

TRANSFER HYDROGENATION PROCESS AND CATALYST

This invention relates to catalytic transfer hydrogenation, particularly in the presence of a complexed transition metal, to a catalyst for such hydrogenation and to a process of making optically active compounds.

Hydrogenation by hydrogen transfer using catalysts containing phosphorus- or nitrogen- ligands was reviewed at length by Zassinovich et al. in Chem. Rev., 1992, 92, 1051-1069. These authors concluded 'in spite of excellent achievements, much work remains to be done'.

Transfer hydrogenation using catalysts in which the transition metal is coordinated to a benzenoid hydrocarbon have been explored. The following publications are of interest:

(1) Noyori et al., J. A. C. S., 1995, 117, 7562-7563: which discloses that use of chloro-ruthenium-mesitylene-N-monotosyl-1,2-diphenylethylenediamine as catalyst in the transfer hydrogenation of acetophenone to 1-phenylethanol by propan-2-ol gave up to a 95% yield of product having 97% enantiomeric excess. Similar results were obtained starting from other alkylaryl ketones. The efficiency of corresponding catalyst containing benzene in place of mesitylene was more sensitive to substituents on the aryl group of the starting ketone. Reaction times were generally rather long, typically 15h; at longer reaction times stereoselectivity decreased, apparently owing to reverse hydrogenation. No turnover numbers are reported. The authors commented that 'the overall catalytic performance is unable to rival that of the current best hydrogenation method' as described in an earlier publication by themselves.

(2) Noyori et al., J. Chem. Soc. Chem. Commun., 1996, 233-234: which discloses that catalysts similar to those of Noyori et al. (1) above but containing other alkylbenzene ligands and various beta-amino alcohols in place of the diphenylethylenediamine were to differing extents effective in the hydrogenation of acetophenone. The beta-amino alcohol ligand gave greater catalyst stability. The preferred arene ligand was hexamethylbenzene. Turnover numbers were up to 227 moles of product per mole of catalyst per hour.

(3) Noyori et al., J. A. C. S., 1996, 118, 2521-2522: which discloses that to prevent reverse hydrogen transfer in the process of Noyori et al. (1) above, formic acid-triethylamine was used as hydrogen source. Reaction times mainly over 14h and up to 90h were used; no turnover numbers are reported.

(4) Noyori et al., J. A. C. S., 1996, 118, 4916-4917: which discloses that the process of Noyori et al. (3) above is effective for reduction of imines (especially cyclic imines) to enantioselected amines.

These processes appear to require relatively long cycle times. As well as involving uneconomic utilisation of chemical plant, such slow reaction can lead to decomposition of the catalytic complex and slow loss of product optical purity; also it

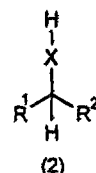
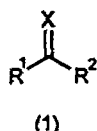
affords limited scope for adjusting reaction conditions such as temperature and reactant concentration to maximise the difference in rate between enantiomerically wanted and unwanted reactions.

Besides the phosphorus-, nitrogen- and benzene- ligated transition metals, complexes based on pentamethylcyclopentadienyl (hereinafter Cp*) have been shown to be effective as catalysts in homogeneous hydrogenation of olefins by free hydrogen (Maitlis, Acc. Chem. Res., 1978, 11, 301-307; Maitlis et al., J. Chem. Soc. Dalton, 1978, 617-626); there was no disclosure of hydrogen transfer in the absence of free hydrogen or of catalysts containing a chelating or chiral-directing ligand.

Complexes of iridium with Cp* and acylated or sulphonylated alpha amino carboxylic acid have been described by Grotjahn et al. (J. A. C. S., 1994, 116, 6969-6970) but without evidence of catalytic activity. Complexes of rhodium with Cp* and 2,2'-bipyridyls and the use of these with formate to hydrogenate nicotinamide adenine dinucleotide (NAD) to NADH have been described by Steckhan et al. (Angew. Chem. Int. Ed. Engl., 1990, 29(4), 388-390). Turnover frequencies up to 67.5 per h are reported, but no activity after 100 catalytic cycles.

We have now found that stereoselective transfer hydrogenation can be efficiently carried out by means of a catalyst comprising a complex of a transition metal, a chelating ligand and a cyclopentadienyl group.

According to a first aspect of the present invention there is provided a process for the transfer hydrogenation of a compound of formula (1) to produce a compound of formula (2)



wherein:

X represents CR³R⁴, NR⁵, (NR⁵R⁶)⁺Q⁻, O or S;
R¹, R², R³, R⁴, R⁵ and R⁶ each independently represents a hydrogen atom, an optionally substituted hydrocarbyl, a perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, one or more of R¹ & R², R¹ & R³, R² & R⁴, R³ & R⁴, R¹ & R⁵, R² & R⁶ and R⁵ & R⁶ optionally being linked in such a way as to form an optionally substituted ring(s); and

Q⁻ represents an anion;

said process comprising reacting the compound of formula (1) with a hydrogen donor in the presence of a catalyst, characterised in that the catalyst has the general formula:



wherein:

R^7 represents an optionally substituted cyclopentadienyl group;

A represents $-NR^8-$, $-NR^9-$, $-NHR^8$ or $-NR^8R^9$ where R^8 is H, $C(O)R^{10}$, SO_2R^{10} , $C(O)NR^{10}R^{14}$, $C(S)NR^{10}R^{14}$, $C(=NR^{14})SR^{15}$ or $C(=NR^{14})OR^{15}$, R^9 and R^{10} each independently represents an optionally substituted hydrocarbyl, perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, and R^{14} and R^{15} are each independently hydrogen or a group as defined for R^{10} ;

B represents $-O-$, $-OH$, OR^{11} , $-S-$, $-SH$, SR^{11} , $-NR^{11}-$, $-NR^{12}-$, $-NHR^{12}$ or $-NR^{11}R^{12}$ where R^{12} is H, $C(O)R^{13}$, SO_2R^{13} , $C(O)NR^{13}R^{16}$, $C(S)NR^{13}R^{16}$, $C(=NR^{16})SR^{17}$ or $C(=NR^{16})OR^{17}$, R^{11} and R^{13} each independently represents an optionally substituted hydrocarbyl, perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, and R^{16} and R^{17} are each independently hydrogen or a group as defined for R^{13} ;

E represents a linking group;

M represents a metal capable of catalysing transfer hydrogenation; and

Y represents an anionic group, a basic ligand or a vacant site;

provided that when Y is not a vacant site that at least one of A or B carries a hydrogen atom.

The catalytic species is believed to be substantially as represented in the above formula. It may be introduced on a solid support.

Hydrocarbyl groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} independently include alkyl, alkenyl and aryl groups, and any combination thereof, such as aralkyl and alkaryl, for example benzyl groups.

Alkyl groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} include linear and branched alkyl groups comprising up to 20 carbon atoms, particularly from 1 to 7 carbon atoms and preferably from 1 to 5 carbon atoms. When the alkyl groups are branched, the groups often comprising up to 10 branch chain carbon atoms, preferably up to 4 branch chain atoms. In certain embodiments, the alkyl group may be cyclic, commonly comprising from 3 to 10 carbon atoms in the largest ring and optionally featuring one or more bridging rings. Examples of alkyl groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} include methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, t-butyl and cyclohexyl groups.

Alkenyl groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} include C_{2-20} , and preferably C_{2-6} alkenyl groups. One or more carbon - carbon double bonds may be present. The alkenyl group may carry one or more substituents, particularly phenyl substituents. Examples of alkenyl groups include vinyl, styryl and indenyl groups. When either of R^1 or R^2 represents an alkenyl group, a carbon - carbon double bond is

preferably located at the position β to the $C=X$ moiety. When either of R^1 or R^2 represents an alkenyl group, the compound of formula (1) is preferably an α,β -unsaturated ketone.

Aryl groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} may contain 1 ring or 2 or more fused rings which may include cycloalkyl, aryl or heterocyclic rings.

5 Examples of aryl groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} include phenyl, tolyl, fluorophenyl, chlorophenyl, bromophenyl, trifluoromethylphenyl, anisyl, naphthyl and ferrocenyl groups.

Perhalogenated hydrocarbyl groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} independently include perhalogenated alkyl and aryl groups, and any
10 combination thereof, such as aralkyl and alkaryl groups. Examples of perhalogenated alkyl groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} include $-CF_3$ and $-C_2F_5$.

Heterocyclic groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} independently include aromatic, saturated and partially unsaturated ring systems and may
15 constitute 1 ring or 2 or more fused rings which may include cycloalkyl, aryl or heterocyclic rings. The heterocyclic group will contain at least one heterocyclic ring, the largest of which will commonly comprise from 3 to 7 ring atoms in which at least one atom is carbon and at least one atom is any of N, O, S or P. When either of R^1 or R^2 represents or comprises a heterocyclic group, the atom in R^1 or R^2 bonded to the $C=X$
20 group is preferably a carbon atom. Examples of heterocyclic groups which may be represented by R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} include pyridyl, pyrimidyl, pyrrolyl, thiophenyl, furanyl, indolyl, quinolyl, isoquinolyl, imidazolyl and triazolyl groups.

