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(54) **A CATALYTICAL ASYMMETRIC EPOXIDATION**

KATALYTISCHE ASYMMETRISCHE EPOXYDIERUNG

EPOXYDATION ASYMETRIQUE CATALYTIQUE

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- **HOSHINO, YUJIRO ET AL: "Novel .alpha.-Amino Acid-Based Hydroxamic Acid Ligands for Vanadium-Catalyzed Asymmetric Epoxidation of Allylic Alcohols" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , 122(42), 10452-10453 CODEN: JACSAT; ISSN: 0002-7863, 2000, XP002322166**
- **ADAM, WALDEMAR ET AL: "Control of enantioselectivity through a hydrogen-bonded template in the vanadium(V)-catalyzed epoxidation of allylic alcohols by optically active hydroperoxides" TETRAHEDRON: ASYMMETRY , 14(10), 1355-1361 CODEN: TASYE3; ISSN: 0957-4166, 2003, XP002322167**

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Description

BACKGROUND OF THE INVENTION

[0001] Catalytic asymmetric epoxidations are extremely useful methods for synthesizing chiral compounds and consequently these types of reactions have broad applicability in the pharmaceutical industry. In the early 1980's Sharpless disclosed an effective method for accessing chiral epoxy alcohols, using a titanium-tartarate complex in the presence of a stoichiometric achiral oxidant. Although this process consistently provides high enantioselectivity, it has a number of disadvantages, which include the required use of molecular sieves, the sensitivity of the catalyst system to air and water, and an extensive and complicated work-up.

[0002] The catalytic asymmetric oxidation, disclosed herein, has one or more of the following advantages over previously used methods. Because the catalyst system is not water sensitive, molecular sieves are not required and an aqueous solution of an organic hydroperoxide can be used as the achiral oxidant. The catalyst system is not air sensitive the reactions are performed under aerobic conditions. Reactions can be easily worked up, which makes this system much more amenable to large-scale reactions. This methodology can also be applied to the catalytic asymmetric oxidation of sulfides.

BRIEF SUMMARY OF THE INVENTION

[0003] The present invention relates to the synthesis of chiral epoxides via a catalytic asymmetric oxidation of olefins. Additionally, the methodology provides a method of asymmetrically oxidizing sulfides. This asymmetric oxidation employs a catalyst system composed of a metal and a chiral bishydroxamic acid ligand, which, in the presence of a stoichiometric quantity of an oxidation reagent, serves to asymmetrically oxidize a variety of substrates.

DETAILED DESCRIPTION OF THE INVENTION

[0004] It is intended that the foregoing detailed description be regarded as illustrative rather than limiting, and that it be understood that it is the following claims, including all equivalents, that are intended to define the spirit and scope of this invention.

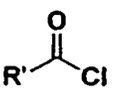
General

[0005] The present invention provides a method of performing a catalytic asymmetric oxidation comprising: reacting a substrate selected from the group consisting of sulfide, alkene and cyclicalkene with catalytic amounts of a chiral bishydroxamic acid ligand and a metal selected from the group consisting of vanadium and molybdenum, in the presence of an oxidation agent, e.g. an organic hydroperoxide, to produce a chiral oxidation product.

Abbreviations and Definitions

[0006] When describing the compounds, compositions, methods and processes of this invention, the following terms have the following meanings, unless otherwise indicated.

[0007] "Acid chloride" refers to a compound of the following formula:



where, R' is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and arylalkyl.

[0008] "Alkene" or "olefin" refers to an unsaturated hydrocarbon group which may be linear, cyclic or branched or a combination thereof. These groups have at leas 1 double bond, but can also include 2 or more double bonds. Possible substituents can be selected from the group consisting of include hydrogen, alkyl, cycloalkyl, hydroxy, alkoxy, amino, alkylamino, halogen, heterocyclyl, aryl, heteroaryl, arylalkyl, O-silyl, and halogen. Alkene groups with 2 to 20 carbon atoms are preferred. Alkene groups with 2 to 16 carbon atoms are more preferred. Examples of alkene groups include ethenyl, n-propenyl, isopropenyl, n-but-2-enyl, n-hex-3-enyl and the like.

[0009] "Alkoxy" refers to those alkyl groups, having from 1 to 10 carbon atoms, attached to the remainder of the molecule via an oxygen atom. Alkoxy groups with 1-8 carbon atoms are preferred. The alkyl portion of an alkoxy may be linear, cyclic, or branched or a combination thereof. Examples of alkoxy groups include methoxy, ethoxy, isopropoxy,

butoxy, cyclopentyloxy, and the like. An alkoxy group can also be represented by the following formula: -OR', where R' is the "alkyl portion" of an alkoxy group.

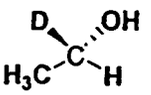
[0010] "Alkyl" by itself or as part of another substituent refers to a hydrocarbon group which may be linear, cyclic, or branched or a combination thereof having from 1 to 10 carbon atoms (preferably 1 to 8 carbon atoms). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, cyclopentyl, (cyclohexyl)methyl, cyclopropylmethyl and the like.

[0011] "Alkylamino" refers to those alkyl groups, having from 1 to 10 carbon atoms, attached to the remainder of the molecule via a nitrogen atom. Alkylamino groups with 1-8 carbon atoms are preferred. The alkyl portion of an alkylamino may be linear, cyclic, or branched or a combination thereof. Examples of alkylamino groups include methyl amine, ethyl amine, isopropyl amine, butyl amine, dimethyl amine, methyl, isopropyl amine and the like. An alkylamino group can also be represented by the following formulae: -NR'- or -NR'R", or -NHR', where R' and R" are alkyl.

[0012] "Aryl" refers to an aromatic hydrocarbon group having a single ring or multiple rings which are fused together or linked covalently with 5 to 14 carbon atoms (preferably 5 to 10 carbon atoms). Examples of aryl groups include phenyl, naphthalene-1-yl, naphthalene-2-yl, biphenyl, anthracene and the like.

[0013] "Arylalkyl" refers to an aryl group, attached to the remainder of the molecule via an alkyl group.. Such groups may have single or multiple substituents on either the aryl ring or on the alkyl side chain. Examples include benzyl, phenylethyl, styryl, 2-(4-methylphenyl)ethyl, triphenylmethane, and 2-phenylpropyl.

[0014] "Asymmetric" refers to a molecule lacking all elements of symmetry. For example, the following carbon center is asymmetric:



[0015] "Catalysis" or "catalyze" refer to a process in which a relatively small amount of a foreign material increases the rate of a chemical reaction and is not itself consumed in the reaction.

[0016] "Catalytic amount" refers to a substoichiometric amount of the catalyst relative to a reactant.

[0017] "Catalytic asymmetric oxidation" refers to the transfer of an oxygen from an organic hydroperoxide to a pair of electrons, using a catalytic amount of a chiral bishydroxamic acid ligand and a metal, to produce an asymmetric product.

[0018] "Chiral" refers to a molecule or conformation which is not superimposable with its mirror image partner. The term "achiral" refers to molecule or conformation which is superimposable with its mirror image partner.

[0019] "Chiral catalyst" refers to a molecule or conformation, which is not superimposable with its mirror image partner and that increases the rate of a chemical reaction without itself being consumed. In an asymmetric catalytic reaction, the chiral catalyst will serve to catalyze the reaction, while also providing enantioselectivity.

[0020] "Chiral ligand" refers to a molecule or ion that surrounds a metal in a metal ion complex as a Lewis base, where the molecule is one which is not superimposable with its mirror image partner.

[0021] "Chiral oxidation product" refers to a molecule or compound which was transformed from a non-chiral to a chiral entity via the oxidation reaction disclosed herein.

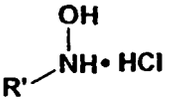
[0022] "CHP" refers to cumene hydroperoxide.

[0023] "Complex" refers to a coordination compound formed by the union of one or more electronically rich molecules or atoms capable of independent existence with one or more electronically poor molecules or atoms, which is also capable of independent existence.

[0024] "Cyclic alkene" refers to alkenes or olefins, in which the unsaturated hydrocarbon group forms to members of a cycloalkyl or heterocyclyl moiety.

[0025] "Cycloalkyl" refers to hydrocarbon rings having from 3 to 12 carbon atoms and being fully saturated or having no more than one double bond between ring vertices (preferably 5 to 6 carbon atoms). Examples of cycloalkyl include cyclopropyl, cyclopentyl, cycloyhexyl and the like. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and the like.

[0026] "Dihydroxylamine hydrochloride" refers to compound having to hydroxylamine hydrochloride moieties. Hydroxylamine hydrochloride refers to a compound of the following formula:



where R' is selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and arylalkyl.

[0027] "Enantiomer" refers to one of a pair of molecular species that are mirror images of each other and not superposable.

[0028] "Enantiomerically enriched" refers to a mixture of enantiomers, in which one of the enantiomers has been selectively created in preference over the other enantiomer. Thus an "enantiomerically enriched" product will have an enantiomeric excess (i.e., % ee), in which one enantiomer is present in a larger amount than the other. To put it another way, "enantiomerically enriched" refers to having an enantiomer excess of more than 0 but less than 100%. "Enantiomeric excess" is equal to 100 times the mole fraction of the major enantiomer minus the more fraction of the minor enantiomer. In a mixture of a pure enantiomer (*R* or *S*) and a racemate, ee is the percent excess of the enantiomer over the racemate.

[0029] "Enantioselective" refers to a process which favors production of one of the two possible enantiomers of a reaction product. For example, a chemical reaction would be enantioselective if it produces the two enantiomers of a chiral product in unequal amounts. Such a reaction is said to exhibit enantioselectivity.

[0030] "Halo" or "halogen", by itself or as part of a substituent refers to a chlorine, bromine, iodine, or fluorine atom. Additionally, terms such as "Haloalkyl" refer to a monohaloalkyl or polyhaloalkyl group, most typically substituted with from 1-3 halogen atoms. Examples include 1-chloroethyl, 3-bromopropyl, trifluoromethyl and the like.

[0031] "Heteroatom" refers to an atom other than carbon. Examples include nitrogen, oxygen, sulfur, phosphorus and the like.

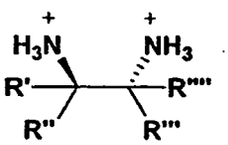
[0032] "Heterocyclyl" refers to a saturated or unsaturated non-aromatic group containing at least one heteroatom and having 3 to 10 members (preferably 3 to 7 carbon atoms). "Heteroaryl group" refers to an aromatic group containing at least one heteroatom and having 3 to 10 members (preferably 3 to 7 carbon atoms). Each heterocyclyl and heteroaryl can be attached at any available ring carbon or heteroatom. Each heterocyclyl may have one or more rings. When multiple rings are present in a heterocyclyl, they can be fused together or linked covalently. Each heteroaryl may have one or more rings. When multiple rings are present in a heteroaryl, they can be fused. Each heterocyclyl and hetroaryl can be fused to a cyclyl, heterocyclyl, heteroaryl, or aryl group. Each heterocyclyl and heteroaryl must contain at least one heteroatom (typically 1 to 5 heteroatoms) selected from nitrogen, oxygen or sulfur. Preferably, these groups contain 0-3 nitrogen atoms and 0-1 oxygen atoms. Examples of saturated and unsaturated heterocyclyl groups include pyrrolidine, imidazolidine, pyrazolidine, piperidine, 1,4-dioxane, morpholine, piperazine, 3-pyrroline and the like. Examples of heteroaryl groups include pyrrole, imidazole, oxazole, furan, triazole, tetrazole, oxadiazole, pyrazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, triazine, indole, benzofuran, benzimidazole, benzopyrazole, quinoline, isoquinoline, quinazoline, quinoxaline and the like. Heterocyclyl and heteroaryl groups can be unsubstituted or substituted. For substituted groups, the substitution may be on a carbon or heteroatom. For example, when the substitution is =O, the resulting group may have either a carbonyl (-C(O)-) or a N-oxide (-N(O)-).

[0033] "Inert atmosphere" refers to reaction conditions in which the mixture is covered with a layer of inert gas such as nitrogen or argon.

[0034] "Ligand" refers to the molecules or ions that surround the metal in a complex and serve as Lewis bases (i.e., electron pair donors).

[0035] "Metal" refers to elements located in Groups 5 and 6 of atomic number 23 to 74.

[0036] "Optically active 1,2-diammonium tartarate" refers to a compound of the following formula:

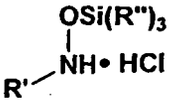


where, R', R", R"', and R"" are selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and arylalkyl. The R" and R"' groups can also form members of the same ring, where the ring is a cycloalkyl or heterocyclyl group.

[0037] "Organic hydroperoxide" refers to an oxidant of the formula R'-O-O-H, where R' is selected from the group consisting of alkyl, cycloalkyl, and arylalkyl. Examples of organic hydroperoxides include tert-butyl hydroperoxide, α,α-dimethylheptyl hydroperoxide, bis-diisobutyl-2,5-dihydroperoxide, 1-methylcyclohexyl hydroperoxide, cumene hydroperoxide, cyclohexyl hydroperocide, and trityl hydroperoxide.

[0038] "Phospine" refers to a phosphorus atom possessing three subsituents. Substituents can be selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and arylalkyl.

[0039] "Silyl protected dihydroxlamine" refers to a compound with two silyl protected hydroxylamines. Silyl hydroxyl amine refers to a compound of the following formula:



where, R' and R" are selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and arylalkyl.

[0040] "Substituted" means that the moiety contains at least one, preferably 1 to 3 substituent(s). Suitable substituents include hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, alkylthio, halogen, heterocyclyl, aryl, heteroaryl, arylalkyl, or O-silyl. These substituents can optionally be further substituted with 1 to 3 substituents. Examples of substituted substituents include alkylamino, dialkylamino, alkylaryl, aralkyl, and the like.

[0041] "Sulfide" refers to a functional group, wherein a sulfur atom possesses two subsituents. A sulfide group can be represented as -S-, where possible subsituents can be selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or arylalkyl.

[0042] "Sulfonyl" refers to a functional group, wherein a sulfur atom possesses four substituents, to of which are double bonded oxygens. A sulfonyl moiety may be represented as $-S(O)_2-$.

[0043] "TBHP" refers to *tert*-butyl hydroperoxide.

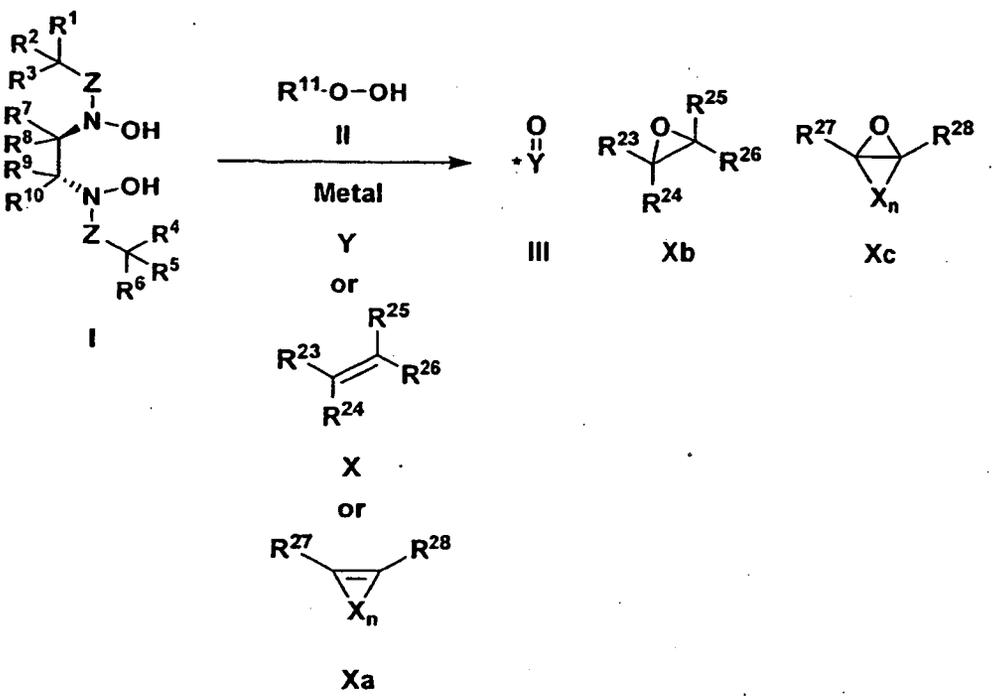
[0044] "*" refers to a center, molecule, or atom which is chiral.

[0045] All of the above terms (*e.g.*, "alkyl," "aryl," "heteroaryl" etc.), in some embodiments, include both substituted and unsubstituted forms of the indicated groups. These groups may be substituted 1 to 10 times, as chemically allowed. Suitable substituents include alkyl, aryl, heteroaryl, heterocyclyl, halogen, alkoxy, oxygen, and nitrogen.

[0046] It is therefore intended that the foregoing detailed description be regarded as illustrative rather than limiting, and that it be understood that it is the following claims, including all equivalents, that are intended to define the spirit and scope of this invention.

Catalytic Asymmetric Oxidation

[0047] The asymmetric oxidation of the present invention can be represented as follows:

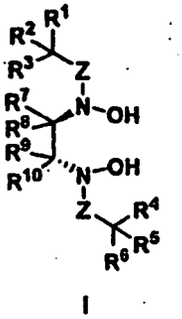


This reaction provides a method for the catalytic asymmetric oxidation of a substrate (**Y**), using catalytic amounts of a metal and a chiral bishydroxamic acid ligand (**I**), in the presence of an oxidation reagent. A number of potential substrates are shown (**Y**, **X**, and **Xa**). The resulting chiral oxidation products, in this example, are represented by compounds **III,**

Xb, and **Xc**. The chiral bishydroxamic acid ligand (**I**), the oxidation reagent, the metal, the substrate, and the chrial oxidation product are all discussed individually below.

Chiral Bishydroxamic Acid Ligand

[0048]



I

[0049] In one embodiment the chiral ligand, is represented by chiral bishydroxamic acid ligand I.

