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57. Abstract: The present invention relates to compounds for use as catalysts, methods for producing said compounds and the use of said compounds as catalysts in catalytic processes, including, but not limited to, the asymmetric reduction of imine and enamine compounds and/or the reduction of animation on the ketone compounds. A compound for use as a catalyst has the formula (I) wherein: R₁, R₂, R₃, R₄ and R₅ are each separately selected from the group consisting of hydrogen, alkyl and aryl; X is oxygen or sulfur; and Z has the formula (II) wherein: R⁶ and R⁷ are each separately selected from the group consisting of hydrogen, alkyl, nitro, halogen, alkyl and aryl, or R⁶ and R⁷ are linked to form a cyclic group; and Y is oxygen, sulfur or NR₈ in which R₈ is selected from the group consisting of hydrogen, alkyl and aryl.
The present invention relates to compounds for use as catalysts, methods for producing said compounds and the use of said compounds as catalysts in catalytic processes including, but not limited to, the asymmetric reduction of imine compounds and/or the reductive animation of aldehyde or ketone compounds.

Many commercially important chemical compounds incorporate amine, particularly chiral amine, groups. Moreover, compounds incorporating amine and chiral amine functionality are valuable chemical intermediates in, for example, the pharmaceutical and fine chemicals industries. A significant amount of work has therefore been undertaken by many different groups to develop new, more efficient methods for preparing compounds incorporating amine groups and, in particular, chiral amine groups.

Different methods have been developed by which chiral amines can be produced from corresponding aldehydes and ketones by stoichiometric or catalytic asymmetric reduction. Unfortunately, each of these methods is a multi-step process, which limits the overall product yield and enantiomeric excess that can be obtained.

Rather than using a carbonyl compound as the starting material, compounds containing imine groups can also be used, whereby the imine group is reduced to the corresponding chiral amine group. The three most widely adopted methods developed to date are transition metal catalysed high pressure hydrogenation, hydrosilylation (typically using trichlorosilane) and transfer hydrogenation. Methods employing metal catalysts, however, suffer from disadvantages associated with metal leaching and catalyst regeneration and so the development of improved catalysts for the generation of chiral amines is of significant commercial interest.

In spite of the clear commercial motivation to explore new methods for producing amine, particularly chiral amine, containing compounds it is widely appreciated that
the development of new catalytic protocols, particularly those which must control the chirality of the final product, is complicated and involves a great deal of optimisation of many different factors which affect the outcome of the catalytic process, such as the catalyst structure, catalyst loading, solvent, temperature and time. Relatively minor changes in any one of these factors can have a significant and often detrimental effect on the stereochemical outcome of the reaction.

An object of the present invention is to obviate or mitigate one or more of the above problems.

According to a first aspect of the present invention there is provided a compound having the formula (I)

![Chemical structure](image)

(I)

wherein: \( R^1, R^2, R^3, R^4 \) and \( R^5 \) are each separately selected from the group consisting of hydrogen, alkyl and aryl; \( X \) is oxygen or sulfur; and \( Z \) has the formula (II)

![Chemical structure](image)

(II)

wherein: \( R^6 \) and \( R^7 \) are each separately selected from the group consisting of hydrogen, alkoxy, nitro, halogen, alkyl and aryl, or \( R^6 \) and \( R^7 \) are linked to form a cyclic group; and \( Y \) is oxygen, sulfur or \( NR^{10} \) in which \( R^{10} \) is selected from the group consisting of hydrogen, alkyl and aryl.
The results presented below in Examples 3 to 7 clearly demonstrate that compounds according to the first aspect of the present invention, in particular but not limited to compound (Villa), are eminently suitable for use as catalysts in the asymmetric reduction of imine compounds to corresponding chiral amine compounds. Moreover, Examples 8 to 11 demonstrate the applicability of compounds according to the first aspect of the present invention to the direct asymmetric reductive amination of aldehydes and ketones to corresponding chiral amine compounds. Furthermore, Example 12 illustrates the ability for compounds according to the first aspect of the present invention to catalyse the asymmetric reduction of enamines to corresponding chiral amine compounds, for example amino acids by selection of appropriate carboxyl/carboxylate group containing substrates.

In a related aspect of the present invention there is provided a compound according to formula (I) wherein Z has formula (III)

![Chemical Structure](image)

(III)

wherein: \( R^8 \) and \( R^9 \) are each separately selected from the group consisting of hydrogen, alkoxy, nitro, halogen, alkyl and aryl; and \( Y \) is oxygen, sulfur or \( NR^{10} \) in which \( R^{10} \) is selected from the group consisting of hydrogen, alkyl and aryl.

A second aspect of the present invention provides a process for the production of a compound according the first aspect of the present invention, the process comprising reacting a compound of formula (IX) with a compound of formula (X) in the presence of a base
wherein $R_{11}$ is a substituted or unsubstituted alkyl group.

A related aspect of the present invention provides a process for the production of a compound according formula (I) in which $Z$ is formula (III), the process comprising reacting a compound of formula (IX) with a compound of formula (XI) in the presence of a base

wherein $R'_{11}$ is a substituted or unsubstituted alkyl group.

Examples 1 and 2 below describe preferred methods for the production of compounds (Villa) and (XVIa), which represent preferred embodiments of the first aspect of the present invention.

According to a third aspect of the present invention there is provided a process for effecting catalytic reduction of an imine compound to provide a corresponding amine compound, the process comprising reacting said imine compound with a reducing agent in the presence of a catalyst compound having a formula according to the first aspect of the present invention.
A fourth aspect of the present invention provides use of a compound having a formula according to the first aspect of the present invention to catalyse the reduction of an imine compound to provide a corresponding amine compound.

According to a fifth aspect of the present invention there is provided a process for effecting the direct asymmetric reductive amination of a first compound including an aldehyde or ketone group with a second compound including a first amine group to provide a third compound including a second amine group, the process comprising reacting said first compound with said second compound and a reducing agent in the presence of a catalyst compound having a formula according to the first aspect of the present invention.

A sixth aspect of the present invention provides use of a compound having a formula according to the first aspect of the present invention to catalyse the direct asymmetric reductive amination of an aldehyde or ketone compound to provide an amine compound.

According to a seventh aspect of the present invention there is provided a process for effecting catalytic reduction of an enamine compound to provide a corresponding amine compound, the process comprising reacting said enamine compound with a reducing agent in the presence of a catalyst compound having a formula according to the first aspect of the present invention.

A eighth aspect of the present invention provides use of a compound having a formula according to the first aspect of the present invention to catalyse the reduction of an enamine compound to provide a corresponding amine compound.

With regard to the seventh and eighth aspects of the present invention it is preferred that reduction of the enamine compound is effected using a chiral catalytic compound according to the first aspect of the present invention such that the process provides a chiral amine compound. In this way, enamines containing carboxyl or
carboxylate groups bonded to the opposite carbon atom of the carbon to carbon double bond to that which the nitrogen atom of the amine group is attached can be used as substrates to afford access to chiral peptide bond containing compounds, such as amino acids (see for example, Example 12 below).

