a is independently selected from aralkyl, alkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen or haloalkyl), aryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), and heterocycloalkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl).

- 10 The present invention also provides a process for producing a chiral compound of the formula (IB') in a stereoisomeric excess:



wherein

R^1 and R^3 are each independently selected from hydrogen, R^a , hydrocarbonyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

R^5 , R^6 , R^7 , R^8 and R^9 are each independently selected from hydrogen, R^a , hydrocarbonyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^5 and one of R^6 and R^8 , or R^6 and R^7 , or R^7 and R^9 , taken together with the carbon atoms to which they are attached, may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

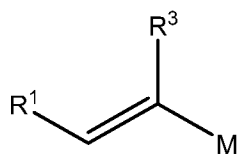
each R^a is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^b$, $-OR^b$, $-C(O)R^b$, $-C(O)N(R^b)R^c$, $-C(O)OR^b$, $-C(O)SR^b$, $-C(O)SeR^b$, $-OC(O)R^b$, $-S(O)_kR^b$, $-S(O)_kN(R^b)R^c$, $-N(R^b)R^c$, $-N(R^b)N(R^b)R^c$, $-N(R^b)C(O)R^c$ and $-N(R^b)S(O)_kR^b$;

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R^b and R^c are each independently hydrogen or selected from hydrocarbyl and $-(CH_2)_j$ -heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, oxo, cyano, amino, hydroxy, alkyl and alkoxy;

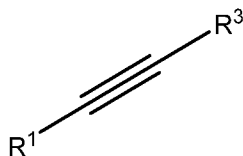
- 5 j is 0, 1, 2, 3, 4, 5 or 6;
 k is 0, 1 or 2; and
 the asterisk * designates a chiral centre of (*R*) or (*S*) configuration.

10 The compound of formula (IB') may be obtained by first contacting a compound comprising an alkyne bond with a hydrometallating agent of the formula HM, wherein M comprises a metal (*e.g.* a transition metal), wherein said compound and the hydrometallating agent are contacted under conditions such that they react to form a compound of the formula (II'):



(II').

Thus, for instance, the process may comprise contacting an alkyne compound of the formula (IV'):

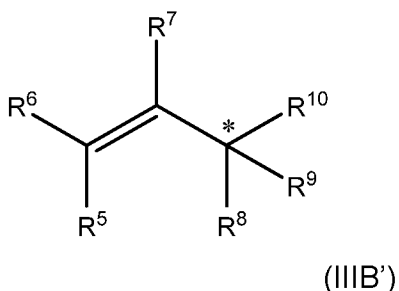


(IV')

25 with a hydrometallating agent of the formula HM under conditions such that the compounds react to form the compound of formula (II').

The compound of formula (II') is then contacted with a compound of the formula (IIIB'):

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wherein

- 5 R^{10} is a leaving group; and
 the asterisk * designates a chiral centre of (*R*) or (*S*) configuration.

In the compound of formula (IIIB'), the radicals R^8 , R^9 and R^{10} are each different, and they are also each different to the moiety $CH(R^1)(R^2)-C(R^3)(R^4)-$, such that a chiral
 10 centre is formed at the position denoted by the asterisk in formula (IB').

The compound of formula (II') and the compound of formula (IIIB') are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a stereoisomeric excess of a compound of formula (IB'). The asymmetric allylic alkylation
 15 reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

In embodiments, one or more of the following apply: (i) R^1 is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; (ii) R^1 is alkyl, cycloalkyl or aralkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a ; (iii) R^3 is hydrogen or hydrocarbyl optionally
 20 substituted with 1, 2, 3, 4 or 5 R^a ; and (iv) R^3 is hydrogen or alkyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, M comprises a metal selected from zirconium, titanium, hafnium, niobium, tantalum, aluminium, tin, magnesium, zinc, palladium, iridium, copper, rhodium,
 25 ruthenium, platinum, rhenium and nickel. Preferably, M comprises a transition metal.

More preferably, the compound of formula (II') is obtained by hydrozirconation of the compound comprising said alkyne bond, *e.g.* by hydrozirconation of a compound of the formula (IV'). Thus, in a preferred embodiment, the hydrometallating agent HM

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comprises zirconium. Preferably, the hydrometallating agent is a zirconium complex of the formula HZrR_2X as defined above. In a preferred embodiment, the hydrometallating agent is a zirconium complex of the formula HZrCp_2X as defined above. Particularly preferred is a zirconium complex of the formula HZrCp_2Cl (the Schwartz reagent).

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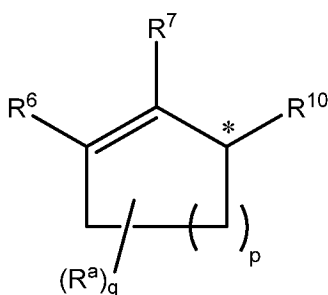
In an embodiment, R^8 and R^9 are each independently selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(\text{CH}_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

- 10 In an embodiment, R^5 and R^8 , taken together with the carbon atoms to which they are attached, form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a .

- 15 In an embodiment, R^5 and R^8 , taken together with the carbon atoms to which they are attached, form a 5-, 6-, 7- or 8-membered carbocyclic or heterocyclic group which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

In an embodiment, R^9 is hydrogen.

- 20 In an embodiment, the compound of formula (IIIB') is a compound of formula (IIIB.1'):



(IIIB.1')

wherein

p is 1, 2, 3 or 4; and

- 25 q is 0, 1, 2, 3, 4 or 5.

In an embodiment, p is 2. In an embodiment, q is 0.

In an embodiment, R^6 is selected from hydrogen and alkyl, *e.g.* hydrogen and methyl.

In an embodiment, R^7 is hydrogen.

- 5 In an embodiment, R^{10} is a leaving group selected from halogen, cyano, cyanate, thiocyanate, $-OR^{11}$, $-C(O)R^{11}$, $-C(S)R^{11}$, $-C(O)N(R^{11})R^{12}$, $-C(O)OR^{11}$, $-C(O)SR^{11}$, $-C(O)SeR^{11}$, $-OC(O)R^{11}$, $-S(O)_mR^{11}$, $-SeR^{11}$, $-S(O)_mN(R^{11})R^{12}$, $-N(R^{11})R^{12}$, $-N(R^{11})N(R^{11})R^{12}$, $-N(R^{11})C(O)R^{12}$, $-N(R^{11})S(O)_mR^{12}$ and $-P(O)(OR^{12})_2$, wherein R^{11} and R^{12} are each independently selected from hydrogen, alkyl, aryl, cycloalkyl, heteroaryl
10 and heterocycloalkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a ; and m is 0, 1 or 2. In an embodiment, R^{10} is a halogen. Preferably, R^{10} is Cl.

In an embodiment, R^{10} is an oxygen atom which forms an epoxide ring within the second compound, and the binding of the hydrometallated first compound to the second
15 compound results in the epoxide ring undergoing ring-opening, forming a hydroxy group in the resulting chiral compound.

In an embodiment, each R^a is independently selected from acyl, alkoxy, alkoxycarbonyl, alkylamino, alkylsulfinyl, alkylsulfonyl, alkylthio, amino, aminoalkyl, aralkyl, cyano,
20 dialkylamino, halo, haloalkoxy, haloalkyl, hydroxy, formyl, nitro, alkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen or haloalkyl), aryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heterocycloalkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen,
25 alkyl or haloalkyl), aminoacyl, aminosulfonyl, acylamino, sulfonylamino, heteroarylalkyl, aryloxy, heteroaryloxy, arylalkyloxy and heteroarylalkyloxy.

In an embodiment, each R^a is independently selected from aralkyl, alkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen or haloalkyl), aryl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl
30 (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl), and heterocycloalkyl (optionally substituted with *e.g.* alkoxy, hydroxy, haloalkoxy, halogen, alkyl or haloalkyl).

Preferably, the compound of formula (IIIB') is formed via a dynamic kinetic resolution process or a dynamic kinetic asymmetric transformation process. Such processes are known in the art to be highly enantioselective and may allow for the conversion of both enantiomers of a racemic compound into a single enantiomerically enriched compound (see *e.g.* Trost *et al*, 1994, J. Am Chem. Soc. 116, 4089-4090; and Langlois *et al*, *supra*). Thus, for example, either or both enantiomers of a compound of formula (IIIB') may be converted into a single enantiomer of a compound of formula (IB'). The resulting chiral compound may have an enantiomeric excess greater than 80%, *e.g.* greater than 90% *e.g.* greater than 95%, *e.g.* greater than 99%. In particular, when starting from a second compound which is racemic, a chiral compound may be formed in a 100% enantiomeric excess. Preferably, the second compound is in racemic form, *e.g.* the second compound is a racemic compound of the formula (IIIB'). Preferably, the second compound is a cyclic and/or substantially symmetrical compound. Thus, for example, a process of the invention may involve the use of a compound of formula (IIIB') which is cyclic and/or substantially symmetrical.

In an embodiment, the chiral compound is formed via desymmetrisation of a meso compound containing an allyl group.

The asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising at least one chiral ligand. In an embodiment, the metal catalyst comprises a metal, one or more chiral ligands and one or more counterions.

In an embodiment, the metal catalyst comprises a transition metal, *e.g.* selected from copper, cobalt, iridium, rhodium, ruthenium, nickel, iron, palladium, gold, silver and platinum.

In a preferred embodiment, the metal catalyst comprises copper. In this regard, it has been found that copper can catalyse asymmetric allylic addition reactions with high overall yield. The reaction tolerates various functionalities; indeed, functional groups that are not compatible with Grignard reagents and organozincs may be compatible with the processes described herein.

The metal catalyst may comprise any catalytic metal and/or catalyst precursor as it is introduced into the reaction vessel and which may be, if needed, converted *in situ* into the active form, as well as the active form of the catalyst which participates in the reaction. In embodiments, the metal catalyst is provided in the reaction mixture in an amount ranging from about 5% to about 10% by weight. The catalyst may be prepared *in situ* by stirring the metal, chiral ligand and any other components (*e.g.* one or more other ligands) together at *e.g.* room temperature.

Preferably, the metal catalyst comprises copper(I). In a particular embodiment, the metal catalyst is formed from a copper (I) salt comprising a non-coordinating counterion. Preferably, the metal catalyst is formed using a copper halide salt, wherein the halide is preferably Cl, Br or I. More preferably the metal catalyst is formed using a copper iodide salt. Using a copper iodide salt in accordance with the process of the present invention has been shown to give high enantioselectivity.

The metal catalyst comprises at least one chiral ligand. Preferably, the chiral ligand is a non-racemic chiral ligand. The chiral ligand may be a chelating ligand or a non-chelating ligand. Examples of suitable ligands include phosphines, bisphosphines, amines, diamines, imines, arsines, sulfides, sulfoxides, carbenes (*e.g.* N-heterocyclic carbenes), peptides and hybrids thereof, including hybrids of phosphines with amines, hybrids of phosphines with peptides, and hybrids of phosphines with sulfides.

In a more preferred embodiment, the non-racemic chiral ligand is a phosphoramidite ligand. Particularly preferred for use in the present processes are the phosphoramidite ligands A and G as described in the Examples herein.

The chiral ligand may be used in the form of a purified stereoisomer. The metal catalyst may comprise one or more other ligands, in addition to the at least one chiral ligand. In particular, the metal catalyst may include one or more additional ligands as is necessary to obtain a stable complex. The or each ligand can be added to the reaction mixture in the form of a metal complex, or added as a separate reagent relative to the addition of the metal.

The various synthetic steps described herein may be performed in separate reaction vessels or in the same reaction vessel (*i.e.* as a “one-pot” reaction). The process may comprise isolating and/or characterising one or more intermediates, *e.g.* the hydrometallated alkyne, of the process.

5

A process of the present invention may be conducted at a temperature of from 0 °C to 60 °C. In particular, the present processes may be conducted at a temperature of from 10 °C to 30 °C, *e.g.* from 20 °C to 25 °C. More preferably, the present processes are conducted at room temperature.

10

A process of the present invention will generally be conducted in the presence of one or more solvents. Examples of suitable solvents include dichloromethane, 1,2-dichloroethane, chloroform, Et₂O, t-BuOMe, i-Pr₂O, 2,2-dimethoxypropane, tetrahydrofuran, 2-methyltetrahydrofuran, diglyme, 1,4-dioxane, toluene, m-xylene and hexane. A preferred solvent is chloroform.

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By way of illustration, a process of the present invention may be conducted in accordance with one of the procedures described in the Examples or elsewhere herein. It will be understood that the processes described in the Examples are solely for the purpose of illustrating the invention and should not be construed as limiting. A process utilising similar or analogous reagents and/or conditions known to one skilled in the art may also be used to obtain a compound of the invention. Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by the formation of a salt if appropriate or possible under the circumstances.

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The present processes produce a chiral compound (*e.g.* the compound of formula (IA), (IB), (IA') or (IB')) in a stereoisomeric excess, *i.e.* such that the concentration of one stereoisomer of the chiral compound exceeds the concentration of another stereoisomer. That is, the present processes yield a chiral compound with a stereoisomeric excess of greater than zero. Preferably, the present processes yield a product with a stereoisomeric excess of greater than 20%, greater than 50%, greater than 70%, greater

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than 80%, or greater than 90%. The chiral compound may be enantiomeric or diastereomeric. For instance, the desired compound may be obtained in a substantially pure form (*e.g.* a form having a purity of greater than 80% purity, in particular greater than 90%, 95% or 99%) of a single enantiomer or diastereomer. In an embodiment, the
5 chiral compound is enantiomeric. All stereoisomers are included within the scope of the present invention. Where a single enantiomer or diastereoisomer is disclosed, the present invention also extends to the other enantiomers or diastereoisomers.

Stereoisomers may be isolated by separation of a racemic or other mixture of the
10 compounds using conventional, *e.g.* fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the stereoisomers by conventional means (*e.g.* HPLC, chromatography
15 over silica).

Compounds of the present invention may also exhibit geometrical isomerism. The present invention contemplates the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond and
20 designates such isomers as of the Z or E configuration, wherein the term "Z" represents substituents on the same side of the carbon-carbon double bond and the term "E" represents substituents on opposite sides of the carbon-carbon double bond.

Compounds of the present invention (especially those containing heteroatoms and
25 conjugated bonds) may also exist in tautomeric forms, and all such tautomers are included in the scope of the present invention. In particular, the present compounds (*e.g.* the compounds of the formula (IA) or (IB)) may be obtained and isolated in the form of enolates and other tautomeric forms; once again, all such tautomeric forms are included within the scope of the present invention. The present invention also extends to
30 all other variant forms of the defined compounds, for example salts, esters, acids or other variants of the present compounds and their tautomers.

Advantageously, a process of the present invention may be efficient, selective, direct,

and may occur at easily accessible temperatures. By avoiding extra steps and protecting groups these methods are environmentally friendly compared to currently available technology. The present invention also introduces the highly practical concept of using inexpensive, functional group tolerant alkenes in a number of useful transformations to synthetic chemists.

The present processes are particularly relevant to industry. A process of the invention may further comprise formulating a product comprising the chiral compound or converting the chiral compound into a product. In an embodiment, the product is a pharmaceutical product, a cosmetic product, a fragrance, a foodstuff, a petrochemical product or a polymer product.

In particular, the present processes may be utilised in the production of active pharmaceutical ingredients, *e.g.* prostaglandins, opiates or terpinoids. In particular, the present processes may be used to prepare compounds having antimicrobial, antibacterial or antibiotic activity, such as hydnocarpic acid, chaulmoogric acid or anthelminthicin C. Thus, the chiral compound may be formulated together with one or more pharmaceutically acceptable carriers or excipients, to provide a pharmaceutical formulation; or chemically converted to a pharmaceutically active ingredient. Moreover, where the chiral compound is an active pharmaceutical ingredient, the compound may be obtained in the form of a free acid or base, or in the form of a pharmaceutically acceptable salt thereof. The term "pharmaceutically acceptable salt" refers to acid addition salts or base addition salts of the compounds in the present invention. Pharmaceutically acceptable salts include salts of both inorganic and organic acids.

The following non-limiting Examples illustrate the present invention.

Materials and Methods

Procedures using oxygen- and/or moisture-sensitive materials were performed with anhydrous solvents (*vide infra*) under an atmosphere of anhydrous argon in flame-dried flasks, using standard Schlenk techniques. Analytical thin-layer chromatography was performed on precoated glass-backed plates (Silica Gel 60 F₂₅₄; Merck), and visualised

using a combination of UV light (254 nm) and aqueous ceric ammonium molybdate (CAM), aqueous basic potassium permanganate stains or vanillin solution. Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), Merck 60 Å silica gel, VWR (40-63 µm) silica gel, Sigma Aldrich silica gel.

5 Pressure was applied at the column head via hand bellows or a flow of nitrogen with the solvent system stated in parentheses.

Cooling of reaction mixtures to 0 °C was achieved using an ice-water bath. Other temperatures were obtained using a Julabo FT902 immersion cooler.

10 Unless stated otherwise, solution NMR spectra were recorded at room temperature; ¹H and ¹³C nuclear magnetic resonance experiments were carried out using Bruker DPX-200 (200/50 MHz), AVN-400 (400/100 MHz), DQX-400 (400/100 MHz) or AVC-500 (500/125 MHz) spectrometers. Chemical shifts are reported in ppm from the residual solvent peak. Chemical shifts (δ) are given in ppm and coupling constants (J) are

15 quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Labels H and H' refer to diastereotopic protons attached to the same carbon and impart no stereochemical information. Assignments were made with the assistance of gCOSY, DEPT-135, gHSQC and gHMBC or gHMQC NMR

20 spectra.