[0050] The -Z- linking groups are each -C(O)-.

[0051] Substituents R^1, R^2, R^3, R^4, R^5, and R^6 are attached to the bishydroxamic backbone via the -Z- linking groups. Substituents R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, heterocyclyl, aryl, heteroaryl and arylalkyl.

[0052] Both of the hydroxamic acid nitrogens are also attached to an ethylene group, which is further substituted with R^7, R^8, R^9, and R^{10}. Substituents R^7, R^8, R^9, and R^{10} are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl and arylalkyl.

[0053] In one embodiment, substituents R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected, such that each is a different group or such that they are the same.

[0054] In another embodiment, substituents R^1, R^2, R^3, R^4, R^5, and R^6 are chosen such that: R^1 and R^4 are the same; R^2 and R^5 are the same; and / or R^3 and R^6 are the same.

[0055] In an additional embodiment, R^1, R^2, R^4, and R^5 may all be the same, while R^3 and R^6 are the same as each other, but different from R^1, R^2, R^4, and R^5.

[0056] In another embodiment, R^1, R^2, and R^3 can be chosen such that any two of these groups, together with the atom to which they are attached, form a ring.

[0057] In an additional embodiment, R^4, R^5, and R^6 can be chosen such that any two of these groups, together with the atom to which they are attached, form a ring.

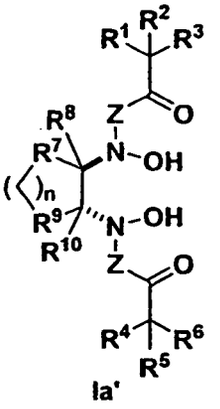
[0058] For example, R^1 and R^2, along with the atom to which they are attached, can form a ring, where the ring is selected from the group consisting of cycloalkyl, heterocyclyl, or aryl. Likewise, R^4 and R^5, along with the atom to which they are attached, can form a ring, where the ring is selected from the group consisting of cycloalkyl, heterocyclyl, or aryl.

[0059] In one embodiment, the ring formed by R^1 and R^2, and the ring formed by R^4 and R^5 are identical and the rings are selected from the group consisting of cycloalkyl, hetercyclyl, and aryl.

[0060] The R^7, R^8, R^9, and R^{10} substituents are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl, such that each group is different or all of these groups are the same.

[0061] In a more preferred embodiment, the R^7 and R^9 substituents can be chosen such that these two groups are identical and the R^8 and R^{10} substituents can be chosen such that these two groups are identical.

[0062] In one embodiment, R^7 and R^9, along with the atoms to which they are attached, form a ring, which is selected from the group consisting of cycloalkyl and heterocyclyl. The resulting chiral bishydroxamic acid ligand is compound **Ia'.**



Ia'

[0063] In chiral bishydroxamic acid ligand **Ia',** R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and Z are defined as previously described.

[0064] The value of n can be 0, 1, 2, 3, or 4.

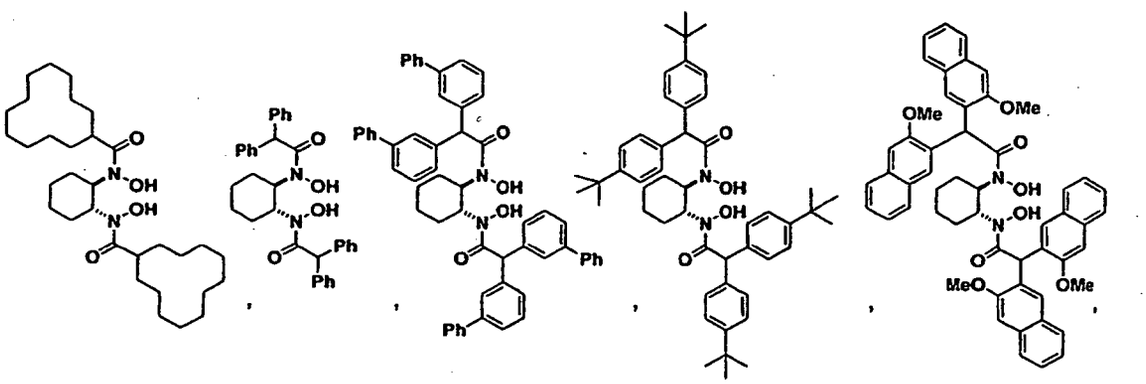
[0065] When R^7 and R^9, along with the atoms to which they are attached, form a ring, R^8 and R^{10} can be the same or different.

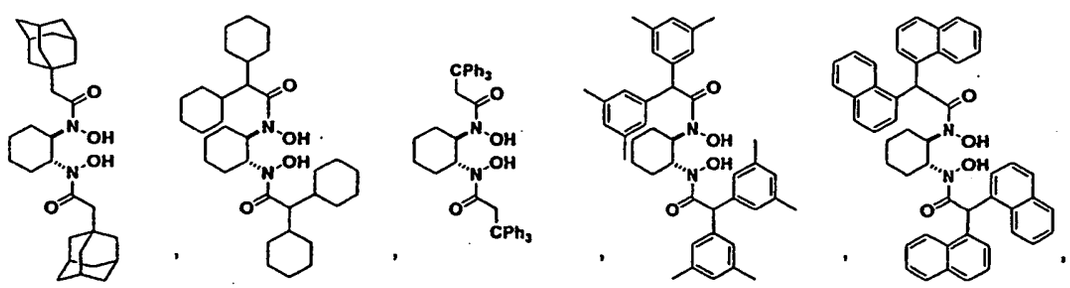
[0066] In a preferred embodiment R^1, R^2, R^4, and R^5, are aryl groups; while R^3 and R^6 are hydrogen.

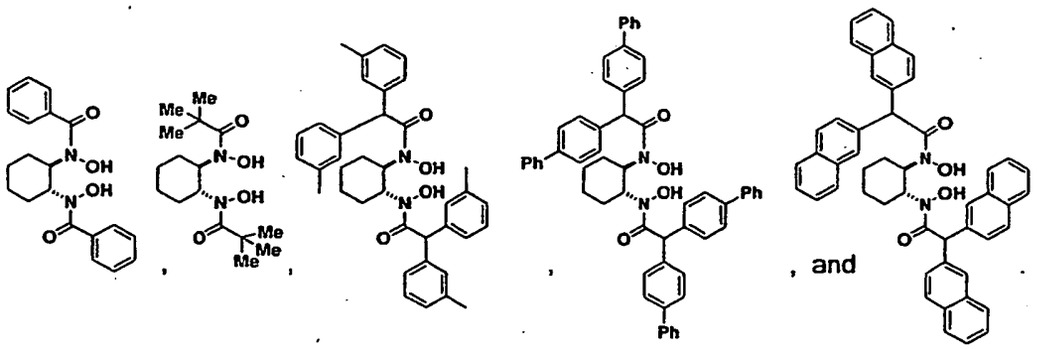
[0067] In a more preferred embodiment, R^1 and R^2 are identical aryl groups, and R^4 and R^5 are identical aryl groups, while R^3 and R^6 are hydrogen.

[0068] In a more preferred embodiment R^1, R^2, R^4, and R^5 are the same or identical aryl group, while R^3 and R^6 are hydrogen.

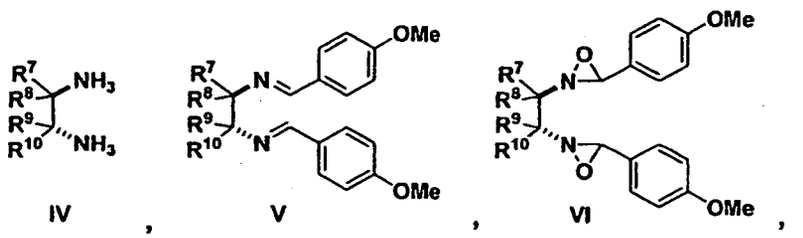
[0069] In another preferred embodiment, the chiral bishydroxamic acid ligand (I) is selected from the group consisting of:



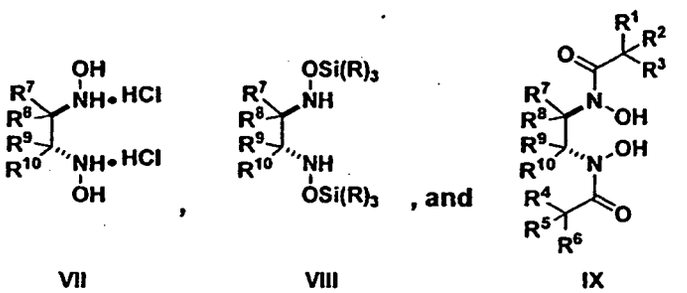




[0070] In one embodiment the chiral bishydroxamic acid ligand is prepared by condensing an optically active 1,2-diammonium tartarate (**IV**) with p-anisaldehyde to provide di-imine **V**. Next, the di-imine (**V**) is oxidized to produce dioxaziridine **VI,** which is subsequently hydrolyzed to generate dihydroxylamine hydrochloride **VII.** The dihydroxylamine hydrochloride **(VII)** is then silylated to provide silyl protected dihydroxlamine **VIII.**
Finally, the silyl protected dihydroxylamine (**VIII**) is condensed with an acid chloride to produce bishydroxamine acid **IX.**

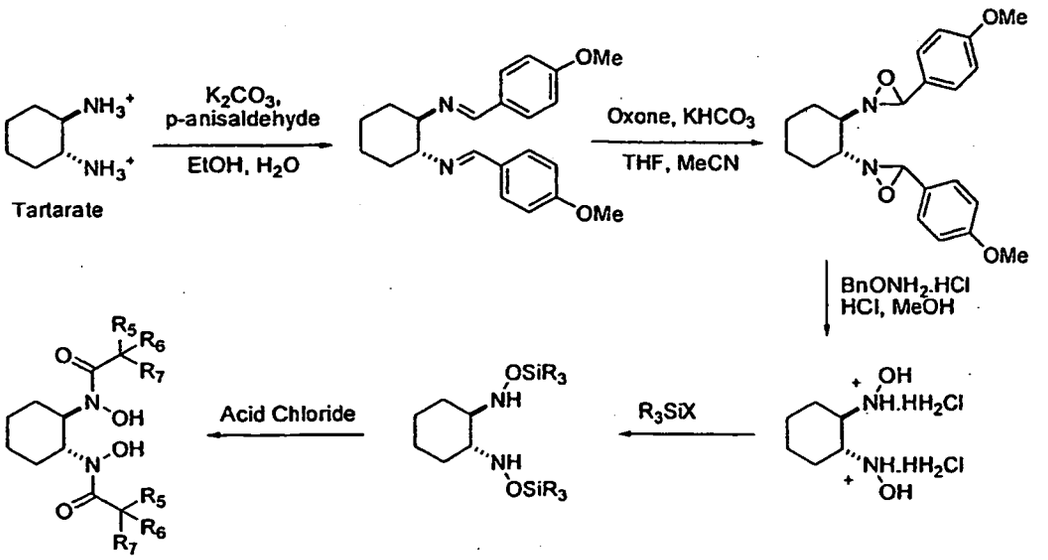


IV , V , VI ,



VII , VIII , and IX

[0071] In another embodiment, the chiral bishydroxamic acid ligand can be prepared by condensing an optically active 1,2-diammonium tartarate with p-anisaldehyde to provide a di-imine, which in turn is oxidized to produce a dioxadirizine. The dioxadirizine is then hydrolyzed to generate a dihydroxylamine hydrochloride. Subsequent, silylation of the dihydroxylamine hydrochloride provides a silyl protected dihydroxlamine, which is then condensed with an acid chloride to produce a chiral bishydroxamic acid ligand. The R group of R_3SiX is typically an alkyl, while the X group can be selected from the group consisting of halo and triflate.

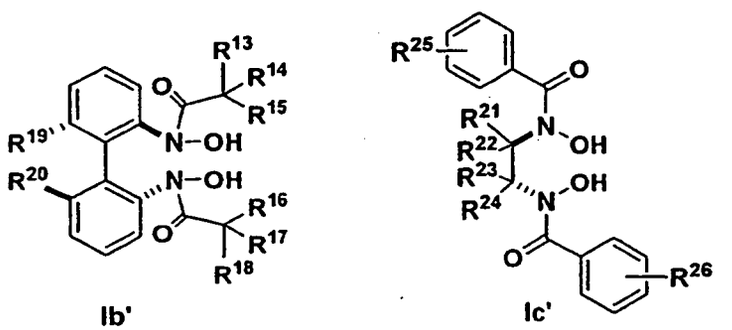


[0072] This synthetic route will provide chiral bishydroxamic acid ligands, wherein -Z- is -C(O)- and the ethylene backbone is part of a cyclohexane ring.

[0073] The R^7 and R^9 substituents, along with the atoms to which they are attached, form a cyclohexane ring, while R^8 and R^{10} are hydrogen.

[0074] The identity of R^1, R^2, R^3, R^4, R^5, and R^6 depend on what acid chloride is condensed with the dihydroxylamine.

[0075] Examples of additional generic chiral bishydroxamic acid ligands include the following compounds:



[0076] With regard to compounds **Ib'** and **Ic',** R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.

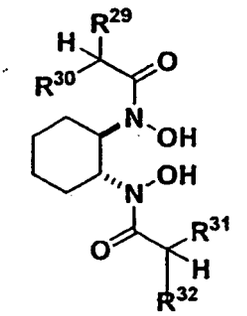
[0077] The R^{19} and R^{20} substituents are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.

[0078] The R^{21}, R^{22}, R^{23}, and R^{24} substituents are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.

[0079] The R^{25} and R^{26} substituents are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.

[0080] It will be apparent to one skilled in the art that the two hydroxamic acids may be connected by more than two atoms. Compound **Ib'** would be an example of one such ligand. In compound **Ib',** the hydroxamic acids are separated by four carbon atoms which are members of a biphenyl backbone. Another example would be a bishydroxamic acid, where the hydroxamic acids are connected to a binaphthyl backbone. Furthermore, the atoms connecting the two hydroxamic acids can be atoms other than carbon, as long as the overall ligand is capable of imparting chirality to the catalytically active species.

[0081] In a more preferred embodiment, the chiral bishydroxamic acid ligand has the following structure **(Id')**:



Id'

[0082] In chiral bishydroxamic acid ligand **Id',** R^{29}, R^{30}, R^{31}, and R^{32} are each independently selected from the group consisting of alkyl ,cycloalkyl, aryl, and arylalkyl. It is important to note that high enantiomeric excesses have resulted when the chiral bishydroxamic acid ligand has had this general structure.

Metal

[0083] In the present invention, the metal can be vanadium (IV) or vanadium (V). Additionally, the metal can be molybdenum (IV), or molybdenum (V). In a preferred embodiment, the metal is selected from the group consisting of $VO(OPr^i)_3$, $VO(acac)_2$, $VO(OEt)_3$, and $MoO(acac)_2$.

Oxidation Reagent

[0084] In the present invention the oxidation is performed by an oxidation reagent. In one embodiment, the oxidation reagent is an organic hydroperoxide. This compound can be represented by the following formula **(II):**

$$R^{11}\text{-O-OH} \qquad \text{II}$$

[0085] The R^{11} substituent is selected from the group consisting of alkyl, cycloalkyl, and arylalkyl.

[0086] Examples of organic hydroperoxides include, but are not limited to, tert-butyl hydroperoxide, α,α-dimethylheptyl hydroperoxide, bis-diisobutyl-2,5-dihydroperoxide, 1-methylcyclohexyl hydroperoxide, cumene hydroperoxide, cyclohexyl hydroperoxide, and trityl hydroperoxide.

[0087] In a preferred embodiment the organic hydroperoxide is selected from the group consisting of tert-butyl hydroperoxide and cumene hydroperoxide.

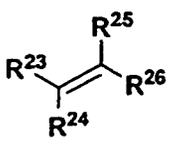
[0088] In another embodiment the oxidation reagent is hydrogen peroxide.

Substrate

[0089] The present invention can be employed in conjunction with a variety of substrates selected from the group consisting of alkene, cyclic alkene and sulfide.

[0090] Additionally, each one of these substrates can be substituted or unsubstituted and can also be a member of a ring.

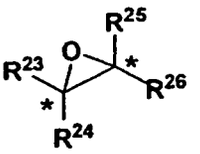
[0091] The present invention can be performed with an alkene substrate. Such an alkene can be represented by the following formula (**X**):



X

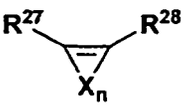
[0092] Substrate **X**, illustrates a potential alkene substrate where the R^{23}, R^{24}, R^{25}, and R^{26} substituents are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.

[0093] This more detailed representation of an alkene substrate, illustrates application of the present invention to an alkene (**X**) substrate, wherein the oxidation is carried out using catalytic amounts of a chiral bishydroxamic acid (**I**) and a metal in the presence of an organic hydroperoxide. The asymmetric oxidation of the alkene provides a chiral oxidation product, in the form of a chiral epoxide (**XII**).



XII

[0094] The present invention can also be used in combination with cyclic alkenes, such as **Xa.**



Xa

[0095] The substituents, R^{27} and R^{28}, are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, aralklyl, heteroaryl, halogen, and alkene.

[0096] The size of the ring is based on the value of n, which can be 1, 2, 3, 4, 5, 6, or 6. For example, when n is 1, the cyclic olefin is a 3-membered ring, with one X group. If n is 2, then the cyclic olefin is a 4-membered ring, with two X groups, and so on.

[0097] Each occurrence of X is independently selected from the group consisting of $-CR^{29}R^{30}-$, $-NR^{31}-$, and -O-, where R^{29}, R^{30}, and R^{31} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, aralklyl, heteroaryl, halogen, and alkene.

[0098] In another embodiment, the substrate is a sulfide.

[0099] It is important to note that one in the art would realize that, as with most organic reactions, this reaction can be performed with a variety of substrates. Furthermore, slight modifications of the substrate will often allow for optimization of the yield and the enantioselectivity.