When any of R^{1-6} , R^9 , R^{10} , R^{11} and R^{13-17} is a substituted hydrocarbyl or heterocyclic group, the substituent(s) should be such so as not to adversely affect the rate or
25 stereoselectivity of the reaction. Optional substituents include halogen, cyano, nitro, hydroxy, amino, thiol, acyl, hydrocarbyl, perhalogenated hydrocarbyl, heterocyclyl, hydrocarbyloxy, mono or di-hydrocarbylamino, hydrocarbylthio, esters, carbonates, amides, sulphonyl and sulphonamido groups wherein the hydrocarbyl groups are as defined for R^1 above. One or more substituents may be present.

30 When any of R^1 & R^2 , R^1 & R^3 , R^2 & R^4 , R^3 & R^4 , R^1 & R^5 , R^2 & R^6 , and R^5 & R^6 are linked in such a way that when taken together with either the carbon atom and/or atom X of the compound of formula (1) that a ring is formed, it is preferred that these be 5, 6 or 7 membered rings. Examples of such compounds of formula (1) include
35 3,4-dihydroisoquinoline, 1-tetralone, 2-tetralone, 4-chromanone, 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline, 1-benzosubarone, 2-indanone and 1-indanone.

Compounds of formula (1) where X is represented by NR^5 or $(NR^5R^6)^+Q^-$, include imines or iminium salts. Where a compound of formula (1) is an imine, it may optionally be converted to an iminium salt. Iminium salts are preferred over imines. Preferred
40 iminium salts are represented by compounds of formula (1) in which X is $(NR^5R^6)^+Q^-$ such that either R^5 or R^6 are hydrogen but that R^5 or R^6 are not identical. When the compound

of formula (1) is an iminium salt, an anion represented by Q^- is present. Examples of anions which may be present are halide, hydrogen sulphate, tosylate, formate, acetate, tetrafluoroborate, trifluoromethanesulphonate and trifluoroacetate.

X is most preferably O.

5 In certain preferred embodiments, R^1 and R^2 are both independently C_{1-6} alkyl, both independently aryl, particularly phenyl, or one is aryl, particularly phenyl and one is C_{1-6} alkyl. Substituents may be present, particularly substituents para to the $C=X$ group when one or both of R^1 and R^2 is a phenyl group.

10 Most advantageously, the compound of formula (1) is prochiral, such that the hydrogenated product of formula (2) comprises a chiral atom to which R^1 , R^2 and X are each bonded. Such an asymmetric transfer hydrogenation process forms an especially preferred aspect of the present invention. Most commonly, when the compound of formula (1) is prochiral, R^1 and R^2 are different, and neither is hydrogen. Usefully, one of R^1 and R^2 is aliphatic and the other is aryl or heterocyclyl.

15 Examples of compounds of formula (1) include acetophenone, 4-chloroacetophenone, 4-methoxyacetophenone, 4-trifluoromethylacetophenone, 4-nitroacetophenone, 2-chloroacetophenone and acetophenone benzylium.

20 Hydrogen donors include hydrogen, primary and secondary alcohols, primary and secondary amines, carboxylic acids and their esters and amine salts, readily dehydrogenatable hydrocarbons, clean reducing agents, and any combination thereof.

25 Primary and secondary alcohols which may be employed as hydrogen donors comprise commonly from 1 to 10 carbon atoms, preferably from 2 to 7 carbon atoms, and more preferably 3 or 4 carbon atoms. Examples of primary and secondary alcohols which may be represented as hydrogen donors include methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol, cyclopentanol, cyclohexanol, benzylalcohol, and menthol. When the hydrogen donor is an alcohol, secondary alcohols are preferred, especially propan-2-ol and butan-2-ol.

30 Primary and secondary amines which may be employed as hydrogen donors comprise commonly from 1 to 20 carbon atoms, preferably from 2 to 14 carbon atoms, and more preferably 3 or 8 carbon atoms. Examples of primary and secondary amines which may be represented as hydrogen donors include ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, hexylamine, diethylamine, dipropylamine, diisopropylamine, dibutylamine, diisobutylamine, dihexylamine, benzylamine, dibenzylamine and piperidine. When the hydrogen donor is an amine, primary amines are preferred, especially primary amines comprising a secondary alkyl group, particularly isopropylamine and isobutylamine.

40 Carboxylic acids or their esters which may be employed as hydrogen donors comprise commonly from 1 to 10 carbon atoms, preferably from 1 to 3 carbon atoms. In certain embodiments, the carboxylic acid is advantageously a beta-hydroxy-carboxylic acid. Esters may be derived from the carboxylic acid and a C_{1-10} alcohol. Examples of

carboxylic acids which may be employed as hydrogen donors include formic acid, lactic acid, ascorbic acid and mandelic acid. When a carboxylic acid is employed as hydrogen donor, at least some of the carboxylic acid is preferably present as an amine salt or ammonium salt. Amines which may be used to form such salts include both aromatic and non-aromatic amines, also primary, secondary and tertiary amines and comprise typically from 1 to 20 carbon atoms. Tertiary amines, especially trialkylamines, are preferred. Examples of amines which may be used to form salts include trimethylamine, triethylamine, di-isopropylethylamine and pyridine. The most preferred amine is triethylamine. When at least some of the carboxylic acid is present as an amine salt, particularly when a mixture of formic acid and triethylamine is employed, the mole ratio of acid to amine is commonly about 5 : 2. This ratio may be maintained during the course of the reaction by the addition of either component, but usually by the addition of the carboxylic acid.

Readily dehydrogenatable hydrocarbons which may be employed as hydrogen donors comprise hydrocarbons which have a propensity to aromatise or hydrocarbons which have a propensity to form highly conjugated systems. Examples of readily dehydrogenatable hydrocarbons which may be employed by as hydrogen donors include cyclohexadiene, cyclohexene, tetralin, dihydrofuran and terpenes.

Clean reducing agents which may be represented as hydrogen donors comprise reducing agents with a high reduction potential, particularly those having a reduction potential relative to the standard hydrogen electrode of greater than about -0.1eV, often greater than about -0.5eV, and preferably greater than about -1eV. Examples of clean reducing agents which may be represented as hydrogen donors include hydrazine and hydroxylamine.

The most preferred hydrogen donors are propan-2-ol, butan-2-ol, triethylammonium formate and a mixture of triethylammonium formate and formic acid.

The optionally substituted cyclopentadienyl group which may be represented by R^7 includes cyclopentadienyl groups capable of η^5 bonding. The cyclopentadienyl group is often substituted with from 1 to 5 hydrocarbyl groups, preferably with 3 to 5 hydrocarbyl groups and more preferably with 5 hydrocarbyl groups. Preferred hydrocarbyl substituents include methyl, ethyl and phenyl. When the hydrocarbyl substituents contain enantiomeric and/or diastereomeric centres, it is preferred that the enantiomerically and/or diastereomerically purified forms of these are used. Examples of optionally substituted cyclopentadienyl groups include cyclopentadienyl, pentamethylcyclopentadienyl, pentaphenylcyclopentadienyl, tetraphenylcyclopentadienyl, ethyltetramethylpentadienyl, menthyltetraphenylcyclopentadienyl, neomenthyltetraphenylcyclopentadienyl, menthylcyclopentadienyl, neomenthylcyclopentadienyl, tetrahydroindenyl, menthyltetrahydroindenyl and neomenthyltetrahydroindenyl groups. Pentamethylcyclopentadienyl is especially preferred.

When either A or B is an amide group represented by $-NR^8$ -, $-NHR^8$, NR^8R^9 ,

-NR¹²-, -NHR¹² or NR¹¹R¹² wherein R⁹ and R¹¹ are as hereinbefore defined, and where R⁹ or R¹² is an acyl group represented by -C(O)R¹⁰ or -C(O)R¹³, R¹⁰ and R¹³ independently are often linear or branched C₁₋₇alkyl, C₁₋₈-cycloalkyl or aryl, for example phenyl. Examples of acyl groups which may be represented by R⁸ or R¹² include benzoyl, acetyl and halogenoacetyl, especially trifluoroacetyl, groups.

When either A or B is present as a sulphonamide group represented by -NR⁸-, -NHR⁸, NR⁸R⁹, -NR¹²-, -NHR¹² or NR¹¹R¹² wherein R⁹ and R¹¹ are as hereinbefore defined, and where R⁸ or R¹² is a sulphonyl group represented by -S(O)₂R¹⁰ or -S(O)₂R¹³, R¹⁰ and R¹³ independently are often linear or branched C₁₋₈alkyl, C₁₋₈cycloalkyl or aryl, for example phenyl. Preferred sulphonyl groups include methanesulphonyl, trifluoromethanesulphonyl and especially p-toluenesulphonyl groups.