Numbering and names of structures accompanying reported data is non-IUPAC, and solely for reference.

25 Low-resolution mass spectra were recorded using a Walters LCT premier XE. High resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer.

Chiral HPLC separations were achieved using an Agilent 1230 Infinity series normal phase HPLC unit and HP Chemstation software. Chiralpak® columns (250 × 4.6 mm), fitted with matching Chiralpak® Guard Cartridges (10 × 4 mm), were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn); all eluent systems were isocratic.

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Infrared measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-600 cm^{-1} .

Optical rotations were recorded using a Perkin-Elmer 241 Polarimeter; $[\alpha]_D$ values are given in $10^{-1} \text{ deg.cm}^2 \text{ g}^{-1}$ (concentration c given as g/100 mL).

Dry THF, CH_2Cl_2 , Et_2O , PhMe, benzene, hexane, pentane, DME, acetonitrile and 1,2-dichloroethane were collected fresh from an mBraun SPS-800 solvent purification system having been passed through anhydrous alumina columns. Dry tert-butyl methyl ether and 2-Me-THF were purchased from Acros with an AcroSeal®. All other dry solvents used were dried over 3 Å molecular sieves and stored under argon. All other solvents were used as purchased from Sigma Aldrich, Rathburn or Fisher Scientific.

Unless stated otherwise, commercially available reagents were purchased from Sigma-Aldrich, Fisher Scientific, Apollo Scientific, Acros Organics, Strem Chemicals, Alfa Aesar or TCI UK and were used without purification. Petroleum ether refers to light petroleum boiling in the range 30-40 °C. Deuterated solvents were purchased from Sigma-Aldrich (CD_2Cl_2 , CDCl_3). Schwartz reagent was prepared from Cp_2ZrCl_2 provided by Alfa Aesar or Strem Chemicals. CuI (98% purity) was purchased from Strem Chemicals and CuI (99.99% purity) was obtained from Sigma-Aldrich; both were directly used without any further purification. All cyclic allylchlorides were distilled fresh and stored in Schlenk flasks under an argon atmosphere. $(t\text{-BuCN})_2\text{Cu}\cdot\text{OTf}$ was synthesised according to literature procedures and carefully maintained under an inert atmosphere. Phosphoramidite ligands A and G (see Table 1 *infra*) were synthesised according to literature procedures (see *e.g.* Teichert *et al*, Angew. Chem. Int. Ed., 2010, 49, 2486-2528; Maksymowicz *et al*, Nat. Chem., 2012, 4(8), 649-654; and Sidera *et al*, Angew. Chem. Int. Ed., 2013; and also the references cited therein).

General procedures

In these examples, an alkene hydrozirconation reaction was first performed using the Schwartz reagent (Cp_2ZrHCl). The hydrozirconated alkene was then reacted with a substrate containing an allylic group. The general procedures employed are as follows.

General procedure 1: Synthesis of racemic products

Cp₂ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH₂Cl₂ (2.0 mL) under an argon atmosphere. After stirring for 40 min, CuBr·Me₂S (82 mg, 0.40 mmol 1.0 eq), was added to the reaction mixture and the resulting black mixture was allowed to stir for an additional 10 min before a compound comprising an allylic group (0.40 mmol, 1.0 eq) was added via syringe over about 1 min. Stirring at room temperature was continued arbitrarily for 15 h before the reaction was quenched by the addition of petrol (*ca* 3 mL) and then NH₄Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with NaHCO₃ (aq. sat., *ca* 10 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the residue (EtOAc/petrol; SiO₂) gave the desired cyclic allylic product. In some cases, further purification was performed to remove excess alkene. This was achieved by distillation using a Kugelrohr, setting up conditions according to the boiling point of the alkene used in each case.

General procedure 2: Synthesis of asymmetric products

CuI (7.7 mg, 0.04 mmol, 0.1 eq) and phosphoramidite ligand A or G (21.2 mg, 0.04 mmol, 0.1 eq) were dissolved in CHCl₃ (0.8 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp₂ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH₂Cl₂ (0.40 mL) under an argon atmosphere. After stirring for 40 min, the resulting clear yellow solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before a compound comprising an allylic group (0.40 mmol, 1.0 eq) was added dropwise via a microsyringe. The reaction was stirred overnight. Afterwards, reaction was quenched by the addition of petrol (*ca* 3 mL) and then NH₄Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with NaHCO₃ (aq. sat., *ca* 10 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the residue

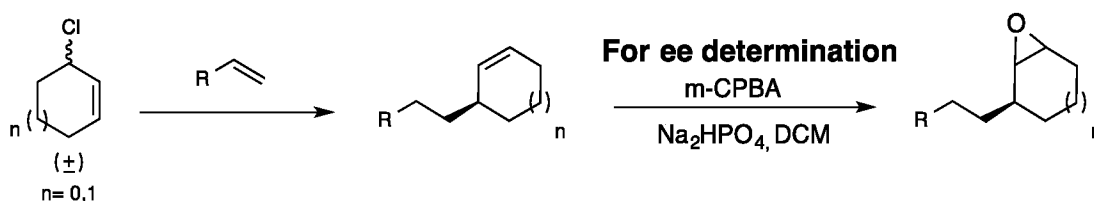
(EtOAc/petrol; SiO₂) gave the desired cyclic allylic product. In some cases, further purification was performed to remove excess alkene. This was achieved by distillation using a Kugelrohr, setting up conditions according to the boiling point of the alkene used in each case.

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General procedure 3: Procedure used in selected optimization experiments

In a 5 mL flame dried flask, the copper source (0.02 mmol, 0.1 eq) and ligand (0.02 mmol, 0.1 eq) were dissolved in a solvent (0.4 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp₂ZrHCl (103 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene (0.08 mL, 0.5 mmol, 2.5 eq) in CH₂Cl₂ (0.20 mL) under an argon atmosphere. After stirring for 20 min, the resulting clear yellow solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before 3-chlorocyclohexene (23.3 mg, 0.20 mmol, 1.00 eq) was added dropwise via a microsyringe. Stirring at room temperature was arbitrarily continued overnight and the reaction was then diluted and then quenched by addition of petrol (ca 3 mL) and then NH₄Cl (1 M aq., ca 1.5 mL). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with NaHCO₃ (aq. sat. ca 10 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude product. The enantiomeric excess was measured directly on the crude reaction products.

25 *General procedure 4: Derivatization of products to epoxides*



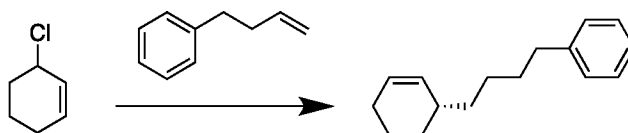
m-CPBA (2 eq) and Na₂HPO₄ (3 eq) were added at room temperature to a stirred solution of the isolated product (1 eq) in CH₂Cl₂ (6 mL, for a 0.4 mmol scale reaction) under an argon atmosphere. The reaction mixture was stirred arbitrarily for 2 h before being diluted and quenched by addition of Et₂O (10 mL) and an aqueous solution of

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saturated $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL). The organic phase was washed with NaOH (1 M aq., 3 × 5 mL), dried over Mg_2SO_4 , filtered and concentrated under vacuum. The resulting crude mixture of diastereomeric epoxides was directly analyzed by GC chromatography using a chiral non-racemic stationary phase.

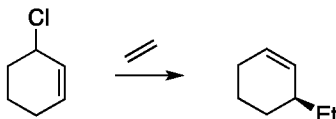
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Example 1: Synthesis of (R)-(+)-4-(Cyclohex-2-en-1-yl)butyl)benzene (3a)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl_3 (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO_3 (sat. aq. ca. 2.0 mL), water (2.0 mL), dried (MgSO_4), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr apparatus ($T = 110^\circ\text{C}$, 55 mbar) gave (*R*)-(-)-4-(cyclohex-2-en-1-yl) butyl) benzene (73.8 mg, 0.34 mmol) in 86% yield. Enantiomeric excess of 93% was determined by HPLC [Chiralpak® IA; flow: 0.6 mL/min; hexane/*i*-PrOH: 99.9: 0.1; $\lambda = 210$ nm; major enantiomer $t_R = 8.2$ min; minor enantiomer $t_R = 8.8$ min]. ^1H NMR (400 MHz, CDCl_3) δ_{H} /ppm: 1.26 - 1.78 (m, 10 H), 1.99 (m, 1 H), 2.07 (m, 2 H), 2.62-2.67 (m, 2 H), 5.58-5.62 (m, 1 H), 5.67-5.71 (m, 1 H), 7.20- 7.23 (m, 3 H), 7.28 - 7.31 (m, 2 H). ^{13}C NMR (100 MHz, CDCl_3) δ_{C} /ppm: 21.5, 25.4, 26.7, 29.1, 31.8, 35.1, 35.9, 36.2, 125.6, 126.7, 128.2, 128.4, 132.3, 142.9 HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{22}$ $[\text{M}]^+$: 214.1721, found: 214.1717. IR (ATR) ν (cm^{-1} , CHCl_3): 698, 1217, 1229, 1366, 1454, 1739, 2855, 2926. $[\alpha]_{589}^{20} = +11.8$ ($c=0.36$ in CHCl_3 , 93% ee).

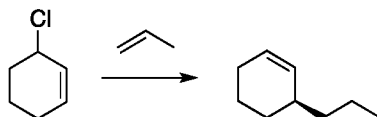
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Example 2: Synthesis of (S)-(-)-3-Ethylcyclohex-1-ene (3b)

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Cul (15.2 mg, 0.08 mmol, 0.10 eq), (S,S,S)-Ligand A (43.2 mg, 0.08 mmol, 0.10 eq) and then CHCl₃ (1.6 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, Cp₂ZrHCl (412 mg, 1.60 mmol, 2.00 eq) and CH₂Cl₂ (0.8 mL) were added to another flame-dried flask, and smoothly stirred at room temperature. A balloon charged with ethylene is bubbled through the later solution for 3 min and the resulting mixture is then vigorously stirred at room temperature under the gaseous alkene atmosphere for 15 min; during this time a clear yellow solution developed, and the resulting organozirconium species is transferred to the copper-ligand solution using a syringe over about 1 minute. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL), dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) gave (S)-(-)-3-ethylcyclohex-1-ene (58.9 mg, 0.54 mmol, 67% yield) as a clear colourless oil. GC analysis of the crude mixture of epoxides derived from 3b indicated an enantiomeric excess of 94% (Hydrodex 6-TBDM, 60-100°C at 5 °C/min, 110-170 °C at 20 °C/min, 10psi); major enantiomer t_R = 9.99, 11.82 min; minor enantiomer t_R = 10.14, 11.09 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm 0.92 (t, J=7.46 Hz, 3 H), 1.13 - 1.43 (m, 3 H), 1.43 - 1.57 (m, 1 H) 1.65 - 1.84 (m, 2 H) 1.89 - 2.03 (m, 3 H) 5.56 - 5.64 (m, 1 H) 5.64 - 5.72 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm 11.5, 21.6, 25.4, 28.6, 29.0, 36.8, 126.7, 132.1. HRMS (ESI) m/z calcd for C₈H₁₄ [M]⁺: 110.1096, found: 110.0944. IR (ATR) ν (cm⁻¹): 2930, 2857, 1764, 1227. [α]_D²⁰ = -83.33 (c 0.04, CHCl₃) for 94% ee [lit. [α]_D²⁰ = -83.34 (c 1.00, CHCl₃)].

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Example 3: Synthesis of (S)-(-)-3-Propylcyclohex-1-ene (3c)

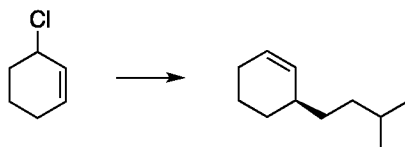
5 CuI (15.2 mg, 0.08 mmol, 0.10 eq), (*S,S,S*)-Ligand A (43.2 mg, 0.08 mmol, 0.10 eq) and then CHCl₃ (1.6 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, Cp₂ZrHCl (412 mg, 1.60 mmol, 2.00 eq) and CH₂Cl₂ (0.8 mL) were added to another flame-dried flask, and smoothly stirred at room temperature. A balloon charged with propylene is bubbled through the later solution for 3

10 min and the resulting mixture is then vigorously stirred at room temperature under the gaseous alkene atmosphere for 15 min; during this time a clear yellow solution developed, and the resulting organozirconium species is transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocyclohex-1-ene (93.3 mg, 0.80 mmol, 1.00 eq) was added

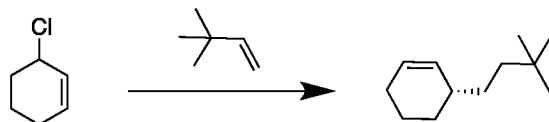
15 dropwise. The reaction mixture was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) gave (*S*)-(-)-3-

20 propylcyclohex-1-ene (78.0 mg, 0.71 mmol, 89% yield) as a colourless oil. GC analysis of the crude mixture of epoxides derived from 3c indicated an enantiomeric excess of 92% (Hydrodex 6-TBDM, 60-100°C at 5 °C/min, 110-170 °C at 20 °C/min, 10psi); major enantiomer *t_R* = 15.301 min; minor enantiomer *t_R* = 14.52 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm 0.91 (t, *J*=7.0 Hz, 3 H), 1.15 - 1.44 (m, 5 H), 1.45 - 1.58 (m, 1 H), 1.65 - 1.86 (m, 2 H), 1.97 (br. s., 2 H), 2.06 (br. s., 1 H), 5.52 - 5.63 (m, 1 H), 5.63 - 5.70 (m, 1 H). ¹³C

25 NMR (100 MHz, CDCl₃) δ_C /ppm 14.3, 20.0, 21.5, 25.4, 29.1, 34.9, 38.7, 126.6, 132.4. HRMS (TOF) *m/z* calcd for C₉H₁₆ [M]⁺: 124.1252, found: 124.1250. IR (ATR) ν (cm⁻¹): 2925.4, 2852.8, 1261. [α]_D²⁰ = -77.0 (*c* 0.27, CHCl₃) for 92% ee.

Example 4: Synthesis of (S)-(-)-3-Isopentylcyclohex-1-ene (3d)

- 5 CuI (15.2 mg, 0.08 mmol, 0.10 eq), (*S,S,S*)-Ligand A (43.2 mg, 0.08 mmol, 0.10 eq) and then CHCl₃ (1.6 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, Cp₂ZrHCl (412 mg, 1.60 mmol, 2.00 eq) and CH₂Cl₂ (0.8 mL) were added to another flame-dried flask, and smoothly stirred at room temperature. A balloon charged with 3-methyl-1-butene is bubbled through the later
- 10 solution for 3 min and the resulting mixture is then vigorously stirred at room temperature under the gaseous alkene atmosphere for 15 min and the resulting organozirconium species is transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (93.3 mg, 0.80 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring
- 15 overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) gave (*S*)-(-)-3-isopentylcyclohex-1-ene (112.0 mg, 0.74 mmol, 93%
- 20 yield). GC analysis of the crude mixture of epoxides derived from 3d indicated an enantiomeric excess of 91% (Hydrodex 6-TBDM, 60-100°C at 5°C/min, 110-170°C at 20°C/min, 10psi); major enantiomer *t_R* = 22.91 min; minor enantiomer *t_R* = 22.62 min.¹H NMR (400 MHz, CDCl₃) δ_H /ppm 0.89 (d, *J*=6.6 Hz, 6 H), 1.13 - 1.41 (m, 5 H), 1.43 - 1.60 (m, 2 H), 1.64 - 1.86 (m, 2 H), 1.98 (br. s., 3 H), 5.59 (d, *J*=10.3 Hz, 1 H), 5.66 (d, *J*=10.5
- 25 Hz, 1 H).¹³C NMR (100 MHz, CDCl₃) δ_C /ppm 21.6, 22.6, 22.7, 25.4, 28.3, 29.2, 34.2, 35.5, 36.3, 126.6, 132.4. HRMS (ESI) *m/z* calcd for C₁₁H₂₀ [M]⁺: 152.1565, found: 152.1559. IR (ATR) ν (cm⁻¹): 2955.3, 2923.0, 2849.1, 1657.7, 1261.5. [α]_D²⁰ = -60.7 (c 1.20, CHCl₃) for 91% ee].

Example 5: Synthesis of (R)-(+)-3-(3,3-Dimethylbutyl)cyclohex-1-ene (3e)

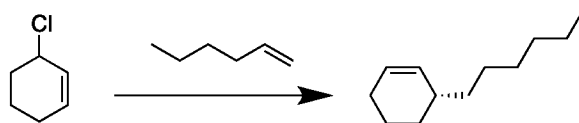
5 Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 3,3-Dimethyl-1-butene (0.13 mL, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.8 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and stirred under an argon atmosphere while heating to reflux

10 (~40 °C) until the solution became clear and yellow (approx. 30 min). After being allowed to cool to room temperature, the resulting organozirconium species was transferred to the copper-ligand solution *via* syringe over about 1 minute. After stirring at room temperature for 5 minutes, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise and the reaction was arbitrarily left stirring overnight before being

15 quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) and further distillation by Kugelrohr (T = 28 °C and 200 mbar pressure) gave (*R*)-(+)-3-(3,3-dimethyl

20 butyl) cyclohex-1-ene (36.6 mg, 0.22 mmol) in 56% yield. GC analysis of the crude mixture of epoxides derived from 3e indicated an enantiomeric excess of 93% (Hydrodex 6-TBDM, 60-170°C at 1 °C/min, 10psi); major enantiomer *t_R* = 50.3, 57.4 min; minor enantiomer *t_R* = 50.7, 61.8 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: 0.88 (s, 9 H), 1.19-1.26 (m, 5 H), 1.48-1.56 (m, 1 H), 1.71-1.81 (m, 2 H), 1.96-1.98 (m, 3 H), 5.58-5.61 (m, 1 H), 5.65-5.66 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm: 21.6, 25.4, 29.2, 29.4, 30.2, 31.2, 35.9, 41.3, 126.6, 132.5. HRMS (ESI) *m/z* calcd for C₁₂H₂₂ [M]⁺: 166.1722, found: 166.1723. IR (ATR) ν (cm⁻¹, CHCl₃): 1262, 1468, 2925. [α]_D²⁰ = + 29.2 (c= 1.75 in CHCl₃, 93% ee).