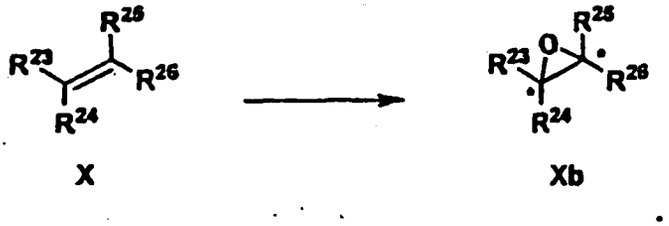
Chiral Oxidation Product

[0100] In one embodiment, the chiral oxidation product can be represented as follows:

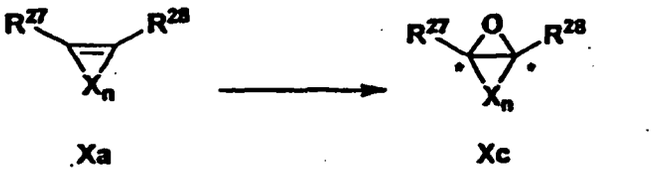
III

where Y is a sulfide substrate.

[0101] In another embodiment, the chiral oxidation product, as it is derived from alkene substrate X is shown below:



[0102] In another embodiment, the chiral oxidation product, as it is derived from alkene substrate Xa is shown below:



[0103] One skilled in the art will realize that the chiral oxidation product will vary depending on the substrate which is used. For example, when the substrate is a sulfide, the chiral oxidation product will be a sulfoxide. In another example, when the substate is an alkene, the chiral oxidation product will be an epoxide.

Reaction Conditions

[0104] The present invention is typically carried out in a solvent. Organic solvents are preferred. More preferrably, the reaction is carried out in a solvent selected from the group consisting of methylene chloride, toluene, chloroform, and ethyl acetate.

[0105] The present invention can be performed at a variety of temperatures. In a preferred embodiment the reacting step is carried out at a temperature of about -20 ˚C to about 25 ˚C.

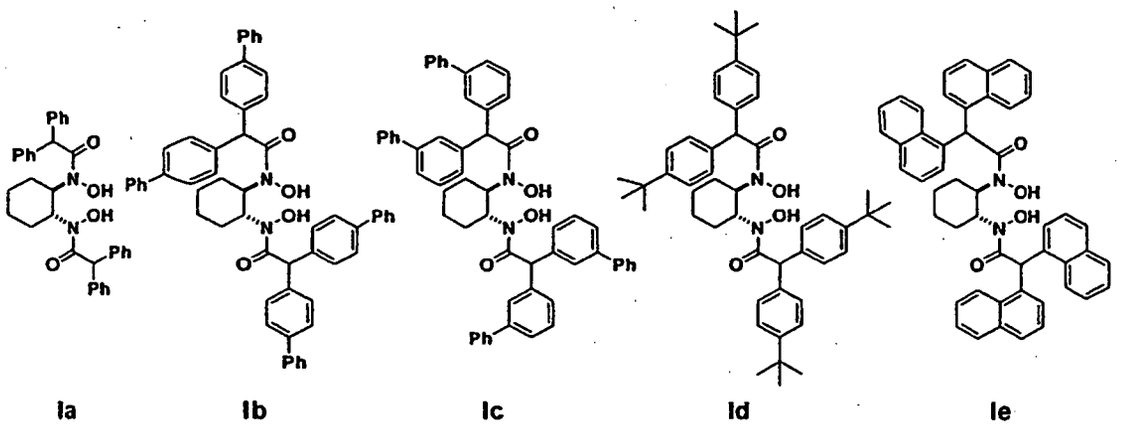
[0106] Furthermore, the reaction disclosed herein is performed with various amounts of the chiral bishydroxamic acid ligand and the metal. In one preferred embodiment the reaction is carried out with about 0.001 to about 0.1 equivalents of the chiral bishydroxamic acid ligand. In another preferred embodiment, the reaction is carried out with about 0.005 to about 0.05 equivalents of the metal.

[0107] It is important to note that one skilled in the art would realize that optimization of the yield and the enantioselectivity can be achieved by altering the reaction conditions. For example, such optimization can include changing the solvent, the temperature of various stages of the reaction, the equivalents of the chiral bishydroxamic acid ligand, and the equivalents of the metal.

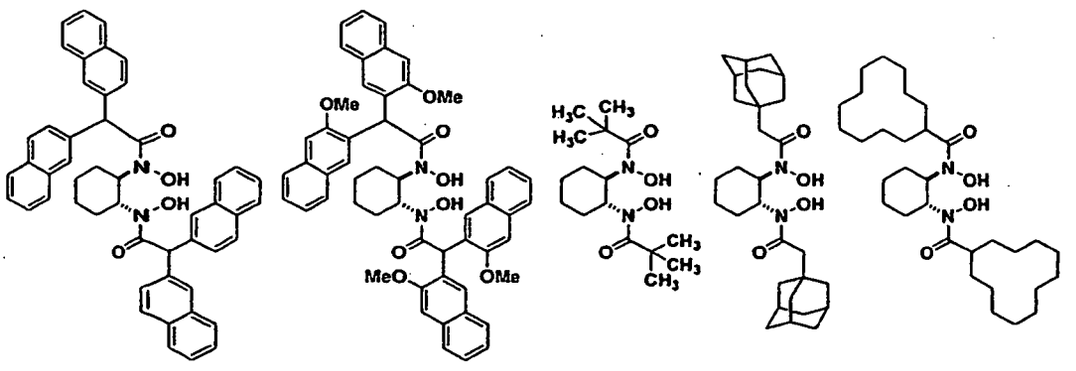
Examples - Scope of the Invention

[0108] The following tables further demonstrate the scope of the invention.

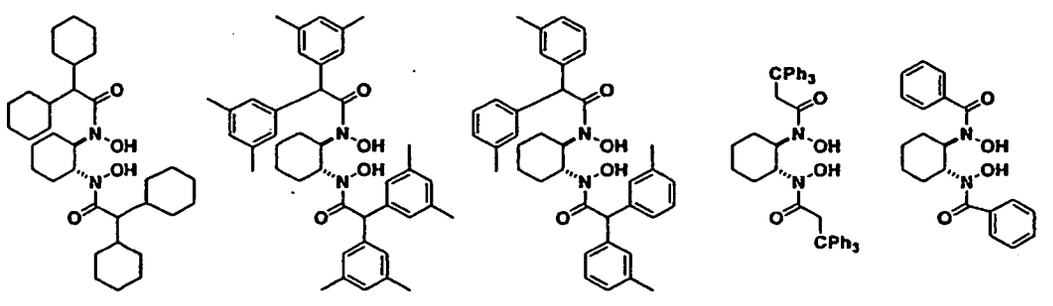
[0109] The ligands, referred to as **Ia** thru **Io** in the following tables, are shown below. These compounds can be made using the procedures provided in the synthetic examples section. It is important to note, that these ligands are illustrative of possible chiral bishydroxamic acid ligands. However, this list is in no way limiting.



Ia Ib Ic Id Ie



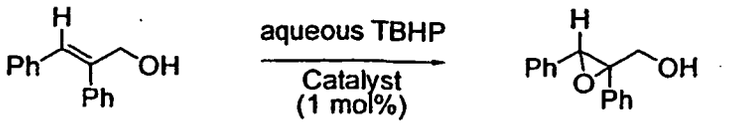
If Ig Ii Ij Ik



Il Im In Io Ip

[0110] Table 1, demonstrates that the catalytic asymmetric oxidation, disclosed herein, can be performed with a variety of chiral bishydroxamic acid ligands. In fact, the results above reveal that this reaction will provide enantiomeric excesses with a wide range of chiral bishydroxamic acid ligands. This table also reveals that this reaction can be employed to epoxidize trans-2,3-diphenyl-2-propenol. It is important to note that one skilled in the art would realize that changing the identity and characteristics of the chiral bishydroxamic acid ligand will provide a means of optimizing both the enantiomeric excess and the yield of this reaction. Furthermore, Table 1 demonstrates that the reaction can be successfully carried out in both methylene chloride and toluene.

Table 1. Epoxidation of trans-2,3-diphenyl-2-propenol.

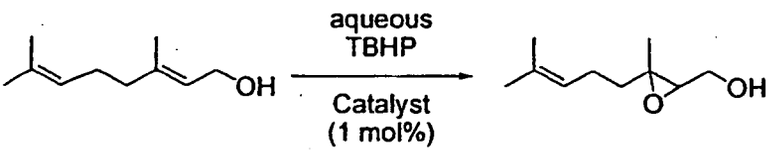


Example	Ligand	Ligand:NO(OPr^i)$_3$	Solvent	Temp/time	% Yield	%ee(config)
1	**Ia**	2.0:1.0	Toluene	0 ˚C, 15 h	87	94 (*RR*)
2	**Ib**	2.0:1.0	Toluene	0 ˚C, 12 h	77	91 (*RR*)
3	**Ic**	2.0:1.0	Toluene	0 ˚C, 12 h	81	94 (*RR*)
4	**Id**	2.0:1.0	Toluene	0 ˚C, 12 h	95	93 (*RR*)
5	**Ie**	1.0:1.0	Toluene	0 ˚C, 1 h	23	92 (*RR*)
6	**If**	2.0:1.0	Toluene	0 ˚C, 11 h	100	92 (*RR*)
7	**Ig**	2.0:1.0	Toluene	0 ˚C, 14.5 h	74	86 (*RR*)
8	**Ii**	1.5:1.0	Toluene	0 ˚C, 12 h	43	5 (*RR*)
9	**Ij**	1.5:1.0	Toluene	0 ˚C, 12 h	79	96 (*RR*)
10	**Ik**	2.0:1.0	CH_2Cl_2	0 ˚C, 20 h	76	98 (*RR*)
11	**Il**	2.0:1.0	CH_2Cl_2	0 ˚C, 20 h	75	99 (*RR*)
12[a]	**Im**	2.0:1.0	CH_2Cl_2	0 ˚C, 9 h	78	91 (*RR*)
13[a]	**In**	2.0:1.0	CH_2Cl_2	0 ˚C, 9 h	84	94 (*RR*)
14	**Io**	2.0:1.0	Toluene	0 ˚C, 18 h	88	90 (*RR*)

[a] anhydrous TBHP solution in CH_2Cl_2 was used.

[0111] Table 2, demonstrates the amenability of this reaction to the epoxidation of a substrate containing multiple alkenes. In fact, the reaction shows selectivity for the allylic alkene. Table 2, also shows that good yields and enantiomeric excesses can be obtained with a large variety of chiral bishydroxamic acid ligands.

Table 2. Epoxidation of Geraniol.



Example	Ligand	Ligand/VO(OPr^i)$_3$	Solvent	Temp/time	% Yield	%ee
1	**Ia**	2.0:1.0	Toluene	0 ˚C, 2 h	50	76
2	**Ib**	2.0:1.0	Toluene	0 ˚C, 24 h	60	63
3	**Ic**	2.0:1.0	Toluene	0 ˚C, 24 h	71	67
4	**Id**	2.0:1.0	Toluene	0 ˚C, 24 h	44	56
5	**If**	2.0:1.0	Toluene	0 ˚C, 5 h	90	76
6	**Ig**	2.0:1.0	Toluene	0 ˚C, 14 h	66	72
7	**Ij**	1.5:1.0	Toluene	0 ˚C, 19 h	47	63
8	**Ik**	2.0:1.0	CH_2Cl_2	0 ˚C, 20 h	70	74
9[a]	**Il**	2.0:1.0	CH_2Cl_2	-10 ˚C, 18 h	60	84
10[a]	**Im**	2.0:1.0	CH_2Cl_2	0 ˚C, 9 h	67	83
11[a]	**In**	2.0:1.0	CH_2Cl_2	0 ˚C, 3 h	37	81
12	**Io**	2.0:1.0	Toluene	0 ˚C, 18 h	74	80
13[a]	**Im**	2.0:1.0	CH_2Cl_2	-10 ˚C, 7 h	31	85
14[a]	**In**	2.0:1.0	CH_2Cl_2	-10 ˚C, 7 h	38	84
15[a]	**Im**	2.0:1.0	CH_2Cl_2	-20 ˚C, 24 h	42	89
16[a]	**In**	2.0:1.0	CH_2Cl_2	-20 ˚C, 24 h	49	88

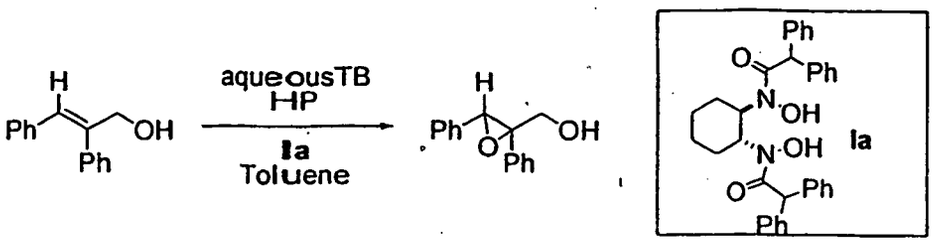
(continued)

Example	Ligand	Ligand/$VO(OPr^i)_3$	Solvent	Temp/time	% Yield	%ee
17	**Io**	2.0:1.0	CH_2Cl_2	0 ˚C, 18 h	73	83

[a] anhydrous TBHP solution in CH_2Cl_2 was utilized.

[0112] Table 3 reveals that this catalytic asymmetric oxidation can be run under a variety of reaction conditions, including a broad range of temperatures. One skilled in the art will realize that changing conditions such as the vanadium source, the temperature, the oxidant, and the ligand to metal ratio will allow optimization of both the yield and the enantiomeric excess. Furthermore, the results provided above demonstrate that both CHP and TBHP can be employed as the hydroperoxide oxidant.

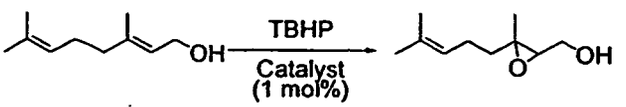
Table 3. The Effect of Variations in Reaction Conditions.



Example	Vanadium	Vandium:Ia	Oxidant	Temp/time	Yield	%ee (config)
1	$VO(OPr^i)_3$	1.0:1.0	CHP	rt, 4 h	93	84 (*RR*)
2	$VO(OPr^i)_3$	1.0:1.0	TBHP	rt, 12 h	94	88 (*RR*)
3	$VO(OPr^i)_3$	1.0:1.0	TBHP	0 ˚C, 6 h	84	94 (*RR*)
4	$VO(OPr^i)_3$	1.0:1.0	TBHP	-20 ˚C, 40 h	84	97 (*RR*)
5	$VO(OPr^i)_3$	1.0:2.0	TBHP	rt, 6 h	96	92 (*RR*)
6	$VO(OPr^i)_3$	1.0:2.0	TBHP	0 ˚C, 15 h	87	95 (*RR*)
7	$VO(OPr^i)_3$	1.0:2.0	TBHP	-20 ˚C, 30 h	89	96 (*RR*)
8	$VO(OPr^i)_3$	1.0:3.0	TBHP	rt, 6 h	96	92 (*RR*)
9	$VO(OPr^i)_3$	1.0:3.0	TBHP	0 ˚C, 15 h	86	94 (*RR*)
10	$VO(acac)_2$	1.0:1.0	TBHP	rt, 6 h	96	90 (*RR*)
11	$VO(acac)_2$	1.0:1.0	TBHP	0 ˚C, 12 h	93	94 (*RR*)
12	$VO(acac)_2$	1.0:1.0	TBHP	-20 ˚C, 40 h	81	97 (*RR*)
13	$VO(acac)_2$	1.0:2.0	TBHP	rt, 6 h	96	92 (*RR*)
14	$VO(acac)_2$	1.0:2.0	TBHP	0 ˚C, 12 h	90	95 (*RR*)
15	$VO(acac)_2$	1.0:2.0	TBHP	-20 ˚C, 30 h	85	96 (*RR*)
16	$VO(acac)_2$	1.0:3.0	TBHP	0 ˚C, 6 h	95	90 (*RR*)
17	$VO(aCaC)_2$	1.0:3.0	TBHP	rt, 12 h	84	93 (*RR*)

[0113] Table 4 shows that the reaction can be performed under a variety of reaction conditions. These results also reveal that the reaction can be carried out under aqueous conditions, since aqueous hydroperoxide provided both good yields and enantiomeric excesses.

Table 4. Epoxidation of Geraniol: The Effect of Variations of the Oxidant, the Solvent, and the Vanadium Source.



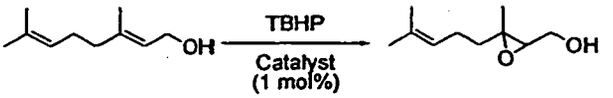
(continued)

	Complexation of the Ligand and Vanadium				*Oxidation Conditions*			
Entry	Ligand	Vanadium	Ligand to Vanadium	Solvent Temp/ time	Oxidant	Temp/time	Yield	%ee
1	**Ia**	$VO(OPr^i)_3$	1.5:1.0	Toluene, rt, 1 h	Trityl hydroperoxide	0 ˚C, 68 h	40%	15
2	**Ia**	$VO(OEt)_3$	1.5:1.0	Toluene, rt, 1 h	Aqueous TBHP	0 ˚C, 19 h	41%	68
3	**Ia**	$VO(OPr^i)_3$	1.5:1.0	Toluene, rt, 1 h	Aqueous TBHP	0 ˚C, 19 h	80%	72
4[a,b]	**Ia**	$VO(OPr^i)_3$	1.5:1.0	CH_2Cl_2,[a] rt, 1 h	Anhydrous TBHP	0 ˚C, 19 h	85%	78
5	**II**	$VO(OPr^i)_3$	2.0:1.0	Toluene, rt, 1 h	Aqueous TBHP	-1.0 ˚C, 18 h	65%	76
6[a]	**II**	$VO(OPr^i)_3$	2.0:1.0	CH_2Cl_2, rt, 1 h	Anhydrous TBHP	-10 ˚C, 18 h	60%	84

[a] Oxidation was performed under an atmosphere of nitrogen. Anhydrous TBHP in CH_2Cl_2 was utilized for the oxidation.
[b] solution of the ligand in CH_2Cl_2 was heated heated with hot gun prior to addition of the vanadium isopropoxide and then stirred at room temperature for 1 h

[0114] Table 5 explores how different oxidants, solvents and vanadium sources influence the yield and the enantiomeric excess of this asymmetric oxidation. The results in Table 5 show that the reaction can be successfully carried out with not only $VO(Opr^i)_3$ and $VO(acac)_3$, but also with $VO(OEt)_3$. This data also reveals that the reaction is compatible with toluene, methylene chloride, and ethyl acetate.