Where the term "alkyl" or "alkyl group" is used herein without any further qualification it is to be interpreted as encompassing both substituted and unsubstituted alkyl groups. Moreover, where the term "alkyl" or "alkyl group" is used herein without any further qualification it will be understood to encompass linear, branched and cyclic alkyl groups.

Where the term "aryl" or "aryl group" is used herein without any further qualification it is to be interpreted as encompassing both substituted and unsubstituted aryl groups. Any substitution may be provided as an appendage to the carbocyclic ring structure and/or within the carbocyclic ring structure wherein at least one carbon atom forming part of the aryl ring structure is replaced with a non-carbon atom so as to provide a heteroaryl ring structure, e.g. a pyridinyl group.

It will be understood that where formulae are used herein to depict chemical structures which include one or more chiral atoms, formulae which depict a particular stereochemistry should be interpreted as relating to a particular enantiomer having the stereochemistry shown, but in formulae where no particular stereochemistry is depicted (e.g. a single solid line is used to represent an interatomic bond, rather than a bold wedge or a hashed wedge) those formulae should be interpreted as encompassing both enantiomers. To aid understanding, where non-stereospecific formulae are used to refer generically to both enantiomers a Roman reference numeral will be used and where a formula is used to depict a specific enantiomer of that compound the Roman reference numeral will be suffixed by a letter 'a' or 'b'. By way of example, a preferred compound according to the first aspect of the present invention has a generic formula denoted '(VIII)' and the (S)-enantiomer of this preferred compound is denoted '(VIIIa)'.

With regard to the compound of formula (I) defined above in the first aspect of the present invention, while X may be oxygen or sulfur, it is preferred that X is oxygen such that compound (I) incorporates a central carbonyl moiety. By virtue of the carbon atom of the carbonyl group being bonded to a nitrogen atom, the preferred embodiment of compound (I), wherein X is oxygen, incorporates an amide functional group. Since the nitrogen atom bonded to the carbonyl carbon atom forms part of a 5-membered heterocyclic ring, the amide functional group is a cyclic amide.

In the group Z which forms part of compound (I), substituent Y may be oxygen, sulfur or NR\(^{10}\), in which R\(^{10}\) is hydrogen, alkyl or aryl. It is preferred that Y is NR\(^{10}\) such that group Z is an imidazole of formula (XXVII) or (XXVIII).

It is preferred that R\(^{10}\) is an alkyl group, more preferably a C\(_1\)-C\(_6\) linear or branched alkyl group, such as a methyl, ethyl or propyl group. Most preferably, R\(^{10}\) is a methyl group.

When group Z has the formula (II) including substituents R\(^6\) and R\(^7\), each of these substituents may be individually selected from the group consisting of hydrogen,
alkoxy (e.g. methoxy, ethoxy), nitro (-NO₂), halogen (e.g. F, Cl, Br, I), alkyl (e.g. C₁-C₆ linear or branched alkyl group, such as methyl, ethyl or propyl) and aryl (e.g. phenyl). It is preferred that at least one of R⁶ and R⁷ is hydrogen, more preferably, both of R⁶ and R⁷ are hydrogen.

In a preferred embodiment of the compound of the first aspect of the present invention, group Z has a formula (V)

\[
\begin{array}{c}
N \\
\hline \\
N
\end{array}
\]

(V)

Alternatively, R⁶ and R⁷ may be linked to form a cyclic group, which may be substituted with one or more substituent selected from the group consisting of hydrogen, alkoxy (e.g. methoxy, ethoxy), nitro (-NO₂), halogen (e.g. F, Cl, Br, I), alkyl (e.g. C₁-C₆ linear or branched alkyl group, such as methyl, ethyl or propyl) and aryl (e.g. phenyl). It is particularly preferred that the cyclic group, which may be substituted or unsubstituted, is a cycloalkyl group or an aromatic group.

A preferred embodiment of the compound having formula (I) incorporates group Z having the formula (VI)

\[
\begin{array}{c}
\text{R}
\end{array}
\]

(VI)

in which, with reference to formula (II) above, Y is nitrogen substituted with a methyl group, and R⁶ and R⁷ are linked to form an unsubstituted phenyl group.

In the compound of formula (I), wherein Z has the formula (III), R⁸ and R⁹ are individually selected from the group consisting of hydrogen, alkoxy (e.g. methoxy,
ethoxy), nitro (-NO₂), halogen (e.g. F, Cl, Br, I), alkyl (e.g. C₁₋C₆ linear or branched alkyl group, such as methyl, ethyl or propyl) and aryl (e.g. phenyl).

At least one of R⁸ and R⁹ may be hydrogen and it is preferred that both R⁸ and R⁹ are hydrogen.

A preferred embodiment of the compound having formula (I) incorporates group Z having the formula (VII)

(VII)

in which, with reference to formula (III) above, Y is nitrogen substituted with a methyl group, and R⁸ and R⁹ are hydrogen.

With regard to the compound of formula (I), R¹ and R² are each separately selected from the group consisting of hydrogen, alkyl (e.g. C₁₋C₆ linear or branched alkyl group, such as methyl, ethyl or propyl) and aryl (e.g. phenyl).

It is preferred that at least one of R¹ and R² is a relatively bulky group, i.e. possessing an atomic radius greater than hydrogen. It is thus preferred that at least one of R¹ and R² is an alkyl group or an aryl group. Suitable alkyl groups incorporate at least one to six carbon atoms and possibly more, and include linear or branched alkyl groups, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl.

At least one of R¹ and R² is preferably an aryl group, preferably both of R¹ and R² are the same or different aryl groups, such as phenyl, benzyl, tolyl or xylyl groups. It is particularly preferred that both R¹ and R² are phenyl groups, such that formula (XXIX) below represents a preferred structure for the compound according to the first aspect of the present invention.
In the compound of formula (I), R^3, R^4 and R^5 are each separately selected from the group consisting of hydrogen, alkyl (e.g. C_1-C_6 linear or branched alkyl group, such as methyl, ethyl or propyl) and aryl (e.g. phenyl). It is preferred that at least one of R^3, R^4 and R^5 is hydrogen, more preferably at least two of R^3, R^4 and R^5 is hydrogen, and most preferably R^3, R^4 and R^5 are all hydrogen.

In a preferred embodiment of the compound of formula (I) according to the first aspect of the present invention said compound has a formula (IV)

![Formula IV](image)

in which, with reference to formula (I), R^1 and R^2 are phenyl, R^3, R^4 and R^5 are hydrogen and X is oxygen.

A particularly preferred embodiment of the first aspect of the present invention has the formula (VIII)

![Formula VIII](image)
which encompasses both the (S)- and (R)-enantiomers which are depicted below in formulae (Villa) and (VIIIb) respectively.

(Villa)  
(VIIIb)

Another preferred embodiment of the first aspect of the present invention has the formula (XIXa)

(XIXa)

which is similar to formula (VIII) but lacks the gem-diphenyl groups bonded to the carbon atom carrying the hydroxyl group.