When either of A or B is present as a group represented by -NR⁸-, -NHR⁸, NR⁸R⁹-, -NR¹²-, -NHR¹² or NR¹¹R¹² wherein R⁹ and R¹¹ are as hereinbefore defined, and where R⁸ or R¹² is a group represented by C(O)NR¹⁰R¹⁴, C(S)NR¹⁰R¹⁴, C(=NR¹⁴)SR¹⁵, C(=NR¹⁴)OR¹⁵, C(O)NR¹³R¹⁶, C(S)NR¹³R¹⁶, C(=NR¹⁶)SR¹⁷ or C(=NR¹⁶)OR¹⁷, R¹⁰ and R¹³ independently are often linear or branched C₁₋₈alkyl, such as methyl, ethyl, isopropyl, C₁₋₈cycloalkyl or aryl, for example phenyl, groups and R¹⁴⁻¹⁷ are often each independently hydrogen or linear or branched C₁₋₈alkyl, such as methyl, ethyl, isopropyl, C₁₋₈cycloalkyl or aryl, for example phenyl, groups.

It will be recognised that the precise nature of A and B will be determined by whether A and/or B are formally bonded to the metal or are coordinated to the metal via a lone pair of electrons.

The groups A and B are connected by a linking group E. The linking group E achieves a suitable conformation of A and B so as to allow both A and B to bond or coordinate to the metal, M. A and B are commonly linked through 2, 3 or 4 atoms. The atoms in E linking A and B may carry one or more substituents. The atoms in E, especially the atoms alpha to A or B, may be linked to A and B, in such a way as to form a heterocyclic ring, preferably a saturated ring, and particularly a 5, 6 or 7-membered ring. Such a ring may be fused to one or more other rings. Often the atoms linking A and B will be carbon atoms. Preferably, one or more of the carbon atoms linking A and B will carry substituents in addition to A or B. Substituent groups include those which may substitute R¹, as defined above. Advantageously, any such substituent groups are selected to be groups which do not coordinate with the metal, M. Preferred substituents include halogen, cyano, nitro, sulphonyl, hydrocarbyl, perhalogenated hydrocarbyl and heterocyclyl groups as defined above. Most preferred substituents are C₁₋₈ alkyl groups, and phenyl groups. Most preferably, A and B are linked by two carbon atoms, and especially an optionally substituted ethyl moiety. When A and B are linked by two carbon atoms, the two carbon atoms linking A and B may comprise part of an aromatic or aliphatic cyclic group, particularly a 5, 6 or 7-membered ring. Such a ring may be fused to one or more other such rings. Particularly preferred are embodiments in which E

represents a 2 carbon atom separation and one or both of the carbon atoms carries an optionally substituted aryl group as defined above or E represents a 2 carbon atom separation which comprises a cyclopentane or cyclohexane ring, optionally fused to a phenyl ring.

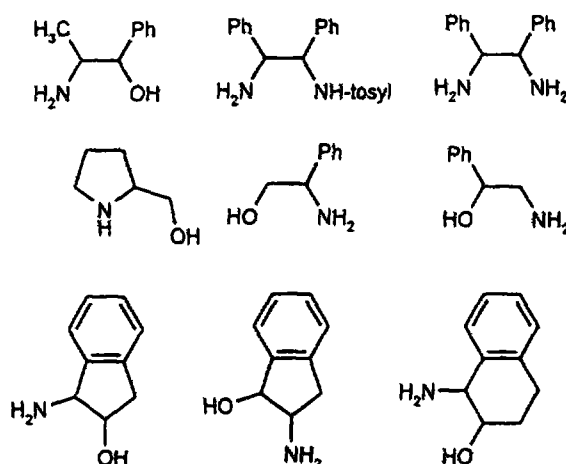
5 E preferably comprises part of a compound having at least one stereospecific centre. Where any or all of the 2, 3 or 4 atom atoms linking A and B are substituted so as to define at least one stereospecific centre on one or more of these atoms, it is preferred that at least one of the stereospecific centres be located at the atom adjacent to either group A or B. When at least one such stereospecific centre is present, it is
10 advantageously present in an enantiomerically purified state.

When B represents -O- or -OH, and the adjacent atom in E is carbon, it is preferred that B does not form part of a carboxylic group.

Compounds which may be represented by A-E-B, or from which A-E-B may be derived by deprotonation, are often aminoalcohols, including 4-aminoalkan-1-ols,
15 1-aminoalkan-4-ols, 3-aminoalkan-1-ols, 1-aminoalkan-3-ols, and especially 2-aminoalkan-1-ols, 1-aminoalkan-2-ols, 3-aminoalkan-2-ols and 2-aminoalkan-3-ols, and particularly 2-aminoethanols or 3-aminopropanols, or are diamines, including 1,4-diaminoalkanes, 1,3-diaminoalkanes, especially 1,2- or 2,3- diaminoalkanes and particularly ethylenediamines. Further aminoalcohols that may be represented by A-E-B
20 are 2-aminocyclopentanol and 2-aminocyclohexanol, preferably fused to a phenyl ring. Further diamines that may be represented by A-E-B are 1,2-diaminocyclopentanes and 1,2-diaminocyclohexanes, preferably fused to a phenyl ring. The amino groups may advantageously be N-tosylated. When a diamine is represented by A-E-B, preferably at least one amino group is N-tosylated. The aminoalcohols or diamines are
25 advantageously substituted, especially on the linking group, E, by at least one alkyl group, such as a C₁₋₄-alkyl, and particularly a methyl, group or at least one aryl group, particularly a phenyl group.

Specific examples of compounds which can be represented by A-E-B and the protonated equivalents from which they may be derived are:

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Preferably, the enantiomerically and/or diastereomerically purified forms of these are used. Examples include (1S,2R)-(+)-norephedrine, (1R,2S)-(+)-cis-1-amino-2-indanol, (1S,2R)-2-amino-1,2-diphenylethanol, (1S,2R)-(-)-cis-1-amino-2-indanol, N-tosyl-(1S,2R)-cis-1-amino-2-indanol, (1R,2S)-(-)-norephedrine, (S)-(+)-2-amino-1-phenylethanol, (1R,2S)-2-amino-1,2-diphenylethanol, (R)-(-)-2-pyrrolidinemethanol and (S)-(+)-2-pyrrolidinemethanol.

Metals which may be represented by M include metals which are capable of catalysing transfer hydrogenation. Preferred metals include transition metals, more preferably the metals in Group VIII of the Periodic Table, especially ruthenium, rhodium or iridium. When the metal is ruthenium it is preferably present in valence state II. When the metal is rhodium or iridium it is preferably present in valence state III.

Anionic groups which may be represented by Y include hydride, hydroxy, hydrocarbyloxy, hydrocarbylamino and halogen groups. Preferably when a halogen is represented by Y, the halogen is chloride. When a hydrocarbyloxy or hydrocarbylamino group is represented by Y, the group may be derived from the deprotonation of the hydrogen donor utilised in the reaction.

Basic ligands which may be represented by Y include water, C₁₋₄ alcohols, C₁₋₈ primary or secondary amines, or the hydrogen donor which is present in the reaction system. A preferred basic ligand represented by Y is water.

Most preferably, the nature of A-E-B, R⁷ and Y are chosen such that the catalyst is chiral. When such is the case, an enantiomerically and/or diastereomerically purified form is preferably employed. Such catalysts are most advantageously employed in asymmetric transfer hydrogenation processes. In many embodiments, the chirality of the catalyst is derived from the nature of A-E-B.

The process is carried out preferably in the presence of a base, especially when Y is not a vacant site. The pK_a of the base is preferably at least 8.0, especially at least 10.0. Convenient bases are the hydroxides, alkoxides and carbonates of alkali metals; tertiary amines and quaternary ammonium compounds. Preferred bases are sodium 2-propoxide and triethylamine. When the hydrogen donor is not an acid, the quantity of base used

can be up to 5.0, commonly up to 3.0, often up to 2.5 and especially in the range 1.0 to 3.5, by moles of the catalyst. The substantial excesses of base used by Noyori et al. appear to be unnecessary. When the hydrogen donor is an acid, the catalyst is preferably contacted with a base prior to the introduction of the hydrogen donor. In such a case, the mole ratio of base to catalyst prior to the introduction of the hydrogen donor is often from 1 : 1 to 3 : 1, and preferably about 1 : 1.

Although gaseous hydrogen may be present, the process is normally operated in the absence of gaseous hydrogen since it appears to be unnecessary.

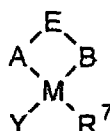
The absence of oxygen is not essential. This has been shown by carrying out the process with sparging of the reactor mixture with pure oxygen: the initial turnover rate was 500h^{-1} and in 2 hours a 40% conversion was obtained. However better results have been obtained under an inert atmosphere, initial rates for example of 1080h^{-1} in static nitrogen and 1500h^{-1} with nitrogen sparging. Advantageously, the process is carried out in the substantial absence of carbon dioxide.