Table 5. Epoxidation of Geraniol: The Effect of Variations of the Oxidant, the Solvent, and the Vanadium Source.



	Complexation of the Ligand and Vanadium					***Oxidation Conditions***			
Entry	Ligand	Vanadium	Ligand/ Vanadium	Solvent	Temp/ time	Oxidant	Temp/time	Yield	%ee[b]
1	**Io**	$VO(OPr^i)_3$	2.0:1.0	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 18 h	74%	81
2	**Io**	$VO(OPr^i)_3$	2.0:1.0	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 18 h	73%	83
3	**Io**	$VO(OPr^i)_3$	2.0:1.0	$CHCl_3$	rt, 1 h	Aqueous TBHP	0 ˚C, 18 h	71%	77
4	**Io**	$VO(OPr^i)_3$	2.0:1.0	EtOAc	rt, 1 h	Aqueous TBHP	0˚C, 18 h	34%	76
5	**Io**	$VO(OPr^i)_3$	2.0:1.0	DMF	rt, 1 h	Aqueous TBHP	0 ˚C, 18 h	-[a]	-
6	**Io**	$VO(OPr^i)_3$	2.0:1.0	Toluene	rt, 1 h	Anhydrous TBHP	0 ˚C, 18 h	70%	81
7	**Io**	$VO(OPr^i)_3$	2.0:1.0	CH_2Cl_2	rt, 1 h	Anhydrous TBHP	0˚C, 18 h	30%	79
8	**Io**	$VO(OEt)_3$	2.0:1.0	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 18 h	90%	83

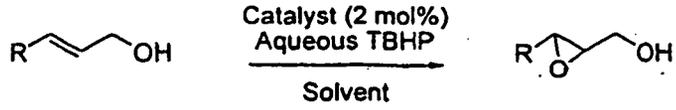
(continued)

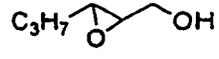
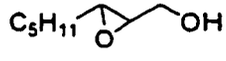
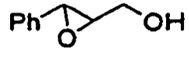
	Complexation of the Ligand and Vanadium					*Oxidation Conditions*			
Entry	Ligand	Vanadium	Ligand/ Vanadium	Solvent	Temp/ time	Oxidant	Temp/time	Yield	%ee[b]
9	**Io**	$VO(acac)_2$	2.0:1.0	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 18 h	80%	83
10	**Io**	$VO(OPr^i)_3$	2.0:1.0	Toluene	rt, 1 h	Aqueous TBHP	-20 ˚C, 43 h	57%	80
11	**Io**	$VO(OPr^i)_3$	2.0:1.0	CH_2Cl_2	rt, 1 h	Aqueous TBHP	-20 ˚C, 43 h	38%	80
12	**Io**	$VO(acac)_2$	2.0:1.0	Toluene	rt, 1 h	Aqueous TBHP	-20 ˚C, 69 h	54%	79
13	**Io**	$VO(acac)_2$	2.0:1.0	CH_2Cl_2	rt, 1 h	Aqueous TBHP	-20 ˚C, 69 h	60%	78

[a] No product was observed in TLC

[0115] Table 6 reveals that several different chiral bishydroxamic acid ligands can be utilitzed to epoxidize cinnamyl alcohol. In each case high enantioselectivies were achieved with respect to the desired epoxidation product.

Table 6. Epoxidation of trans disubstituted allylic alcohols.

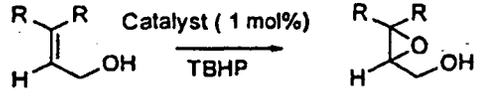


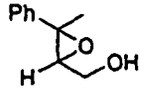
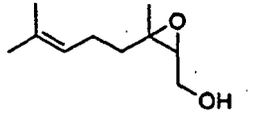
		Complexation of the Ligand and Vanadium					*Oxidation Conditions*		
Example	Product	Ligand	Vanadium	Solvent	Temp/time	Oxidant	Temp/time	%Yield	%ee
1		**Ia**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 45 h	50[a]	93
2		**Io**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 45 h	59[a]	77
3		**Ia**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 49 h	40%	92
4		**Io**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 49 h	55%	78
5		**Ia**[b]	$VO(acac)_2$	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 43 h	45%[a]	95
6		**Ia**	$VO(acac)_2$	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 69 h	33%	93
7		**Ia**	$VO(acac)_2$		rt, 1 h	Aqueous TBHP	0 ˚C, 69 h	40%	94
8		**Ik**[b]	$VO(OPr^i)_3$	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 43 h	49%[a]	83
9		**Io**[b]	$VO(acac)_2$	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 48 h	40%[a]	84

[a] determined by 1 H NMR analysis of the unpurified product. [b]Catalyst 1 mol%

[0116] Table 7 explores the ability of this asymmetric oxidation to epoxidize nerol and (*E*)-3-phenylbut-2-en-1-ol. In this case, enantiomeric excesses, in conjunction with high yields, were obtained with regard to the epoxidation of the allylic alkene. Furthermore, these successful results were obtained with a number of different chiral bishydroxamic acid ligands.

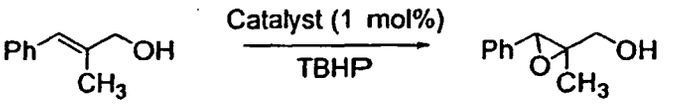
Table 7. Epoxidation of Nerol and (*E*)-3-phenylbut-2-en-1-ol.



			Complexation of the Ligand and Vanadium				***Oxidation Conditions***		
Entry	Product	Ligand	Vanadium	Solvent	Temp/ time	Oxidant	Temp/time	%Yield	%
1		**Ia**	$VO(acac)_2$	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 20.5 h	8[a]	8
2		**Io**	$VO(acac)_2$	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 20.5 h	23[a]	8
3		**Ia**	$VO(OPr^i)_3$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 22 h	36	8
4		**Io**	$VO(OPr^i)_3$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 22 h	81	9
5		**Il**	$VO(OPr^i)_3$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 18 h	83	8
6		**Ia**	$VO(acac)_2$	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 20.5 h	83	7
7		**Io**	$VO(acac)_2$	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 20.5 h	82	8
8		**In**	$VO(OPr^i)_3$	CH_2Cl_2	rt, 1 h	Anhydrous TBHP	0˚C, 18 h	92	8
9		**If**	$VO(OPr^i)_3$	CH_2Cl_2	rt, 1 h	Anhydrous TBHP	0 ˚C, 10 h	96	8

[0117] Table 8 provides results for the epoxidation of α-methylcinnamyl alcohol. In this case, both high yields and enantiomeric excesses were obtained with a number of different chiral bishydroxamic acid ligands.

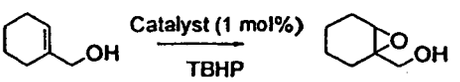
Table 8. Epoxidation of α-Methylcinnamyl Alcohol.



Entry	Ligand	Vanadium Source	Catalyst loading	Oxida nt	Solvent Temp/time	Isolated Yield %ee	
1	**Ia**	$VO(acac)_2$	1 mol %	Aqueous TBHP	Toluene, 0 ˚C, 44 h	76 %	95
2	**Io**	$VO(acac)_2$	1 mol %	Aqueous TBHP	Toluene, 0˚C, 44 h	86%	87
3	**In**	$VO(OPr^i)_3$	1 mol %	Anhydrous TBHP	CH_2Cl_2 0 ˚C, 18 h	92 %	93
4	**If**	$VO(OPr^i)_3$	1 mol %	Anhydrous TBHP	CH_2Cl_2 0 ˚C, 10 h	96%	90
5	**Il**	$VO(OPr^i)_3$	1 mol %	Aqueous TBHP	CH_2Cl_2 0 ˚C, 17 h	88 %	95

[0118] Table 9 demonstrates that this reaction can be successfully applied to cyclic alkene substrates, in this case cyclohex-1-enyl-methanol. In fact, high enantiomeric excess were obtained , in good yields, with three different chiral bishydroxamic acid ligands.

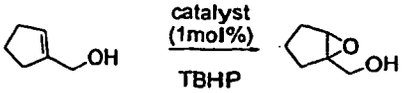
Table 9. Epoxidation of Cyclohex-1-enyl-methanol.



	Complexation of the Ligand and Vanadium					***Oxidation Conditions***			
Entry	Ligand	Vanadium	Ligand/ Vanadium	Solvent	Temp/ time	Oxidant	Temp/time	Yield	%ee
1	**Ia**	$VO(acac)_2$	2.0:1.0	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 21.5 h	66	**93**
2	**Io**	$VO(acac)_2$	2.0:1.0	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 21.5 h	76	73
3	**Il**	$VO(OPr^i)_2$	2.0:1.0	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 17 h	59	88
4	**If**	$VO(OPr^i)_3$	2.0:1.0	CH_2Cl_2	rt, 1 h	Anhydrous TBHP	0 ˚C, 12 h	94%	92

[0119] Table 10 reveals that the reaction disclosed herein can also successfully epoxidize a five membered cyclic alkene.

Table 10. Epoxidation of Cyclopent-1-enyl-methanol.

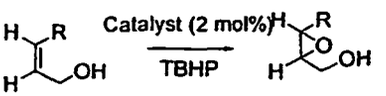


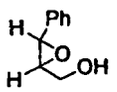
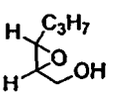
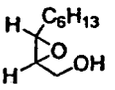
(continued)

		Complexation of the Ligand and Vanadium					*Oxidation Conditions*		
Entry	Ligand	Vanadium	Ligand/ Vanadium	Solvent	Temp/ time	Oxidant	Temp/time	Yield	%ee
1	**Ia**	$VO(acac)_2$	2.0:1.0	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 20.5 h	52%	90
2	**Io**	$VO(acac)_2$	2.0:1.0	Toluene	rt, 1 h	Aqueous TBHP	0 ˚C, 20.5 h	72%	75
3	**If**	$VO(OPr^i)_3$	2.0:1.0	CH_2Cl_2	rt, 1 h	Anhydrous TBHP	0 ˚C, 10 h	94%	69
4	**Im**	$VO(OPr^i)_3$	2.0:1.0	CH_2Cl_2	rt, 1 h	Anhydrous TBHP	0 ˚C, 18 h	95%	78

[0120] Table 11 demonstrates that a cis-alkene can be utilized as the epoxidation substrate. The data shows that the yield may vary with changes in the nature of the bishyroxamic acid ligand. However, it appears that drastic changes in the character of the chiral bishydroxamic acid ligand may have only a minimal influence with respect to the enantiomeric excess.

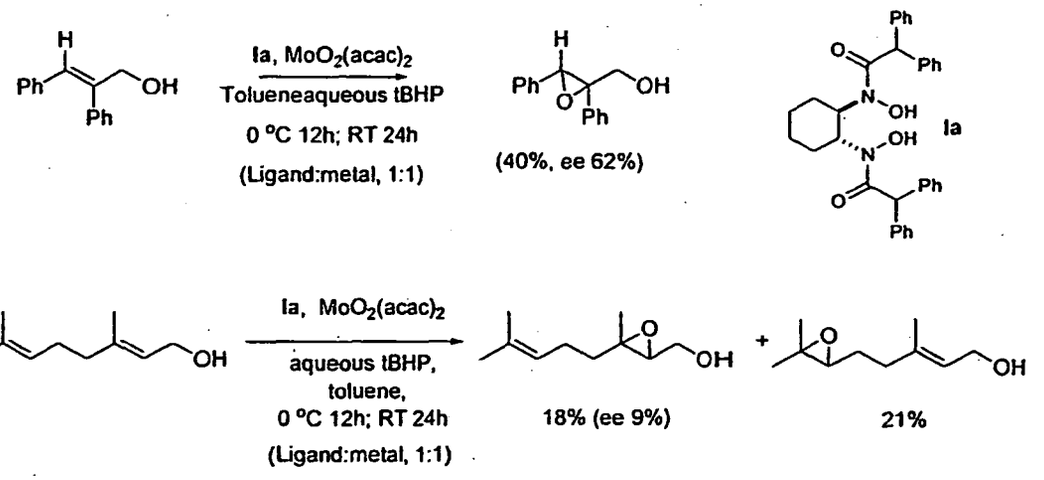
Table 11. Epoxidation of (Z)-Hex-2-en-ol.



		Complexation of the Ligand and Vanadium					*Oxidation Conditions*		
Entry	**Ligand**		**Vanadium**	**Solvent**	**Temp/ time**	**Oxidant**	**Temp/ time**	**%Yield**	**%ee**
1		**Ia**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0˚C, 5 days	11	74
2		**Io**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0˚C, 5 days	55	91
3		**Io**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	RT, 26 h	68	89
4		**II**	$VO(OPr^i)_3$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0˚C, 5 days	49	87
5		**Ia**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0 ˚C, 92 h	28	80
6		**II**	$VO(OPr^i)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0˚C, 92 h	50	87
7		**Io**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	RT, 21 h	89	91
8		**Io**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0˚C, 46 h	64	93
9		**Io**	$VO(acac)_2$	CH_2Cl_2	rt, 1 h	Aqueous TBHP	0˚C, 46 h	60%	95

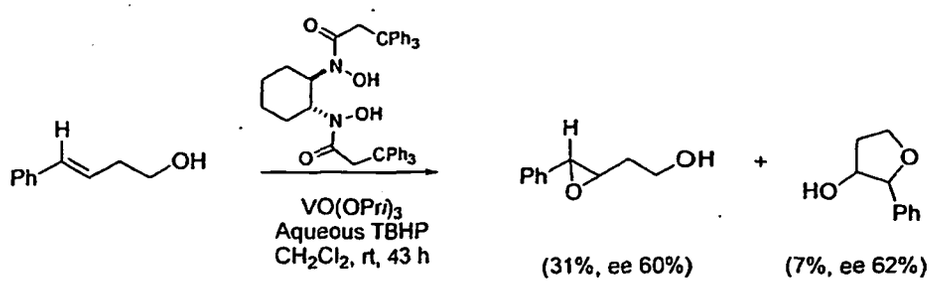
[0121] Table 12 demonstrates that the epoxidation of trans-2,3-diphenyl-2-propenol and geraniol can be successfully carried out using molybdenum as the metal, in this case $MoO(acac)_2$.

Table 12. Molybdenum Catalyzed Epoxidation.



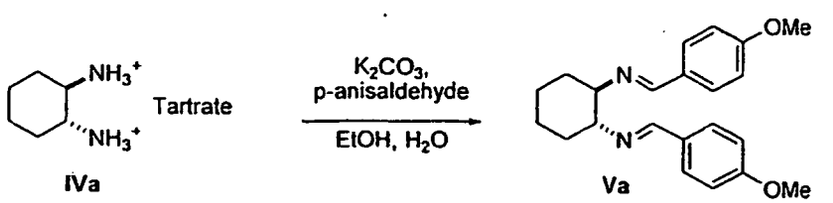
[0122] Table 13 shows that this reaction is also capable of successfully epoxidizing homoallylic alcohols.

Table 13. Epoxidation of Homoallylic Alcohol.



Synthetic and Spectroscopic Examples

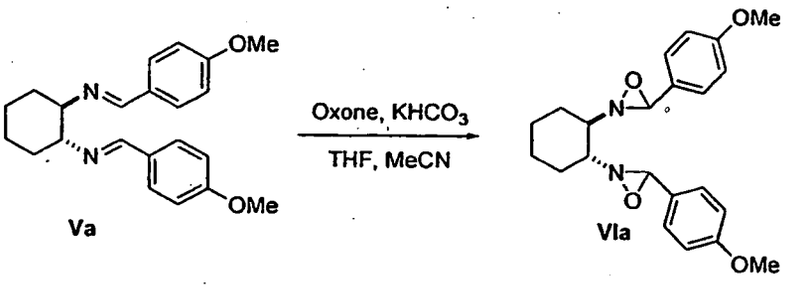
[0123] Example 1. The preparation (*R,R*)-*N, N'- Bis*-(4-methoxybenzylidene)-cyclohexane-1,2-diamine **(IVa)** is shown below.



[0124] In this preparation, a mixture of diammonium salt **(IVa)** (21.2 g, 80.1 mmol), K_2CO_3 (22.1 g, 160 mmol), and de-ionized water (107 mL) was stirred until dissolution was achieved, and then ethanol (429 mL) was added. The resulting cloudy mixture was heated at 80 °C, and a solution of *p*-anisaldehyde (21.8 g, 160 mmol) in ethanol (36 mL) was added in a steady stream over 30 min. The yellow slurry was stirred at the same temperature for 5 h before heating was discontinued. The reaction mixture was cooled to room temperature, and the water phase was separated and discarded. The organic phase was concentrated and toluene was added to the residue. It was then concentrated to remove any traces of water. The resulting residue was dissolved in chloroform, dried (Na_2SO_4) and filtered. The filtrate was evaporated to give crude **Va** as light yellow solid, which was purified by recrystalization from chloroform and hexanes: R_f 0.6 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 2929, 2855, 1643, 1606, 1579, 1512, 1463, 1303, 1250, 1165, 1032, 831 cm^{-1}; ^1H NMR

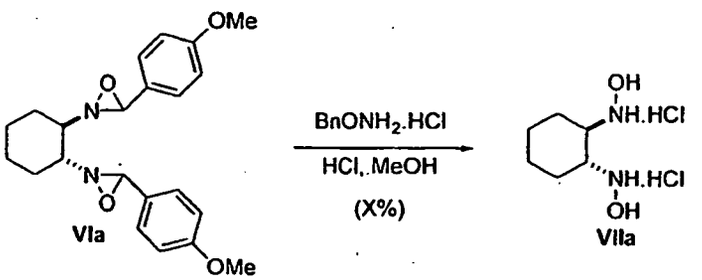
(500 MHz, $CDCl_3$) δ 8.13 (s, 2 H), 7.52 (d, *J* = 8.5 Hz, 4 H), 6.83 (d, *J* = 8.5 Hz, 4 H), 3.79 (s, 6 H), 3.37-3.32 (m, 2 H), 1.87-1.77 (m, 6 H), 1.49-1.46 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (C), 160.5 (CH), 129.7 (CH), 114.0 (CH), 74.0 (CH_3), 55.5 (CH), 33.3 (CH_2), 24.8 (CH_2). HRMS-ESI calcd for $C_{22}H_{27}O_6N_2$ $[M+H]^+$ 351.2073, found 351.2076.