A still further preferred embodiment of the first aspect of the present invention has the formula (XXXXVIa)

(XXXXVIa)

which is again similar to formula (VIII) but replaces the gem-diphenyl groups with larger gem-di(β-naphthyl) groups.
There is provided a process for the production of a compound of formula (I) comprising reacting a compound of formula (IX) with a compound of formula (X) or formula (XI) in the presence of a base

\[
\begin{align*}
(IX) \\
(X) \\
(XI)
\end{align*}
\]

wherein \( R^{11} \) is a substituted or unsubstituted alkyl group.

It will be appreciated that the selection of compound (X) or (XI) will determine whether a compound incorporating a \( Z \) group (see formula (I)) of formula (II) or (III) is obtained. Thus, if it is desired to produce a compound of formula (I) according to the first aspect of the present invention wherein \( Z \) corresponds to formula (II) then compound (IX) above should be reacted with compound (X). Alternatively, if it is desired to produce a compound of formula (I) in which \( Z \) corresponds to formula (III), then compound (IX) should be reacted with compound (XI). This is represented below.

\[
\begin{align*}
(X) + (IX) & \rightarrow (I), Z=(II) \\
(XI) + (IX) & \rightarrow (I), Z=(III)
\end{align*}
\]
Where it is desired to produce the (S)-enantiomer of compound (I) the (S)-
enantiomer of compound (IX) should be used and when the (R)-enantiomer of
compound (I) is desired, the (R)-enantiomer of compound (IX) should be used.

Preferred embodiments of the compound of formula (I) incorporate a central
carbonyl moiety, i.e. where X is oxygen, and so preferred processes for producing
these preferred embodiments of compound (I) utilise an ester derivative of
compounds (X) and (XI).

A preferred method for producing preferred compound (Villa) is set out below in
Example 1, wherein a preferred embodiment of compound (X), ester compound
(XII), is reacted with a preferred embodiment of compound (IX), compound (XIIIa),
to produce compound (Villa).

\[
\text{N} \quad \text{N} \\
\text{OEt} \quad \text{OH} \\
\text{(XII)} \quad \text{(XIIIa)} \\
\rightarrow \\
\text{N} \quad \text{N} \\
\text{O} \quad \text{OH} \\
\text{(Villa)}
\]

A further preferred method for producing a different preferred compound (XVIa) is
set out below in Example 2, wherein a preferred embodiment of compound (X), ester
compound (XIV), is reacted with a preferred embodiment of compound (IX),
compound (XVa), to produce compound (XVIa).

\[
\text{N} \quad \text{N} \\
\text{OEt} \quad \text{OH} \\
\text{(XIV)} \quad \text{(XVa)} \\
\rightarrow \\
\text{N} \quad \text{N} \\
\text{O} \quad \text{OH} \\
\text{(XVIa)}
\]
In the above two reaction schemes, the (S)-enantiomers of preferred compounds (Villa) and (XVIa) have been produced using the (S)-enantiomers of starting materials (XIIIa) and (XVa) respectively. It will be appreciated that the (R)-enantiomers of compounds (VIIIb) and (XVIb) may be produced by using the (R)-enantiomer of compounds (XIIIb) and (XVb) respectively.

While any appropriate base may be used, it is preferred that the base is sodium hydride.

The reaction of compound (IX) with compound (X) or (XI) may be effected at any suitable temperature. It is preferred that the reaction is carried out at an elevated temperature, that is, a temperature above room temperature. Preferably, the reaction is effected at a temperature of at least around 40 °C, more preferably at least around 50 °C, more preferably at least around 60 °C, and most preferably at a temperature of around 70 °C.

Compound (IX) may be reacted with compound (X) or (XI) over any appropriate time period. It is desirable that the reaction time should be sufficiently long to ensure that as much of starting material as possible has been converted to product. Preferably the reaction is effected over a time period of at least around 10 hours, more preferably at least around 20 hours and still more preferably at least around 30 hours. Most preferably the reaction is effected over a time period of around 40 hours.

The third aspect of the present invention relates to a process for effecting catalytic reduction of an imine compound to provide a corresponding amine compound, the process comprising reacting said imine compound with a reducing agent in the presence of a catalyst compound having a formula according to the first aspect of the present invention, that is, a compound of formula (I).

It is preferred that the imine nitrogen atom is bonded to an electron-withdrawing group. Preferably the imine nitrogen atom is bonded to an atom or group of atoms of
higher electronegativity than the imine nitrogen atom. The imine nitrogen atom may be bonded to an atom or group of atoms which polarises the bond connecting said atom or group of atoms to the imine nitrogen atom. Preferably said polarisation produces a dipole across the bond such that a partial positive charge (sometimes referred to as a "delta positive" charge) resides on the imine nitrogen atom and a partial negative charge (sometimes referred to as a "delta negative" charge) resides on the atom or group of atoms bonded to the imine nitrogen atom.

In an alternative preferred embodiment the imine nitrogen atom is bonded to an electron-donating group, which is of lower electronegativity than the imine nitrogen atom, such that a partial negative charge resides on the imine nitrogen atom and a partial positive charge resides on the atom or group of atoms bonded to the imine nitrogen atom.

In a preferred embodiment the imine nitrogen atom is bonded directly to a cyclic group, such as a carbocyclic or heterocyclic group which may be aromatic or non-aromatic. Alternatively, the imine nitrogen atom may be bonded to a cyclic group (e.g. an aryl group) via a bivalent alkyl group, such as a C\textsubscript{6} alkyl group, e.g. methylene.

In a preferred embodiment the imine nitrogen atom is bonded directly to an aromatic group, which is preferably substituted with one or more atoms or groups of atoms which are other than hydrogen atoms. It is particularly preferred that the aromatic group is substituted with one or more electron donating group, for example an alkoxide group, such as a methoxy group. Most preferably the or each electron donating group is provided at the position on the aromatic group which maximises the electron donating ability of that group. By way of example, in a preferred embodiment where the imine nitrogen atom is bonded directly to a six-membered aryl group (e.g. phenyl), it is preferred that the aryl group is substituted with a methoxy group at the carbon atom of the aryl group that is \textit{para} to the carbon bonded to the imine nitrogen atom.
This aspect of the present invention is depicted in general terms below with reference to the conversion of imine compound (XXX) to the corresponding chiral amine compound (XXXI).

![Diagram](image)

wherein each of \( R^{12} \), \( R^{13} \) and \( R^{14} \) is a chemical group, for example but not limited to, hydrogen, alkyl or aryl, moreover, \( R^{12} \) and \( R^{13} \) may be linked to form a carbocyclic or heterocyclic ring structure.

When defining the third aspect of the present invention with reference to the above reaction scheme, it is preferred that \( R^{14} \) is an electron withdrawing group, although in other preferred embodiments \( R^{14} \) may be an electron donating group. It will be appreciated that the electronegativity of the imine nitrogen atom will be affected to some extent by the nature of the other two atoms or groups (\( R^{12} \) and \( R^{13} \)) bonded to the imine nitrogen. Accordingly, the electron donating/withdrawing ability of a particular \( R^{14} \) group relative to the imine nitrogen atom may also be affected by the nature of \( R^{12} \) and/or \( R^{13} \).