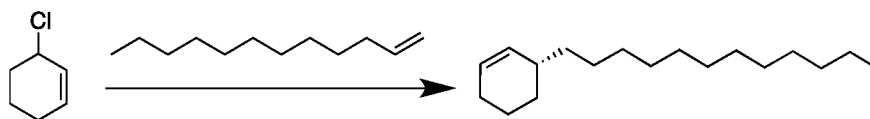
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Example 6: Synthesis of (R)-(+)-3-Hexylcyclohex-1-ene (3f)

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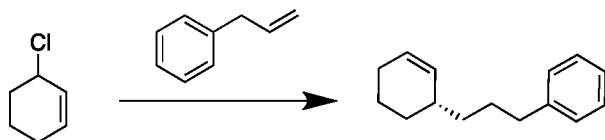
Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (0.12 mL, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until a clear yellow solution was obtained (approx. 15 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (~1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL), dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) and further distillation by Kugelrohr (T = 30 °C and 100 mbar pressure) gave (*R*)-(+)-3-hexylcyclohex-1-ene (55.7 mg, 0.34 mmol) in 84% yield. GC analysis of the crude mixture of epoxides derived from 3f indicated an enantiomeric excess of 95% (Hydrodex 6-TBDM, 60-170°C at 1 °C/min, 10psi); major enantiomer t_R = 64.6, 68.1 min; minor enantiomer t_R = 65.3, 70.5 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: 0.88-0.91 (t, 3 H, J = 6.8 Hz), 1.25-1.31 (m, 11 H), 1.48-1.56(m, 1H), 1.69-1.81(m, 2 H), 1.95- 2.04 (m, 3 H), 5.57-5.60 (m, 1 H), 5.64-5.67 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm: 14.1, 21.6, 22.7, 25.4, 26.9, 29.2, 29.6, 31.9, 35.2, 36.5, 126.6, 132.4. HRMS (ESI) *m/z* calcd for C₁₂H₂₂ [M]⁺: 166.1722, found: 166.1725. IR (ATR) ν (cm⁻¹, CHCl₃): 1216, 1229, 1367, 1739, 2924. [α]_D²⁰ = + 4.7 (c=2.285 in CHCl₃, 95% ee).

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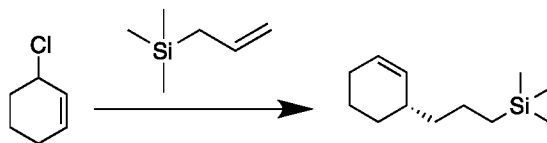
Example 7: Synthesis of (R)-(+)-3-Dodecylcyclohex-1-ene (3g)

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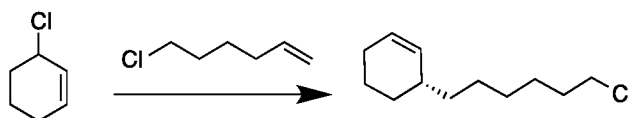
Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-Dodecene (0.22 mL, 1.00 mmol, 2.50 eq),
 10 CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until a clear yellow solution was obtained (approx. 20 min). The resulting organozirconium species was transferred over about 1 minute to the copper-ligand solution using a syringe. After stirring at room temperature for 5 additional min, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq)
 15 was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL), dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) and further
 20 distillation by Kugelrohr (T = 150 °C and 50 mbar pressure) gave (*R*)-(+)-3-dodecylcyclohex-1-ene (78.1 mg, 0.32 mmol) in 78% yield. GC analysis of the crude mixture of epoxides derived from 3g indicated an enantiomeric excess of 95% (Hydrodex 6-TBDM, 60-170°C at 1 °C/min, hold for 70 min, 10psi); major enantiomer t_R = 140.3 min; minor enantiomer t_R = 141.4 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: 0.87-0.91 (t, 3 H, J = 6.85 Hz), 1.22-1.32 (m, 23 H), 1.48-1.56 (m, 1 H), 1.71-1.81 (m, 2 H), 1.95-2.06 (m, 3 H), 5.57-5.60 (m, 1 H), 5.64-5.68 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm: 21.6, 22.7, 25.4, 27.0, 29.1, 29.3, 29.7 (br. m, 6C), 29.9, 31.9, 35.2, 36.5, 126.6, 132.4. HRMS (ESI) *m/z* calcd for C₁₈H₃₄ [M]⁺: 250.2661, found: 250.2664. IR (ATR) ν (cm⁻¹, CHCl₃): 1733, 1739, 1742. [α]_D²⁰ = + 18.0 (c = 0.84 in CHCl₃, 95% ee).
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Example 8: Synthesis of (R)-(+)-(3-(Cyclohex-2-en-1-yl)propyl)benzene (3h)

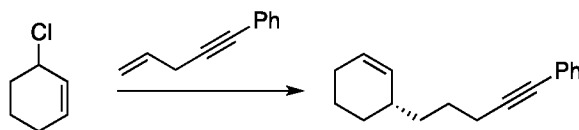
5 Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, allylbenzene (0.13 mL, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear
 10 solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0
 15 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) and further distillation by Kugelrohr (T = 100 °C and 50 mbar pressure) gave (*R*)-(+)-(3-(cyclohex-2-en-1-yl) propyl) benzene (60.9 mg, 0.31 mmol) in 76% yield. GC analysis of the crude
 20 mixture of epoxides derived from 3h indicated an enantiomeric excess of 91% (Hydrodex 6-TBDM, 60-170°C at 1 °C/min, hold for 70 min, 10psi); major enantiomer *t_R* = 114.9, 118.6 min; minor enantiomer *t_R* = 113.2, 118.8 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: 1.22-1.43 (m, 3H), 1.50-1.56 (m, 1 H), 1.68-1.83 (m, 4 H), 1.97-2.01 (m, 2 H), 2.08-2.13 (m, 1 H), 2.62-2.66 (t, 2 H, J = 7.77 Hz), 5.58-5.62 (m, 1 H), 5.67-5.71 (m, 1H), 7.21-7.23
 25 (m, 3H), 7.29-7.33 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm: 21.6, 25.4, 28.9, 29.1, 35.1, 36.1, 36.2, 125.6, 126.8, 128.3, 128.4, 132.1, 142.8. HRMS (ESI) *m/z* calculated for C₁₅H₂₀ [M]⁺: 200.1565, found: 200.1563. IR (ATR) ν (cm⁻¹, CHCl₃): 1736, 1743. [α]_D²⁰₅₈₉ = + 30.7 (c= 2.66 in CHCl₃, 95% ee).

Example 9: Synthesis of (R)-(+)-(3-(Cyclohex-2-en-1-yl)propyl)trimethylsilane (3i)

- 5 Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl_3 (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, Allyltrimethylsilane (0.16 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow
- 10 solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0
- 15 mL). The phases were partitioned and the organic phase was washed with NaHCO_3 (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO_4), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr ($T = 40^\circ\text{C}$ and 40 mbar pressure) gave (*R*)-(+)-(3-(cyclohex-2-en-1-yl) propyl) trimethylsilane (40.8 mg, 0.21 mmol) in 52% yield. GC analysis of the
- 20 crude mixture of epoxides derived from 3i indicated an enantiomeric excess of 95% (Hydrodex 6-TBDM, 60-170°C at 1 °C/min, 10psi); major enantiomer $t_R = 65.8, 69.5$ min; minor enantiomer $t_R = 65.3, 71.5$ min. ^1H NMR (400 MHz, CDCl_3) δ_H /ppm: 0.005 (s, 9H), 0.49-0.53 (m, 2 H), 1.23-1.39 (m, 5 H), 1.50-1.57 (m, 1 H), 1.72-1.82 (m, 2 H), 1.98-2.01 (m, 2 H), 2.06-2.10 (m, 1 H), 5.58-5.62 (m, 1H), 5.66-5.70 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ_C /ppm: -1.6, 16.8, 21.2, 21.5, 25.4, 29.1, 34.9, 40.4, 126.6, 132.4. HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{24}\text{Si}$ $[\text{M}]^+$: 196.1647, found: 196.1641. IR (ATR) ν (cm^{-1} , CHCl_3): 836.5, 860.8, 1247.7, 1457.3, 2853.9, 2923.1. $[\alpha]_{589}^{20} = +28$ ($c = 0.7$ in CHCl_3 , 93% ee).
- 25

Example 10: Synthesis of (R)-(+)-3-(6-Chlorohexyl)cyclohex-1-ene (3j)

- 5 Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 6-chlorohex-1-ene (106 μL, 1.0 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear
- 10 solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0
- 15 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) gave (*R*)-(+)-3-(6-chlorohexyl)cyclohex-1-ene as a colourless oil (66.2 mg, 0.34 mmol, 84%). GC analysis of the crude mixture of epoxides derived from 3j indicated an enantiomeric excess of
- 20 91% (Hydrodex 6-TBDM, 60-165°C at 1 °C/min, hold for 30 min, 10psi); *t_R* = 1st diastereomer: 107.4 min, 2nd diastereomer: 113.8 min (major enantiomer), 116.2 min (minor enantiomer). ¹H NMR (400 MHz, CDCl₃) δ ppm 5.72-5.62 (m, 1H), 5.61-5.53 (m, 1H), 3.54 (t, *J*=6.8 Hz, 2H), 2.09-2.00 (m, 1H), 2.00-1.91 (m, 2H), 1.83-1.74 (m, 3H), 1.73-1.66 (m, 1H), 1.55-1.48 (m, 1H), 1.48-1.39 (m, 2H), 1.38-1.28 (m, 5H), 1.28-1.15
- 25 (m, 2H); ¹³C NMR NMR (100 MHz, CDCl₃) δ ppm 132.2, 126.8, 45.2, 36.3, 35.1, 32.6, 29.1, 29.1, 26.9, 26.8, 25.4, 21.5; HRMS (EI/CI) *m/z* calcd for C₁₂H₂₁Cl [M]⁺: 200.1335; found: 200.1332; IR (ν_{max}/cm⁻¹) 2924, 2855, 1648, 1446, 1310, 885, 721, 698, 675, 653. [α]_D²⁰ = +14.89 (c 0.47, CHCl₃, 91% ee).

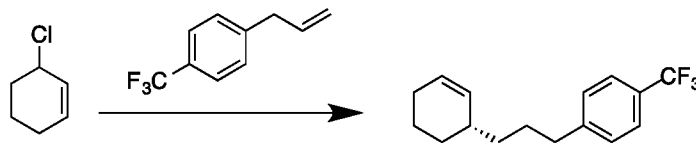
Example 11: Synthesis of (S)-(+)-3-(5-Phenylpent-4-yn-1-yl)cyclohex-1-ene (3k)

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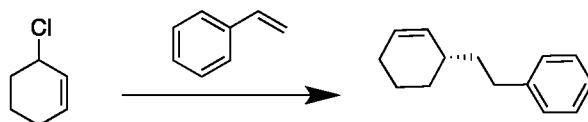
Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-phenyl-4-penten-1-yne (0.15 mL, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) gave (S)-(+)-3-(5-phenylpent-4-yn-1-yl)cyclohex-1-ene (80.7 mg, 0.36 mmol) in 90% yield. Enantiomeric excess of 81% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; 100% hexane; λ = 210 nm; major enantiomer t_R = 14.52 min; minor enantiomer t_R = 13.63 min]. ¹H NMR (500 MHz, CDCl₃) δ_H /ppm 1.19 - 1.33 (m, 1 H), 1.35 - 1.60 (m, 3 H), 1.60 - 1.88 (m, 4 H), 1.93 - 2.04 (m, 2 H), 2.12 (br. s., 1 H), 2.42 (t, *J*=7.0 Hz, 2 H), 5.60 (d, *J*=10.1 Hz, 1 H), 5.69 (d, *J*=10.3 Hz, 1 H), 7.19 - 7.33 (m, 3 H), 7.40 (d, *J*=6.7 Hz, 2 H). ¹³C NMR (126 MHz, CDCl₃) δ_C /ppm 19.6, 21.4, 25.3, 26.1, 29.0, 34.8, 35.6, 80.6, 90.2, 124.0, 126.9, 127.4, 128.1 (2C), 131.5 (2C), 131.8. HRMS (TOF+) *m/z* calcd for C₁₇H₂₀ [M]⁺: 224.1565; found: 224.1574. [α]_D²⁰₅₈₉ = +49.54 (c 0.72, CHCl₃). IR (ν_{max} /cm⁻¹): 3016.8, 2927.3, 2857.4, 1598.6, 1489.9.

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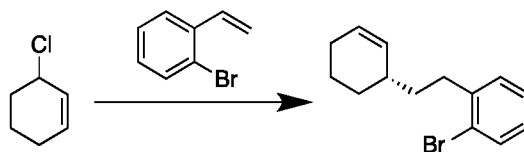
Example 12: Synthesis of (S)-(+)-1-(3-(Cyclohex-2-en-1-yl)propyl)-4-(trifluoromethyl)-benzene (3l)



5 Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-allyl-4-(trifluoromethyl)benzene (0.17 mL, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it
10 became a clear solution (approx. 25 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by
15 addition of CH₂Cl₂ (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) and further distillation by Kugelrohr (T = 30 °C and 400 mbar pressure) gave (S)-(+)-1-(3-(cyclohex-2-en-1-yl)propyl)-4-(trifluoromethyl) benzene (100.6 mg, 0.37
20 mmol) in 93% yield. GC analysis of the crude mixture of epoxides derived from 3l indicated an enantiomeric excess of 87% (Hydrodex 6-TBDM, 90-180°C at 10 °C/min, hold for 10 min, 180-220°C at 1 °C/min, 10psi); major enantiomer t_R = 28.4 min; minor enantiomer t_R = 28.8 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: 1.20-1.43 (m, 3H), 1.50-1.56 (m, 1 H), 1.68-1.74 (m, 3 H), 1.76-1.83 (m, 1 H), 1.96-2.00 (m, 2 H), 2.06-2.13 (m, 1
25 H), 2.66-2.70 (t, 2 H, J = 7.74 Hz), 5.56-5.60 (m, 1H), 5.66-5.71 (m, 1H), 7.29-7.32 (m, 2 H), 7.53-7.55 (d, 2H, J = 7.87 Hz). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm: 21.5, 25.4, 28.6, 29.0, 35.0, 35.9, 36.0, 125.2 (2C), 127.1, 128.0 (q, J (C, F) = 31.0 Hz), 128.7, 131.8, 146.8. ¹⁹F NMR (380 MHz, CDCl₃) δ_F /ppm: -62.3. HRMS (ESI) *m/z* calcd for C₁₆H₁₉F₃ [M]⁺: 268.1439, found: 268.1437. IR (ATR) ν (cm⁻¹, CHCl₃): 720, 843, 1018, 1067, 1122,
30 1162, 1323, 1618, 2928. [α]_D²⁰ = +41.3 (c = 2.62 in CHCl₃, 87% ee).