[0125] Example 2. The preparation of Dioxaziridine **VIa** is shown below.



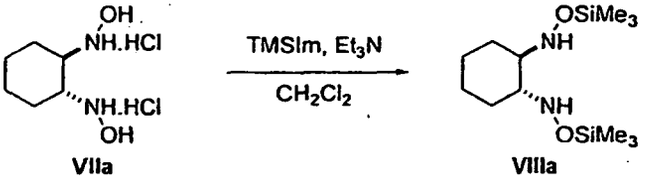
[0126] To a stirred solution of diimine **Va** (10.5 g, 30.0 mmol) in MeCN (180 mL) and THF (360 mL), at room temperature, was added an aqueous solution (300 mL) of $KHCO_3$ (50.5 g, 504 mmol) followed by an aqueous solution (300 mL) of oxone (44 g, 72 mmol). After stirring for 2 h 15 min, the reaction mixture was diluted with CH_2Cl_2 (600 mL). The biphasic mixture was separated and the aqueous portion was extracted with CH_2Cl_2 (2 x 300 mL) and the combined organic extracts dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to provide crude dioxaziridine **VIa** (11.1 g) which was used in the following step without further purification: Major diastereomer FTIR (film) υ_{max} 2935, 1615, 1517, 1309, 1456, 1437, 1310, 1252, 1171, 1031, 821, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.02-6.79 (m, 4 H), 6.59-7.6.56 (m, 4 H), 4.39 (s, 2 H), 3.81 (s, 6 H), 2.39-2.37(m, 2 H, CHH'), 2.22-2.20 (m, 2 H), 1.83-1.81 (m, 2 H), 1.58-1.51 (m, 2 H), 1.31-1.27 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (C), 129.0 (CH), 126.5 (C), 113.8 (CH), 81.6 (CH), 72.4 (CH_3/CH), 55.4 (CH_3/CH), 30.3 (CH_2), 24.1 (CH_2). HRMS-ESI calcd. for $C_{22}H_{26}O_4N_2Na$ $[M+Na]^+$ 405.1788, found 405.1790.

[0127] Example 3. The preparation of *Bis*-hydroxylamine dihydrochloride **VIIa** is shown below.



[0128] To a mixture of the unpurified product VIa (11.1 g) obtained from the previous oxidation reaction and benzyloxyhydroxyl amine hydrochloride ($BnONH_2$·HCl) (8.8 g, 55.1 mmol) was treated with anhydrous methanol (immediately) followed by 1 M HCl in MeOH (94 mL, 94 mmol). The resulting mixture was stirred for 20 minutes. The reaction mixture was then concentrated under reduced pressure to dryness. Et_2O (200 mL) and de-ionized water (100 mL) was added. The bi-layer was separated and the organic part was extracted with de-ionized water (20 mL). Combined aqueous portion was washed with Et_2O (2 x 100 mL). The aqueous portion was concentrated to 60-75 mL and resulting white solid ($BnONH_2$.HCl) was filtered off and the filtrate was concentrated under reduced pressure to provide bis-hydroxylamine dihydrochloride **VIIa** (6.95 g) as an oily solid which contained 5-10% of $BnONH_2$.HCl This material was utilized in the next step without any purification: ^1H NMR (400 MHz, D_2O) δ 3.66-3.62 (m, 2 H), 2.02-1.98 (m, 2 H), 1.69-1.66 (m, 2 H), 1.41-1.37 (m, 4 H), 1.20-1.15 (m, 2 H; ^{13}C NMR (100 MHz, D_2O) δ 58.6 (CH), 25.1 (CH_2), 22.1 (CH_2).

[0129] Example 4. Two methods for the preparation of (*R*,*R*)-O, *O*'-bistrimethylsilyl cyclohexyl-1,2-dihydroxylamine **(VIIIa)** are shown below as Method A and Method B.

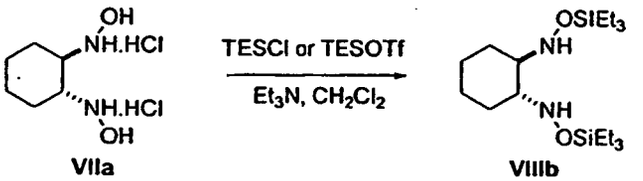


VIIa VIIIa

[0130] Method A: To a suspension of dihydroxylamine dihydrochloride **VIIa** (5.52 g, 25.2 mmol) in pentane (30 mL) at room temperature was added triethylamine (8.5 mL, 60.6 mmol) under nitrogen atmosphere. After stirring for 12 h at room temperature, the mixture was treated drop wise with 1-(trimethylsilyl)imidazole (TMSIm) (7.7 mL, 50.5 mmol) and stirred for another 9 h. The resulting suspension was filtrated through pad of Celite and the filtrate was concentrated under reduced pressure to give *O,O'*-bistrimethylsilylcyclohexyl-1,2-dihydroxylamine (**VIIIa**) as yellow oil (5.85 g, 80% yield), which was used in the following reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (br s, 2 H), 2.68-2.65 (m, 2 H), 2.19-2.15 (m, 2 H), 1.23-1.13 (m, 4 H), 0.14 (s, 18 H).

[0131] Method B: To a stirred suspension of **VIIa** (382 mg, 1.74 mmol) and pyridine (1 mL) in CH_2Cl_2 (4 mL) at room temperature was added Et_3N (384 μL, 2.75 mmol). After 15 min, trimethylsilyl imidazole (620 μL, 4.2 mmol) was added and stirring was continued for 16 h. The reaction mixture was then diluted pentane (15 mL) and filtered through a pad of celite. The filtrate was concentrated under reduced pressure to provide **VIIIa** (432 mg, 86%) which was used in the coupling reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (br s, 2 H), 2.68-2.65 (m, 2 H), 2.19-2.15 (m, 2 H), 1.23-1.13 (m, 4 H), 0.14 (s, 18 H).

[0132] Example 5. Three methods for the preparation of (*R,R*)-*O,O'*-bistriethylsilylcyclohexyl-1,2-dihydroxylamine **(XIIIb)** are shown below and are designated Method A, Method B, and Method C. When referring triethylsilyl chloride, it can be abbreviated as TESCl.



VIIa VIIIb

[0133] Method A: To a suspension of **VIIIa** (6.95 g) in CH_2Cl_2 (70 mL) at room was added Et_3N (12.6 mL, 90 mmol). After stirring 30 min, the reaction mixture was cooled to -30 ˚C, and 2,6-lutidine (17.4 mL, 150 mmol) then triethylsilyl trifluoromethanesulfonate (TESOTf) (34 mL, 150 mmol). After 2 min, the CO_2/acetone cooling bath was removed and the reaction mixture stirred for 6 h at room temperature, then poured into brine (10 mL) and extracted with CH_2Cl_2 (2 x 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1:99) to provide **VIIIb** (5.60 g, 50%) as a colorless oil: R_f 0.6 (EtOAc/hexanes, 1:9); FTIR (film) υ_{max} 2954, 2876, 1557, 1540, 1458, 1417, 1238, 1072, 1008, 883, 841, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (br s, 2 H), 2.66-2.63 (m, 2 H), 2.19-2.18 (m, 2 H), 1.71-170 (m, 2 H), 0.98 (t, J = 8.0 Hz, 18 H), 0.67 (q, J = 8.0 Hz, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.1 (CH), 30.6 (CH_2), 24.8 (CH_2), 7.11 (CH_3), 4.3 (CH_2). HRMS-ESI calcd for $C_{18}H_{42}O_2N_2Si_2Na$ [M+Na]$^+$ 397.2683, found 397.2690.

[0134] Method B: To a stirred suspension of **VIIa** (170 mg, 0.77 mmol) and pyridine (2 mL) in CH_2Cl_2 (1 mL) at room temperature was added Et_3N (215 μl, 0.15 mmol). After 30 min, triethylsilyl chloride (TMSCl) (775 μL, 4.62 mmol) was added and stirring was continued for 48 h, then poured into brine and extracted with CH_2Cl_2 (2 x 20 mL) The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (EtOAc/hexanes,0.5:99.5) to provide **VIIIb** (156 mg, 54%) as a colorless oil: R_f 0.6 (EtOAc/hexanes, 1:9); FTIR (film) υ_{max} 2954, 2876, 1557, 1540, 1458, 1417, 1238, 1072, 1008, 883, 841, 738 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$) δ 5.46 (br s, 2 H), 2.66-2.63 (m, 2 H), 2.19-2.18 (m, 2 H), 1.71-170 (m, 2 H), 0.98 (t, J = 8.0 Hz, 18 H), 0.67 (q, J = 8.0 Hz, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.1 (CH), 30.6 (CH_2), 24.8 (CH_2), 7.11 (CH_3), 4.3 (CH_2).

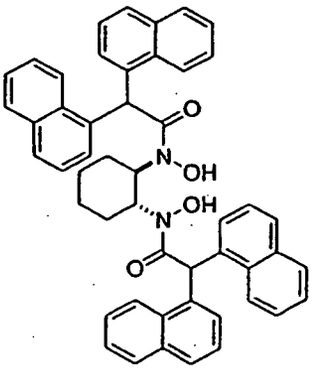
[0135] Method C: To a stirred suspension of **VIIa** (2.24 g, 10.2 mmol) in CH_2Cl_2 (40 mL) at room temperature was added Et_3N (3.70 mL, 25.6 mmol). After 1 h (to the resulting cloudy white suspension) dimethyl aminopyridine (DMAP) (374 mg, 3.06 mmol), imidazole (4.17 g, 61.4 mmol) followed by triethylsilyl chloride (6.90 mL, 40.9 mmol) were added and stirring was continued 16 h, then poured into an aqueous solution of $NaHCO_3$ (5.16 g, 61.4 mmol) and extracted

with EtOAc (2 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (EtOAc/hexanes, 0.5:99.5) to provide **VIIIb** (4.23g) which contained diethylsilyl ether as 1:1 mixture. This compound was kept under reduced pressure to remove diethylsilyl ether: R_f 0.6 (EtOAc/hexanes, 1:9); FTIR (film) υ_{max} 2954, 2876, 1557, 1540, 1458, 1417, 1238, 1072, 1008, 883, 841, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.46 (br s, 2 H), 2.66-2.63 (m, 2 H), 2.19-2.18 (m, 2 H), 1.71-170 (m, 2 H), 0.98 (t, J = 8.0 Hz, 18 H), 0.67 (q, J = 8.0 Hz, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.1 (CH), 30.6 (CH_2), 24.8 (CH_2), 7.11 (CH_3), 4.3 (CH_2).

[0136] Example 6. Three general procedures for condensation of the silyl protected dihydroxyl amine with an acid chloride are provided below and are labeled Method A, Method B, and Method C. The resulting product is a chiral bishydroxamic acid ligand. The corresponding spectroscopic data for some of the ligands synthesized with these methods are provided, following each of the methods below.

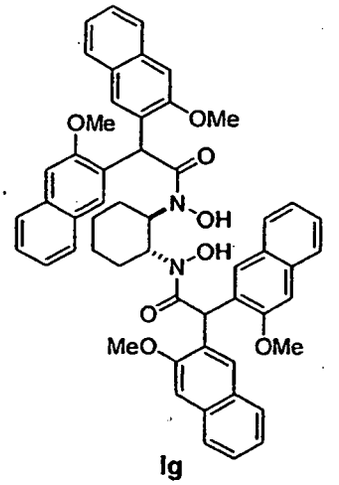
[0137] Method A: A mixture of the acid chloride (40.4 mmol) and lithium iodide (16.2 g, 121.2 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 6 h and then cooled to -10˚C to be treated drop wise with a solution of **VIII** (5.85 g, 20.2 mmol) and diisopropylethylamine (8.9 mL, 52.2 mmol) in CH_2Cl_2 (25 mL). After stirring for 12 h at room temperature, 3 M aqueous HCl was added and stirring was continued for 30 min. The mixture was then extracted with methylene chloride (2 x 50 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to provide the chiral bishydroxamic acid ligand (I).

[0138] Example 7. This example provides spectroscopic data for (*R,R*)-*N*-{2-[(2,2-Dinaphthalen-1-ylacetyl)-hydroxyamino]-cyclohexyl}-*N*-hydroxy-2,2-dinaphthalen-1-ylacetamide (Ie) (3% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 2 H), 7.98-7.14 (m, 28 H), 6.40 (s, 2 H), 4.40 (m 2 H), 2.96-1.82 (m, 6 H), 1.30 (m, 2 H).



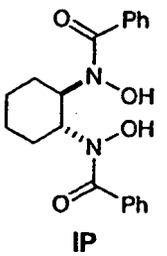
Ie

[0139] Example 8. This example provides spectroscopic data for (*R,R*)-*N*-(2-{[2,2-Bis-(3-methoxynaphthalen-2-yl)-acetyl]-hydroxyamino}-cyclohexyl)-*N*-hydroxy-2,2-bis-(3-methoxynaphthalen-2-yl)-acetamide (**Ig**) (Yield, 15%). R_f 0.5 (EtOAc/hexanes, 1:1); ^1H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 2 H), 7.81 (d, J = 8.2 Hz, 2 H), 7.65 (d, J = 8.1 Hz, 2 H), 7.66 (d, J = 6.6 Hz, 2 H), 7.46-7.07 (m, 16 H), 6.92-6.89 (m, 2 H), 6.35 (s, 2 H), 4.36-4.33 (m 2 H), 3.78 (s, 6 H), 3.62 (s, 6 H), 1.86-1.83 (m, 2 H), 1.66-1.64 (s, 2 H), 1.52-1.50 (s, 2 H), 1.20-1.18 (m, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.4, 156.6, 156.4, 134.5, 134.4, 130.9, 130.0, 129.8, 129.0, 128.7, 128.5, 128.3, 127.3, 127.1, 127.0, 126.8, 124.6, 124.1, 106.3, 106.3, 57.4, 56.7, 56.4, 28.3, 25.0.



Ig

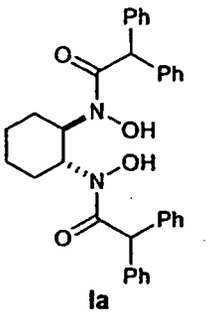
[0140] Example 9 This example provides spectroscopic data for **Ip** Yield, 55%; white solid: R_f 0.42 (EtOAc/hexanes, 1:1); FTI R (KBr) υ_{max} 3150, 2940, 2863, 1609, 1572, 1501, 1449, 1451, 1406, 1316, 1254, 1175, 795, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 2 H), 7.65 (d, J = 7.8 Hz, 2 H), 7.50 (t, J = 7.2 Hz, 2 H), 7.37 (d, J = 7.8 Hz, 1 H), 4.52-4.49 (m, 2 H), 2.09-1.98 (m, 6 H), 1.52-1.42 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (C=O), 132.2 (C), 132.0 (C), 130.4 (CH), 127.8 (CH), 55.9 (CH), 28.2 (CH_2), 24.8 (CH_2).



IP

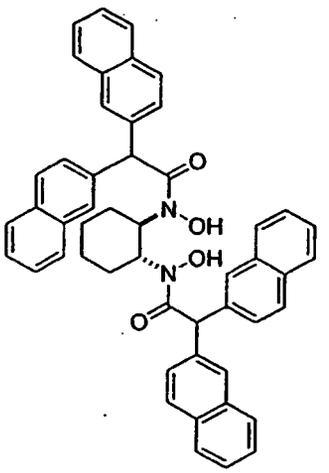
[0141] Method B: A general procedure for the preparation of chiral bishydroxamic acid ligands is herein provided. To a stirred solution of **VIII** (1 equiv) and DIEA (6 equiv) in CH_2Cl_2 was added acid chloride (3 equiv). After 24-72 h, the reaction mixture was concentrated under reduced pressure. To the residue, methanol followed by 0.5 M aqueous HCl was added. After stirring for 15-20 min the reaction mixture was extracted with CH_2Cl_2 (or EtOAc), washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to provide the chiral bis-hydroxamic acid ligand.

[0142] Example 10. This example provides spectroscopic data for (*R*,*R*)-*N*-[2-(Diphenylacetylhydroxyamino)-cyclohexyl]-*N*-hydroxy-2,2-diphenylacetamide (**Ia**) (Yield, 55%). White solid: R_f 0.5 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 3195, 3062, 3029, 2961, 2940, 2862, 1750, 1687, 1658, 1620, 1600, 1495, 1451, 1401, 1309, 1251, 1166, 1079, 1032, 909, 733, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 2 H, OH), 7.31-7.26 (m, 5 H), 7.21-7.18 (m, 5 H), 7.16-7.05 (m, 10 H), 5.49 (s, 2 H), 4.49-4.48 (m 2 H), 1.78-1.68 (m, 6 H), 1.24-1.21 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (C=O), 139.4 (C), 139.2 (C), 129.5 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 127.3 (CH), 127.1 (CH), 56.7 (CH), 53.4 (CH), 27.9 (CH_2), 24.6 (CH_2); HRMS-ESI calcd for $C_{34}H_{34}O_4N_2Na$ $[M+Na]^+$ 557.2416, found 557.2438.