When the product(s) from dehydrogenation of the hydrogen donor is volatile, for example boils at under 100°C , the removal of this volatile product is preferred. The removal can be accomplished by the use of inert gas sparging. More preferably, the removal is accomplished by distillation preferably at less than atmospheric pressure. When reduced pressure distillation is employed, the pressure is often no more than 500 mmHg, commonly no more than 200 mmHg, preferably in the range of from 5 to 100 mmHg, and most preferably from 10 to 80 mmHg.

Suitably the process is carried out at temperatures in the range of from minus 78°C to plus 150°C , preferably from minus 20°C to plus 110°C and more preferably from minus 5°C to plus 60°C . The initial concentration of the substrate, a compound of formula (1), is suitably in the range 0.05 to 1.0 and, for convenient larger scale operation, can be for example up to 6.0 more especially 0.75 to 2.0, on a molar basis. The molar ratio of the substrate to catalyst is suitably no less than 50:1 and can be up to 50000:1, preferably between 250:1 and 5000:1 and more preferably between 500:1 and 2500:1. The hydrogen donor is preferably employed in a molar excess over the substrate, especially from 5 to 20 fold or, if convenience permits, greater, for example up to 500 fold. Reaction times are typically in the range of from 1.0 min to 24h, especially up to 8h and conveniently about 3h. It appears that substantially shorter times than those disclosed in the above-mentioned publications are made practicable by the invention. After reaction, the mixture is worked up by standard procedures. A reaction solvent may be present, for example acetonitrile or, conveniently, the hydrogen donor when the hydrogen donor is liquid at the reaction temperature, particularly when the hydrogen donor is a primary or secondary alcohol or a primary or secondary amine. Usually it is preferred to operate in substantial absence of water, but water does not appear to inhibit the reaction. If the hydrogen donor or the reaction solvent is not miscible with water and the desired product is water soluble, it may be desirable to have water present as a second phase extracting

the product, pushing the equilibrium and preventing loss of product optical purity as the reaction proceeds. The concentration of substrate may be chosen to optimise reaction time, yield and enantiomeric excess.

According to a second embodiment of the present invention there is provided a
5 catalyst of general formula:



wherein:

- R^7 represents an optionally substituted cyclopentadienyl group;
- 10 A represents $-NR^8$, $-NR^9$, $-NHR^9$, or $-NR^9R^9$ where R^8 is H, $C(O)R^{10}$, SO_2R^{10} , $C(O)NR^{10}R^{14}$, $C(S)NR^{10}R^{14}$, $C(=NR^{14})SR^{15}$ or $C(=NR^{14})OR^{15}$, R^9 and R^{10} each independently represents an optionally substituted hydrocarbyl, perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, and R^{14} and R^{15} are each independently hydrogen or a group as defined for R^{10} ;
- 15 B represents $-O-$, $-OH$, OR^{11} , $-S-$, $-SH$, SR^{11} , $-NR^{11}-$, $-NR^{12}-$, $-NHR^{12}$, or $-NR^{11}R^{12}$ where R^{12} is H, $C(O)R^{13}$, SO_2R^{13} , $C(O)NR^{13}R^{16}$, $C(S)NR^{13}R^{16}$, $C(=NR^{16})SR^{17}$ or $C(=NR^{16})OR^{17}$, R^{11} and R^{13} each independently represents an optionally substituted hydrocarbyl, perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, and R^{16} and R^{17} are each independently hydrogen or a group as defined for R^{13} ;
- 20 E represents a linking group;
- M represents a metal capable of catalysing transfer hydrogenation; and
- Y represents an anionic group, a basic ligand or a vacant site;
- provided that (i) when Y is not a vacant site that at least one of A or B carries a hydrogen atom and (ii) when B represents $-O-$ or $-OH$, that B is not part of a carboxylate group.
- 25

In the catalysts according to the present invention, A, E, B, M, R^7 and Y can be as described above for the transfer hydrogenation process.

The catalytic species is believed to be substantially as represented in the above formula. It may be employed as an oligomer or metathesis product, on a solid support or
30 may be generated in situ.

In certain embodiments it has advantageously been found that certain catalysts are preferred in the transfer hydrogenation of certain substrate types. Catalysts in which A-E-B is derived from aminoalcohols, particularly norephedrine and cis-aminoindanol, are preferred in the transfer hydrogenation of aldehydes and ketones to give alcohols.
35 Especially, M is also rhodium (III) and R^7 represents pentamethylcyclopentadienyl. Further, isopropanol is preferably employed as hydrogen donor and sodium isopropoxide is employed as a base. Catalysts in which A-E-B is derived from N-tosyldiamines are preferred in transfer hydrogenation reactions of imines and iminium salts. Especially, M is

also rhodium (III) and R^7 represents pentamethylcyclopentadienyl. Further, sodium isopropoxide or triethylamine are often employed as a base. When the compound of formula (1) is an imine, a mixture of formic acid and triethylamine is preferably employed as hydrogen donor and when the compound of formula (1) is a preformed imminium salt, preferably a trifluoroacetate salt, isopropanol is preferably employed as hydrogen donor.

The catalyst can be made by reacting a metal cyclopentadienyl halide complex with a compound of formula A-E-B as defined above or a protonated equivalent from which it may be derived, and, where Y represents a vacant site, reacting the product thereof with a base. The metal cyclopentadienyl halide complex preferably has the formula $[MR^7Z_2]_2$, wherein M and R^7 are as defined above, and Z represents a halide, particularly chloride.

For the preparation of the catalysts according to the present invention, a solvent is preferably present. Suitable reaction temperatures are in the range 0-100, for example 20-70, °C, often giving reaction times of 0.5-5.0 h. After reaction is complete, the catalyst may if desired be isolated, but is more conveniently stored as the solution or used soon after preparation. The solution can contain the hydrogen donor and this, if a secondary alcohol, may be present in or used as the solvent for steps (a) and/or (b). The preparation and after-handling should preferably be under an inert atmosphere, and particularly in carbon dioxide and oxygen-free conditions.

The catalyst or catalyst solution is generally treated with base either just prior to use in a transfer hydrogenation reaction, or during use. This can be accomplished by adding base to the catalyst in solution, or to the compound of formula (1) in solution, or by addition to the transfer hydrogenation reaction.

Transfer hydrogenation can be accomplished by transferring the solution of catalyst to a solution of substrate, a compound of general formula I. Alternatively a solution of substrate can be added to a solution of catalyst. Base may be pre-added to the catalyst solution and/or the substrate solution, or can be added later. The hydrogen donor if not already present in the catalyst solution may be added to the substrate solution, or may be added to the reaction mixture.

The invention is illustrated by the following Examples.

Unless otherwise stated, % conversions and % enantiomeric excess (e.e.) were determined by GC.

EXAMPLE 1

Preparation of catalyst and reduction of acetophenone

Reactant	Wt used	Mol.Wt	Mol ratio	
$[Rh(Cp^*)Cl_2]_2^{**}$ (1S,2R)-(+)-	0.0254g	618.08	1.0	41.2 μ mol
Norephedrine	0.0209g	151.21	3.36	138.2 μ mol
2-propanol (anhydrous)	100ml	60.10	31677	1.305mol

KOH 0.1M in

2-propanol	3.3ml	56.11	4.01	0.33mmol
Acetophenone	2.06g	120.15	209	17mmol

5 Notes: ** purchased from STREM Chemicals

Prior to the reaction, the solvent was degassed:

100ml of anhydrous 2-propanol was added by syringe to a sealed clean dry round bottomed flask and degassed in vacuo at under 20°C for 30 min.

10 (a) Catalyst Preparation

The (+)-norephedrine and rhodium compound were weighed out into a clean dry Schlenk flask. The flask was stoppered with a 'Suba-seal' (RTM). Its contents were evacuated, then purged at room temperature by 15 changes of nitrogen. Then 2-propanol (20ml) was added by cannula. The flask tap was closed and the flask swirled until the starting solids dissolved. The result was an orange-coloured supernatant and a dark solid. The flask tap was re-opened, a current of nitrogen fed in, and the flask contents heated at 60°C for 2h 5min. The catalyst was checked at 30 min intervals. At each interval it was a dark brown solution, with a black solid at the bottom.