Example 13: Synthesis of (S)-(+)-(2-(Cyclohex-2-en-1-yl)ethyl)benzene (3m)

- 5 Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, styrene (0.12 mL, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution
- 10 (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0 mL). The
- 15 phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) and further distillation by Kugelrohr (T = 85 °C and 20 mbar pressure) gave (S)-(+)-(2-(cyclohex-2-en-1-yl)ethyl)benzene (49 mg, 0.26 mmol) in 66% yield. GC analysis of the crude mixture
- 20 of epoxides derived from 3m indicated an enantiomeric excess of 87% (Hydrodex 6-TBDM, 90-200°C at 1 °C/min, 10psi); major enantiomer *t_R* = 78.0 min; minor enantiomer *t_R* = 79.9 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: 1.25-1.33 (m, 1 H), 1.50-1.79 (m, 4H), 1.82-1.87 (m, 1 H), 1.98-2.02 (m, 2 H), 2.08-2.13 (m, 1 H), 2.64-2.69 (m, 2 H), 5.62-5.66 (m, 1H), 5.69-5.74 (m, 1H), 7.16-7.23 (m, 3H), 7.28-7.32 (m, 2H). ¹³C NMR (100
- 25 MHz, CDCl₃) δ_C /ppm: 21.4, 25.4, 29.0, 33.3, 34.7, 38.2, 125.6, 127.1, 128.3, 128.4, 131.7, 142.8. HRMS (ESI) *m/z* calcd for C₁₄H₁₈ [M]⁺: 186.1409, found: 186.1407. IR (ATR) ν (cm⁻¹, CHCl₃): 772.7, 1219.7, 2922.0. [α]_D²⁰ = +14.4 (c= 0.25 in CHCl₃, 83% ee)

Example 14: Synthesis (S)-(+)-1-Bromo-2-(2-(cyclohex-2-en-1-yl)ethyl)benzene (3n)

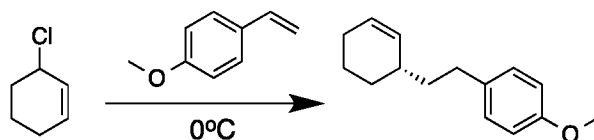
5 Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 2-bromostyrene (0.13 mL, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow

10 solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional min, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0

15 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) and further distillation by Kugelrohr (T = 60 °C and 10 mbar pressure) gave (S)-(+)-1-bromo-2-(2-(cyclohex-2-en-1-yl)ethyl)benzene (82.7 mg, 0.31 mmol) in 78% yield. GC analysis of the

20 crude mixture of epoxides derived from 3n indicated an enantiomeric excess of 87% (Hydrodex 6-TBDM, 90-200°C at 1 °C/min, 10psi); major enantiomer *t_R* = 102.9 min; minor enantiomer *t_R* = 103.8 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: 1.34-1.40 (m, 1H), 1.57-1.66 (m, 3 H), 1.76-1.81 (m, 1 H), 1.87-1.92 (m, 1 H), 2.01-2.04 (m, 2 H), 2.15-2.20 (m, 1 H), 2.75-2.85 (m, 2 H), 5.66-5.70 (m, 1H), 5.72-5.76 (m, 1H), 7.04-7.08 (m, 1 H), 7.24-7.25 (m, 2H), 7.53-7.55 (d, 1H, J = 7.89 Hz). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm: 21.5, 25.4, 28.9, 33.7, 35.1, 36.6, 124.5, 127.3, 127.4, 127.5, 130.3, 131.6, 132.8, 142.2.

25 HRMS (ESI) *m/z* calcd for C₁₄H₁₇Br [M]⁺: 264.0514, found: 264.0515. IR (ATR) ν (cm⁻¹, CHCl₃): 658.3, 721.1, 1023.2, 1438.9, 1470.6, 1567.2, 2855.3, 2924.6, 3015.7 [α]_D²⁰ = + 37.2 (c = 2.85 in CHCl₃, 87% ee).

Example 15: Synthesis of (S)-(+)-1-(2-(Cyclohex-2-en-1-yl)ethyl)-4-methoxybenzene (3o)

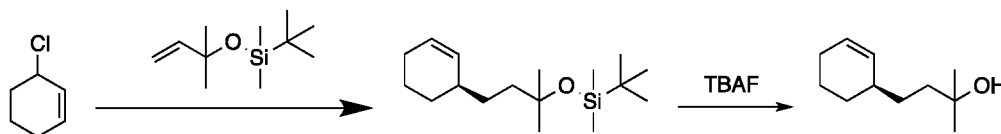
5 Cul (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature before cooled with ice bath for 10 min. Meanwhile, 4-Vinylanisole (0.13 mL, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at

10 room temperature until it became a clear solution (approx. 20 min), then cooled with ice bath for 10 min. The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring in the ice bath for 10 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight at 0°C before being

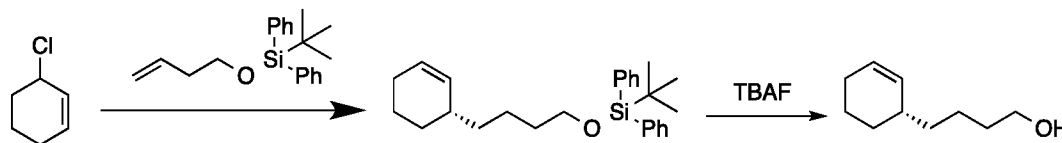
15 quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) and further distillation by Kugelrohr (T = 120 °C and 25 mbar pressure) gave (*S*)-(+)-1-(2- (cyclohex-

20 2-en-1-yl) ethyl)-4-methoxybenzene (54.6 mg, 0.26 mmol) in 63% yield. GC analysis of the crude mixture of epoxides derived from 3o indicated an enantiomeric excess of 95% (Hydrodex 6-TBDM, 60-200°C at 1 °C/min, 10psi); major enantiomer *t_R* = 136.5 min; minor enantiomer *t_R* = 137.2 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: 1.53-1.66 (m, 2H), 1.74-1.77 (m, 1 H), 1.84-1.86 (m, 1 H), 1.98-2.03 (m, 2 H), 2.07-2.13 (m, 1 H), 2.60-2.65 (m, 2 H), 3.81 (s, 3 H), 5.63-5.66 (m, 1H), 5.70-5.74 (m, 1H), 6.84-6.86 (m, 2H), 7.12-7.14 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm: 21.5, 25.4, 29.1, 32.3, 34.7, 38.5, 55.3, 113.7, 127.1, 129.2, 131.8, 134.9, 157.6. HRMS (ESI) *m/z* calcd for C₁₅H₂₀O [M]⁺: 216.1514, found: 216.1520. IR (ATR) ν (cm⁻¹, CHCl₃): 822.1, 1038.9, 1177.1, 1246.0, 1463.6, 1511.9, 1612.6, 2925.5. [α]_D²⁰ = +45.7 (c= 0.505 in CHCl₃, 95% ee).

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Example 16: Synthesis of (R)-(-)-(Cyclohex-2-en-1-yl)-2-methylbutan-2-ol (3p)

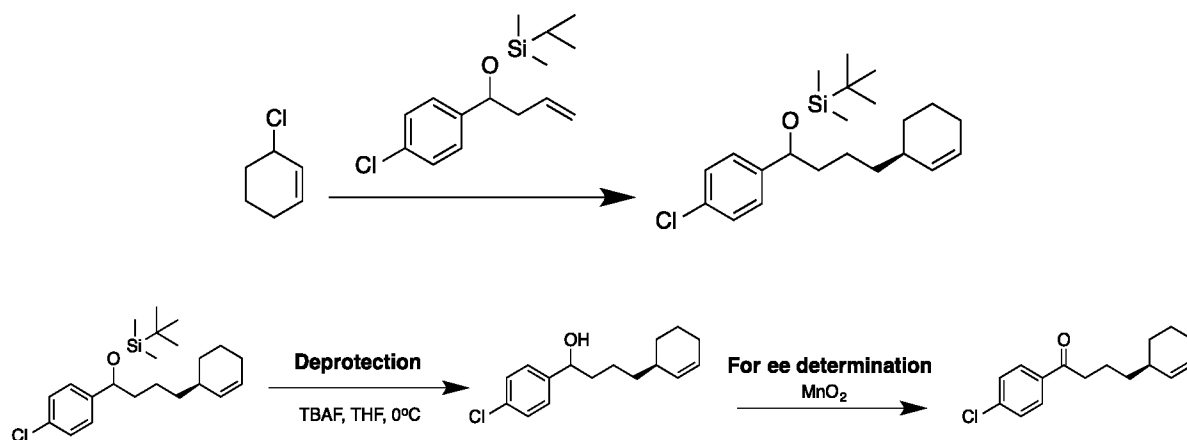
In a 5ml flame dried flask, tert-butyldimethyl((2-methylbut-3-en-2-yl)oxy)silane (200 mg, 1.00 mmol, 2.50 eq) is dissolved in CH_2Cl_2 (0.40 mL) and then Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) is added in one portion. The mixture is smoothly stirred at room temperature under an argon atmosphere until it becomes a clear yellow solution (overnight). In another 5ml flame-dried flask CuI (7.6 mg, 0.04 mmol, 0.10 eq) and (S,S,S)- Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) are dissolved in CHCl_3 (0.8 mL) under an argon atmosphere. The mixture is stirred for 1 h at room temperature. The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional min, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO_3 (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO_4), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave crude product which was then dissolved in THF (5 mL) and treated with tetrabutylammonium fluoride solution (1M in THF, 6.4 mL, 6.4 mmol, 16 eq) while stirring under an argon atmosphere. The reaction was heated to reflux overnight to affording (R)-(-)-4-(cyclohex-2-en-1-yl)-2-methylbutan-2-ol which has an aromatic smell. Flash column chromatography (silica gel; 20% ethyl acetate in petrol) provided the pure alcohol in 45% yield based on the isolated alcohol (30 mg, 0.18 mmol). GC analysis of the crude mixture of epoxides derived from the alcohol indicated an enantiomeric excess of 94% (Hydrodex 6-TBDM, 60-150°C at 1 °C/min, 10psi); major enantiomer t_R = 63.7, 83.9 min; minor enantiomer t_R = 64.4, 85.0 min. ^1H NMR (400 MHz, CDCl_3) δ_H /ppm: 1.22 (s, 6 H), 1.25-1.26 (m, 1 H), 1.31-1.45 (m, 2 H), 1.48-1.56 (m, 3 H), 1.70-1.81 (m, 2 H), 1.95-2.05 (m, 3 H), 5.57-5.60 (m, 1H), 5.67-5.70 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ_C /ppm: 21.5, 25.4, 29.1, 29.20, 29.25, 30.8, 35.5, 41.1, 71.1, 127.1, 131.9. HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{20}\text{O}$ $[\text{M}]^+$: 168.1514, found: 168.1511. IR (ATR) ν (cm^{-1} , CHCl_3): 676.8, 719.4, 932.7, 1149.3, 1377.3, 1454.2, 2858.3, 2927.9, 2967.9, 3016.7, 3362.4. $[\alpha]_D^{20} = -31.3$ ($c = 0.75$ in CHCl_3 , 94% ee).

Example 17: Synthesis of (S)-(+)-4-(Cyclohex-2-en-1-yl)butan-1-ol (3g)

- 5 Cp₂ZrHCl (206 mg, 0.8 mmol, 2.0 eq.) was added in one portion to a stirred solution of (but-3-en-1-yloxy)(tert-butyl)diphenylsilane (310 mg, 1.0 mmol, 2.5 eq.) in CH₂Cl₂ (0.4 mL) and stirred until a clear yellow solution was obtained (20 min). Simultaneously, in a different round-bottom flask, CuI (7.7 mg, 0.04 mmol, 0.1 eq.) and (*R,R,R*)-Ligand A (21.6 mg, 0.04 mmol, 0.1 eq.) were dissolved in CHCl₃ (0.8 mL) and stirred for 1 h. The
- 10 resulting mixture was then added to the freshly prepared alkenylzirconium species. After 10 min, 3-chlorocyclohex-1-ene (48 µL, 0.4 mmol, 1 eq.) was added to the resulting black solution and stirred was continued for 12 h. The reaction mixture was diluted with Et₂O (2 mL) and then NH₄Cl (aq., 1M) was added. The mixture was partitioned and the aqueous phase extracted with Et₂O (3 x 10 mL). The combined organic materials were
- 15 washed with NaHCO₃ (aq., sat.), dried over MgSO₄, filtered and concentrated under reduced pressure. After flash column chromatography (SiO₂, 0-2% Et₂O in pentane), a mixture of (S)-tert-butyl(4-(cyclohex-2-en-1-yl) butoxy)diphenylsilane and (but-3-en-1-yloxy)(tert-butyl)diphenylsilane was obtained as a pale yellow oil. This yellow oil was oil dissolved in THF (3 mL) before TBAF (0.8 mL, 1M in THF, 0.8 mmol, 2.0 eq.) was
- 20 added. The reaction mixture was stirred for 3.5 h before being diluted with Et₂O (1 mL) and NaCl (aq., sat. 1 mL) was added. The mixture was partitioned and the aqueous phase extracted with Et₂O (3 x 3 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. Flash column chromatography (SiO₂, 30% Et₂O in hexane), provided (S)-(+)-4-(cyclohex-2-en-1-yl)butan-1-ol as a colourless oil (34 mg, 0.22 mmol, 55%). The enantiomeric excess (89%), was determined by GC on a chiral stationary phase after derivatization into the corresponding epoxides (Hydrodex 6TBDM column, Method: 60-0-1-150-30, 10 psi, major enantiomer t_R = 95.5, 104.6 min; minor enantiomer t_R = 94.8, 107.5 min. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.71-5.64 (m, 1H), 5.58 (dd, ³J=9.8, 2.1 Hz, 1H), 3.66 (t, ³J=6.6 Hz, 2H), 2.11-2.01 (m, 1H), 2.01-1.94 (m, 2H), 1.84-1.67 (m, 2H), 1.64-1.55 (m, 2H), 1.55-1.45 (m, 1H), 1.45-1.37 (m, 2H), 1.37-1.28 (m, 1H), 1.28-1.16 (m, 2H); ¹³C
- 25
- 30

NMR (100 MHz, CDCl₃) δ ppm 132.0, 126.9, 63.0, 36.1, 35.1, 33.0, 29.1, 25.4, 23.1, 21.5; HRMS (EI/CI) m/z calcd for C₁₀H₁₈O [M]⁺: 154.1358; found: 154.1354; IR ($\nu_{\max}$ /cm⁻¹) 3327, 3016, 2928, 2858, 1447, 1059, 720, 675. [α]_D²⁰₅₈₉ = +26.64 (c 1.02, CHCl₃, 89% ee).

5 Example 18: Synthesis of (S)-(-)-tert-Butyl(1-(4-chlorophenyl)-4-(cyclohex-2-en-1-yl)butoxy)dimethylsilane (3r)



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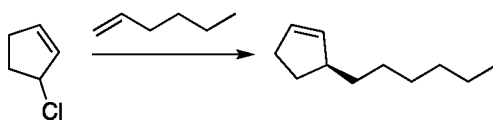
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CuI (7.6 mg, 0.04 mmol, 0.10 eq), (S,S,S)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, tert-butyl((1-(4-chlorophenyl) but-3-en-1-yl)oxy)dimethylsilane (297 mg, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional min, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~1.0 mL) and diluted by addition of CH₂Cl₂ (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) gave (S)-(-)-tert-butyl(1-(4-chlorophenyl)-4-(cyclohex-2-en-1-yl)butoxy)-dimethylsilane (137.9 mg, 0.36 mmol) in 91% yield. For ee determination, the product was treated with tetrabutylammonium fluoride solution (1M in THF, 1.6 ml, 1.6 mmol, 4 eq) in THF (5 mL) at 0 °C. After stirring under an argon

atmosphere at 0 °C for 4h, Et₂O (1 mL) and then NaCl (aq., sat.) were added. The mixture was partitioned, and then the aqueous phase was extracted with Et₂O (3 x 3 mL). The combined organic materials were dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was dissolved in Et₂O (6 mL) and then MnO₂ (1 g, 12 mmol, 30 eq.) was added and the resulting mixture was left stirring overnight before being filtering through a cotton plug. After removal of the solvent the product was used directly for enantiomeric excess determination. Enantiomeric excess of 91% was determined by HPLC of the derived ketone [Chiralpak® IA; flow: 1.0 mL/min; hexane/i-PrOH: 100: 0; λ = 210 nm; major enantiomer t_R = 57.5 min; minor enantiomer t_R = 72.1 min]. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: -0.12 (s, 3H), 0.05 (s, 3 H), 0.9 (s, 9 H), 1.17-1.36 (m, 4 H), 1.39-1.46 (m, 1 H), 1.49-1.60 (m, 2 H), 1.65-1.78 (m, 3 H), 1.95-2.03 (m, 3H), 4.61-4.64 (m, 1H), 5.54-5.56 (d, 1H, J=10.13 Hz), 5.64-5.68 (m, 1H), 7.22-7.30 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm: -4.9, -4.5, 18.2, 21.5, 22.9, 25.4, 25.8, 29.1, 35.1, 36.3, 41.2, 74.4, 126.8, 127.2, 128.2, 132.1, 132.3, 144.5. HRMS (ESI) *m/z* calcd for C₂₂H₃₅ClOSi [M]⁺: 378.2146, found: 378.2180. IR (ATR) ν (cm⁻¹, CHCl₃): 675.8, 718.4, 775.3, 835.3, 1014.1, 1084.9, 1251.9, 1360.9, 1471.5, 1489.2, 2856.4, 2928.3. [α]_D²⁰ = -30.9 (c= 3.5 in CHCl₃, 91% ee).

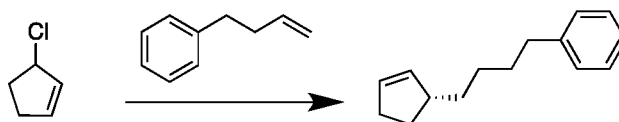
Example 19: Synthesis of (S)-(-)-3-Hexylcyclopent-1-ene (4a)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (S,S,S)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl₃ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (84 μL, 1.00 mmol, 2.50 eq), CH₂Cl₂ (0.4 mL) and Cp₂ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional min, 3-chlorocyclopent-1-ene (41.0 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by

addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO_3 (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO_4), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*S*)-(-)-3-hexylcyclopent-1-ene (46.4 mg, 0.31 mmol) in 77% yield. GC analysis of the crude mixture of epoxides derived from 4a indicated an enantiomeric excess of 90% (Hydrodex 6-TBDM, 60-110°C at 5 °C/min, 110-170°C at 20°C/min, hold for 20 min, 10psi); major enantiomer t_R = 22.79, 24.58 min; minor enantiomer t_R = 23.04, 24.24 min. ^1H NMR (400 MHz, CDCl_3) δ_H /ppm 0.89 (t, J =6.0 Hz, 3 H), 1.29 (br. s., 9 H), 1.33 - 1.46 (m, 2 H), 2.05 (m, 1 H), 2.30 (m, 2 H), 2.63 (m, 1 H), 5.70 (m, 2 H). ^{13}C NMR (100 MHz, CDCl_3) δ_C /ppm 14.1, 22.7, 27.9, 29.6, 29.9, 31.9, 32.0, 36.2, 45.6, 130.0, 135.5. HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{20}$ $[\text{M}]^+$: 152.1565, found: 152.1559. IR (ATR) ν (cm^{-1}): 2323.8, 2854.9, 1462.9. $[\alpha]_D^{20} = -105.1$ (c 0.92, CHCl_3) for 90% ee].