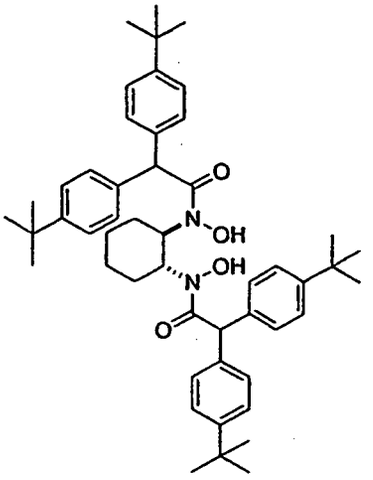


Ia

[0143] Example 11. This example provides spectroscopic data for (*R*,*R*)-*N*-{2-[(2,2-Di-naphthalen-2-ylacetyl)-hydroxyamino]-cyclohexyl}-*N*-hydroxy-2,2-dinaphthalen-2-ylacetamide (**If**) (31% yield): R_f 0.6 (EtOAc/hexane, 1:2); FTIR (film) $\square_{max}$ 2937, 2862, 1605, 1507, 1406, 1264, 1235, 1168, 1017, 923, 854, 811, 741, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) □ 9.06 (s, 2 H), 7.89-7.32 (m, 28 H), 5.91 (s, 2 H), 4.53-4.51 (m 2 H), 1.86-1.76 (m, 6 H), 1.31-1.21(m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) □ 175.1 (C=O), 136.5 (C), 133.4 (C), 133.3 (C), 132.5 (C), 132.4 (C), 128.3 (CH), 128.1 (CH), 127.97 (CH), 127.94 (CH), 127.61 (CH), 127.57 (CH), 127.19 (CH), 127.15 (CH), 127.0 (CH), 126.12 (CH), 126.09 (CH), 125.9 (CH), 56.6 (CH), 53.5 (CH), 27.8 (CH_2), 24.3 (CH_2).

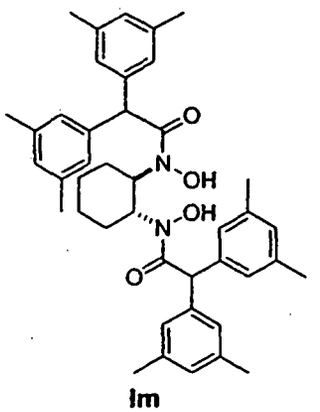


[0144] Example 12. This example provides spectroscopic data for (*R,R*)-*N*-(2-{[2,2-Bis-(4-tert-butylphenyl)-acetyl]-hydroxyamino}-cyclohexyl)-2,2-bis-(4-tert-butylphenyl)-*N*-hydroxyacetamide (**Id**) (Yield, 71%). White solid: R_f 0.7 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 3419, 2961, 2904, 2870, 1652, 1622, 1511, 1456, 1410, 1363, 1269, 1169, 819, 737, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.99 (s, 2 H, OH), 7.32-7.28 (m, 6 H), 7.21-7.15 (m, 12 H), 5.53 (s, 2 H), 4.32-4.30 (m 2 H), 1.77-1.71 (m, 6 H), 1.27-1.25 (m, 2 H), 1.22 (s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1 (C=O), 150.1 (C), 150.0 (C), 138.4 (C), 136.93 (C), 136.88 (C), 129.5 (CH), 128.9 (CH), 128.7 (CH), 126.1 (CH),126.0 (CH), 126.0 (CH), 56.9 (CH), 53.5 (CH), 34.98 (C), 34.97 (C), 31.95 (CH_3), 31.92 (CH_3), 28.2 (CH_2), 24.9 (CH_2).



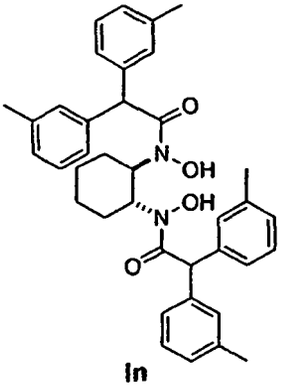
Id

[0145] Example 13. This example provides spectroscopic data for (*R*,*R*)-*N*-(2-{[2,2-Bis-(3,5-dimethylphenyl)-acetyl]-hydroxyamino}-cyclohexyl)-2,2-bis-(3,5-dimethylphenyl)-*N*-hydroxyacetamide (**Im**) (45% yield): R_f 0.5 (EtOAc/hexane, 1:4); FTIR (film) υ_{max} 3172, 3007, 2919, 2861, 1621, 1602, 1452, 1404, 1309, 1264, 1233, 1166, 1132, 1037, 958, 897, 851, 823, 790, 770, 736, 710, 688, 660 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 2 H), 6.87-6.72 (m, 12 H), 5.35 (s, 2 H), 4.52-4.50 (m 2 H), 2.27 (s, 12 H), 2.14 (s, 12 H), 1.89-1.77 (m, 6 H), 1.26 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C=O), 139.2 (C), 139.0 (C), 137.9 (C), 137.5 (C), 128.6 (CH), 128.5 (CH), 126.8 (CH), 126.4 (CH), 56.5 (CH), 53.0 (CH), 27.7 (CH_2), 24.5, (CH_2), 21.4 (CH_3), 21.3 (CH_3); HRMS-ESI calcd for $C_{42}H_{50}O_4N_2Na$ $[M+Na]^+$ 669.3668, found 669.3668.



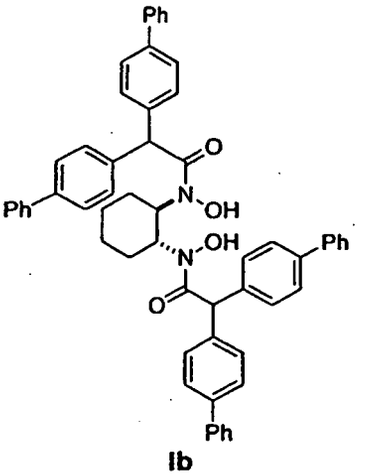
Im

[0146] Example 14. This example provides spectroscopic data for (*R,R*)-*N*-(2-{[2,2-Bis-(3-methylphenyl)-acetyl]-hydroxyamino}-cyclohexyl)-2,2-bis-(3-methylphenyl)-*N*-hydroxyacetamide (**In**) (Yield, 50%). White solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 2 H), 7.21-7.18 (m, 2 H), 7.06-6.84 (m, 14 H), 5.43 (s, 2 H), 4.42-4.50 (m 2 H), 2.30 (s, 6 H), 2.21 (s, 6 H), 1.83-1.71 (m, 6 H), 1.30-1.25 (m, 2 H); HRMS-ESI calcd for $C_{38}H_{42}O_4N_2Na$ $[M+Na]^+$ 613.3042, found 613.3029.



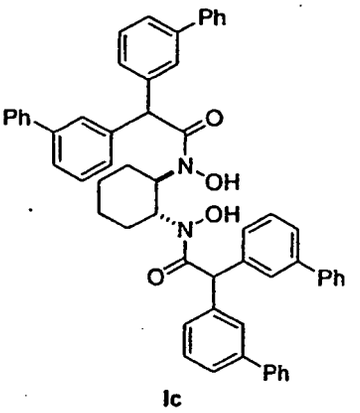
In

[0147] Example 15. This example provides spectroscopic data for (*R,R*)-2,2-Bis-biphenyl-3-yl-*N*-{2-[(2,2-bis-biphenyl-3-yl-acetyl)-hydroxyamino]-cyclohexyl}-*N*-hydroxyacetamide (**Ib**) (Yield ,55%). White solid; R_f 0.4 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 3383, 3057, 3030, 2938, 2862, 1634, 1617, 1559, 1540, 1520, 1486, 1419, 1167, 1008, 911, 826, 764, 735, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 2 H), 7.55-7.50 (m, 4 H), 7.40-7.37 (m, 4 H), 7.33-7.28 (m, 14 H), 7.22-7.17 (m, 10 H), 5.69 (s, 2 H), 4.54-4.50 (m 2 H), 1.85-1.76 (m, 6 H), 1.27-1.25 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1 (C=O), 140.9 (C), 140.4 (C), 141.2 (C), 140.0 (C), 138.4 (C), 138.3 (C), 129.9 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH),127.3 (CH), 127.1 (CH), 56.9 (CH), 52.9 (CH), 28.0 (CH_2), 24.6 (CH_2).



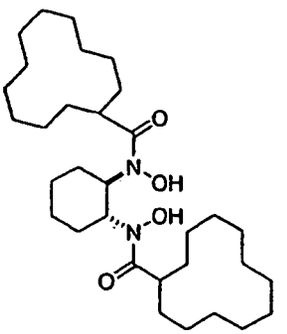
Ib

[0148] Example 16. This example provides spectroscopic data for (*R,R*)-2,2-Bis-biphenyl-3-yl-*N*-{2-[(2,2-bis-biphenyl-3-yl-acetyl)-hydroxyamino]-cyclohexyl}-*N*-hydroxy-acetamide (**Ic**) (Yield, 46%). White solid: R_f 0.4 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 3420, 1623, 1599, 1478, 1455, 1419, 1170, 908, 755, 733, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 2 H), 7.52-7.50 (m, 4 H), 7.46-7.42 (m, 10 H), 7.39-7.36 (m, 4 H), 7.34-7.24 (m, 12 H), 7.19 (d, J = 7.5 Hz, 2 H), 7.10 (d, J = 8.0 Hz, 2 H), 6.94-6.91 (m, 2 H), 5.65 (s, 2 H), 4.50-4.49 (m 2 H), 1.80-1.74 (m, 6 H), 1.26-1.24 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0 (C=O), 141.7 (C), 141.6 (C), 141.2 (C), 141.0 (C), 138.9 (C), 139.6 (C), 129.2 (CH), 129.1 (CH), 129.0 (CH), 127.9 (CH), 127.73 (CH), 127.66 (CH), 127.6 (CH),127.5 (CH), 127.44 (CH), 127.38 (CH), 126.2 (CH), 126.1 (CH), 56.7 (CH), 53.8 (CH), 28.1 (CH_2), 24.5 (CH_2).



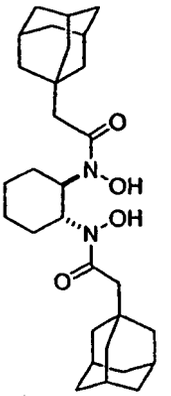
Ic

[0149] Example 17. This example provides spectroscopic data for **Ik** (Yield, 41%): white solid: R_f 0.4 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 3141, 2930, 2860, 1603 1470, 1169, 714, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 2 H), 4.53-4.51 (m 2 H), 3.21-3.16 (m, 2 H), 1.90-1.82 (m, 6 H), 1.61-1.52 (m, 6 H), 1.43-1.25 9m 40 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3 (C=O), 56.2 (CH), 36.3 (CH), 28.3 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 24.9 (CH_2), 24.0 (CH_2), 23.93 (CH_2), 23.90 (CH_2), 23.87 (CH_2), 23.7 (CH_2), 23.61 (CH_2), 23.56 (CH_2), 22.8 (CH_2), 22.6 (CH_2).



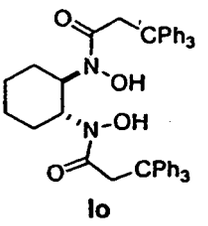
Ik

[0150] Example 18. This example provides spectroscopic data for (*R*,*R*)-2-Adamantan-1-yl-*N*-{2-[(2-adamantan-1-ylacetyl)-hydroxyamino]-cyclohexyl}-N-hydroxyacetamide (**Ij**) (Yield, 94%). White solid: R_f 0.68 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 3151, 2902, 2848, 1602, 1450, 1172, 909, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 2 H, OH), 4.44-4.39 (m 2 H), 2.59 (d, J = 12.7 Hz, 2 H), 1.90 (d, J = 12.7 Hz, 2 H), 1.86-1.80 (m, 6 H), 1.70-1.57 (m, 28 H), 1.40-1.30 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C=O), 55.3 (CH), 46.0 (CH_2), 42.8 (CH_2), 37.0 (CH_2), 33.8 (C), 28.9 (CH), 28.4 (CH_2), 24.8 (CH_2).



Ij

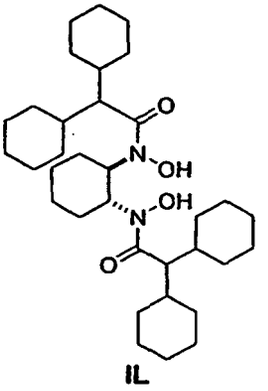
[0151] Example 19. This example provides spectroscopic data for (*R*,*R*)-*N*-Hydroxy-*N*-{2-[hydroxy-(3,3,3-triphenyl-propionyl)-amino]-cyclohexyl}-3,3,3-triphenylpropionamide (**Io**) (Yield, 72%). White solid: R_f 0.63 (EtOAc/hexanes, 1:3); FTIR (film) υ_{max} 3150, 2938, 2859, 1616, 1493, 1446, 1419, 1170, 769, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 2 H), 7.28-7.17(m, 30 H), 4.19 (d, *J* = 16.1 Hz, 2 H), 3.94-3.92 (m, 2 H), 3.55 (d, *J* = 16.1 Hz, 2 H), 1.68-1.65 (m, 2 H), 1.50-1.38 (m, 4 H), 1.12-1.07 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6 (C=O), 147.2 (C), 129.6 (CH), 127.8 (CH), 126.3 (CH), 56.2 (C), 55.2 (CH), 42.5 (CH_2), 27.5 (CH_2), 24.6 (CH_2); HRMS-ESI calcd for $C_{48}H_{46}O_4N_2Na$ $[M+Na]^+$ 737.3355, found 737.3379.



Io

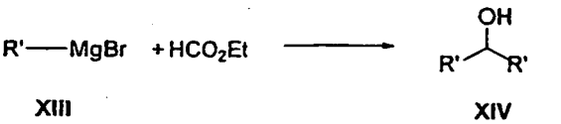
[0152] Method C: To a stirred solution of **VIII** (1 equiv) and DIEA (6 equiv) in CH_2Cl_2 was added acid chloride. After 48 h, the reaction mixture was concentrated under reduced pressure and methanol followed by 0.5 M aqueous HCl was added to the residue. After stirring for 15-20 min the reaction mixture was extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to provide monohydroxamic acid. To a stirred solution of monohydroxamic acid in CH_2Cl_2 was added freshly prepared acid chloride and DIEA. After 48 h, the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with EtOAc, washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to provide the chiral bishydroxamic acid ligand.

[0153] Example 20. This example provides spectroscopic data for (*R,R*)-2,2-Dicyclohexyl-*N*-{2-[(2,2-dicyclohexyl-acetyl)-hydroxy-amino]-cyclohexyl}-*N*-hydroxy-acetamide (**IL**) (Yield, 28%). White solid: R_f 0.6 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 3149, 2930, 2849, 1616, 1577, 1445, 1374, 1177 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 2 H, OH), 4.57-4.50 (m, 2 H), 2.96 (dd, *J* = 9.0, 5.0 Hz, 2 H), 1.89- 0.89 (series of m, 52 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9 (C=O), 57.8 (CH), 51.2 (CH), 38.9 (CH_2), 36.9 (CH_2), 32.3 (CH_2), 32.1 (CH_2), 31.2 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 27.5 (CH_2), 27.2, 27.14 (CH_2), 27.10 (CH_2), 25.3 (CH_2); ; HRMS-ESI calcd for $C_{34}H_{58}O_4N_2Na$ $[M+Na]^+$ 581.4294, found 581.4294.



IL

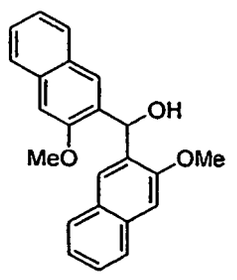
[0154] Example 21. The general procedure for the preparation of the alcohol (a precursor to the acid chloride used in the preparation of the acid chloride) is shown below. The R' substituent can be selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.



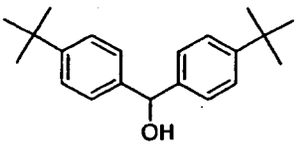
XIII XIV

[0155] To a stirred suspension of magnesium (1.1 equiv) in THF (10 mL), under an atmosphere of argon at room temperature, was added a small crystal of iodine, the resulting mixture was heated at reflux. To this refluxing solution, a small portion of aryl bromide (**XIII**) (~5% of the total amount: 1 equiv) was added and the heating was continued. After 5 minutes, the remaining aryl bromide was added and was heated at reflux in an oil bath for 1-2 h according to substrate. The oil bath was removed, ethyl formate was added drop wise over 5 min to the hot reaction mixture, and then stirred for 1-2 h at room temperature. The reaction mixture was poured into saturated aqueous NH_4Cl. After stirring for 30 minutes, the biphasic mixture was extracted with EtOAc (3 times) and the combined organic extracts washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide crude alcohol **XIV,** which was purified by column chromatography on silica gel or recrystalization according to the substrate.

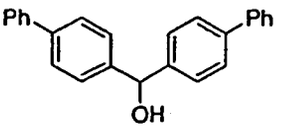
[0156] Example 22. This example provides spectroscopic data for bis-(3-methoxynaphthalen-2-yl)-methanol (Yield, 74%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2 H), 7.69 (d, J = 8.0 Hz, 2 H), 7.66 (s, 2 H), 7.46-7.41 (m, 2 H), 7.32-7.29 (m, 2 H), 7.17 (s, 2 H), 6.60 (s, 1 H), 3.93 (s, 6 H), 3.50(br s, 1 H).



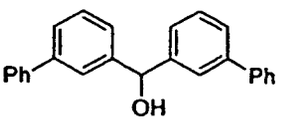
[0157] Example 23. This example provides spectroscopic data for *bis*-(4-*tert*-butylphenyl)-methanol Yield, 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.6 Hz, 4 H), 7.34 (d, J = 8.6 Hz, 4 H), 5.83 (s, 1 H), 2.16 (br s, 1 H), 1.34 (s, 18 H).



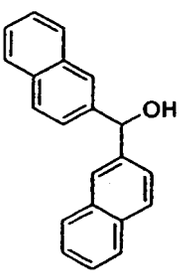
[0158] Example 24. This example provides spectroscopic data for *bis*-biphenyl-4-yl-methanol (Yield, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) 7.62-7.59 (m, 8 H), 7.52 (d, J = 8.2 Hz, 4 H), 7.47-7.44 (m, 4 H), 7.32-7.29 (m, 4 H), 5.97 (s, 1 H), 2.31 (br s, 1 H).