20 (b) Hydrogenation

The acetophenone was dissolved in 2-propanol (80ml) then degassed for 40min. This solution was added to the catalyst-containing flask by cannula, followed via syringe by the degassed 0.1M solution of KOH in 2-propanol. The mixture was left at room temperature, samples being taken at intervals and examined by gas chromatography. At the small scale of operation the reaction mixture was not sparged with the nitrogen, but sparging would be used in larger scale production. Results for production of (R)-1-phenylethanol were:

	conversion %	ee %
1h	92	84

30 The turnover number, integrated over 1h was 189h⁻¹.

EXAMPLE 2

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.2mg	618.08	1.0	10.1μmol
35 (1R,2S)-(+)-cis-1-amino-2-indanol	1.64mg	149.19	1.09	11μmol
acetophenone	2.06g	120.15	1547	17mmol
2-propanol			129974	

(a) Catalyst Preparation

The rhodium compound and (1R,2S)-(+)-cis-2-aminoindanol were suspended in degassed 2-propanol (50ml) under nitrogen, heated to 60°C and held at 60°C for 1h, then cooled to ambient temperature. The resulting orange-red solution of the catalyst: [(+)-cis-(1R)-amino-(2S)-hydroxyindanyl]-[(μ⁵)-pentamethylcyclopentadienyl]-rhodium chloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation

The catalyst solution was added to a degassed 0.1M solution of KOH in 2-propanol, followed by a solution of acetophenone in 2-propanol. The mixture was stirred at ambient temperature under nitrogen for 2h, then worked up by neutralising with dilute hydrochloric acid and concentrating by vacuum distillation. The residue was diluted with ethyl acetate and washed with an equal volume of saturated aqueous sodium chloride. The organic layer was separated, dried over magnesium sulphate, separated from the solid and freed of solvent to give crude (S)-1-phenylethanol (1.76g). Yield 84%, ee 89%. The turnover number, integrated over 1h, was 324h⁻¹.

EXAMPLE 3

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.3mg	618.08	1.0	10.2μmol
(1S,2R)-(-)-cis-1-amino-2-indanol	3.1mg	149.19	2.0	20.8μmol
acetophenone	1.29g	120.15	1039	10.6mmol
2-propanol			63857	

(a) Catalyst Preparation

The rhodium compound was suspended in 50ml of 2-propanol and degassed by 3 cycles of vacuum and nitrogen flush. The mixture was heated to gentle reflux until the solid dissolved, then cooled to ambient temperature. (1S,2R)-(-)-cis-1-amino-2-indanol was added to the solution with stirring. The mixture was degassed by cycles of vacuum and nitrogen flush and warmed at 30°C for 30min. The resulting orange-red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ⁵)-pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation

The acetophenone was added to the catalyst solution. The mixture was stirred at ambient temperature for 1h. Sodium 2-propoxide (0.25ml of freshly prepared 0.1M solution in 2-propanol) was added. The mixture was stirred for 2h and sampled; 57% of

the acetophenone had reacted to give (R)-1-phenylethanol of 79% ee. The turnover number, integrated over 1h, was 241h⁻¹.

EXAMPLE 4

5	Reactant	Wt used	Mol wt	mol ratio	
	[Ir(Cp*)Cl ₂] ^{**}	7.1mg	796.71	1.0	8.9μmol
	(1R,2S)-(+)-cis-1-amino-2-indanol	1.64mg	149.19	1.23	11μmol
	acetophenone	2.06g	120.15	1908	17mmol
10	2-propanol			146550	

^{**} purchased from STREM Chemicals

(a) Catalyst Preparation

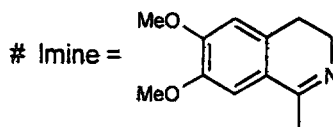
15 The Iridium compound and (1R,2S)-(+)-cis-1-amino-2-indanol were suspended in degassed 2-propanol (50 ml) under nitrogen, heated to 60°C and held at 60°C for 1h, then cooled to ambient temperature. The resulting orange-red solution of the catalyst: [(+)-cis-(1R)-amino-(2S)-hydroxyindanyl]-[(μ5)-pentamethylcyclopentadienyl]-iridium chloride was passed to the next stage but could be stored under argon or nitrogen.

20 (b) Hydrogenation

To the catalyst solution was added a degassed 0.1M solution of KOH in 2-propanol, followed by a solution of acetophenone in 2-propanol. The mixture was warmed to 60°C and stirred at ambient temperature under nitrogen for 1h, then worked up by neutralising with dilute hydrochloric acid and concentrating by vacuum distillation. 25 The residue was diluted with ethyl acetate and washed with an equal volume of saturated aqueous sodium chloride. The organic layer was separated, dried over magnesium sulphate, separated from the solid and freed of solvent to give crude (S)-1-phenylethanol (0.9g). Yield 43%, ee 80%. The turnover number, integrated over 1h, was 410h⁻¹.

30 EXAMPLE 5

	Reactant	Wt used	Mol Wt	Mol ratio	
	[Rh(Cp*)Cl ₂] ₂	6.2mg	618.08	1.0	10 μmol
	(1S,2R)-2-amino-1,2-diphenylethanol	4.3mg	213.28	2.01	20.1μmol
35	triethylamine	7μl	101.19		
	[#] Imine	53mg	205.26	26	0.26mmol
	CF ₃ CO ₂ H	20μl	114.02		0.26mmol
	2-propanol	11ml		144000	



(a) Catalyst Preparation

(1S,2R)-2-amino-1,2 diphenylethanol (Aldrich : 4.3mg, 20.1 μ mol) was dissolved in 2-propanol (10ml) in a small vial with magnetic stirrer flushed with nitrogen. The rhodium compound (6.2mg, 10 μ mol) was added to the solution, together with triethylamine (7 μ l). The solution was warmed to 60°C for 45 min during which it turned brown. The resulting solution of the catalyst: [(1S)-amino-(2R)-hydroxydiphenylethyl]-[(μ 5)-pentamethylcyclopentadienyl]-rhodium chloride was used directly in the following reaction.

(b) Hydrogenation

Iminium trifluoroacetate was prepared by adding trifluoroacetic acid (20 μ l, 0.26mmol) to the imine (53mg, 0.26mmol) in 2-propanol (1ml). This solution was added to the catalyst solution and heated at 60°C for 20 h. After quenching into aqueous acid, the aqueous solution was made basic before extracting into methylene chloride, the product was analysed by ¹Hn.m.r. and found to be 54% of the desired product, the remainder was imine starting material.

EXAMPLE 6

Reactant	Wt used	Mol wt	Mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.2mg	618.08	1.0	9.73 μ mol
N-tosyl-(1S,2R)-cis-1-amino-2-indanol	6.8mg	303.38	2.3	22.4 μ mol
2-propanol	1ml			
triethylamine	7 μ l	101.19		
#Imine	40mg	205.26		0.195mmol
CF ₃ CO ₂ H	15 μ l			0.195mmol

(a) Catalyst Preparation

N-tosyl-(1S,2R)-cis-1-amino-2-indanol (6.8 mg, 22.4 μ mol) was dissolved in 2-propanol (1ml) in a small nitrogen flushed vial with magnetic stirrer. The rhodium compound (6.2mg, 9.73 μ mol) was added to the solution, which was then warmed to 60°C for 1h. Triethylamine (7 μ l) was added. The solution colour changed from orange to purple. The solution was maintained at 60°C for a further 20 min, then cooled to ambient temperature. The resulting solution of the catalyst: [N-tosyl-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ 5)-pentamethylcyclopentadienyl]-rhodium chloride was stored under nitrogen.

(b) Hydrogenation

The iminium trifluoroacetate was prepared by adding trifluoroacetic acid (15 μ l, 0.195mmol) to the imine (40mg, 0.195mmol) in 2-propanol (1ml). The catalyst solution was added and the mixture heated at 60°C for 16 h. After quenching into aqueous sodium bicarbonate and extracting into methylene chloride, the product was analysed by ¹Hn.m.r. and found to be 42% of the desired product; the remainder was the imine starting material.

EXAMPLE 7

Reactant	Wt used	Mol wt	Mol Ratio	
[Rh(Cp*)Cl ₂] ₂	6.3mg	618.08	1.0	10.2 μ mol
N-Tosyl-(1R,2R)-1,2-diphenylethylenediamine	7.3mg	366.48	1.93	20 μ mol
triethylamine	6 μ l	101.19	4.18	43 μ mol
2-propanol	10ml	60.1		
CH ₃ CN	6.4ml	41.05		
*Imine	109mg	205.26		0.53mmol
triethylamine/formic acid 2:5	0.25ml			

(a) Catalyst Preparation

N-Tosyl-(1R,2R)-1,2-diphenylethylenediamine (7.3mg, 20 μ mol) and the rhodium compound (6.3mg, 10.2 μ mol) were suspended in 2-propanol (10ml) in a small vial flushed with nitrogen. Triethylamine (6 μ l) was added. The mixture was stirred at 55°C until all the solid had dissolved and then heated to 80°C for 30 min then cooled to ambient temperature. The resulting solution of the catalyst: [N-tosyl-(1R)-amino-(2R)-aminodiphenylethyl]-[(μ 5)-pentamethylcyclopentadienyl]-rhodium chloride was stored under nitrogen.