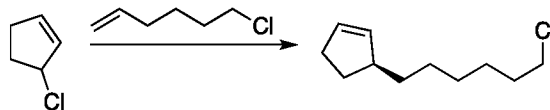
15 Example 20: Synthesis of (R)-(+)-(4-(Cyclopent-2-en-1-yl)butyl)benzene (4b)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl_3 (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocyclopent-1-ene (41.0 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO_3 (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO_4), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further

distillation by Kugelrohr ($T = 110\text{ }^{\circ}\text{C}$ and 55 mbar pressure) gave (*R*)-(+)-(4-(cyclopent-2-en-1-yl)butyl)benzene (45.7 mg, 0.23 mmol) in 57% yield. GC analysis of the crude mixture of epoxides derived from 4b indicated an enantiomeric excess of 92% (Hydrodex 6-TBDM, 60-110 $^{\circ}\text{C}$ at 5 $^{\circ}\text{C}/\text{min}$, 110-140 $^{\circ}\text{C}$ at 10 $^{\circ}\text{C}/\text{min}$, hold for 10 min, 140-170 $^{\circ}\text{C}$ at 5 $^{\circ}\text{C}/\text{min}$, hold for 10 min, 170-210 $^{\circ}\text{C}$ at 5 $^{\circ}\text{C}/\text{min}$, 10psi); major enantiomer $t_{\text{R}} = 39.5$ min, 41.3 min; minor enantiomer $t_{\text{R}} = 39.2$ min, 41.7 min. ^1H NMR (400 MHz, CDCl_3) δ_{H} /ppm: 1.33-1.49 (m, 5 H), 1.66-1.68 (m, 2 H), 2.05-2.09 (m, 1H), 2.32-2.37 (m, 2 H), 2.65- 2.69 (t, 3 H, $J = 7.8$ Hz), 5.71-5.73 (m, 1 H), 5.74-5.77 (m, 1 H), 7.22- 7.24 (m, 3 H), 7.28 - 7.33 (m, 2 H). ^{13}C NMR (100 MHz, CDCl_3) δ_{C} /ppm: 27.7, 29.9, 31.8, 32.0, 36.0, 45.6, 125.6, 128.2, 128.4, 130.1, 135.3, 142.9 HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{20}$ $[\text{M}]^+$: 200.1564, found: 200.1565. IR (ATR) ν (cm^{-1} , CHCl_3): 698, 718, 1454, 1496, 1604, 2853, 2926, 3027. $[\alpha]_{\text{D}}^{20} = +59.2$ ($c = 1.759$ in CHCl_3 , 92% ee).

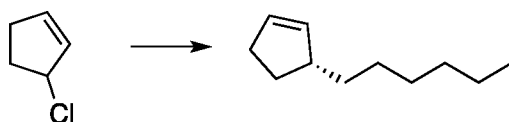
Example 21: Synthesis of (*S*)-(-)-3-(6-Chlorohexyl)cyclopent-1-ene (4c)



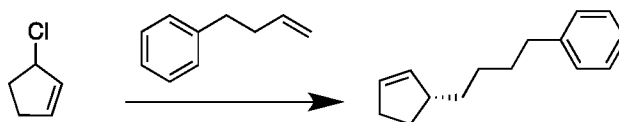
CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S,S*)-Ligand A (21.6 mg, 0.04 mmol, 0.10 eq) and then CHCl_3 (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 6-chloro-1-hexene (0.13 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclopent-1-ene (41.0 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~ 1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with NaHCO_3 (sat. aq. ca. 2.0 mL), water (2.0 mL) dried (MgSO_4), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*S*)-(-)-3-(6-chlorohexyl) cyclopent-1-ene (54.3 mg, 0.29 mmol) in 72% yield. GC analysis of the crude mixture of epoxides derived from 4c indicated an enantiomeric excess of 90%

(Hydrodex 6-TBDM, 60-110 °C at 5 °C/min, 110-170 °C at 1 °C/min, hold for 20 min, 10psi); major enantiomer t_R = 33.47, 38.45 min; minor enantiomer t_R = 33.78, 37.82 min. ^1H NMR (400 MHz, CDCl_3) δ_H /ppm 1.25 - 1.48 (m, 9 H), 1.74 - 1.83 (m, 2 H), 1.99 - 2.08 (m, 1 H), 2.28 (m, 1 H), 2.31 - 2.40 (m, 1 H), 2.56 - 2.69 (m, 1 H), 3.54 (t, J =6.8 Hz, 2 H), 5.65 - 5.70 (m, 1 H), 5.71 (dt, J =5.8, 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3) δ_C /ppm 26.9, 27.8, 29.1, 29.8, 32.0, 32.6, 36.0, 45.2, 45.5, 130.1, 135.3. HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{19}\text{Cl}$ $[\text{M}]^+$: 186.1175, found: 186.1168. IR (ATR) ν (cm^{-1}): 3050.9, 2925.8, 2853.2, 1461.5, 719.8. $[\alpha]_D^{20} = -85.7$ (c 1.12, CHCl_3) for 90% ee].

10 Example 22: Gram-scale synthesis of (*R*)-(+)-3-Hexylcyclopent-1-ene (4a)

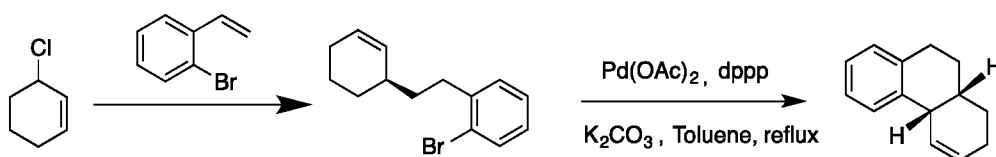


In a 50 mL flame dried flask, CuI (190.5 mg, 1.10 mmol, 0.10 eq) and (*R,R,R*)-Ligand (593.6 mg, 1.10 mmol, 0.10 eq) were dissolved in CHCl_3 (22 mL) and the mixture was stirred at room temperature for 1 h. Meanwhile, in another 25 mL flame-dried flask, 1-hexene (2.32 mL, 84.16 mmol, 1.70 eq) was dissolved in CH_2Cl_2 (11 mL) and then Cp_2ZrHCl (4.25 g, 16.5 mmol, 1.50 eq) added in one portion at room temperature. The mixture was stirred rapidly until it becomes a clear yellow solution (approx. 20 min). The resulting organozirconium reagent was transferred to the copper-ligand solution using a syringe. After 5 min of additional stirring, 3-chlorocyclopent-1-ene (0.90 mL, 11.0 mmol, 1.00 eq) was added dropwise. Stirring was continued arbitrarily overnight and the reaction quenched by addition of NH_4Cl 1M (15 mL) and then dilution with CH_2Cl_2 (15 mL). The phases were partitioned and the organic phase was washed with NaHCO_3 (aq. sat. ca., 30.0 mL), water (30.0 mL), dried (MgSO_4), and filtered. The solvent was then carefully removed by rotary evaporator (bath T = 30 °C, 350 mbar pressure). Flash column chromatography of the residue (pentane; SiO_2) gave (*R*)-(+)-3-hexylcyclopent-1-ene (1.20 g, 9.46 mmol) in 86% yield. GC analysis of the crude mixture of epoxides derived from 4a indicated an enantiomeric excess of 91% (Hydrodex 6-TBDM, 60-110 °C at 5 °C/min, 110-170 °C at 20 °C/min, hold for 20 min, 10 psi); major enantiomer t_R = 22.90, 24.08 min; minor enantiomer t_R = 22.77, 24.59 min.

Example 23: Gram-scale synthesis of (R)-(+)-(4-(cyclopent-2-en-1-yl)butyl)benzene (4b)

- 5 In a 50 mL flame dried flask, CuI ((291.4 mg, 1.53 mmol, 0.10 eq) and (*R,R,R*)-Ligand A (825.7 mg, 1.53 mmol, 0.10 eq) were dissolved in CHCl₃ (30 mL) and the mixture stirred at room temperature for 1 h. Meanwhile, in another 50 mL flame-dried flask, 4-Phenyl-1-butene (5.75 mL, 38.25 mmol, 2.50 eq) was dissolved in CH₂Cl₂ (15 mL) and then Cp₂ZrHCl (7.89 g, 30.60 mmol, 2.00 eq) was added in one portion at room temperature.
- 10 The mixture is rapidly stirred until a clear yellow solution was obtained (approx. 20 min). The resulting organozirconium reagent was transferred to the copper-ligand solution using a syringe and after 5 min of additional stirring 3-chlorocyclopent-1-ene (1.49 mL, 15.30 mmol, 1.00 eq) was added dropwise. Stirring was continued arbitrarily overnight before the reaction was quenched by addition of NH₄Cl 1M (35.0 mL) and diluted with
- 15 CH₂Cl₂ (40.0 mL). The organic phase was washed with NaHCO₃ (aq. sat. *ca.*, 40.0 mL), and then water (40.0 mL), dried (MgSO₄), filtered and then the solvent was carefully removed by rotary evaporator (bath T = 30 °C, 400 mbar pressure). Flash column chromatography of the residue (pentane; SiO₂) and further distillation by Kugelrohr (T = 110 °C, 55 mbar) gave (*R*)-(+)-3-isopentylcyclohex-1-ene (1.77 g, 22.2 mmol) in 58%
- 20 yield. GC analysis of the crude mixture of epoxides derived from 4b indicated an enantiomeric excess of 94% (Hydrodex 6-TBDM, 60-110 °C at 5 °C/min, 110-140 °C at 10 °C/min, hold for 10 min, 140-170 °C at 5 °C/min, hold for 10 min, 170-210 °C at 5 °C/min, 10 psi); major enantiomer *t_R* = 39.5 min, 41.3 min; minor enantiomer *t_R* = 39.2 min, 41.7 min.

25

Example 24: Synthesis of (-)-(4aR,10aS)-1,2,4a,9,10,10a-Hexahydrophenanthrene (5)

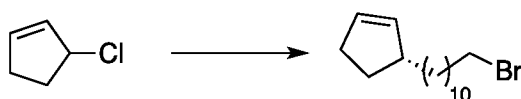
- a) CuI (61.6 mg, 0.32 mmol, 0.10 eq), (*S,S,S*)-Ligand A (172.8 mg, 0.32 mmol, 0.10 eq) and then CHCl₃ (6.4 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 2-Bromostyrene (1.1 mL, 8.00 mmol, 2.50 eq), CH₂Cl₂ (3.2 mL) and Cp₂ZrHCl (1.648 g, 6.40 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until a clear yellow solution was obtained (approx. 25 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 10 additional minutes, 3-chlorocyclohex-1-ene (0.373 g, 3.20 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH₄Cl (1M, aq. ~10 mL) and diluted by addition of CH₂Cl₂ (10 mL). The phases were partitioned and the organic phase was washed with NaHCO₃ (sat. aq. ca. 10 mL), water (10 mL), dried (MgSO₄), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO₂) and further distillation by Kugelrohr (T = 60 °C and 10 mbar pressure) gave (*R*)-1-bromo-2-(2-(cyclohex-2-en-1-yl)ethyl)benzene (750.3 mg, 2.81 mmol) in 88% yield. GC analysis of the crude mixture of epoxides derived from (*R*)-1-bromo-2-(2-(cyclohex-2-en-1-yl)ethyl)benzene indicated an enantiomeric excess of 87% (Hydrodex 6-TBDM, 90-200°C at 1 °C/min, 10psi); major enantiomer t_R = 101.1 min; minor enantiomer t_R = 99.4 min. ¹H NMR (400 MHz, CDCl₃) δ_H /ppm: 1.34-1.40 (m, 1H), 1.57-1.66 (m, 3 H), 1.76-1.81 (m, 1 H), 1.87-1.92 (m, 1 H), 2.01-2.04 (m, 2 H), 2.15-2.20 (m, 1 H), 2.75-2.85 (m, 2 H), 5.66-5.70 (m, 1H), 5.72-5.76 (m, 1H), 7.04-7.08 (m, 1 H), 7.24-7.25 (m, 2H), 7.53-7.55 (d, 1H, J = 7.89 Hz). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm: 21.5, 25.4, 28.9, 33.7, 35.1, 36.6, 124.5, 127.3, 127.4, 127.5, 130.3, 131.6, 132.8, 142.2.
- b) In a flame-dried 25 ml round-bottom flask, a solution of (*R*)-1-bromo-2-(2-(cyclohex-2-en-1-yl)ethyl)benzene (250 mg, 0.943 mmol, 1.00 eq), Pd(OAc)₂ (32.5 mg, 0.141 mmol, 0.15 eq), 1,3-Bis(diphenylphosphino)propane (dppp) (118.8 mg, 0.283 mmol, 0.3 eq) and K₂CO₃ (533 mg, 3.772 mmol, 4.00 eq) and toluene (10 mL) was heated to reflux condition under an argon atmosphere for 28 h. The reaction mixture was allowed to cool to room temperature, filtered through Celite and rinsed with EtOAc before NaCl was added (sat. solution, 10 mL), the phases partitioned. The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried (MgSO₄) and the solvent was evaporated. Flash column chromatography of the residue (pentane; SiO₂)

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gave (–)-(4a*R*, 10a*S*)-1,2,4a,9,10,10a-hexahydro phenanthrene (152.7 mg, 0.829 mmol) in 88% yield. Enantiomeric excess of 87% was determined by HPLC [Chiralpak® IB; flow: 0.5 mL/min; hexane/*i*-PrOH: 100: 0; λ = 210 nm; major enantiomer t_R = 10.7 min; minor enantiomer t_R = 11.7 min]. ^1H NMR (400 MHz, CDCl_3) δ_{H} /ppm: 1.73-1.81 (m, 2H), 1.82-1.91 (m, 2 H), 2.09-2.15 (m, 2 H), 2.21-2.26 (m, 1 H), 2.85-2.89 (m, 2 H), 3.53-3.55 (m, 1 H), 5.72-5.76 (m, 1H), 5.80-5.83 (m, 1H), 7.13-7.19 (m, 2 H), 7.21-7.25 (m, 1H), 7.28-7.30 (m, 1 H). ^{13}C NMR (100 MHz, CDCl_3) δ_{C} /ppm: 21.9, 24.6, 27.1, 29.1, 32.2, 39.2, 125.6, 125.8, 125.9, 128.8, 128.9, 131.2, 136.8, 140.3. HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{16}$ $[\text{M}]^+$: 184.1252, found: 184.1249. IR (ATR) ν (cm^{-1} , CHCl_3): 630.4, 666.5, 739.4, 1257.5, 1449.7, 1487.5, 2919.5 $[\alpha]_{589}^{20} = -101$ ($c = 0.702$ in CHCl_3 , 87% ee).