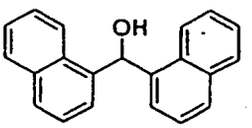
[0159] Example 25. This example provides spectroscopic data for *bis*-biphenyl-4-yl-methanol: Yield, 81%; ^{1}H NMR (500 MHz, $CDCl_3$) 7.70 (s, 2 H), 7.62-7.60 (m, 4 H), 7.48-7.47 (m, 2 H), 7.46-7.43 (m, 8 H), 7.38-7.37 (m, 2 H), 5.32 (s, 2 H);



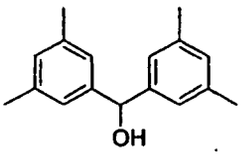
[0160] Example 26. This example provides spectroscopic data for bis-(naphthalen-2-yl)-methanol^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 2 H), 7.86-7.79 (m, 6 H), 7.50-7.46 (m, 6 H), 6.16 (s, 1 H), 2.53 (s, 1 H).



[0161] Example 27. This example provides spectroscopic data for bis-(naphthalen-1-yl)-methanol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2 H), 7.91 (d, J = 8.0 Hz, 2 H), 7.82 (d, J = 7.8 Hz, 2 H), 7.53-7.37 (m, 8 H), 7.20 (s, 1 H), 2.73 (s, 1 H).



[0162] Example 28. This example provides spectroscopic data for bis-(3,5-dimethyl-phenyl)-methanol: (81% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 4 H), 6.90 (s, 2 H), 5.70 (d, J = 3.2 Hz, 1 H), 2.30 (s, 12 H), 2.12 (d, J = 3.4 Hz, 1H).

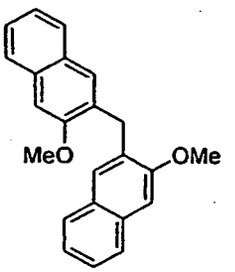


[0163] Example 29. The general procedure for the reduction of the Alcohol is shown below.

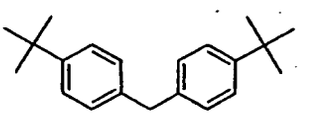
XIV **XV**

[0164] To a stirred suspension of NaI (6 equiv) in MeCN, under an atmosphere of nitrogen at room temperature, was added trimethylsilylchloride (6 equiv). After stirring for 20 min, the reaction mixture was cooled to 0 ˚C, a solution of alcohol **XIV** (1 equiv) in CH_2Cl_2 and MeCN (1:1 mixture), was added over 1 h. After stirring for a further 30 min. at the same temperature, the reaction mixture was allowed to warm to room temperature over 5 min. and then immediately cooled to 0 ˚C, poured into aqueous NaOH (4 equiv), additional NaOH solution was added to adjust pH of aqueous layer to 7. The biphasic mixture was extracted with EtOAc (2 times) and the organic phase was washed with saturated aqueous $Na_2S_2O_3$ to completely remove any color of iodine. The aqueous portion was extracted with small amount EtOAc and he combined organic extracts were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by the flash column chromatography on silica gel or recrystalization to provide the desired compound (XV).

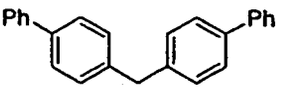
[0165] Example 30. This example provides spectroscopic data for bis-(3-methoxynaphthalen-2-yl)-methane: Yield, 89%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2 H), 7.58 (d, *J* = 8.2 Hz, 2 H), 7.39 (s, 2 H), 7.36-7.33 (m, 2 H), 7.26-7.23 (m, 2 H), 7.10 (s, 2 H), 4.21 (s, 2 H), 3.87 (s, 6 H).



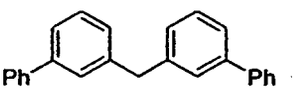
[0166] Example 31. This example provides spectroscopic data for *bis*-(4-*tert*-butyl-phenyl)-methanol: Yield, 90%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 4 H), 7.10 (d, *J* = 8.0 Hz, 4 H), 3.89 (s, 2 H), 1.26 (s, 18 H).



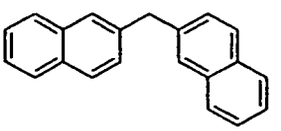
[0167] Example 32. This example provides spectroscopic data for *bis*-biphenyl-4-yl-methane: Yield, 92%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.54 (m, 4 H), 7.41-7.40 (m, 4 H), 7.47-7.44 (m, 4 H), 7.38-7.27 (m, 6 H), 4.04 (s, 2 H).



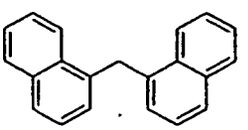
[0168] Example 33. This example provides spectroscopic data for *bis*-biphenyl-4-yl-methane Yield, 64%; FTIR (film) υ_{max} cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56-7.54 (m, 4 H), 7.44-7.38 (m, 8 H), 7.34-7.29 (m, 4 H), 7.20-7.19 (m, 2 H), 4.09 (s, 2 H).



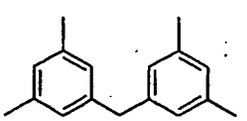
[0169] Example 34. This example provides spectroscopic data for *bis*-(naphthalen-2-yl)-methane: 66% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (m, 6 H), 7.73 (s, 2 H), 7.53-7.46 (m, 4 H), 7.39 (dd, *J* = 8.4 Hz, 1.6 Hz, 2 H), 4.35 (s, 2 H).



[0170] Example 35. This example provides spectroscopic data for *bis*-(naphthalen-1-yl)-methane: 67% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 2 H), 7.94 (d, *J* = 7.6 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.57-7.50 (m, 4 H), 7.36 (t, *J* = 8.0 Hz, 2 H), 7.11 (d, *J* = 6.8 Hz, 2H), 4.92 (s, 2 H).



[0171] Example 36. This example provides spectroscopic data for *bis*-(3,5-dimethylphenyl)-methane: 82% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2 H), 6.81 (s, 4 H), 3.82 (s, 2 H), 2.27 (s, 12 H).



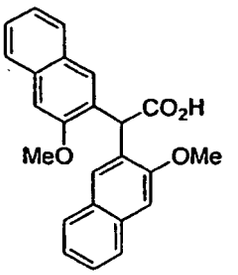
[0172] Example 37. The general procedure for preparation of the carboxylic acid is shown below.

XVI **XVII**

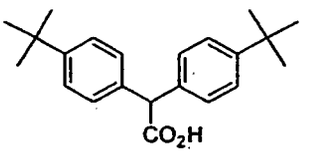
[0173] To a stirred suspension of diarylmethane (**XVI**) (1 equiv) in THF, under an atmosphere of argon, at room temperature was added n-butyl lithium (1.3 equiv). After 1 h, anhydrous CO_2 was bubbled through the reaction mixture and stirred for additional 1 h. Once all the alkyl lithium species were consumed, the reaction mixture was concentrated

under reduced pressure and aqueous NaOH (10-15 equiv) was added. The aqueous solution was washed with ether and separated, acidified with 1 M HCl to pH 2-3 which was extracted with EtOAc (3 times). The combined organic extracts were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by recrystalization, to provide carboxylic acid **XVII.**

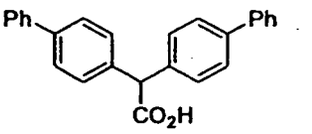
[0174] Example 38. This example provides spectroscopic data for bis-(3-methoxy-naphthalen-2-yl)-acetic acid: Yield, 83%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (d, J = 8.1 Hz, 2 H), 7.73 (d, J = 8.2 Hz, 2 H), 7.48-7.42 (m, 6 H), 7.32-7.30 (m, 2 H), 5.68 (s, 1 H), 3.90 (s, 6 H).



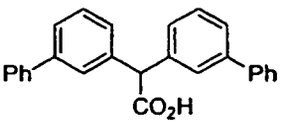
[0175] Example 39. This example provides spectroscopic data for bis-(4-*tert*-butylphenyl)-acetic acid: Yield, 63%; ^{1}H NMR (500 MHz, DMSO-d_6 + 1 M HCl) δ 7.19-7.17 (m, 4 H), 7.10-7.07 (m, 4 H), 4.78 (s, 1 H), 1.11 (s, 9 H), 1.09 (s, 9 H).



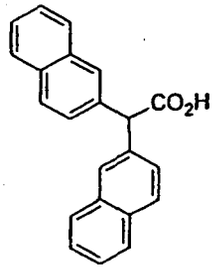
[0176] Example 40. This example provides spectroscopic data for *bis*-biphenyl-4-yl-acetic acid: Yield, 87%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54-7.52 (m, 8 H), 7.34-7.33 (m, 8 H), 7.26-7.25 (m, 2 H), 5.07 (s, 1 H).



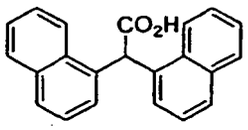
[0177] Example 41. This example provides spectroscopic data for bis-biphenyl-3-yl-acetic acid: Yield, 83%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56-7.54 (m, 2 H), 7.51-7.33-7.49 (m, 4 H), 7.37-7.35 (m, 2 H), 7.31-7.24 (m, 10 H), 5.15 (s, 1 H).



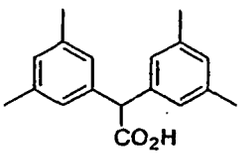
[0178] Example 42. This example provides spectroscopic data for bis-(naphthalen-2-yl)-acetic acid: 72% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (bs, 1 H), 7.90-7.88 (m, 8 H), 7.54-7.48 (m, 6 H), 5.45 (s, 1 H).



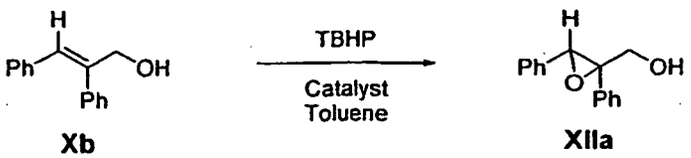
[0179] Example 43. This example provides spectroscopic data for bis-(naphthalen-1-yl)-acetic acid (57% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (bs, 1 H), 8.06-8.02 (m, 4 H), 7.93 (d, J = 8.2 Hz, 2 H) 7.61-7.47 (m, 6 H), 7.22 (d, J = 7.1 Hz, 2 H), 6.54 (s, 1 H).



[0180] Example 44. This example provides spectroscopic data for bis-(3,5-dimethyl-phenyl)-acetic acid (58% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (bs, 1 H), 6.90 (s, 4 H), 6.86 (s, 2 H), 4.85 (s, 1 H), 2.23 (s, 12 H).



[0181] Example 45. The general Procedure for asymmetric epoxidation of allylic alcohols in the presence of VO(OPr^i)$_3$ and hydroxamic acid ligand is shown below.



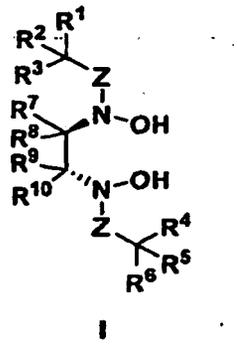
Xb **XIIa**

[0182] To a solution of hydroxamic acid (0.02 equiv) in toluene was added VO(OPr^i)$_3$ (0.01 equiv), and the mixture was stirred for 1 h at room temperature. The resulting solution was cooled to 0 ˚C, 70% aqueous *tert*-butylhydroperoxide (TBHP) (1.5 equiv) and allyl alcohol Xb (1 equiv) were added and stirring was continued at the same temperature for several hours at the same temperature monitoring the progress of the reaction by TLC. When the epoxidation was complete according to TLC, a saturated aqueous Na_2SO_3 was added and the mixture was warmed to room temperature over a period of 15 min, extracted with Et_2O, dried (Na_2SO_4) and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography on silica gel to provide epoxy alcohol. The enantiomeric excess of the epoxy alcohol **XIIa** was determined by HPLC using chiral OD-H column (hexanes/2-propanol, 95:5), 0.5 mL/min; major enantiomer t_r = 13.9 min, minor enatiomer t_r = 12.0 min.

Claims

1. A method of performing a catalytic asymmetric oxidation comprising: reacting a substrate selected from the group consisting of sulfide, alkene and cyclic alkene with catalytic amounts of a chiral bishydroxamic acid ligand and a metal selected from the group consisting of vanadium and molybdenum, in the presence of an oxidation reagent, to produce a chiral oxidation prod uct.

2. The method of claim 1, where the chiral bishydroxamic acid ligand has a structure I:



I

where:

R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;
or where R^1 and R^2, together with the atom to which they are attached, form a substituted or unsubstituted ring selected from the group consisting of cycloalkyl, heterocyclyl, or aryl;
or where R^4 and R^5, together with the atom to which they are attached, form a substituted or unsubstituted ring selected from the group consisting of cycloalkyl, heterocyclyl, and aryl;
R^7, R^8, R^9, and R^{10} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;
or where R^7 and R^9, together with the atoms to which they are attached, form a substituted or non-subsituted ring selected from the group consisting of cycloalkyl and heterocyclyl;
-Z- is -C(O)-.

3. The method of claim 1, where the metal is selected from the group consisting of vanadium (IV), vanadium (V), molybdenum (IV), molybdenum (V), and molybdenum (VI).

4. The method of claim 3, where the metal is selected from the group consisting of vanadium (IV) and vanadium (V).

5. The method of claim 3, where the metal is selected from the group consisting of molybdenum (IV), molybdenum (V), and molybdenum (VI).

6. The method of claim 1, where the substrate is sulfide.

7. The method of claim 1, where the substrate is selected from the group consisting of alkene and cyclic alkene.

8. The method of claim 1, where the oxidation reagent is an organic hydroperoxide with the following structure (**II**):

$$R^{11}\text{-O-OH} \qquad \text{II}$$

where, R^{11} is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl.

9. The method of claim 1 wherein the chiral oxidation product has a structure III:

III

where Y is a sulfide.

10. The method of claim 2, where the substrate is an alkene or cyclic alkene.

11. The method of claim 2, where R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, and alkylamino.

12. The method of claim 2, where R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from the group consisting of cycloalkyl and heterocyclyl.

13. The method of claim 2, where R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from the group consisting of aryl, arylalkyl, heteroaryl, and halogen.

14. The method of claim 2, where:

R^1 and R^2, together with the atom to which they are attached, form a substituted or unsubstituted ring;
R^4 and R^5, together with the atom to which they are attached, form a substituted or unsubstituted ring; and
the ring formed by R^1 and R^2 is identical to the ring formed by R^4 and R^5.

15. The method of claim 2, where R^7, R^8, R^9, and R^{10} are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, and alkylamino.

16. The method of claim 2, where R^7, R^8, R^9, and R^{10} are each independently selected from the group consisting of cycloalkyl and heterocyclyl.

17. The method of claim 2, where R^7, R^8, R^9, and R^{10} are each independently selected from the group consisting of aryl, arylalkyl, and heteroaryl.

18. The method of claim 2, where R^7 and R^9, together with the atoms to which they are attached, form a ring.

19. The method of claim 18, where R^8 and R^{10} are identical.

20. The method of claim 16, where R^7 and R^9, together with the atoms to which they are attached, form a ring.

21. The method of claim 20, where R^8 and R^{10} are identical.

22. The method of claim 2, where:

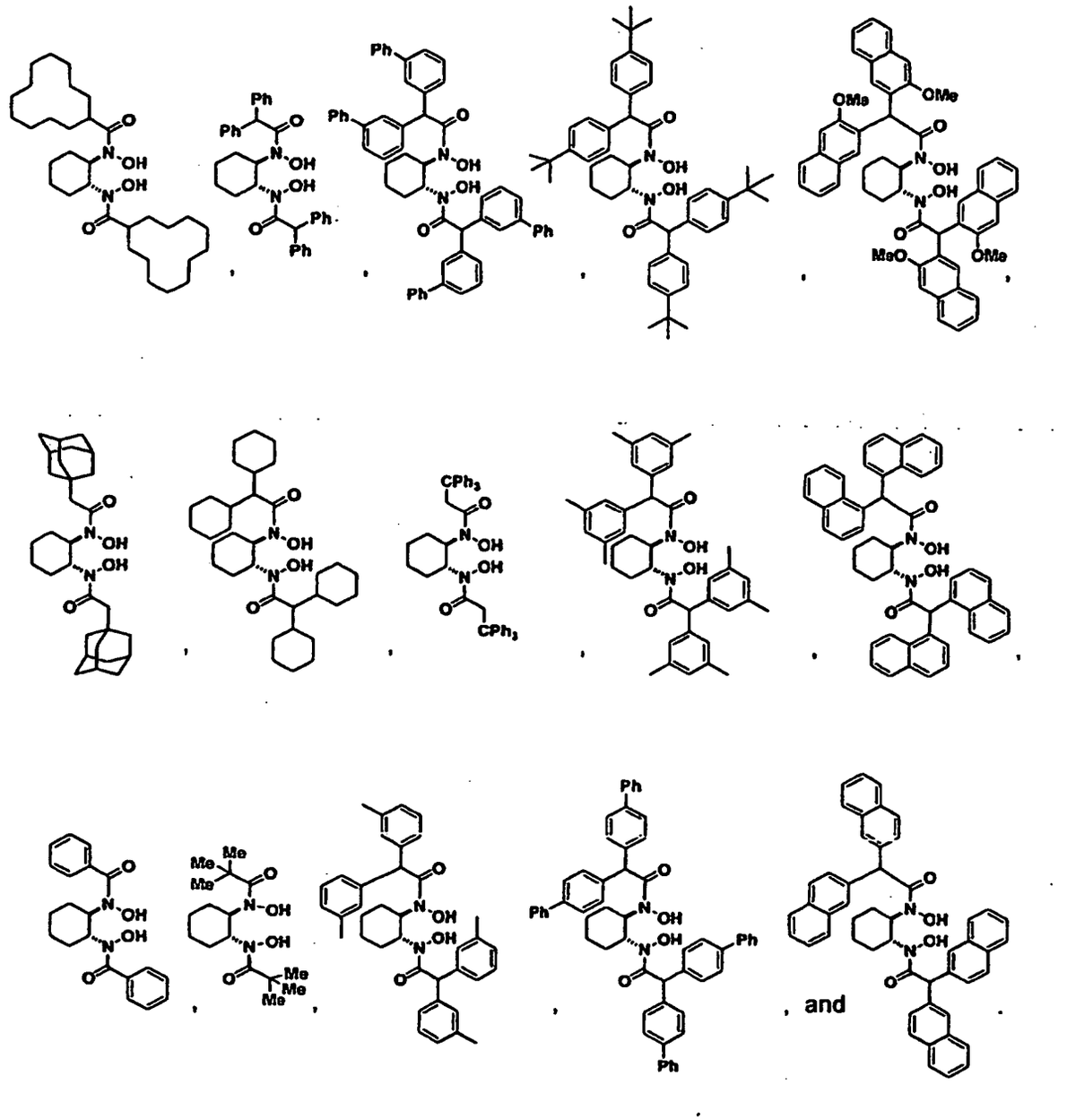
R^1 and R^2 are aryl groups;
R^3 is hydrogen;
R^4 and R^5 are aryl groups; and
R^6 is hydrogen.