In a particularly preferred embodiment, compound (XXX) is not an oxime. Thus, \( R^{14} \) is preferably any chemical group, subject to the proviso that it is other than a hydroxide group or alkoxide group bonded to the imine nitrogen atom via the alkoxide oxygen atom. In further preferred embodiments, compound (XXX) is other than an enamide and/or phosphinoylimine.

The third aspect of the present invention therefore provides a means by which an imine, preferably a ketimine, functional group present in a compound can be
selectively converted, via asymmetric reduction, to a chiral amine group. Moreover, by appropriate selection of the stereochemistry of the catalyst compound of formula (I), the achiral imine functionality can be converted to a chiral amine possessing the desired stereochemistry in high enantiomeric excess.

In a preferred embodiment of the third aspect of the present invention the catalyst is provided in an amount of around 0.01 mol % to around 10 mol % of the amount of the reducing agent. The catalyst loading may be lowered further, such that the catalyst may be provided in an amount of around 0.01 mol % to around 5 mol % of the amount of the reducing agent, or an amount of around 0.01 mol % to around 2 mol % of the amount of the reducing agent. More preferably still lower catalyst loadings may be employed, such as around 1 mol % of the amount of the reducing agent. Most preferably the catalyst is provided in an amount of around 0.01 mol % to around 1 mol % of the amount of the reducing agent.

Any suitable reducing agent may be used provided it shows the potential to reduce a carbon-nitrogen double bond to a carbon-nitrogen single bond, that is, reduce an imine to a corresponding amine. Preferred reducing agents are silanes and a particularly preferred reducing agent is trichlorosilane, not least because it is known to be a cheap, versatile reducing agent.

Preferably the initial molar amount of the reducing agent is in excess of the initial molar amount of the imine that is to undergo asymmetric reduction to a corresponding amine. The initial molar ratio of the reducing agent compared to the imine may lie in the range around 1 : 1 (reducing agent : imine) to around 5 : 1. That is, the reducing agent and imine may be provided initially in approximately equal molar amounts or up to an amount whereby the reducing agent is provided in a five-fold excess compared to the amount of the imine starting material.

The initial molar ratio of the reducing agent compared to the imine may be in the range around 1.5 : 1 (reducing agent : imine) to around 4 : 1, and may lie in the range
around 1.5 : 1 to around 2 : 1. Most preferably, the reducing agent is provided in about two-fold excess compared to the initial amount of imine, i.e. a molar ratio of around 2 : 1 (reducing agent : imine).

As is demonstrated below in Example 5, the asymmetric reduction reaction may be effected over a wide range of reaction temperatures without detriment to the enantiomeric excess obtained. The process may be effected at a reaction temperature in the range around -20 °C to around 30 °C, more preferably at a reaction temperature in the range around 0 °C to around 25 °C. Still more preferably, the process is effected at a reaction temperature in the range around 0 °C to around 15 °C.

Any appropriate reaction solvent or mixture of solvents may be employed in the asymmetric reduction reaction. Preferred solvents are selected from the group consisting of trichloromethane, dichloromethane and toluene.

Any suitable reaction time may be adopted in order to obtain the optimum yield. The process may be effected over a time period of up to around 15 hours, more preferably a time period in the range around 1 hour to around 13 hours, or most preferably a time period of around 4 hours.

The fifth aspect of the present invention provides a process for effecting the direct, i.e. single-step or 'one-pot', asymmetric reductive animation of a first compound including an aldehyde or ketone group with a second compound including a first amine group to provide a third compound including a second amine group, the process comprising reacting said first compound with said second compound and a reducing agent in the presence of a catalyst compound having a formula according to the first aspect of the present invention.

This aspect of the present invention is depicted in general terms below, with reference to the asymmetric reductive amination of an aldehyde or ketone (XXXII)
to an amine (XXXIV) by reaction with an amine (XXXIII) in the presence of a reducing agent (e.g. trichlorosilane) and a catalyst (e.g. compound (VIIIa)). As can be seen, the basis of the reductive animation process is to couple compound (XXXII) to compound (XXXIII) by linking the carbonyl carbon atom of compound (XXXII) to the amine nitrogen atom of compound (XXXIII). In this way, the new amine compound (XXXIV) is generated in which groups R\textsubscript{15}, R\textsubscript{16} and R\textsubscript{17} are linked via a new carbon-nitrogen bond and resulting in that carbon atom being a chiral centre when R\textsubscript{16} and R\textsubscript{17} are different chemical groups.

![Chemical structure](attachment:structure.png)

wherein each of R\textsubscript{15}, R\textsubscript{16} and R\textsubscript{17} is any chemical group, for example but not limited to, hydrogen, alkyl or aryl. R\textsubscript{15} and R\textsubscript{16} can also be linked to form a carbocyclic or heterocyclic ring.

Any appropriate reducing agent may be employed in the direct asymmetric reductive amination process, for example, the reducing agent may be a silane, and is preferably trichlorosilane.

In a preferred embodiment of the fifth aspect of the present invention the catalyst is provided in an amount of around 0.01 mol % to around 10 mol % of the amount of the reducing agent. The catalyst loading may be lower, for example 0.01 mol % to around 5 mol %, or around 0.01 mol % to around 2 mol % of the amount of the reducing agent. Yet more preferably even lower catalyst loadings may be employed, such as around 1 mol % of the amount of the reducing agent. Most preferably the catalyst is provided in an amount of around 0.01 mol % to around 1 mol % of the amount of the reducing agent.
While the first compound (i.e. the aldehyde or ketone starting material) and the second compound (i.e. the amine starting material) are preferably provided in approximately equal amounts, i.e. a molar ratio of around 1 : 1 (first compound : second compound), the initial molar amount of the reducing agent is preferably in excess of the initial molar amount of the aldehyde or ketone that is to undergo reductive amination to the third compound (i.e. the product incorporating the second amine group). The initial molar ratio of the reducing agent compared to the aldehyde or ketone may lie in the range around 1 : 1 to around 5 : 1. That is, the reducing agent and aldehyde/ketone may be provided initially in approximately equal molar amounts or up to an amount whereby the reducing agent is provided in a five-fold excess compared to the amount of the aldehyde/ketone starting material.

The initial molar ratio of the reducing agent compared to the aldehyde/ketone may be in the range around 1.5 : 1 (first compound : second compound) to around 4 : 1, and may lie in the range around 1.5 : 1 to around 2 : 1. Most preferably, the reducing agent is provided in about two-fold excess compared to the initial amount of aldehyde/ketone, i.e. a molar ratio of around 2 : 1.

The solvent in which the reductive amination process is carried out may be any appropriate solvent. It is preferred that the process in carried out in a non-polar solvent. A preferred reaction solvent is dichloromethane.