Example 25: Synthesis of Hydnocarpic Acid (6)

(+)-(S)-3-(Bromoundecenyl)cyclopent-1-ene (4d)

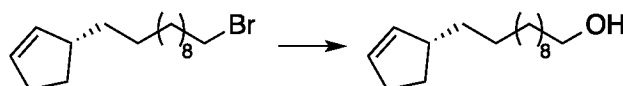


CuI 98% (23.4 mg, 0.12 mmol, 0.10 eq) and (*R,R,R*)-Ligand A (65.0 mg, 0.12 mmol, 0.10 eq) were stirred in CHCl_3 (4.8 mL) at room temperature for 1 h. In another flask Cp_2ZrHCl (618.9 mg, 2.40 mmol, 2.00 eq) was added to a solution of 11-bromoundec-1-ene (0.65 mL, 3.00 mmol, 2.50 eq) in CH_2Cl_2 (2.4 mL) at room temperature and stirred until a clear yellow solution was obtained (15-20 min). The freshly prepared organozirconium reagent was then transferred to the copper-ligand solution dropwise, using a 5 mL syringe, over 3 min. The resulting orange solution was stirred for 10 minutes before 3-chlorocyclopent-1-ene (0.12 mL, 1.20 mmol, 1.00 eq) was added and stirring was arbitrarily continued for an additional 12 h before the reaction was quenched by the addition of Et_2O (7 mL) and NH_4Cl (1 M, 5 mL). The aqueous phase was extracted with Et_2O (2x3 mL) and the combined organic materials were washed with NaHCO_3 (sat. sol. ~5 mL), water (5 mL) and brine (5 mL), dried (MgSO_4), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography using 100% pentane yielded the desired product contaminated with 11-bromoundec-1-ene in a 1:1.1 ratio. To remove the alkene the oil was subjected to kugelrohr distillation at 125 °C under high vacuum (~0.1 mmHg). The desired product, which constituted the residue

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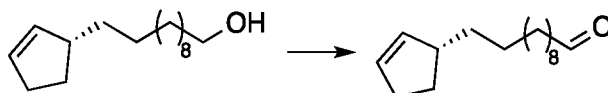
after distillation, was obtained in 42% yield (153.0 mg, 0.51 mmol). GC analysis of the crude mixture of epoxides derived from 4d indicated an enantiomeric excess of 92% (Hydrodex 6-TBDM in the following conditions: 60-190 °C at 5 °C /min, held for 50 min and 1 °C /min to 210 °C and held 10 min); major enantiomer t_R = 69.5 min, minor enantiomer t_R = 67.7 min. ^1H NMR (500 MHz, CDCl_3) δ_H /ppm 1.28 (br. s., 14 H), 1.32 - 1.48 (m, 5 H), 1.86 (quin, $J=7.2$ Hz, 2 H), 1.97 - 2.11 (m, 1 H), 2.19 - 2.42 (m, 2 H), 2.62 (br. s., 1 H), 3.42 (t, $J=6.8$ Hz, 2 H), 5.59 - 5.81 (m, 2 H) ^{13}C NMR (126 MHz, CDCl_3) δ_C /ppm 28.0, 28.2, 28.8, 29.4, 29.5, 29.6, 29.6, 29.9 (2C), 32.0, 32.9, 34.0, 36.2, 45.6, 130.0, 135.5. HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{29}\text{Br}$ $[\text{M}]^+$: 300.1453, found: 300.1456. IR (ATR) ν (cm^{-1}): 2923, 2852, 1463. $[\alpha]_{589}^{20} = +50.33$ (c 1.01, CHCl_3) for 92% ee.

i. 11-((*R*)-Cyclopent-2-enyl)-undecan-1-ol



NaHCO_3 (44.6 mg, 0.53 mmol, 3.11 eq) was added to a stirred solution of bromide 4d (50.0 mg, 0.17 mmol, 1.00 eq) in a mixture of DMSO (0.85 mL) and water (0.22 mL). The resulting suspension was stirred 22 h at 95 °C before being quenched by addition of water (2 mL). The aqueous phase was extracted with Et_2O (3 x 1 mL) and the combined organic extracts were washed with water, brine, dried (MgSO_4), filtered and concentrated under reduced pressure to afford crude product that was used in the next step without further purification.

ii. 11-((*R*)-Cyclopent-2-enyl)-undecanal

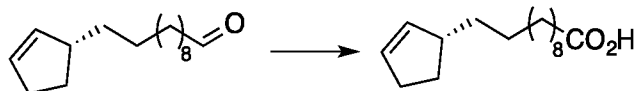


Dess-Martin periodinane (148.4 mg, 0.35 mmol, 2.00 eq) was added to a stirred solution of the crude alcohol (0.17 mmol) in CH_2Cl_2 (8.5 mL). The suspension was stirred for 30 min at room temperature before 5 mL of mixture of NaHCO_3 : $\text{Na}_2\text{S}_2\text{O}_3$ (1:5, both sat. aq.) was added in one portion. 5 mL of CH_2Cl_2 was added, the phases were separated, and

the aqueous phase extracted with CH_2Cl_2 (3x2 mL). The crude aldehyde was used in the next step without further purification.

iii. (+)-(R)-11-(Cyclopent-2-enyl)-undecanoic acid (*Hydnocarpic acid*)

5

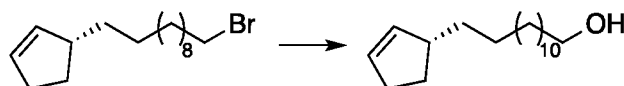


A freshly prepared solution of NaClO_2 (153.7 mg, 1.70 mmol, 10.00 eq) in 20% aqueous NaH_2PO_4 (0.94 mL) was added to a vigorously stirred solution of the crude aldehyde (0.17 mmol, 1.00 eq) in *t*BuOH (2.8 mL). After vigorous stirring at room temperature 1 h the reaction mixture was then poured into EtOAc (5 mL) and the phases separated. The aqueous phase was extracted with EtOAc (4 x 2 mL) and a rotary evaporator was used to remove the volatiles. The crude oil was purified by flash column chromatography (SiO_2) eluting with hexane:EtOAc (8:2) to give the desired product in 79% yield after three steps (33.0 mg, 0.13 mmol). ^1H NMR (500 MHz, CDCl_3) δ_{H} /ppm 1.16 - 1.46 (m, 18 H), 1.57 - 1.71 (m, 2 H), 2.03 (m, 1 H), 2.22 - 2.34 (m, 2 H), 2.36 (t, $J=7.7$ Hz, 2 H), 2.62 (br. s., 1 H), 5.62 - 5.79 (m, 2 H). ^{13}C NMR (126 MHz, CDCl_3) δ_{C} /ppm 24.7, 28.0, 29.0, 29.2, 29.4, 29.6, 29.6, 29.9 (2C), 32.0, 33.8, 36.2, 45.6, 130.0, 135.5, 178.8. HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{28}\text{O}_2$ $[\text{M}]^+$: 252.2089, found: 252.2078. IR (ATR) ν (cm^{-1}): 3015.2, 2918.9, 2851.7, 1700.9. $[\alpha]_{\text{D}}^{20} = +48.51$ (c 0.67, CHCl_3).

Example 26: Synthesis of Chaulmoogric Acid (7)

i. 13-Cyclopent-2-en-1-yltridecan-1-ol (9)

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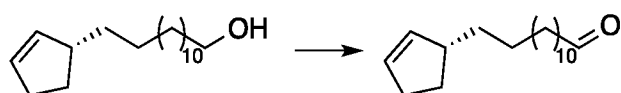


In a flame-dried flask equipped with a condenser under Ar, Mg (48.2 mg, 1.98 mmol, 2.50 eq) and an I_2 crystal were flamed with a Bunsen burner until the I_2 sublimed. The reaction flask was allowed to cool to room temperature before a minimum amount of THF (0.10 mL) was added. While this mixture was stirring, a solution of bromide 4d

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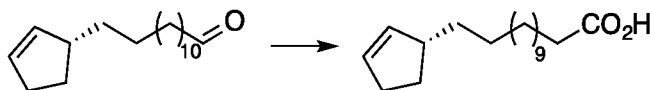
(239.2 mg, 0.79 mmol, 1.00 eq) in THF (1.0 mL) was added at an adequate rate to achieve, and then keep, a constant reflux. (If necessary, the reaction can be initiated by heating to reflux). Once the addition was finished, the mixture was heated to reflux for 1 h and then allowed to cool to room temperature. The Grignard reagent was then transferred via syringe over 20 min to another flask containing ethylene oxide (2.5 M in THF, 1.07 mL, 2.69 mmol, 3.40 eq) and CuI (15.0 mg, 0.08 mmol, 0.10 eq) at 0 °C and the reaction mixture became dark grey. After stirring at 0 °C for 75 min, one portion of saturated aqueous NH₄Cl (4 mL) was added. The mixture was partitioned and the aqueous phase was extracted with Et₂O (3x2 mL) and the combined organic extracts were washed with water (3 mL), brine (3 mL), dried (MgSO₄), filtered and concentrated. The crude oil was purified by flash column chromatography using hexane:EtOAc (8:2) which afforded the desired product as a white solid in 76% yield (160.2 mg, 0.60 mmol). ¹H NMR (400 MHz, CDCl₃) δ_H /ppm 1.17 - 1.46 (m, 24 H), 1.51 - 1.66 (m, 2 H), 1.95 - 2.11 (m, 1 H), 2.18 - 2.42 (m, 2 H), 2.62 (m, 1 H), 3.65 (t, *J*=6.6 Hz, 2 H), 5.62 - 5.77 (m, 2 H). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm 25.7, 28.0, 29.4, 29.6, 29.6, 29.7 (4C), 29.9, 29.9, 32.0, 32.8, 36.2, 45.6, 63.1, 129.9, 135.5. HRMS (ESI) *m/z* calcd for C₁₈H₃₄O [M]⁺: 266.2610, found: 266.2611. IR (ATR) ν (cm⁻¹): 3451.3, 2922.1, 2851.9, 1538.9.

ii. 13-cyclopent-2-en-1-yltridecanal



Dess-Martin periodinane (415.7 mg, 0.98 mmol, 2.00eq) was added to a stirred solution of the crude alcohol (0.49 mmol, 1.00 eq) in 4.9 mL of CH₂Cl₂. The resulting suspension was stirred for 30 min at room temperature before 5 mL mixture of NaHCO₃:Na₂S₂O₃ (1:5) was added in one portion. After dilution with 5 mL of CH₂Cl₂, the phases were separated and the aqueous phase extracted with CH₂Cl₂ (3 x 2 mL). The crude aldehyde was used in the next step without further purification.

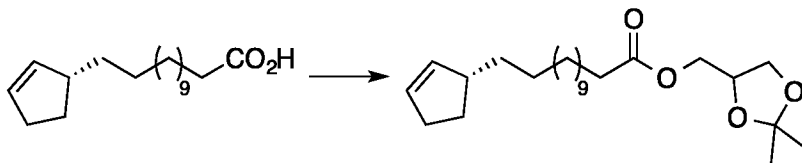
iii. (+)-(R)-13-(cyclopent-2-en-1-yl)tridecanoic acid (*Chaulmoogric acid*)



- 5 A freshly prepared solution of NaClO₂ (443.0 mg, 4.90 mmol, 10.00 eq) in 20% aqueous NaH₂PO₄ (2.72 mL) was added to a vigorously stirred solution of the crude aldehyde (0.49 mmol, 1.00 eq) in *t*BuOH (8.2 mL). After further vigorously stirred at room temperature 1 h the reaction mixture was poured into EtOAc (10 mL) and the phases separated. The aqueous phase was extracted with EtOAc (4 x 4 mL) and the residue
- 10 concentrated under vacuum. The crude oil was purified by flash column chromatography (SiO₂; 8 hexane: 2 EtOAc) to give the desired product as a white solid in 90% yield after two steps (124.7 mg, 0.44 mmol). ¹H NMR (500 MHz, CDCl₃) δ_H /ppm 1.16 - 1.36 (m, 21 H), 1.56 (quin, *J*=7.4 Hz, 2 H), 1.95 (m, 1 H), 2.10 - 2.26 (m, 3 H), 2.28 (t, *J*=7.5 Hz, 2 H), 2.48 - 2.60 (m, 1 H), 5.55 - 5.69 (m, 2 H). ¹³C NMR (126 MHz, CDCl₃) δ_C /ppm 24.7,
- 15 28.0, 29.1, 29.3, 29.4, 29.6, 29.6, 29.7, 29.7, 29.9, 29.9, 32.0, 34.0, 36.2, 45.6, 130.0, 135.5, 179.9. HRMS (ESI) *m/z* calcd for C₁₈H₃₂O₂ [M]⁺: 280.2402, found: 280.2397. IR (ATR) ν (cm⁻¹): 3120.1, 2918.9, 2850.9, 1699.7. [α]_D²⁰₅₈₉ = +61.57 (*c* 0.38, CHCl₃) [lit. +61.7, *c* 4.82 CHCl₃]. m.p. = 67.0–68.5 °C [lit. 67.5 - 68.5 °C].

20 Example 27: Synthesis of Anthelminthicin C (8)

i. (+)-4-[13-((R)-cyclopent-2-enyl-tridecanoyloximethyl)-2,2-dimethyl-[1,3]dioxolane

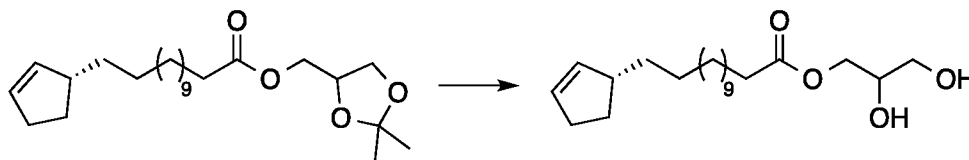


- DCC (17.7 mg, 0.09 mmol, 1.00 eq) and DMAP (1.05 mg, 0.009, 0.10) were added to a
- 25 stirred solution of **7** (24.0 mg, 0.09 mmol, 1.00 eq) in CH₂Cl₂ at 0 °C. The mixture was stirred at 0 °C for 30 min and then a solution of solketal (11.1 μL, 0.09 mmol, 1.01 eq) in CH₂Cl₂ (0.1 mL) was added over 5 min and stirring of the resulting suspension, at room temperature, was continued for 2 h. EtOAc (2 mL) was added and stirred was continued for 10 additional minutes before filtration to remove a precipitate. The filtrate was

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concentrated, then diluted with EtOAc (3 mL) and water (3 mL) and the phases separated. The organic phase was washed with a saturated solution of NaHCO₃ (2 mL), brine (2 mL), dried (MgSO₄), filtered and the solvent removed under vacuum. The crude oil was purified by silica gel flash column chromatography by eluting with hexane:EtOAc (9:1) to afford the product as a colourless oil in 94% yield (33.5 mg, 0.084 mmol). ¹H NMR (400 MHz, CDCl₃) δ_H /ppm 1.22 - 1.31 (m, 17 H), 1.36 - 1.41 (m, 2 H), 1.38 (s, 3 H), 1.47 (s, 3 H), 1.63 (m, 2 H), 1.95 - 2.09 (m, 1 H), 2.20 - 2.32 (m, 3 H), 2.35 (t, *J*=7.6 Hz, 2 H), 2.62 (m, 1 H), 3.74 (dd, *J*=8.4, 6.3 Hz, 1 H), 4.06 - 4.12 (m, 2 H), 4.17 (dd, *J*=11.2, 4.6 Hz, 1 H), 4.32 (quin, *J*=5.8 Hz, 2 H), 5.61 - 5.78 (m, 2 H). ¹³C NMR (100 MHz, CDCl₃) δ_C /ppm 24.9, 25.4, 26.7, 28.0, 29.1, 29.2, 29.4, 29.6, 29.6, 29.6, 29.7, 29.9, 29.9, 32.0, 34.1, 36.2, 45.6, 64.5, 66.4, 73.7, 109.8, 130.0, 135.5, 173.6. HRMS (ESI) *m/z* calcd for C₂₄H₄₂O₄ [M]⁺: 394.3083, found: 394.3094. IR (ATR) ν (cm⁻¹): 2924.1, 2853.3, 1742.1. [α]_D²⁰₅₈₉ = +43.51 (c 0.41, CHCl₃).

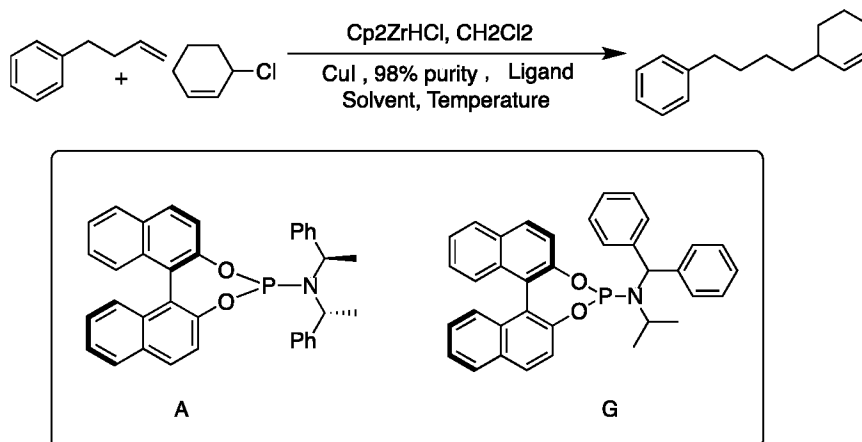
ii. (+)-2,3-Dihydroxypropyl 9-((*R*)-cyclopent-2-en-1-yl)tridecanoate, Anthelminthicin C



Amberlyst 15 (1.0 mg) was added to a stirred solution of the ester (11.5 mg, 0.029 mmol) in dry MeOH (0.6 mL). The resulting solution was stirred for 20 h at room temperature before the resin was filtered off and the filtrate concentrated. Flash column chromatography of the residue using silica gel and eluting with CH₂Cl₂:MeOH (95:5) gave anthelminthicin C as a colorless oil in 97% yield (11.1 mg, 0.028 mmol) that was slightly contaminated (approx. 3%) by an inseparable 1,2-*O*-acyl migration product. ¹H NMR (500 MHz, CDCl₃) δ_H /ppm 1.24 - 1.32 (m, 18 H), 1.35 - 1.45 (m, 2 H), 1.61 - 1.68 (m, 2 H), 1.99-2.06 (m, 1 H), 2.13 (m, 1 H), 2.22 - 2.29 (m, 1 H), 2.31 - 2.37 (m, 1 H), 2.36 (t, *J*=8.0, 2 H), 2.62 (m, 1 H), 3.62 (m, 1 H), 3.70 (m, 1 H), 3.94 (m, 1 H), 4.15 (dd, *J*=11.7, 6.1 Hz, 1 H), 4.21 (dd, *J*=11.7, 4.6 Hz, 1 H), 5.64 - 5.76 (m, 2 H). ¹³C NMR (126 MHz, CDCl₃) δ_C /ppm 24.9, 28.0, 29.1, 29.3, 29.5, 29.6, 29.6, 29.7, 29.7, 29.9, 29.9, 32.0, 34.2, 36.2, 45.6, 63.3, 65.2, 70.3, 130.0, 135.5, 174.4. HRMS (ESI) *m/z* calcd for C₂₁H₃₈O₄ [M]⁺: 354.2770, found: 354.2778. IR (ATR) ν (cm⁻¹): 3393.5, 2918.5, 2850.0, 1735.8. [α]_D²⁰₅₈₉ = +28.00 (c 0.20, CHCl₃).