(b) Hydrogenation [Substrate:Catalyst ratio 266:1]

A portion (8ml) of the above catalyst solution was placed into a vial and the solvent evaporated by applying vacuum. The residue was redissolved in acetonitrile (6.4ml) and degassed with nitrogen. A nitrogen-purged vial was charged with the Imine (109mg, 0.53mmol) and 0.8ml of the catalyst solution followed by a 2:5 triethylamine:formic acid mixture (0.25ml). The mixture was heated at 60°C for 1 h, quenched by addition of water and then extracted into methylene chloride, dried over magnesium sulfate and the crude product analysed by ¹HNMR that showed it to be >95% of the desired amine. Chiral shift ¹Hn.m.r. showed the amine to be 74.8% ee.

EXAMPLE 8

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6mg	618.08	1.0	9.7μmol
(1S,2R)-(-)-cis-				
1-amino-2-indanol	3.2mg	149.19	2.1	22.1μmol
acetophenone	0.126g	120.15		1mmol
2-butanol	20ml	74.12		0.22mol

(a) Catalyst Preparation

The rhodium compound and (1S,2R)-(-)-cis-1-amino-2-indanol were suspended in degassed 2-butanol (20ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The yellow mixture was heated to 35°C for 0.5h, during which time the colour intensified to orange/red, then cooled to ambient temperature. The resulting orange-red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ5)-pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation [Substrate:Catalyst ratio 539:1]

Acetophenone (0.126g, 1mmol) was added to a dry vial. Then a portion (2ml) of the catalyst solution was added followed by sodium 2-propoxide solution (25μl of 0.2M solution in 2-propanol). The mixture was stirred at ambient temperature under nitrogen for 2h. This gave (R)-1-phenylethanol Yield 66.2%, ee 87%. The initial turnover number, integrated over 1h, was 574h⁻¹.

EXAMPLE 9

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.1mg	618.08	1.0	9.9μmol
(1S,2R)-(-)-cis-				
1-amino-2-indanol	3mg	149.19	2.03	20μmol
acetophenone	1.089g	120.15		9.1mmol
2-butanol	20ml	74.12		0.22mol

(a) Catalyst Preparation

The rhodium compound and (1S,2R)-(-)-cis-1-amino-2-indanol were suspended in degassed 2-butanol (20ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The yellow mixture was heated to 35°C for 20min, during which time the colour intensified to orange/red, then cooled to ambient temperature. The resulting orange-red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ5)-pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation [Substrate:Catalyst ratio 460:1]

Sodium 2-propoxide (0.45ml of 0.2M solution in 2-propanol) was charged to the catalyst solution. After 2 minutes, the acetophenone (1.0889g, 9.1mmol) was added. The mixture was stirred under vacuum at 35°C for 1.5h, then heated to maintain a temperature between 40-45°C for 4hours. This gave (R)-1-phenylethanol Yield 87.1%, ee 87%. The turnover number, integrated over 1h, was 1502h⁻¹.

EXAMPLE 10

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	5.9mg	618.08	1.0	9.57μmol
(1S,2R)-(-)-cis-1-amino-2-indanol	3.1mg	149.19	2.17	20.8μmol
α-tetralone	0.5ml	146.19	393	3.76mmol
2-propanol	50ml	60.1		0.653mol

(a) Catalyst Preparation

The rhodium compound and (1S,2R)-(-)-cis-1-amino-2-indanol were suspended in degassed 2-propanol (50ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 35°C for 10min. The resulting orange solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ₅)-pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation

Sodium 2-propoxide (0.38ml of 0.1M solution in 2-propanol) was charged to the catalyst solution followed by the α-tetralone (0.5ml, 3.76mmol). The mixture was stirred under vacuum (80mmHg) at 35°C for 2h, after the first hour the flask was back filled with nitrogen and sufficient 2-propanol charged to compensate for the volume removed by distillation. This gave (R)-1-tetralol Yield 98.4%, ee 95.7%. The turnover number, integrated over 1h, was 185h⁻¹

EXAMPLE 11

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	24.4mg	618.08	1.0	39.48μmol
(1R,2S)-(-)-norephedrine	12.1mg	151.21	2.03	80μmol
α-tetralone	5ml	146.19	952	37.6mmol
2-propanol	125ml	60.1		1.63mol

(a) Catalyst Preparation

The rhodium compound and (1R,2S)-(-)-norephedrine were suspended in degassed 2-propanol (75ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 35°C for 30min. The resulting orange solution of the catalyst: [(-)-(1R,2S)-norephedriny]-[(μ 5)-pentamethylcyclopentadieny]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation

Sodium 2-propoxide (1.55ml of 0.1M solution in 2-propanol) was charged to the catalyst solution and the pressure reduced (40-80mmHg). The α -tetralone (5ml, 37.6mmol) in 2-propanol (75ml) was then added over a period of 15min. The mixture was stirred under vacuum (40-80mmHg) at 35°C for 4h, at hourly intervals the flask was back filled with nitrogen and sufficient 2-propanol charged to compensate for the volume removed by distillation. This gave (S)-1-tetralol Yield 96%, ee 96.2%. The turnover number, integrated over 1h, was 382h⁻¹.

EXAMPLE 12

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	26.4mg	618.08	1.0	42.7 μ mol
(1S,2R)-(-)-cis-1-amino-2-indanol	13.4mg	149.19	2.1	89.8 μ mol
acetophenone	5ml	120.15		42.9mmol
2-propanol	270ml			

(a) Catalyst Preparation

The rhodium compound and (1S,2R)-(-)-cis-1-amino-2-indanol were suspended in degassed 2-propanol (20 ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 40-50°C for 30min, during which time the colour intensified to deep red, then cooled to ambient temperature. The resulting red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindany]-[(μ 5)-pentamethylcyclopentadieny]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation [Substrate:Catalyst ratio 5018:1]

Acetophenone (5ml, 42.9mmol) was added to a dry Schlenck flask containing 250ml 2-propanol. Then a portion (2ml) of the catalyst solution was added followed by sodium 2-propoxide solution (0.3ml of 0.1M solution in 2-propanol). The mixture was stirred at 18°C under vacuum (28mmHg) for 5h. This gave (R)-1-phenylethanol Yield 74%, ee 86.8%. The initial turnover number, integrated over 1h, was 1947h⁻¹.

EXAMPLE 13

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.2mg	618.08	1.0	10μmol
(1S,2R)-(-)-cis-				
1-amino-2-indanol	4.3mg	149.19	2.88	28.8μmol
p-methylacetophenone	0.280g	134.18		2.1mmol
2-propanol				

(a) Catalyst Preparation

The rhodium compound and (1S,2R)-(-)-cis-1-amino-2-indanol were suspended in degassed 2-propanol (10ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 90°C for 20min, during which time the colour intensified to orange/red, then cooled to ambient temperature. The resulting orange-red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ⁵)-pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation [Substrate:Catalyst ratio 523:1]

p-Methylacetophenone (0.28g, 2.1mmol) was added to a dry vial. Then a portion (2ml) of the catalyst solution was added followed by sodium 2-propoxide solution (90μl of 0.1M solution in 2-propanol). The mixture was stirred at ambient temperature under nitrogen for 2h. This gave 1-(p-methylphenyl)ethanol Yield 56.8%, ee 56%. The initial turnover number, integrated over 1h, was 1064h⁻¹.

EXAMPLE 14

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.2mg	618.08	1.0	10μmol
(1S,2R)-(-)-cis-				
1-amino-2-indanol	4.3mg	149.19	2.88	28.8μmol
p-trifluoromethyl-				
acetophenone	0.384g	188.15		2mmol
2-propanol				

(a) Catalyst Preparation

The rhodium compound and (1S,2R)-(-)-cis-1-amino-2-indanol were suspended in degassed 2-propanol (10ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 90°C for 20min, during which time the colour intensified to orange/red, then cooled to ambient temperature. The resulting orange-red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ⁵)-

pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation [Substrate:Catalyst ratio 498:1]

p-Trifluoromethylacetophenone (0.384g, 2mmol) was added to a dry vial. Then a portion (2ml) of the catalyst solution was added followed by sodium 2-propoxide solution (90 μ l of 0.1M solution in 2-propanol). The mixture was stirred at ambient temperature under nitrogen for 2h. This gave 1-(*p*-trifluoromethylphenyl)ethanol Yield 96.7%, ee 73.8%. The initial turnover number, integrated over 1h, was 412h⁻¹.

EXAMPLE 15

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.2mg	618.08	1.0	10 μ mol
(1S,2R)-(-)-cis-1-amino-2-indanol	3.3mg	149.19	2.2	22.1 μ mol
<i>p</i> -chloroacetophenone	0.162g	154.6	517	1.05mmol
2-propanol				

(a) Catalyst Preparation

The rhodium compound and (1S,2R)-(-)-cis-1-amino-2-indanol were suspended in degassed 2-propanol (10ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 90°C for 20min, during which time the colour intensified to orange/red, then cooled to ambient temperature. The resulting orange-red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ 5)-pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation [Substrate:Catalyst ratio 524:1]

p-Chloroacetophenone (0.162g, 1.05mmol) was added to a dry vial. Then a portion (2ml) of the catalyst solution was added followed by sodium 2-propoxide solution (50 μ l of 0.1M solution in 2-propanol). The mixture was stirred at ambient temperature under nitrogen for 19h. This gave 1-(*p*-chlorophenyl)ethanol Yield 90.6%, ee 71.6%. The initial turnover number, integrated over 1h, was 846h⁻¹.