The reductive amination can be conducted at any suitable temperature, for example, a temperature in the range around 0 °C to around 50 °C. The reaction is more preferably carried out at a temperature in the range around 10 °C to around 40 °C, still more preferably around 20 °C to around 30 °C. The reaction is most preferably carried out at around room temperature.

Any appropriate reaction time period may be adopted to provide optimum generation of the chiral amine product, that is, a satisfactory yield over a realistic and economically viable time period. It is preferred that the reaction is carried out over a
time period of up to around 30 hours, more preferably around 1 hour to around 20 hours, and still more preferably around 5 hours to around 20 hours. It is most preferred that the process is carried out over a time period of around 15 hours.

A further related aspect of the present invention relates to a compound for use as a catalyst, said compound comprising a catalytic moiety linked to a polymer support, wherein said compound has the formula (XXXV)

\[
\text{\text{(XXXV)}}
\]

wherein R^{18} is alkyl or alkoxy; A is alkyl, aryl or -(CH_2O)_m-CH_2- in which m is an integer that may be zero or higher; p is a non-zero integer; and n is a non-zero integer representing the number of repeating units of the structure shown comprised in the backbone of the polymer support.

It will be appreciated that the catalytic moiety is the oxazaborolidine functional group and the polymer support is the bracketed portion of formula (XXXV) incorporating the cyclopentane ring. The polyether containing chain incorporating the group A may be considered as a linking group which connects the catalytic moiety to the polymer support.

The compound of general formula (XXXV) may be used to catalyse the reduction of an imine or oxime functional group within a molecule to an amine, typically chiral amine, functional group, as depicted generically below.
wherein $R^{19}$, $R^{20}$ and $R^{21}$ may be any chemical group, such as but not limited to, hydrogen, alkyl or aryl. $R^{22}$ may be an alkyl group. Moreover, $R^{19}$ and $R^{20}$ may be linked to form a carbocyclic or heterocyclic ring.

A further related aspect of the present invention relates to a process for the reduction of an imine or oxime functional group present in a molecule to provide an amine functional group, wherein the process comprises reacting the molecule containing the imine or oxime functional group with a reducing agent in the presence of a compound of formula (XXXV).

Another aspect of the present invention relates to use of a compound of formula (XXXV) to catalyse the reduction of an imine or oxime functional group present in a molecule to provide an amine functional group in said molecule.

The compound of general formula (XXXV) may be used to catalyse the reduction of a ketone functional group within a molecule to an alcohol, typically chiral alcohol, functional group, as depicted generically below.
wherein $R^{19}$ and $R^{20}$ may be alkyl or aryl. Moreover, $R^{19}$ and $R^{20}$ may be linked to form a carbocyclic or heterocyclic ring.

A still further related aspect of the present invention relates to a process for the reduction of a ketone functional group present in a molecule to provide an alcohol functional group, wherein the process comprises reacting the molecule containing the ketone functional group with a reducing agent in the presence of a compound of formula (XXXV). Another aspect of the present invention relates to use of a compound of formula (XXXV) to catalyse the reduction of a ketone functional group present in a molecule to provide an alcohol functional group in said molecule.

Any appropriate reducing agent may be used, such as a borane, e.g. BH$_3$. The reducing agent may be provided in any suitable amount to provide the desired yield of the amine or alcohol. The reaction time and temperature may each be selected to suit a particular application. While the reduction reaction may be carried out in any suitable solvent, it is preferred that the reaction is carried out in tetrahydrofuran.

The catalyst compound (XXXV) may be provided in any desirable amount. For example, a catalyst loading of around 10% compared to the molar amount of the imine/oxime/ketone starting material may be used. More preferably a catalyst loading of around 0.1% to around 10% is used, more preferably from around 0.1% to around 5%. Most preferably a lower catalyst loading of around 0.1% to around 2% is used. Most preferably a catalyst loading of around 1% compared to the molar amount of the imine/oxime/ketone starting material is used.

With regard to catalyst compound (XXXV), $R^{18}$ may be an alkyl group or an alkoxy group. It is preferred that $R^{18}$ is a C$_6$ linear or branched alkyl group. More preferably $R^{18}$ is a C$_3$ linear alkyl group, most preferably a methyl group.

Group A which forms part of the linker connecting the catalytic moiety to the polymer support may be an alkyl, aryl or -(CH$_2$O)$_n$-CH$_2$- group. The alkyl group is
preferably a C$_i$-C$_6$ linear or branched alkyl group, such as methyl, ethyl or propyl group. Alternatively, group A may be an aryl group, such as a phenyl, benzyl, tolyl or xylyl group. With regard to the option of A being a -(CH$_2$O)$_m$-CH$_2$- group, it is preferred that m is an integer from 1 to 6, more preferably 1 to 4 and most preferably 1 to 2. It will be appreciated that when integer m is zero, the -(CH$_2$O)- repeating unit is not present such that a methylene group connects the oxygen atom bonded to the benzene ring of the catalytic moiety to the oxygen atom linked via a methylene group to the cyclopentane ring forming part of the backbone of the polymer support.

The polymer support may incorporate any appropriate number of cyclopentane-containing repeating units, in other words, n may take any appropriate value. The provision of the polymer support significantly eases separation of the catalytic moiety from the reaction mixture once the reaction has run to completion or reached the desired end point.

Another aspect of the present invention provides a process for the production of compound (XXXV). It is preferred that the process comprises ring opening metathesis polymerisation (ROMP) of appropriate starting materials. A generalised scheme for the production of the compound (XXXV) is set out below.
Aspects of the present invention will be further described, by way of example only, with reference to the following non-limiting Examples.
EXAMPLES

EXAMPLE 1

Compound (Villa), which represents a preferred embodiment of the first aspect of the present invention, was prepared by reacting compound XII with compound XIIIa in the presence of a base as follows:

\[ \text{(XII)} \] + \[ \text{(XIIIa)} \] → \[ \text{(Villa)} \]

NaH, toluene, 70°C, 40 h

EXAMPLE 2

Compound (XVIa), which represents a further preferred embodiment of the first aspect of the present invention, was prepared by reacting compound XIV with compound XVa in the presence of a base as follows:

\[ \text{(XIV)} \] + \[ \text{(XVa)} \] → \[ \text{(XVIa)} \]

NaH, toluene, 70°C, 40 h
EXAMPLE 3
A compound having the formula (Villa) in accordance with a preferred embodiment of the present invention was tested as a catalyst in the asymmetric reduction of the ketimine, N-phenyl acetophenone (XVII), to the corresponding chiral amine (XVIIIa).

![Chemical structures](image)

The asymmetric reduction reaction was carried out by addition of trichlorosilane to a stirred solution of the ketimine (XVII) and catalyst (Villa) in dry dichloromethane under an atmosphere of nitrogen at 0 °C. After 4 hours, the reaction was quenched with 1 M hydrochloric acid and subjected to standard work-up procedures.