Example 28: Screening reaction conditions

Using 3-butenylbenzene and 3-chlorocyclohexene as model substrates, a variety of reaction conditions (ligand, solvent and temperature) were examined. The results of this experiment are presented in Table 1:



Entry	Solvent	CH ₂ Cl ₂ : Solvent	CuI : Ligand	Ligand	Temperature	ee	Yield
1	CHCl ₃	0.2ml : 1ml	0.1 eq : 0.12eq	G	RT	91%	
2	CHCl ₃	0.2ml : 1ml	0.12 eq : 0.1eq	G	RT	91%	
3	CHCl ₃	0.2ml : 0.4ml	0.1 eq : 0.1eq	G	RT	91%	
4	CHCl ₃	0.2ml : 2.2ml	0.1 eq : 0.1eq	G	RT	91%	
5	CHCl ₃	0.2ml : 0.4ml	0.1 eq : 0.1eq	G	0°C	95%	
6	CHCl ₃	0.2ml : 0.4ml	0.1 eq : 0.1eq	G	0 ~ 10°C	93%	
7	CHCl ₃	0.2ml : 0.4ml	0.1 eq : 0.1eq	G	60°C	77%	
8	CHCl ₃	0.2ml : 0.4ml	0.1 eq : 0.1eq	G	0°C	93%	>67%, 24h
9	CH ₂ Cl ₂	0.2ml : 0.4ml	0.1 eq : 0.1eq	G	0°C	91%	>75%, 24h
10	CHCl ₃	0.2ml : 0.4ml	0.1 eq : 0.1eq	A	0°C	93~95%	114.3%, 24h
11	CHCl ₃	0.2ml : 0.4ml	0.1 eq : 0.1eq	A	0°C	95%	88%, 18h
12	CH ₂ Cl ₂	0.2ml : 0.4ml	0.1 eq : 0.1eq	A	0°C	93%	>45%, 24h

Table 1

The results in Table 1 demonstrate that the present processes can be performed under a variety of reaction conditions and achieve desirable stereoselectivity. In particular, it can be seen that the reactions can be performed at room temperature.

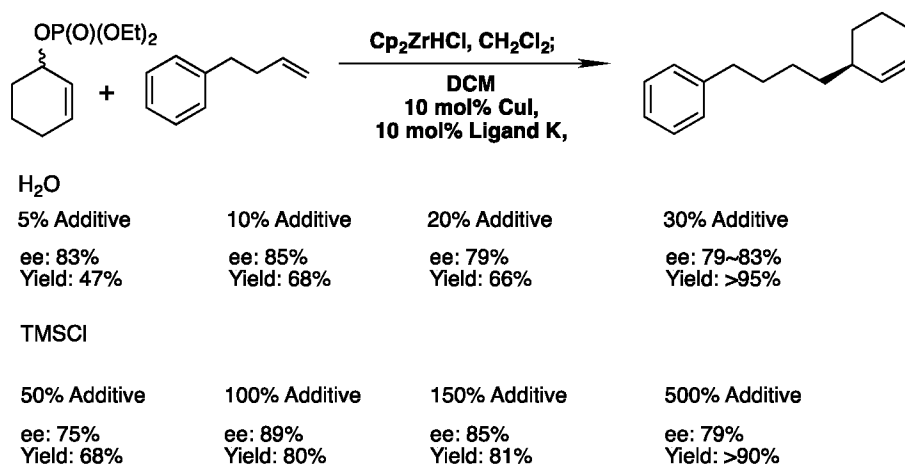
Similar experiments were performed using different copper sources, solvents and leaving groups. Chlorine was found to be a particularly preferred leaving group, while copper iodide was found to be a particularly effective source of copper.

5

Example 29: Effect of additives

Additives were also screened to see if they would have an effect on the yield and enantiomeric excess of reactions. Various amounts of water and TMSCl were added to the reaction. As can be seen from the results presented in the table below, procedures where 5 equivalents of TMSCl were added gave good results.

10



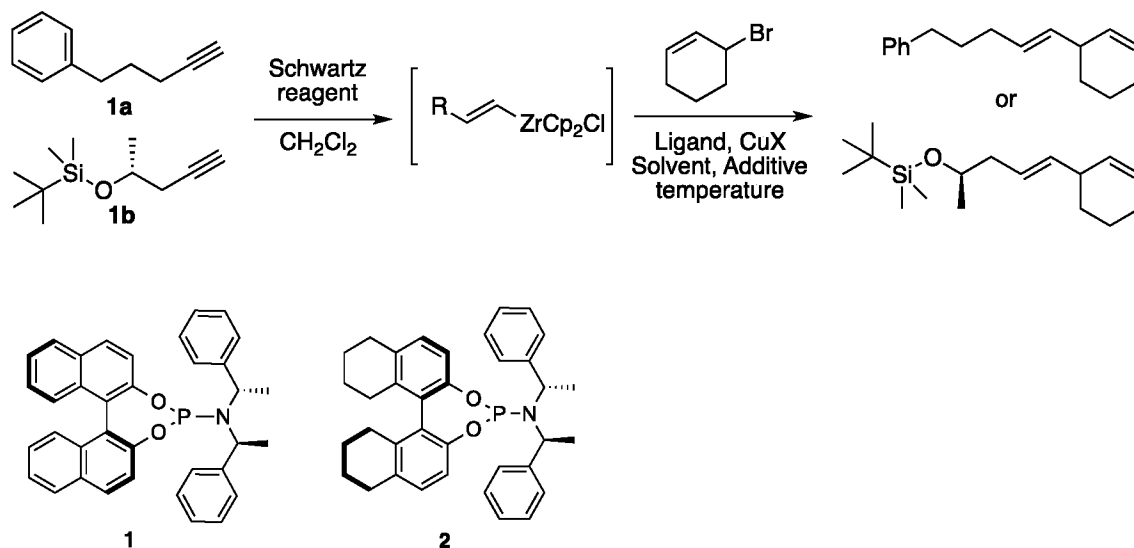
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Example 30: Use of alkyne substrates

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Following similar procedures to those described above, alkyne hydrozirconation reactions were first performed using the Schwartz reagent (Cp₂ZrHCl). The hydrozirconated alkynes were then reacted with a substrate containing an allylic group. Using an allylbromide is used as the allylic substituent, a variety of reaction conditions (ligand, solvent and temperature) were examined. The syntheses and phosphoramidite ligands employed in these experiments are described below:

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5 The results of this experiment are presented in the table below:

<i>Alkyne</i>	<i>CuX</i>	<i>Ligand</i>	<i>Solvent</i>	<i>T (°C)</i>	<i>ee</i>
1a	CuCl/AgOTs	2	CH_2Cl_2	rt	53
1a	CuCl/AgOTs	2	1,4-dioxane	rt	53
1b	CuCl/AgOTs	1	CH_2Cl_2	-40 °C	51
1b	CuCl/AgOTs	2	CH_2Cl_2	rt	51
1b	CuCl/AgOTs	2	CH_2Cl_2	-40 °C	83

It will be understood that the present invention has been described above purely by way of example, and modification of detail can be made within the scope of the invention.

10 Each feature disclosed in the description and the claims may be provided independently or in any appropriate combination.

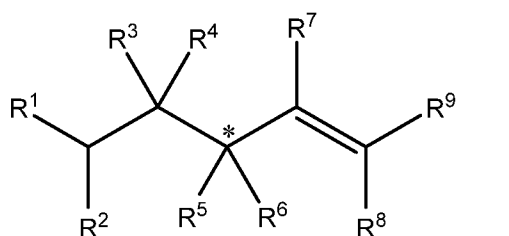
CLAIMS

1. A process for producing a chiral compound in a stereoisomeric excess, the process comprising:

(i) contacting a first compound comprising an alkene bond with a hydrometallating agent, wherein the first compound and the hydrometallating agent are contacted under conditions such that the first compound is hydrometallated by said hydrometallating agent; and

(ii) contacting the hydrometallated first compound with a second compound comprising an allylic group, wherein the hydrometallated first compound and the second compound are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction in which a carbon atom of the hydrometallated first compound binds to a carbon atom of said allylic group, forming a stereoisomeric excess of a compound having a chiral centre in an allylic position, said chiral centre being located at the carbon atom bound by said first compound, wherein said asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

2. A process for producing a chiral compound of the formula (IA) in a stereoisomeric excess:



(IA)

wherein

R^1 , R^2 , R^3 and R^4 are each independently selected from hydrogen, R^a , hydrocarbonyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^1 and R^3 taken together with the carbon atoms to which they are attached may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

R^5 , R^6 , R^7 , R^8 and R^9 are each independently selected from hydrogen, R^a ,

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hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^5 and one of R^6 and R^8 , or R^6 and R^7 , or R^7 and R^9 , taken together with the carbon atoms to which they are attached, may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

each R^a is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^b$, $-OR^b$, $-C(O)R^b$, $-C(O)N(R^b)R^c$, $-C(O)OR^b$, $-C(O)SR^b$, $-C(O)SeR^b$, $-OC(O)R^b$, $-S(O)_kR^b$, $-S(O)_kN(R^b)R^c$, $-N(R^b)R^c$, $-N(R^b)N(R^b)R^c$, $-N(R^b)C(O)R^c$ and $-N(R^b)S(O)_kR^b$;

R^b and R^c are each independently hydrogen or selected from hydrocarbyl and $-(CH_2)_j$ -heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, oxo, cyano, amino, hydroxy, alkyl and alkoxy;

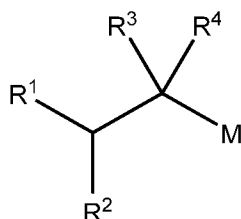
j is 0, 1, 2, 3, 4, 5 or 6;

k is 0, 1 or 2; and

the asterisk * designates a chiral centre of (*R*) or (*S*) configuration;

wherein the process comprises:

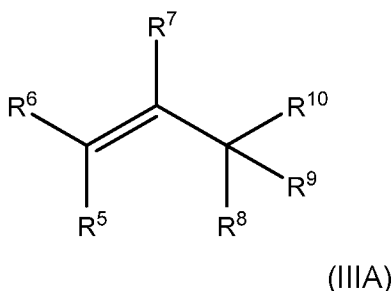
(i) contacting a compound comprising an alkene bond with a hydrometallating agent of the formula HM, wherein M comprises a metal, and wherein said compound and the hydrometallating agent are contacted under conditions such that they react to form a compound of the formula (II):



(II); and

(ii) contacting the compound of formula (II) with a compound of the formula (IIIA):

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wherein R¹⁰ is a leaving group;

5

wherein the compound of formula (II) and the compound of formula (IIIA) are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a stereoisomeric excess of a compound of formula (IA), wherein said asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

10

3. A process according to claim 2, wherein R⁷ is hydrogen.

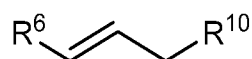
4. A process according to claim 2 or claim 3, wherein R⁸ and R⁹ are each independently selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a; and -(CH₂)_j-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a.

15

5. A process according to claim 4, wherein R⁸ and R⁹ are each independently selected from hydrogen and alkyl optionally substituted with 1, 2, 3, 4 or 5 R^a.

20

6. A process according to claim 2, wherein the compound of formula (IIIA) is a compound of the formula (IIIA.1):



(IIIA.1).

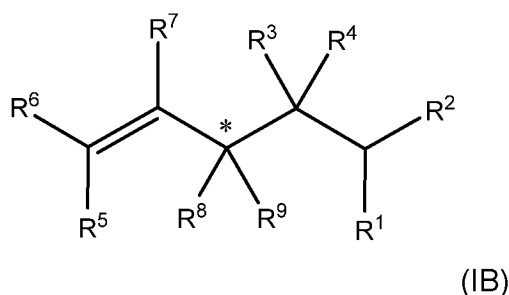
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7. A process according to any of claims 2 to 6, wherein R⁶ is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a.

8. A process according to claim 7, wherein R^6 is selected from alkyl, aryl, aralkyl and cycloalkyl, each of which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

9. A process according to claim 8, wherein R^6 is aryl or aralkyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

10. A process for producing a chiral compound of the formula (IB) in a stereoisomeric excess:



wherein

R^1 , R^2 , R^3 and R^4 are each independently selected from hydrogen, R^a , hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^1 and R^3 taken together with the carbon atoms to which they are attached may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

R^5 , R^6 , R^7 , R^8 and R^9 are each independently selected from hydrogen, R^a , hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

or R^5 and one of R^6 and R^8 , or R^6 and R^7 , or R^7 and R^9 , taken together with the carbon atoms to which they are attached, may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

each R^a is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^b$, $-OR^b$, $-C(O)R^b$, $-C(O)N(R^b)R^c$, $-C(O)OR^b$, $-C(O)SR^b$, $-C(O)SeR^b$, $-OC(O)R^b$, $-S(O)_kR^b$, $-S(O)_kN(R^b)R^c$, $-N(R^b)R^c$, $-N(R^b)N(R^b)R^c$, $-N(R^b)C(O)R^c$ and $-N(R^b)S(O)_kR^b$;

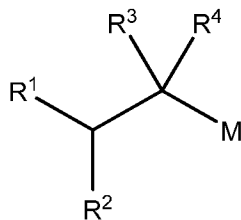
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R^b and R^c are each independently hydrogen or selected from hydrocarbyl and $-(CH_2)_j$ -heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, oxo, cyano, amino, hydroxy, alkyl and alkoxy;

- 5 j is 0, 1, 2, 3, 4, 5 or 6;
 k is 0, 1 or 2; and
 the asterisk * designates a chiral centre of (*R*) or (*S*) configuration;

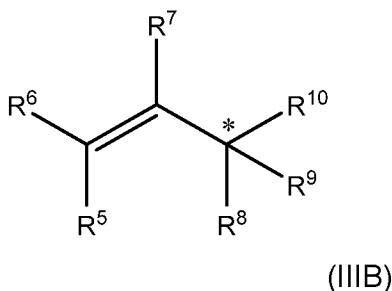
wherein the process comprises:

- 10 (i) contacting a compound comprising an alkene bond with a hydrometallating agent of the formula HM, wherein M comprises a metal, and wherein said compound and the hydrometallating agent are contacted under conditions such that they react to form a compound of the formula (II):



(II); and

- (ii) contacting the compound of formula (II) with a compound of the formula (IIIB):



(IIIB)

wherein

- 25 R^{10} is a leaving group; and

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the asterisk * designates a chiral centre of (*R*) or (*S*) configuration;

wherein the compound of formula (II) and the compound of formula (IIIB) are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a stereoisomeric excess of a compound of formula (IB), wherein said asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

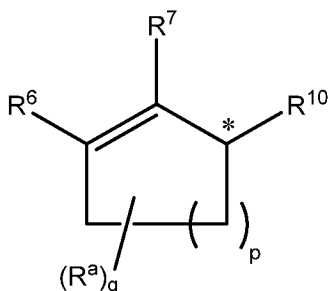
11. A process according to claim 10, wherein R^8 and R^9 are each independently selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

12. A process according to claim 10, wherein R^5 and R^8 , taken together with the carbon atoms to which they are attached, form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a .

13. A process according to claim 12, wherein R^5 and R^8 , taken together with the carbon atoms to which they are attached, form a 5-, 6-, 7- or 8-membered carbocyclic or heterocyclic group which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

14. A process according to claim 12 or claim 13, wherein R^9 is hydrogen.

15. A process according to claim 10, wherein the compound of formula (IIIB) is a compound of formula (IIIB.1):



(IIIB.1)

wherein

p is 1, 2, 3 or 4; and

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q is 0, 1, 2, 3, 4 or 5.

16. A process according to claim 15, wherein p is 2.

5 17. A process according to claim 15 or claim 16, wherein q is 0.

18. A process according to any of claims 10 to 17, wherein R⁶ is selected from hydrogen and alkyl.

10 19. A process according to claim 18, wherein R⁶ is hydrogen.

20. A process according to any of claims 10 to 19, wherein R⁷ is hydrogen.

15 21. A process according to any of claims 10 to 20, wherein the compound of formula (IIIB) is in racemic form.

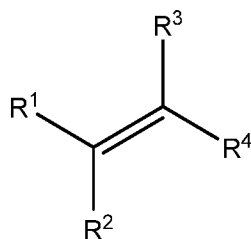
22. A process according to any of claims 2 to 21, wherein R¹⁰ is a leaving group selected from halogen, cyano, cyanate, thiocyanate, -OR¹¹, -C(O)R¹¹, -C(S)R¹¹, -C(O)N(R¹¹)R¹², -C(O)OR¹¹, -C(O)SR¹¹, -C(O)SeR¹¹, -OC(O)R¹¹, -S(O)_mR¹¹, -SeR¹¹,
20 -S(O)_mN(R¹¹)R¹², -N(R¹¹)R¹², -N(R¹¹)N(R¹¹)R¹², -N(R¹¹)C(O)R¹², -N(R¹¹)S(O)_mR¹² and -P(O)(OR¹²)₂, wherein R¹¹ and R¹² are each independently selected from hydrogen, alkyl, aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a; and m is 0, 1 or 2.

25 23. A process according to claim 22, wherein R¹⁰ is halo, *e.g.* Cl, Br or I.

24. A process according to any of claims 2 to 21, wherein R¹⁰ is -OP(O)(OR¹²)₂, wherein each R¹² is independently selected from hydrogen, alkyl, aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5
30 R^a.

25. A process according to any of claims 2 to 24, wherein the compound comprising an alkene bond is a compound of the formula (IV):

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(IV).