EXAMPLE 16

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.2mg	618.08	1.0	10μmol
(1S,2R)-(-)-cis-				
5 1-amino-2-indanol	3.3mg	149.19	2.2	22.1μmol
o-chloroacetophenone	0.160g	154.6		1mmol
2-propanol				

(a) Catalyst Preparation

10 The rhodium compound and (1S,2R)-(-)-cis-1-amino-2-indanol were suspended in degassed 2-propanol (10ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 90°C for 20min, during which time the colour intensified to orange/red, then cooled to ambient temperature. The resulting orange-red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ5)-

15 pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation [Substrate:Catalyst ratio 517:1]

20 o-Chloroacetophenone (0.16g, 1mmol) was added to a dry vial. Then a portion (2ml) of the catalyst solution was added followed by sodium 2-propoxide solution (50μl of 0.1M solution in 2-propanol). The mixture was stirred at ambient temperature under nitrogen for 19h. This gave 1-(o-chlorophenyl)ethanol Yield 94.3%, ee 69.1%. The turnover number, integrated over 1h, was 195h⁻¹.

EXAMPLE 17

Reactant	Wt used	Mol wt	mol ratio	
[Ir(Cp*)Cl ₂] ₂	32.8mg	796.67	1.0	41.2μmol
(1S,2R)-(+)-				
norephedrine	20mg	151.21	3.2	132μmol
30 acetophenone	2ml	120.15	413	17mmol
2-propanol	100ml			

(a) Catalyst Preparation

35 The iridium compound and (+)-norephedrine were suspended in degassed 2-propanol (20ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 60°C for 90min, then cooled to ambient temperature. The resulting solution of the catalyst: [(+)-(1S,2R)-norephedriny]-[(μ5)-pentamethylcyclopentadienyl]-iridium chloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation

Acetophenone (2ml, 17mmol) was dissolved in 2-propanol (80ml) and purged with nitrogen. Then the catalyst solution was added followed by potassium hydroxide solution (3.3ml of 0.1M solution in 2-propanol). The mixture was stirred at ambient temperature under nitrogen for 10h. This gave 1-phenylethanol Yield 68%, ee 49%. The initial turnover number, integrated over 1h, was 318h⁻¹.

EXAMPLE 18

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	1g	618.08	1.0	1.62mmol
(1S,2R)-(-)-cis-1-amino-2-indanol	0.5g	149.19	2.08	3.36mol
tetralone	200ml	146.19	928	1.5mol
2-propanol	10l			

(a) Catalyst Preparation

2-Propanol (9.5l) was charged to a 20l reaction flask which was deoxygenated and back-filled with nitrogen. The rhodium compound and (1S,2R)-(-)-cis-2-aminoindanol were charged to the vessel with stirring and the mixture was deoxygenated and back-filled with nitrogen. The orange suspension was heated to 35°C until a clear red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ⁵)-pentamethylcyclopentadienyl]-rhodiumchloride was formed.

(b) Hydrogenation

Tetralone (200ml, 1.5mol) was charged to the catalyst solution, followed by 2-propanol (0.5l). The pressure was reduced (28.5mmHg) and then a sodium 2-propoxide solution (120ml of 0.1M solution in 2-propanol) was charged. The mixture was stirred at ambient temperature under nitrogen for 4.5h, at hourly intervals the flask was back filled with nitrogen and sufficient 2-propanol charged to compensate for the volume removed by distillation. This gave (R)-1-tetralol Yield 96.9%, ee 86.9%. The turnover number, integrated over 1h, was 358h⁻¹.

EXAMPLE 19

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	1g	618.08	1.0	1.62mmol
(1S,2R)-(-)-cis-1-amino-2-indanol	0.49g	149.19	2.04	3.31mol
acetophenone	179g	120.15	920	1.49mol
2-propanol	10l			

(a) Catalyst Preparation

2-Propanol (9.5l) was charged to a 20l reaction flask which was deoxygenated and back-filled with nitrogen. The rhodium compound and (1S,2R)-(-)-cis-1-amino-2-indanol were charged to the vessel with stirring and the mixture was deoxygenated and back-filled with nitrogen. The orange suspension was heated to 35°C until a clear red solution of the catalyst: [(-)-cis-(1S)-amino-(2R)-hydroxyindanyl]-[(μ 5)-pentamethylcyclopentadienyl]-rhodiumchloride was formed.

(b) Hydrogenation

Acetophenone (200ml, 1.5mol) was charged to the catalyst solution, followed by 2-propanol (0.5l). The pressure was reduced (28.5mmHg) and then a sodium 2-propoxide solution (120ml of 0.1M solution in 2-propanol) was charged. The mixture was stirred at ambient temperature under nitrogen for 2.5h, at hourly intervals the flask was back filled with nitrogen and sufficient 2-propanol charged to compensate for the volume removed by distillation. This gave (R)-1-phenylethanol Yield 99.6%, ee 82.9%. The turnover number, integrated over 1h, was 454h⁻¹.

EXAMPLE 20

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.3mg	618.08	1.0	10 μ mol
(1R,2S)-(-)-				
2-amino-1,2-diphenylethanol	4.5mg	213.28	2.07	21.1 μ mol
acetophenone	0.120g	120.15	490	0.99mmol
2-propanol				

(a) Catalyst Preparation

The rhodium compound and (1R,2S)-(-)-2-amino-1,2-diphenylethanol were suspended in degassed 2-propanol (20ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 80°C for 30min, then cooled to ambient temperature. The resulting solution of the catalyst: [(-)-(2S)-amino-(1R)-hydroxydiphenylethyl]-[(μ 5)-pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation

Acetophenone (0.12g, 0.99mmol) was added to a dry vial. Then a portion (2ml) of the catalyst solution was added followed by sodium 2-propoxide solution (50 μ l of 0.1M solution in 2-propanol). The mixture was stirred at ambient temperature under nitrogen for 2h. This gave 1-phenylethanol Yield 90.7%, ee 66%. The turnover number, integrated over 1h, was 826h⁻¹.

EXAMPLE 21

Reactant	Wt used	Mol wt	mol ratio	
[Rh(Cp*)Cl ₂] ₂	6.2mg	618.08	1.0	10.4μmol
(S)-(+)-2-amino-1-phenylethanol	2.7mg	137.18	1.96	19.7μmol
acetophenone	0.140g	120.15		1.17mmol
2-propanol				

(a) Catalyst Preparation

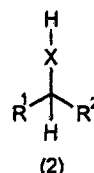
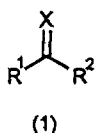
The rhodium compound and (S)-(+)-2-amino-1-phenylethanol were suspended in degassed 2-propanol (20ml) under nitrogen, and the reaction purged with nitrogen for 30 minutes. The mixture was heated to 80°C for 30min, then cooled to ambient temperature. The resulting solution of the catalyst: [(+)-(2)-amino-(1S)-hydroxyphenylethyl]-[(μ5)-pentamethylcyclopentadienyl]-rhodiumchloride was passed to the next stage but could be stored under argon or nitrogen.

(b) Hydrogenation [Substrate:Catalyst ratio 580:1]

Acetophenone (0.14g, 1.17mmol) was added to a dry vial. Then a portion (2ml) of the catalyst solution was added followed by sodium 2-propoxide solution (50μl of 0.1M solution in 2-propanol). The mixture was stirred at ambient temperature under nitrogen for 2h. This gave 1-phenylethanol Yield 62.4%, ee 77.4%. The initial turnover number, integrated over 1h, was 487h⁻¹.