The reaction produced a product yield of 55% (based on isolated product) with an enantiomeric excess of 86% of the (S)-enantiomer of the chiral amine, compound (XVIIIa). The enantiomeric excess was determined by integration of the appropriate signals in the HPLC chromatogram of the crude reaction mixture. The configuration of the final product was confirmed by comparison of HPLC retention times and specific rotations which those in the literature.
EXAMPLE 4
A compound having the formula (XIXa) in accordance with a preferred embodiment of the present invention was tested as a catalyst in the asymmetric reduction of the ketimine, N-phenyl acetophenone (XVII), to the corresponding chiral amine (XVIIIa).

![Chemical Structure](image)

The asymmetric reduction reaction was carried out by addition of trichlorosilane to a stirred solution of the ketimine (XVII) and catalyst (XIXa) in dry dichloromethane under an atmosphere of nitrogen at 0 °C. After 4 hours, the reaction was quenched with 1 M hydrochloric acid and subjected to standard work-up procedures.

The reaction produced a product yield of 67 % (based on isolated product) with an enantiomeric excess of 42 % of the (S)-enantiomer of the chiral amine, compound (XVIIIa). The enantiomeric excess was determined by integration of the appropriate signals in the HPLC chromatogram of the crude reaction mixture. The configuration of the final product was confirmed by comparison of HPLC retention times and specific rotations which those in the literature.
EXAMPLE 5
A compound having the formula (XXXXVIa) in accordance with a preferred embodiment of the present invention was tested as a catalyst in the asymmetric reduction of the ketimine, N-phenyl acetophenone (XVII), to the corresponding chiral amine (XVIIIa).

![Chemical structure](image)

(XVII)

(XVIIIa)

The asymmetric reduction reaction was carried out by addition of trichlorosilane to a stirred solution of the ketimine (XVII) and catalyst (XIXa) in dry dichloromethane under an atmosphere of nitrogen at 0 °C. After 4 hours, the reaction was quenched with 1 M hydrochloric acid and subjected to standard work-up procedures.

The reaction produced a product yield of 72 % (based on isolated product) with an enantiomeric excess of 86 % of the (S)-enantiomer of the chiral amine, compound (XVIIIa). The enantiomeric excess was determined by integration of the appropriate signals in the HPLC chromatogram of the crude reaction mixture. The configuration of the final product was confirmed by comparison of HPLC retention times and specific rotations which those in the literature.
EXAMPLE 6
A series of reactions were carried out to investigate the optimum conditions for the asymmetric reduction of ketimine (XVII) to chiral amine (XVIIIa) using the catalyst compound (Villa).

![Diagram](image)

Each asymmetric reduction reaction was carried out by addition of trichlorosilane to a stirred solution of the ketimine (XVII) and catalyst (Villa) in a dry solvent under an atmosphere of nitrogen at a predefined temperature. After a predetermined amount of time (indicated in Table 1 below) each reaction was quenched with 1 M hydrochloric acid and subjected to standard work-up procedures.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (hrs)</th>
<th>Solvent</th>
<th>Cl$_3$SiH (equiv.)</th>
<th>(VIIIa) (equiv.)</th>
<th>[I(XVII)]$_0$ (mol. L$^{-1}$)</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>13</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>0.1</td>
<td>0.4</td>
<td>59</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>13</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>0.05</td>
<td>0.4</td>
<td>65</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>13</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>0.01</td>
<td>0.4</td>
<td>45</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>13</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>0.01</td>
<td>0.4</td>
<td>39</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>-20</td>
<td>13</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>0.01</td>
<td>0.4</td>
<td>42</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>13</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>0.01</td>
<td>2.0</td>
<td>56</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>13</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>0.01</td>
<td>2.0</td>
<td>32</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>13</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>0.01</td>
<td>0.4</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>4</td>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
<td>0.01</td>
<td>2.0</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>4</td>
<td>CHCl$_3$</td>
<td>2</td>
<td>0.01</td>
<td>2.0</td>
<td>81</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>4</td>
<td>PhCH$_3$</td>
<td>2</td>
<td>0.01</td>
<td>2.0</td>
<td>87</td>
<td>86</td>
</tr>
</tbody>
</table>

Table 1
The results of this series of reactions are set out below in Table 1. Product yields were based on isolated product. The enantiomeric excess was determined by integration of the appropriate signals in the HPLC chromatogram of the crude reaction mixture. In all cases the (S)-enantiomer of the chiral amine, compound (XVIIIa) was formed as the major product.

It can be appreciated from the results presented in Table 1 that compound (Villa) exhibited good enantioselectivity over a wide range of different reaction conditions when catalysing the conversion of imine (XVII) to the (S)-enantiomer of the chiral amine, compound (XVIIIa).

The most unexpected result, which is of great commercial significance, was that the enantioselectivity of the reaction was essentially unaffected by reducing the catalyst loading from 10 % to 1 % (see entries 1 to 3). At a catalyst loading of 1 %, varying the reaction temperature from -20 °C to 0 °C to 25 °C was not detrimental to the product yield or e.e. (see entries 3 to 5), while increasing the amount of trichlorosilane above 1.5 eq. significantly increased the product yield without affecting the e.e. (see entries 6 to 9). Switching the solvent from dichloromethane to trichloromethane marginally increased the e.e. and using toluene as solvent increased the product yield obtained (see entries 9 to 11).

It therefore appears that a very low catalyst loading can be employed at an economically viable reaction temperature (e.g. 15 °C) without concern that either of these factors will harm the enantioselectivity of the reaction. Moreover, the product yield can be improved by increasing the amount of trichlorosilane reducing agent, increasing the initial concentration of the imine starting material and/or using toluene as solvent.
EXAMPLE 7
The applicability of compound (Villa) to the asymmetric reduction of different imine substrates ((XX) to (XXVI)) was investigated using a series of reactions. The results were compared to the results obtained in respect of imine (XVII) in Example 6.

Each asymmetric reduction reaction was carried out by addition of trichlorosilane (2 eq.) to a stirred solution of the ketimine under investigation and catalyst (Villa) (1 mol %) in dry CH₂Cl₂ under an atmosphere of nitrogen at 0 °C. After 4 hours each reaction was quenched with 1 M hydrochloric acid and subjected to standard work-up procedures.
The results of this series of reactions are set out below in Table 2. E/Z ratio was determined by comparison to literature precedent and nOe studies. Product yields were based on isolated product. The enantiomeric excess was determined by integration of the appropriate signals in the HPLC chromatogram of the crude reaction mixture. In all cases the (S)-enantiomer was formed as the major product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>E/Z ratio</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(XVII)</td>
<td>100/0</td>
<td>82*</td>
<td>85*</td>
</tr>
<tr>
<td>2</td>
<td>(XX)</td>
<td>100/0</td>
<td>96</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>(XXI)</td>
<td>91/9</td>
<td>59</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>(XXII)</td>
<td>88/12</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>(XXXIII)</td>
<td>100/0</td>
<td>42</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>(XXIV)</td>
<td>100/0</td>
<td>41</td>
<td>22</td>
</tr>
<tr>
<td>7</td>
<td>(XXV)</td>
<td>100/0</td>
<td>85</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>(XXVI)</td>
<td>80/20</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>(XXXXII)</td>
<td>-</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>(XXXXIII)</td>
<td>-</td>
<td>81</td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td>(XXXXIV)</td>
<td>-</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>12</td>
<td>(XXXXV)</td>
<td>-</td>
<td>quant.*</td>
<td>-</td>
</tr>
</tbody>
</table>