- 5 26. A process according to any of claims 2 to 25, wherein R^1 is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a .
27. A process according to claim 26, wherein R^1 is alkyl, cycloalkyl or aralkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a .
- 10 28. A process according to any of claims 2 to 27, wherein R^3 is hydrogen or hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a .
29. A process according to claim 28, wherein R^3 is hydrogen or alkyl optionally substituted with 1, 2, 3, 4 or 5 R^a .
- 15 30. A process according to any of claims 2 to 29, wherein R^2 and R^4 are each hydrogen.
- 20 31. A process according to any preceding claim, wherein the chiral compound is formed via a dynamic kinetic resolution process or a dynamic kinetic asymmetric transformation process.
32. A process according to any preceding claim, wherein the chiral compound is formed via desymmetrisation of a meso compound containing an allyl group.
- 25 33. A process according to any preceding claim, wherein the hydrometallating agent comprises zirconium.

34. A process according to claim 33, wherein the hydrometallating agent is of the formula HZrCp_2X , wherein each Cp is an optionally substituted π -cyclopentadienyl group; and X is selected from halogen, triflates, alcohols and nitrogen-containing compounds.

5

35. A process according to claim 34, wherein the hydrometallating agent is of the formula HZrCp_2Cl .

10

36. A process according to any preceding claim, wherein the metal catalyst comprises a metal, one or more ligands and one or more counterions, wherein the one or more ligands include said chiral ligand.

15

37. A process according to any preceding claim, wherein the metal catalyst comprises a transition metal.

38. A process according to claim 37, wherein the metal catalyst comprises copper, *e.g.* Cu(I) .

20

39. A process according to claim 38, wherein the metal catalyst comprises a copper halide, *e.g.* copper iodide.

40. A process according to any preceding claim, wherein the chiral ligand is a non-racemic chiral ligand.

25

41. A process according to claim 40, wherein the non-racemic chiral ligand is a phosphoramidite ligand.

42. A process according to any preceding claim, wherein the chiral compound is produced in an enantiomeric excess.

30

43. A process according to any preceding claim, wherein the chiral compound is a prostaglandin, an opiate or a terpinoid, or the process comprises converting the chiral compound into a prostaglandin, an opiate or a terpinoid.

44. A process according to any preceding claim, wherein the process further comprises formulating a product comprising the chiral compound or converting the chiral compound into a product.

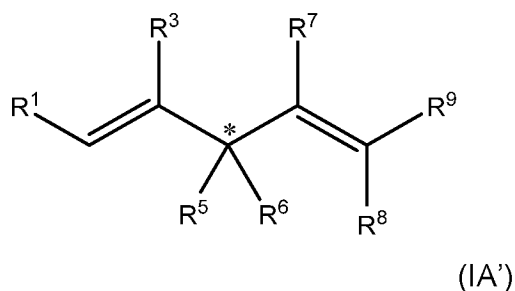
5 45. A process according to claim 44, wherein the product is a pharmaceutical product.

46. A process for producing a chiral compound in a stereoisomeric excess, the process comprising:

10 (i) contacting a first compound comprising an alkyne bond with a hydrometallating agent, wherein the first compound and the hydrometallating agent are contacted under conditions such that the first compound is hydrometallated by said hydrometallating agent; and

(ii) contacting the hydrometallated first compound with a second compound
15 comprising an allylic group, wherein the hydrometallated first compound and the second compound are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction in which a carbon atom of the hydrometallated first compound binds to a carbon atom of said allylic group, forming a stereoisomeric excess of a compound having a chiral centre in an allylic position, said chiral centre being located at the carbon
20 atom bound by said first compound, wherein said asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

47. A process for producing a chiral compound of the formula (IA') in a stereoisomeric excess:



wherein

R^1 and R^3 are each independently selected from hydrogen, R^a , hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl

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optionally substituted with 1, 2, 3, 4 or 5 R^a ;

R^5 , R^6 , R^7 , R^8 and R^9 are each independently selected from hydrogen, R^a , hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

5 or R^5 and one of R^6 and R^8 , or R^6 and R^7 , or R^7 and R^9 , taken together with the carbon atoms to which they are attached, may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

each R^a is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^b$, $-OR^b$, $-C(O)R^b$, $-C(O)N(R^b)R^c$, $-C(O)OR^b$, $-C(O)SR^b$, $-C(O)SeR^b$,
10 $-OC(O)R^b$, $-S(O)_kR^b$, $-S(O)_kN(R^b)R^c$, $-N(R^b)R^c$, $-N(R^b)N(R^b)R^c$, $-N(R^b)C(O)R^c$ and $-N(R^b)S(O)_kR^b$;

R^b and R^c are each independently hydrogen or selected from hydrocarbyl and $-(CH_2)_j$ -heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, oxo, cyano, amino, hydroxy,
15 alkyl and alkoxy;

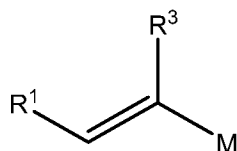
j is 0, 1, 2, 3, 4, 5 or 6;

k is 0, 1 or 2; and

the asterisk * designates a chiral centre of (*R*) or (*S*) configuration;

20 wherein the process comprises:

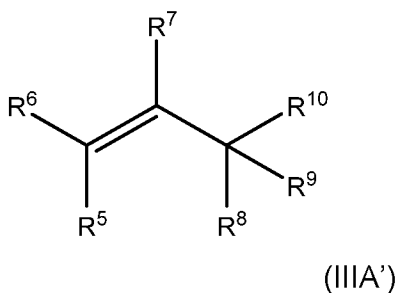
(i) contacting a compound comprising an alkyne bond with a hydrometallating agent of the formula HM, wherein M comprises a metal, and wherein said compound and the hydrometallating agent are contacted under conditions such that they react to form a
25 compound of the formula (II'):



(II'); and

30 (ii) contacting the compound of formula (II') with a compound of the formula (IIIA'):

- 90 -



5 wherein R^{10} is a leaving group;

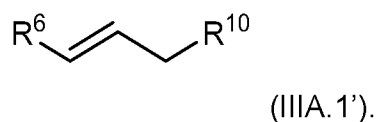
wherein the compound of formula (II') and the compound of formula (IIIA') are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a stereoisomeric excess of a compound of formula (IA'), wherein said asymmetric allylic alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

48. A process according to claim 47, wherein R^7 is hydrogen.

15 49. A process according to claim 47 or claim 48, wherein R^8 and R^9 are each independently selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

50. A process according to claim 49, wherein R^8 and R^9 are each independently selected from hydrogen and alkyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

51. A process according to claim 47, wherein the compound of formula (IIIA') is a compound of the formula (IIIA.1'):



52. A process according to any of claims 47 to 51, wherein R^6 is hydrocarbyl

optionally substituted with 1, 2, 3, 4 or 5 R^a .

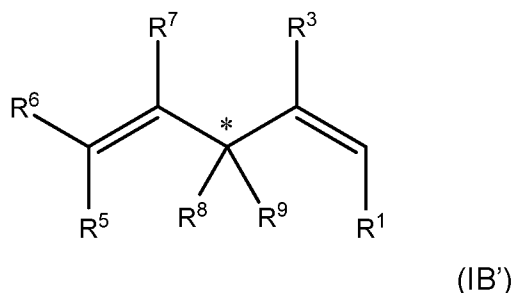
53. A process according to claim 52, wherein R^6 is selected from alkyl, aryl, aralkyl and cycloalkyl, each of which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

5

54. A process according to claim 53, wherein R^6 is aryl or aralkyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

55. A process for producing a chiral compound of the formula (IB') in a stereoisomeric excess:

10



wherein

15

R^1 and R^3 are each independently selected from hydrogen, R^a , hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

R^5 , R^6 , R^7 , R^8 and R^9 are each independently selected from hydrogen, R^a , hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a ;

20

or R^5 and one of R^6 and R^8 , or R^6 and R^7 , or R^7 and R^9 , taken together with the carbon atoms to which they are attached, may form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a ;

each R^a is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^b$, $-OR^b$, $-C(O)R^b$, $-C(O)N(R^b)R^c$, $-C(O)OR^b$, $-C(O)SR^b$, $-C(O)SeR^b$, $-OC(O)R^b$, $-S(O)_kR^b$, $-S(O)_kN(R^b)R^c$, $-N(R^b)R^c$, $-N(R^b)N(R^b)R^c$, $-N(R^b)C(O)R^c$ and $-N(R^b)S(O)_kR^b$;

25

R^b and R^c are each independently hydrogen or selected from hydrocarbyl and $-(CH_2)_j$ -heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or

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5 substituents independently selected from halogen, oxo, cyano, amino, hydroxy, alkyl and alkoxy;

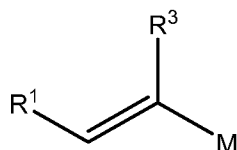
j is 0, 1, 2, 3, 4, 5 or 6;

k is 0, 1 or 2; and

5 the asterisk * designates a chiral centre of (*R*) or (*S*) configuration;

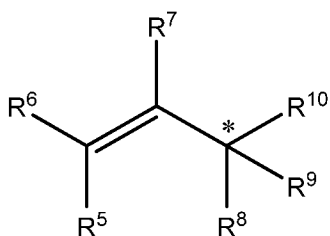
wherein the process comprises:

- (i) contacting a compound comprising an alkyne bond with a hydrometallating agent of the formula HM, wherein M comprises a metal, and wherein said compound and the hydrometallating agent are contacted under conditions such that they react to form a compound of the formula (II'):



15 (II'); and

- (ii) contacting the compound of formula (II') with a compound of the formula (IIIB'):



20 (IIIB')

wherein

R¹⁰ is a leaving group; and

the asterisk * designates a chiral centre of (*R*) or (*S*) configuration;

- 25 wherein the compound of formula (II') and the compound of formula (IIIB') are contacted under conditions such that they undergo an asymmetric allylic alkylation reaction to form a stereoisomeric excess of a compound of formula (IB'), wherein said asymmetric allylic

alkylation reaction is performed in the presence of a metal catalyst comprising a chiral ligand.

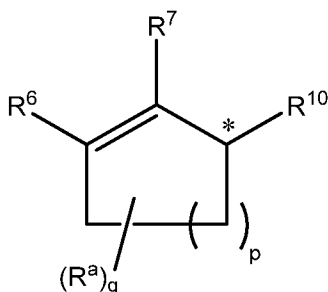
56. A process according to claim 55, wherein R^8 and R^9 are each independently selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a ; and $-(CH_2)_j$ -heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

57. A process according to claim 55, wherein R^5 and R^8 , taken together with the carbon atoms to which they are attached, form a carbocyclic or heterocyclic group, which group is optionally substituted with 1, 2, 3, 4 or 5 R^a .

58. A process according to claim 57, wherein R^5 and R^8 , taken together with the carbon atoms to which they are attached, form a 5-, 6-, 7- or 8-membered carbocyclic or heterocyclic group which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

59. A process according to claim 57 or claim 58, wherein R^9 is hydrogen.

60. A process according to claim 55, wherein the compound of formula (IIIB') is a compound of formula (IIIB.1'):



(IIIB.1')

wherein

p is 1, 2, 3 or 4; and

q is 0, 1, 2, 3, 4 or 5.

61. A process according to claim 60, wherein p is 2.

62. A process according to claim 60 or claim 61, wherein q is 0.

63. A process according to any of claims 55 to 62, wherein R^6 is selected from hydrogen and alkyl.

64. A process according to claim 63, wherein R^6 is hydrogen.

65. A process according to any of claims 55 to 64, wherein R^7 is hydrogen.

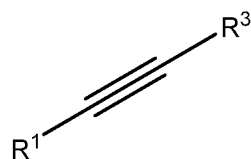
66. A process according to any of claims 55 to 65, wherein the compound of formula (IIIB) is in racemic form.

67. A process according to any of claims 47 to 66, wherein R^{10} is a leaving group selected from halogen, cyano, cyanate, thiocyanate, $-OR^{11}$, $-C(O)R^{11}$, $-C(S)R^{11}$, $-C(O)N(R^{11})R^{12}$, $-C(O)OR^{11}$, $-C(OS)R^{11}$, $-C(O)SeR^{11}$, $-OC(O)R^{11}$, $-S(O)_mR^{11}$, $-SeR^{11}$, $-S(O)_mN(R^{11})R^{12}$, $-N(R^{11})R^{12}$, $-N(R^{11})N(R^{11})R^{12}$, $-N(R^{11})C(O)R^{12}$, $-N(R^{11})S(O)_mR^{12}$ and $-P(O)(OR^{12})_2$ and $-OP(O)(OR^{12})_2$, wherein R^{11} and R^{12} are each independently selected from hydrogen, alkyl, aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a ; and m is 0, 1 or 2.

68. A process according to claim 67, wherein R^{10} is halo, e.g. Cl, Br or I.

69. A process according to claim 68, wherein R^{10} is Cl.

70. A process according to any of claims 47 to 69, wherein the compound comprising an alkyne bond is a compound of the formula (IV'):



(IV').

71. A process according to any of claims 47 to 70, wherein R^1 is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

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72. A process according to claim 71, wherein R^1 is alkyl, cycloalkyl or aralkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^a .

73. A process according to any of claims 47 to 72, wherein R^3 is hydrogen or hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

74. A process according to claim 73, wherein R^3 is hydrogen or alkyl optionally substituted with 1, 2, 3, 4 or 5 R^a .

75. A process according to any of claims 46 to 74, wherein the chiral compound is formed via a dynamic kinetic resolution process or a dynamic kinetic asymmetric transformation process.

76. A process according to any of claims 46 to 75, wherein the chiral compound is formed via desymmetrisation of a meso compound containing an allyl group.

77. A process according to any of claims 46 to 76, wherein the hydrometallating agent comprises zirconium.

78. A process according to claim 77, wherein the hydrometallating agent is of the formula $HZrCp_2X$, wherein each Cp is an optionally substituted π -cyclopentadienyl group; and X is selected from halogen, triflates, alcohols and nitrogen-containing compounds.

79. A process according to claim 78, wherein the hydrometallating agent is of the formula $HZrCp_2Cl$.

80. A process according to any of claims 46 to 79, wherein the metal catalyst comprises a metal, one or more ligands and one or more counterions, wherein the one or more ligands include said chiral ligand.

81. A process according to any of claims 46 to 80, wherein the metal catalyst comprises a transition metal.

82. A process according to claim 81, wherein the metal catalyst comprises copper, *e.g.* Cu(I).

83. A process according to claim 82, wherein the metal catalyst comprises a copper
5 halide, *e.g.* copper iodide.

84. A process according to any of claims 46 to 83, wherein the chiral ligand is a non-racemic chiral ligand.

10 85. A process according to claim 84, wherein the non-racemic chiral ligand is a phosphoramidite ligand.

86. A process according to any of claims 46 to 85, wherein the chiral compound is
15 produced in an enantiomeric excess.

87. A process according to any of claims 46 to 86, wherein the process further comprises formulating a product comprising the chiral compound or converting the chiral compound into a product.

20 88. A process according to claim 87, wherein the product is a pharmaceutical product.

89. Use of a hydrometallated alkene for the production of a chiral compound in a stereoisomeric excess, wherein the chiral compound is produced via an asymmetric
25 allylic addition reaction involving said hydrometallated alkene and wherein said reaction is catalysed using a metal catalyst comprising a chiral ligand.

90. Use of a metal catalyst for the production of a chiral compound in a stereoisomeric excess, wherein said metal catalyst comprises a chiral ligand and
30 wherein the chiral compound is produced via an asymmetric allylic addition reaction which involves a hydrometallated alkene and said metal catalyst.

91. Use according to claim 89 or claim 90, wherein the hydrometallated alkene is a

hydrozirconated alkene.

92. Use according to any of claims 89 to 91, wherein the chiral ligand is a non-racemic chiral ligand.

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93. Use of a hydrometallated alkyne for the production of a chiral compound in a stereoisomeric excess, wherein the chiral compound is produced via an asymmetric allylic addition reaction involving said hydrometallated alkyne and wherein said reaction is catalysed using a metal catalyst comprising a chiral ligand.

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94. Use of a metal catalyst for the production of a chiral compound in a stereoisomeric excess, wherein said metal catalyst comprises a chiral ligand and wherein the chiral compound is produced via an asymmetric allylic addition reaction which involves a hydrometallated alkyne and said metal catalyst.

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95. Use according to claim 93 or claim 94, wherein the hydrometallated alkyne is a hydrozirconated alkyne.

96. Use according to any of claims 93 to 95, wherein the chiral ligand is a non-racemic chiral ligand.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/052230

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07B53/00 C07C2/86
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)
C07B 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/054131 A1 (ISIS INNOVATION [GB]; FLETCHER STEPHEN P [GB]; MAKSYMOWICZ REBECCA M []) 18 April 2013 (2013-04-18) the whole document	1,31-96
X	MAKSYMOWICZ ET AL: "Catalytic asymmetric carbon carbon bond formation using alkenes as alkylmetal equivalents", NATURE CHEMISTRY,, vol. 4, 1 January 2012 (2012-01-01), pages 649-654, XP009166674, the whole document	1,31-96



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"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

6 October 2014

Date of mailing of the international search report

15/10/2014

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/052230

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JEAN-BAPTISTE LANGLOIS ET AL: "Dynamic kinetic asymmetric transformation in copper catalyzed allylic alkylation", CHEMICAL COMMUNICATIONS, no. 26, 1 January 2009 (2009-01-01), page 3868, XP55144252, ISSN: 1359-7345, DOI: 10.1039/b907722g the whole document -----	1-96

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2014/052230

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013054131 A1	18-04-2013	EP 2766324 A1 WO 2013054131 A1	20-08-2014 18-04-2013