CLAIMS

1. A process for the transfer hydrogenation of a compound of formula (1) to produce a compound of formula (2);



wherein:

X represents CR^3R^4 , NR^5 , $(\text{NR}^5\text{R}^6)^+\text{Q}^-$, O or S;

R^1 , R^2 , R^3 , R^4 , R^5 and R^6 each independently represents a hydrogen atom, an optionally substituted hydrocarbyl, a perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, one or more of R^1 & R^2 , R^1 & R^3 , R^2 & R^4 , R^3 & R^4 , R^1 & R^5 , R^2 & R^6 and R^5 & R^6 optionally being linked in such a way as to form an optionally substituted ring(s); and

Q^- represents an anion;

said process comprising reacting the compound of formula (1) with a hydrogen donor in the presence of a catalyst, characterised in that the catalyst has the general formula:



wherein:

R^7 represents an optionally substituted cyclopentadienyl group;

A represents $-\text{NR}^8-$, $-\text{NR}^9-$, $-\text{NHR}^8$ or $-\text{NR}^8\text{R}^9$ where R^8 is H, $\text{C}(\text{O})\text{R}^{10}$, SO_2R^{10} , $\text{C}(\text{O})\text{NR}^{10}\text{R}^{14}$, $\text{C}(\text{S})\text{NR}^{10}\text{R}^{14}$, $\text{C}(=\text{NR}^{14})\text{SR}^{15}$ or $\text{C}(=\text{NR}^{14})\text{OR}^{15}$, R^9 and R^{10} each independently represents an optionally substituted hydrocarbyl, perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, and R^{14} and R^{15} are each independently hydrogen or a group as defined for R^{10} ;

B represents $-\text{O}-$, $-\text{OH}$, OR^{11} , $-\text{S}-$, $-\text{SH}$, SR^{11} , $-\text{NR}^{11}-$, $-\text{NR}^{12}-$, $-\text{NHR}^{12}$ or $-\text{NR}^{11}\text{R}^{12}$ where R^{12} is H, $\text{C}(\text{O})\text{R}^{13}$, SO_2R^{13} , $\text{C}(\text{O})\text{NR}^{13}\text{R}^{16}$, $\text{C}(\text{S})\text{NR}^{13}\text{R}^{16}$, $\text{C}(=\text{NR}^{16})\text{SR}^{17}$ or $\text{C}(=\text{NR}^{16})\text{OR}^{17}$, R^{11} and R^{13} each independently represents an optionally substituted hydrocarbyl, perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, and R^{16} and R^{17} are each independently hydrogen or a group as defined for R^{13} ;

E represents a linking group;

M represents a metal capable of catalysing transfer hydrogenation; and

Y represents an anionic group, a basic ligand or a vacant site;

provided that when Y is not a vacant site that at least one of A or B carries a hydrogen atom.

2. A process according to claim 1, in which the compound of formula (1) is a ketone, an imine or an iminium salt.

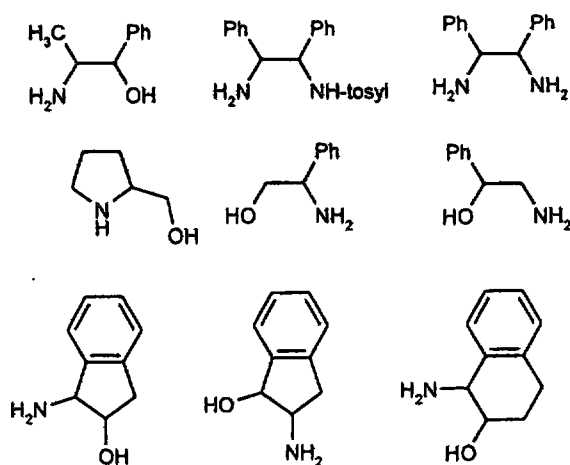
3. A process according to either of claims 1 or 2, wherein M is a group VIII transition metal, especially ruthenium, rhodium or iridium.

4. A process according to any one of claims 1 to 3, wherein R⁷ is a cyclopentadienyl group substituted with between 3 and 5 substituents, preferably 5 substituents, and especially a pentamethylcyclopentadienyl group.

5. A process according to any one of claims 1 to 4, in which A-E-B is, or is derived from, an aminoalcohol or a diamine, preferably selected from an optionally substituted 2-aminoethanol, an optionally substituted 3-aminopropanol and an optionally substituted ethylenediamine.

6. A process according to claim 5, wherein either of A or B carries an acyl or sulphonyl group, preferably a toluenesulphonyl, methanesulphonyl, trifluoromethanesulphonyl or acetyl group.

7. A process according to claim 5 in which A-E-B is, or is derived from, one of the following:



8. A process according to any preceding claim, wherein the compound of formula (1) is prochiral and the catalyst is chiral, an enantiomerically and/or diastereomerically

purified form of the catalyst being employed, whereby the compound of formula (1) is asymmetrically hydrogenated.

9. A process according to claim 8, in which A-E-B comprises at least one stereospecific centre.

10. A process according to any one of claims 1 to 9, in which the hydrogen donor is selected from hydrogen, primary and secondary alcohols, primary and secondary amines, carboxylic acids and their esters and amine salts, readily dehydrogenatable hydrocarbons, clean reducing agents, and any combination thereof.

11. A process according to claim 10, in which the hydrogen donor is propan-2-ol, butan-2-ol or a mixture of triethylamine and formic acid.

12. A process according to any one of claims 1 to 11, in which the products from dehydrogenation of the hydrogen donor are removed by vacuum distillation.

13. A process according to any of claims 1 to 12, in which a ketone of formula (1) is transfer hydrogenated in the presence of a catalyst in which A-E-B is, or is derived from, an aminoalcohol.

14. A process according to claim 1 to 12 in which an imine or iminium salt of formula (1) is transfer hydrogenated in the presence of a catalyst in which A-E-B is, or is derived from, an N-tosyldiamine.

15. A process according to any one of the preceding claims, in which the process is carried out in presence of a base having a pK_a of at least 8.0.

16. A catalyst of general formula:



wherein:

R^7 represents an optionally substituted cyclopentadienyl group;

A represents $-NR^8$ -, $-NR^9$ -, $-NHR^8$ or $-NR^8R^9$ where R^8 is H, $C(O)R^{10}$, SO_2R^{10} , $C(O)NR^{10}R^{14}$, $C(S)NR^{10}R^{14}$, $C(=NR^{14})SR^{15}$ or $C(=NR^{14})OR^{15}$, R^9 and R^{10} each

independently represents an optionally substituted hydrocarbyl, perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, and R^{14} and R^{15} are each independently hydrogen or a group as defined for R^{10} ;

B represents -O-, -OH, OR¹¹, -S-, -SH, SR¹¹, -NR¹¹-, -NR¹²-, -NHR¹² or -NR¹¹R¹² where R¹² is H, C(O)R¹³, SO₂R¹³, C(O)NR¹³R¹⁶, C(S)NR¹³R¹⁶, C(=NR¹⁶)SR¹⁷ or C(=NR¹⁶)OR¹⁷, R¹¹ and R¹³ each independently represents an optionally substituted hydrocarbyl, perhalogenated hydrocarbyl or an optionally substituted heterocyclyl group, and R¹⁶ and R¹⁷ are each independently hydrogen or a group as defined for R¹³;

E represents a linking group;

M represents a metal capable of catalysing transfer hydrogenation; and

Y represents an anionic group, a basic ligand or a vacant site;

provided that (i) when Y is not a vacant site that at least one of A or B carries a hydrogen atom and (ii) when B represents -O- or -OH, that B is not part of a carboxylate group.

17. A catalyst according to claims 16, wherein M is a group VIII transition metal, especially ruthenium, rhodium or iridium.

18. A catalyst according to either of claims 16 or 17, wherein R⁷ is a cyclopentadienyl group substituted with between 3 and 5 substituents, preferably 5 substituents, and especially a pentamethylcyclopentadienyl group.

19. A catalyst according to any one of claims 16 to 18, in which A-E-B is derived from an aminoalcohol or a diamine, preferably an optionally substituted 2-aminoethanol, an optionally substituted 3-aminopropanol or an optionally substituted ethylenediamine.

20. A catalyst according to claim 19, wherein either or both of A or B, when an amino group, carries an acyl or sulphonyl group, preferably a toluenesulphonyl, methanesulphonyl, trifluoromethanesulphonyl or acetyl group, especially a trifluoroacetyl or p-toluenesulphonyl group.

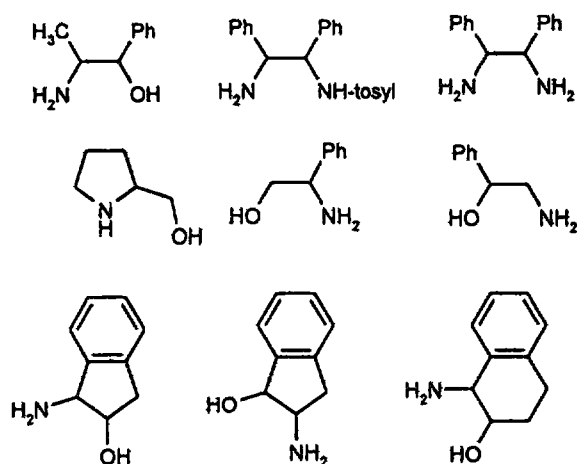
21. A catalyst according to claim 19 in which A-E-B is, or is derived from, one of the following:



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22. A catalyst according to any one of claims 16 to 21 in which the catalyst is chiral, and resolved forms thereof.

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23. A catalyst according to claim 22, in which A-E-B comprises at least one stereospecific centre.

24. A process for the preparation of a catalysts according to any one of claims 16 to 23, which comprises reacting a metal cyclopentadienyl halide complex with a compound of formula A-E-B or a protonated equivalent from which it may be derived.

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