*From Example 5
Table 2
From the results presented in Table 2 it can be seen that a significant improvement in product yield was obtained when imine (XVII) was replaced with imine (XX) (see entries 1 and 2). While the inventors do not wish to be bound by any particular theory, this observation may be due to imine (XX) being more electron rich than imine (XVII) which could enable imine (XX) to undergo more efficient binding to the trichlorosilane reducing agent. A similar trend was observed in respect of imines (XXI) and (XXII) (see entries 3 and 4). Good yields and e.e.s were also observed for substrate imines (XXV) and (XXVI) (see entries 7 and 8).
**EXAMPLE 8**

The use of compounds according to the first aspect of the present invention to catalyse reductive processes, other than those described in Examples 3 to 7, was investigated. Specifically, the ability of a preferred embodiment of the first aspect of the present invention, compound (Villa), to catalyse the asymmetric reductive amination of a ketone to the corresponding chiral amine was studied. The starting materials were the ketone, acetophenone (1-phenylethanone) and the amine, \( p \)-methoxyaniline. The reducing agent was trichlorosilane, as in Examples 3 to 7. The reaction was carried out in dichloromethane, at room temperature over a period of 15 hours. A catalyst loading of 10 % was used.

\[
\text{Ph} - \overset{\text{Cl}_3\text{SiH}}{\longrightarrow} - \text{NHMe} \rightarrow \text{Ph} - \overset{10\% \text{(Villa)}}{\longrightarrow} - \text{Ph} - \overset{10\% \text{(Villa)}}{\longrightarrow} - \text{NHMe}
\]

Eighty-four percent of the starting material was converted to product with an enantiomeric excess (\((S)-\)enantiomer) of 80 %.

**EXAMPLE 9**

The use of compound (Villa) to catalyse the asymmetric reductive amination of a different ketone was investigated. The starting ketone was 1-phenylpropanone. The amine starting material and the reducing agent were the same as in Example 8. The reaction was again carried out in dichloromethane, at room temperature over a period of 15 hours. A catalyst loading of 10 % was used, as in Example 8.

\[
\text{Ph} - \overset{\text{Cl}_3\text{SiH}}{\longrightarrow} - \text{NH}_2 \rightarrow \text{Ph} - \overset{10\% \text{(Villa)}}{\longrightarrow} - \text{Ph} - \overset{10\% \text{(Villa)}}{\longrightarrow} - \text{NHMe}
\]

Twenty percent of the starting material was converted to product with an enantiomeric excess (\((S)-\)enantiomer) of 80 %.
EXAMPLE 10

The use of compound (Villa) to catalyse the asymmetric reductive animation of another ketone was investigated.

In this Example, the starting ketone was 1-cyclohexylethanone. The amine starting material and the reducing agent were the same as in Example 8, that is, $p$-methoxyaniline and trichlorosilane respectively. The reaction was again carried out in dichloromethane, at room temperature but over a longer time period of 24 hours. A catalyst loading of 10% was again used.

\[
\begin{align*}
\text{C}_6\text{H}_{12}\text{CHO} + \text{Cl}_3\text{SiH} + \text{C}_6\text{H}_4\text{NH}_2 &\rightarrow \text{C}_6\text{H}_{12}\text{HCH} - \text{OMe} \\
\text{CH}_2\text{Cl}_2, \text{RT}, 24\text{h} &\rightarrow \text{C}_6\text{H}_{12}\text{HCH} - \text{OMe}
\end{align*}
\]

Thirty-one percent of the starting material was converted to product with an enantiomeric excess ((S)-enantiomer) of 71%.
EXAMPLE 11
The use of compound (Villa) to catalyse the asymmetric reductive amination of a still further ketone was investigated.

In this Example, the starting ketone was 1-(4-nitrophenyl)ethanone. The amine starting material and the reducing agent were again the same as in Example 8, i.e. p-methoxyaniline and trichlorosilane respectively. The reaction was carried out in dichloromethane, at room temperature over 24 hours. A catalyst loading of 10% was used.

Thirty-three percent of the starting material was converted to product with an enantiomeric excess ((S)-enantiomer) of 60%.

Significantly, the asymmetric reductive amination reactions described in Examples 8 to 11 were carried out as direct, single-step, 'one-pot' procedures, requiring no isolation of intermediate compounds. This has not previously been possible. Given the extent to which asymmetric reductive amination processes are employed in synthetic chemistry to generate chiral amine functionalities, it will be appreciated that the above methodology represents an important breakthrough, which has been made possible by the development of the new class of compounds according to the first aspect of the present invention.
EXAMPLE 12

The use of compounds according to the first aspect of the present invention to catalyse the stereoselective reduction of enamines was investigated. A reaction was carried out to assess the ability of compound (Villa) to produce peptide bond-containing compounds, such as amino acids, from appropriate substrates.

In this example, the reaction shown below was carried out by addition of trichlorosilane (2 eq.) to a stirred solution of a para-methoxyphenyl protected enamine and catalyst (Villa) (10 mol %) in dry CH₂Cl₂ under an atmosphere of nitrogen at 0 °C. After 4 hours the reaction was quenched with 1 M hydrochloric acid and subjected to standard work-up procedures.

Thirty-two percent of the starting material was converted to product with an enantiomeric excess ((S)-enantiomer) of 70 %.
1. A compound having the formula (I)

\[
\begin{align*}
\text{R}^5 & \quad \text{R}^4 \\
\text{Z} & \quad \text{X} \\
\text{N} & \quad \text{OH} \\
\text{X} & \quad \text{R}^1 \\
\text{R}^2 & \quad \text{R}^3 \\
\end{align*}
\]

wherein: R\(^1\), R\(^2\), R\(^3\), R\(^4\) and R\(^5\) are each separately selected from the group consisting of hydrogen, alkyl and aryl; X is oxygen or sulfur; and Z has the formula (II)

\[
\left(\begin{array}{c}
\text{R}^6 \\
\text{N} \\
\text{R}^7
\end{array}\right)
\]

wherein: R\(^6\) and R\(^7\) are each separately selected from the group consisting of hydrogen, alkoxy, nitro, halogen, alkyl and aryl, or R\(^6\) and R\(^7\) are linked to form a cyclic group; and Y is oxygen, sulfur or NR\(^i\) in which R\(^i\) is selected from the group consisting of hydrogen, alkyl and aryl.

2. A compound according to claim 1, wherein X is oxygen.

3. A compound according to claim 1 or 2, wherein Y is NR\(^i\).

4. A compound according to claim 3, wherein R\(^i\) is an alkyl group.

5. A compound according to claim 3, wherein R\(^i\) is a Ci-C\(_6\) linear or branched alkyl group.
6. A compound according to claim 3, wherein R\textsuperscript{10} is selected from the group consisting of methyl, ethyl and propyl.

7. A compound according to any preceding claim, wherein at least one of R\textsuperscript{1} and R\textsuperscript{2} is an alkyl group or an aryl group.

8. A compound according to claim 7, wherein said aryl group is a phenyl group.

9. A compound according to any preceding claim, wherein at least one of R\textsuperscript{3}, R\textsuperscript{4} and R\textsuperscript{5} is hydrogen.

10. A compound according to any preceding claim, wherein said compound has a formula (IV)

\[
\begin{align*}
\text{(IV)}
\end{align*}
\]

11. A compound according to any preceding claim, wherein at least one of R\textsuperscript{6} and R\textsuperscript{7} is hydrogen.

12. A compound according to any preceding claim, wherein group Z has a formula (V)

\[
\begin{align*}
\text{(V)}
\end{align*}
\]

13. A compound according to any one of claims 1 to 10, wherein R\textsuperscript{6} and R\textsuperscript{7} are linked to form a cyclic group and said cyclic group is substituted with one or
more substituent selected from the group consisting of hydrogen, alkoxy, nitro, halogen, alkyl and aryl.

14. A compound according to claim 13, wherein the cyclic group is a cycloalkyl group or an aromatic group.

15. A compound according to any one of claims 1 to 10, wherein group Z has the formula (VI)

\[
\text{(VI)}
\]

16. A compound according to claim 1, wherein the compound has the formula (VIII)

\[
\text{(VIII)}
\]

17. A compound having the formula (XXXV)

\[
\text{(XXXV)}
\]
wherein R^{18} is alkyl or alkoxy; A is alkyl, aryl or -(CH_{2}O)_{m}-CH_{2} in which m is an integer that may be zero or higher; p is a non-zero integer; and n is a non-zero integer.

18. A compound according to claim 17, wherein R^{18} is a methyl group and/or m is 1 or 2.

19. A process for the production of a compound according to any one of claims 1 to 16, the process comprising reacting a compound of formula (IX) with a compound of formula (X) in the presence of a base

\[ \text{IX} \]

\[ \text{X} \]

wherein R^{11} is a substituted or unsubstituted alkyl group.

20. A process according to claim 19, wherein the base is sodium hydride.

21. A process according to claim 19 or 20, wherein the reaction is effected at a temperature of around 70 \(^{\circ}\)C.

22. A process according to claim 19, 20 or 21, wherein the reaction is effected over a time period of around 40 hours.

23. A process for the production of a compound of formula (XXXV) according to claim 17, the process comprising the reaction steps shown below
24. A process for effecting catalytic reduction of an imine compound to provide a corresponding amine compound, the process comprising reacting said imine compound with a reducing agent in the presence of a catalyst compound having a formula according to any one of claims 1 to 18.

25. A process according to claim 24, wherein the catalyst is provided in an amount of around 0.01 mol % to around 10 mol % of the amount of the reducing agent.

26. A process according to claim 24, wherein the catalyst is provided in an amount of around 0.01 mol % to around 5 mol % of the amount of the reducing agent.

27. A process according to claim 24, wherein the catalyst is provided in an amount of around 0.01 mol % to around 2 mol % of the amount of the reducing agent.
28. A process according to claim 24, wherein the catalyst is provided in an amount of around 1 mol % of the amount of the reducing agent.

29. A process according to any one of claims 24 to 28, wherein the reducing agent is a silane.

30. A process according to any one of claims 24 to 28, wherein the reducing agent is trichlorosilane.

31. A process according to any one of claims 24 to 30, wherein the initial molar amount of the reducing agent is in excess of the initial molar amount of the imine.

32. A process according to any one of claims 24 to 30, wherein the initial molar ratio of the reducing agent compared to the imine is in the range around 1 : 1 to around 5 : 1.

33. A process according to any one of claims 24 to 30, wherein the initial molar ratio of the reducing agent compared to the imine is in the range around 1.5 : 1 to around 4 : 1.

34. A process according to any one of claims 24 to 30, wherein the initial molar ratio of the reducing agent compared to the imine is in the range around 1.5 : 1 to around 2 : 1.

35. A process according to any one of claims 24 to 34, wherein the process is effected at a reaction temperature in the range around -20 °C to around 30 °C.

36. A process according to any one of claims 24 to 34, wherein the process is effected at a reaction temperature in the range around 0 °C to around 25 °C.
37. A process according to any one of claims 24 to 34, wherein the process is
effected at a reaction temperature in the range around 0 °C to around 15 °C.

38. A process according to any one of claims 24 to 37, wherein the process is
effected in a solvent selected from the group consisting of trichloromethane,
dichloromethane and toluene.

39. A process according to any one of claims 24 to 38, wherein the process is
effected over a time period of up to around 15 hours.

40. A process according to any one of claims 24 to 38, wherein the process is
effected over a time period of around 4 hours.

41. Use of a compound having a formula according to any one of claims 1 to 18
to catalyse the reduction of an imine compound to provide a corresponding
amine compound.

42. A process for effecting the direct asymmetric reductive animation of a first
compound including an aldehyde or ketone group with a second compound
including a first amine group to provide a third compound including a second
amine group, the process comprising reacting said first compound with said
second compound and a reducing agent in the presence of a catalyst
compound having a formula according to any one of claims 1 to 18.

43. A process according to claim 42, wherein the catalyst is provided in an
amount of around 0.01 mol % to around 10 mol % of the amount of the
reducing agent.

44. A process according to claim 42 or 43, wherein the reducing agent is a silane.
45. A process according to claim 42 or 43, wherein the reducing agent is trichlorosilane.

46. A process according to any one of claims 42 to 45, wherein the initial molar amount of the reducing agent is in excess of the initial molar amount of the first compound.

47. A process according to any one of claims 42 to 45, wherein the initial molar ratio of the reducing agent compared to the first compound is in the range around 1:1 to around 5:1.

48. A process according to any one of claims 42 to 47, wherein the process is carried out in a non-polar solvent.

49. A process according to any one of claims 42 to 47, wherein the process is carried out in dichloromethane.

50. A process according to any one of claims 42 to 49, wherein the process is carried out at around room temperature.

51. A process according to any one of claims 42 to 49, wherein the process is carried out over a time period of around 15 hours.

52. Use of a compound having a formula according to any one of claims 1 to 18 to catalyse the direct asymmetric reductive animation of an aldehyde or ketone compound to provide an amine compound.

53. A process for effecting catalytic reduction of an enamine compound to provide a corresponding amine compound, the process comprising reacting said enamine compound with a reducing agent in the presence of a catalyst compound having a formula according to any one of claims 1 to 18.
54. Use of a compound having a formula according to any one of claims 1 to 18 to catalyse the reduction of an enamine compound to provide a corresponding amine compound.