23. The method of claim 22, where:

R^1 and R^2 are identical; and
R^4 and R^5 are identical.

24. The method of claim 23, where R^1, R^2, R^4, and R^5 are identical.

25. The method of claim 2, where the chiral bishydroxamic acid ligand (I) is selected from the group consisting of:



26. The method of claim 7, where the metal is selected from the group consisting of molybdenum (IV), molybdenum (V), and molybdenum (VI).

27. The method of claim 3, where the metal is selected from the group consisting of $VO(OPr^i)_3$, $VO(acac)_2$, $VO(OEt)_3$, and $MoO_2(acac)_2$.

28. The method of claim 7, where the metal is selected from the group consisting of $VO(OPr^i)_3$, $VO(acac)_2$, $VO(OEt)_3$, and $MoO_2(acac)_2$.

29. The method of claim 8, where the organic hydroperoxide is selected from the group consisting of tert-butyl hydroperoxide and cumene hydroperoxide.

30. The method of claim 8, where the organic hydroperoxide is tert-butyl hydroperoxide.

31. The method of claim 8, where the organic hydroperoxide is cumene hydroperoxide.

32. The method of claim 7, where the oxidation reagent is selected from the group consisting of tert-butyl hydroperoxide and cumene hydroperoxide.

33. The method of claim 7, where the oxidation reagent is tert-butyl hydroperoxide.

34. The method of claim 7, where the oxidation reagent is cumene hydroperoxide.

35. The method of claim 1, where the oxidation reagent is hydrogen peroxide.

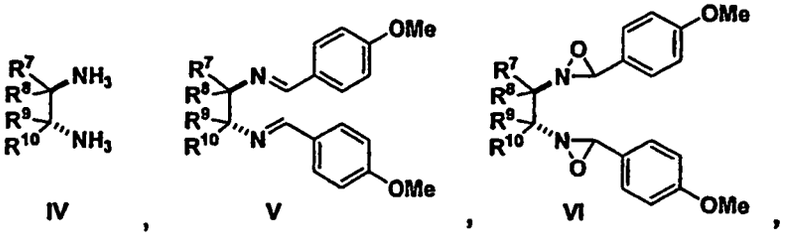
36. The method of claim 7, where the oxidation reagent is hydrogen peroxide.

37. A method of preparing a chiral bishydroxamic acid ligand comprising:

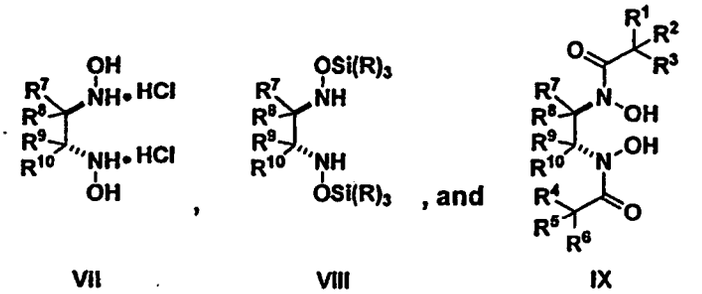
condensing an optically active 1,2-diammonium tartarate with p-anisaldehyde to provide a di-imine;
oxidizing the di-imine to produce a dioxaziridine;
hydrolyzing the dioxaziridine to generate a dihydroxylamine hydrochloride;
silylating the dihydroxylamine hydrochloride to provide a silyl protected dihydroxyamine;
condensing the silyl protected dihydroxylamine with an acid chloride to produce the chiral bishydroxamic acid ligand.

38. The method of claim 37, where the chiral bishydroxamic acid ligand is prepared by a method comprising:

condensing an optically active 1,2-diammonium tartrate (IV) with p-anisaldehyde to provide a di-imine (V);
oxidizing the di-imine (V) to produce a dioxaziridine (VI);
hydrolyzing the dioxaziridine (VI) to generate a dihydroxylamine hydrochloride (VII);
silylating the dihydroxylamine hydrochloride (VII) to provide a silyl protected dihydroxylamine (VIII);
condensing the silyl protected dihydroxylamine with an acid chloride to produce the bishydroxamic acid (IX).

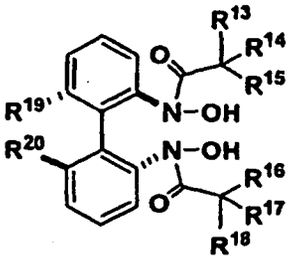


IV , V , VI ,

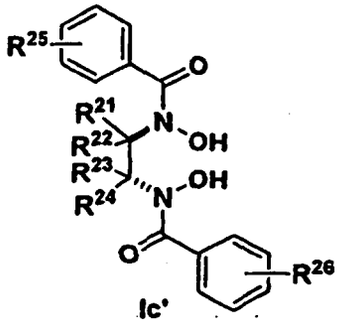


VII , VIII , and IX .

39. The method of claim 1, where the chiral bishydroxamic acid ligand (I) is selected from the following formulae:



Ib'

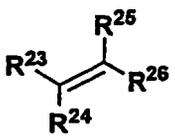


Ic'

where:

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;
R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;
R^{21}, R^{22}, R^{23}, and R^{24} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;
R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.

40. The method of claim 7, where the alkene is of the formula (X):

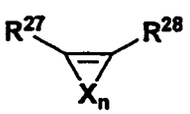


X

where:

R^{23}, R^{24}, R^{25}, and R^{28} are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.

41. The method of claim 7, where the alkene is a cyclic alkene of the formula (Xa):



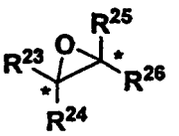
Xa

where:

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, aralkyl, heteroaryl, halogen, and alkene;
n is 1, 2, 3, 4, 5, 6, or 6;

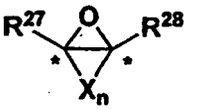
each X is independently selected from the group consisting of - CR'R", -NR'-, and -O-;
R' and R" are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, aralkyl, heteroaryl, and halogen.

42. The method of claim 40, where the chiral oxidation product is of the formula (Xb):



Xb

43. The method of claim 41, where the chiral oxidation product is of the formula (Xc):



Xc .

44. The method of claim 1, where the reacting step is carried out in a solvent.

45. The method of claim 44, where the reacting step is carried out in a solvent selected from the group consisting of methylene chloride, toluene, chloroform, and ethyl acetate.

46. The method of claim 1, where the reacting step is carried out at a temperature of about -20 to about 25 ˚C.

47. The method of claim 1, where the reaction is carried out with about 0.001 to about 0.1 equivalents of the chiral bishydroxamic acid ligand (I).

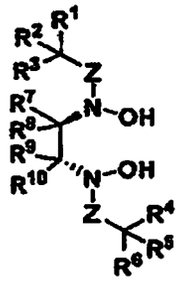
48. The method of claim 1, where the reaction is carried out with about 0.005 to about 0.05 equivalents of metal.

Patentansprüche

1. Verfahren zur Durchführung einer katalytischen asymmetrischen Oxidation, umfassend:

das Umsetzen eines Substrats, ausgewählt aus der Gruppe, bestehend aus Sulfid, Alken und cyclischem Alken, mit katalytischen Mengen eines chiralen Bishydroxamsäureliganden und eines Metalls, ausgewählt aus der Gruppe, bestehend aus Vanadium und Molybdän, in der Gegenwart eines Oxidationsreagenzes, wobei ein chirales Oxidationsprodukt hergestellt wird.

2. Verfahren nach Anspruch 1, wobei der chirale Bishydroxamsäureligand eine Struktur **I** aufweist:



I

wobei:

R^1, R^2, R^3, R^4, R^5 und R^6 jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Alkyl, Cycloalkyl, Alkoxy, Alkylamino, Heterocyclyl, Aryl, Heteroaryl und Arylakyl, ausgewählt sind;
oder wobei R^1 und R^2 zusammen mit dem Atom, an welches sie gebunden sind, einen substituierten oder nicht substituierten Ring, ausgewählt aus der Gruppe, bestehend aus Cycloalkyl, Heterocyclyl oder Aryl, bilden;
oder wobei R^4 und R^5 zusammen mit dem Atom, an welches sie gebunden sind, einen substituierten oder nicht substituierten Ring, ausgewählt aus der Gruppe, bestehend aus Cycloalkyl, Heterocyclyl oder Aryl, bilden;
R^7, R^8, R^9 und R^{10} jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Alkyl, Cycloalkyl, Alkoxy, Alkylamino, Heterocyclyl, Aryl, Heteroaryl und Arylakyl, ausgewählt sind;
oder wobei R^7 und R^9 zusammen mit den Atomen, an welche sie gebunden sind, einen substituierten oder nicht substituierten Ring, ausgewählt aus der Gruppe, bestehend aus Cycloalkyl und Heterocyclyl, bilden;
-Z- für -C(O)- steht.

3. Verfahren nach Anspruch 1, wobei das Metall aus der Gruppe, bestehend aus Vanadium (IV), Vanadium (V), Molybdän (IV), Molybdän (V) und Molybdän (VI), ausgewählt ist.

4. Verfahren nach Anspruch 3, wobei das Metall aus der Gruppe, bestehend aus Vanadium (IV) und Vanadium (V), ausgewählt ist.

5. Verfahren nach Anspruch 3, wobei das Metall aus der Gruppe, bestehend aus Molybdän (IV), Molybdän (V) und Molybdän (VI), ausgewählt ist.

6. Verfahren nach Anspruch 1, wobei das Substrat Sulfid ist.

7. Verfahren nach Anspruch 1, wobei das Substrat aus der Gruppe, bestehend aus Alken und cyclischem Alken, ausgewählt ist.

8. Verfahren nach Anspruch 1, wobei das Oxidationsreagenz ein organisches Hydroperoxid mit der folgenden Struktur (**II**) ist:

$$R^{11}\text{-O-OH} \qquad \textbf{II}$$

wobei R^{11} aus der Gruppe, bestehend aus Alkyl, Cycloalkyl, Aryl, Heteroaryl und Heterocyclyl, ausgewählt ist.

9. Verfahren nach Anspruch 1, wobei das chirale Oxidationsprodukt eine Struktur **III** aufweist:

wobei Y ein Sulfid ist.

10. Verfahren nach Anspruch 2, wobei das Substrat ein Alken oder cyclisches Alken ist.

11. Verfahren nach Anspruch 2, wobei R^1, R^2, R^3, R^4, R^5 und R^6 jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Alkyl, Alkoxy und Alkylamino, ausgewählt sind.

12. Verfahren nach Anspruch 2, wobei R^1, R^2, R^3, R^4, R^5 und R^6 jeweils unabhängig aus der Gruppe, bestehend aus Cycloalkyl und Heterocyclyl, ausgewählt sind.

13. Verfahren nach Anspruch 2, wobei R^1, R^2, R^3, R^4, R^5 und R^6 jeweils unabhängig aus der Gruppe, bestehend aus Aryl, Arylalkyl, Heteroaryl und Halogen, ausgewählt sind.

14. Verfahren nach Anspruch 2, wobei:

R^1 und R^2 zusammen mit dem Atom, an welches sie gebunden sind, einen substituierten oder nicht substituierten Ring bilden;
R^4 und R^5 zusammen mit dem Atom, an welches sie gebunden sind, einen substituierten oder nicht substituierten Ring bilden; und
der Ring, der durch R^1 und R^2 gebildet wird, identisch mit dem Ring, der durch R^4 und R^5 gebildet wird, ist.

15. Verfahren nach Anspruch 2, wobei R^7, R^8, R^9 und R^{10} jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Alkyl, Alkoxy und Alkylamino, ausgewählt sind.

16. Verfahren nach Anspruch 2, wobei R^7, R^8, R^9 und R^{10} jeweils unabhängig aus der Gruppe, bestehend aus Cycloalkyl und Heterocyclyl, ausgewählt sind.

17. Verfahren nach Anspruch 2, wobei R^7, R^8, R^9 und R^{10} jeweils unabhängig aus der Gruppe, bestehend aus Aryl, Arylalkyl und Heteroaryl, ausgewählt sind.

18. Verfahren nach Anspruch 2, wobei R^7 und R^9 zusammen mit den Atomen, an welche sie gebunden sind, einen Ring bilden.

19. Verfahren nach Anspruch 18, wobei R^8 und R^{10} identisch sind.

20. Verfahren nach Anspruch 16, wobei R^7 und R^9 zusammen mit den Atomen, an welche sie gebunden sind, einen Ring bilden.

21. Verfahren nach Anspruch 20, wobei R^8 und R^{10} identisch sind.

22. Verfahren nach Anspruch 2, wobei:

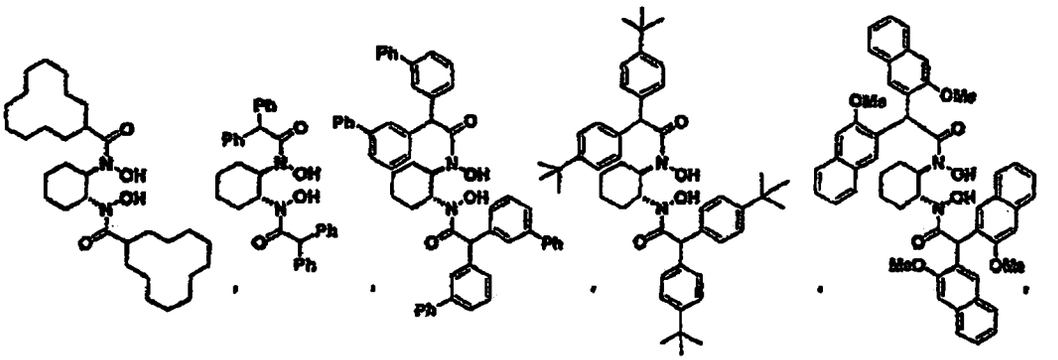
R^1 und R^2 Arylreste sind;
R^3 Wasserstoff ist;
R^4 und R^5 Arylreste sind; und
R^6 Wasserstoff ist.

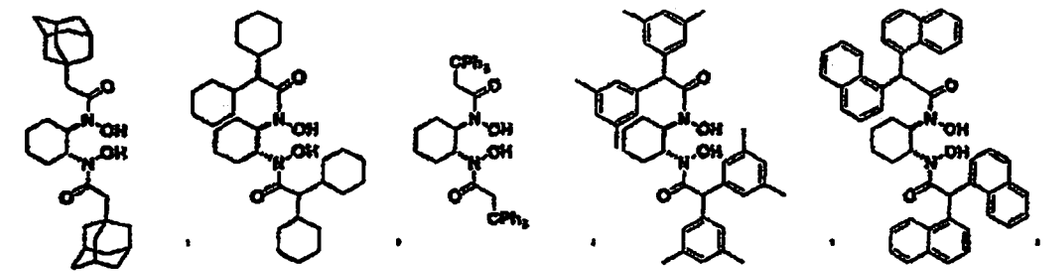
23. Verfahren nach Anspruch 22, wobei

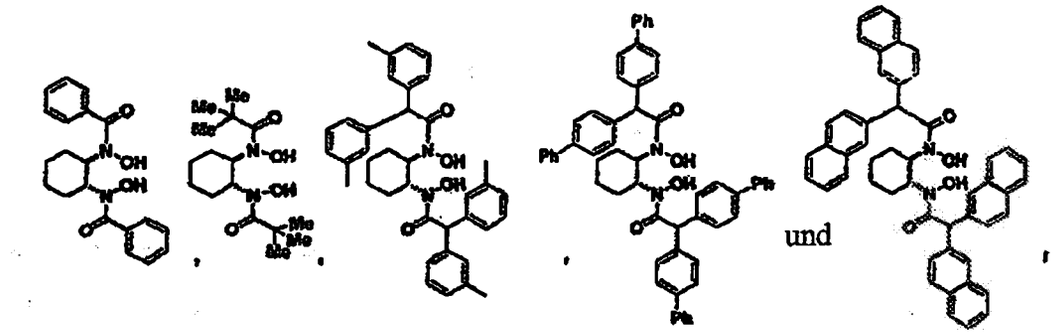
R^1 und R^2 identisch sind; und
R^4 und R^5 identisch sind.

24. Verfahren nach Anspruch 23, wobei R^1, R^2, R^4 und R^5 identisch sind.

25. Verfahren nach Anspruch 2, wobei der chirale Bishydroxamsäureligand (I) aus der Gruppe, bestehend aus







und

ausgewählt ist.

26. Verfahren nach Anspruch 7, wobei das Metall aus der Gruppe, bestehend aus Molybdän (IV), Molybdän (V) und Molybdän (VI), ausgewählt ist.

27. Verfahren nach Anspruch 3, wobei das Metall aus der Gruppe, bestehend aus $VO(OPr^i)_3$, $VO(acac)_2$, $VO(OEt)_3$ und $MoO_2(acac)_2$, ausgewählt ist.

28. Verfahren nach Anspruch 7, wobei das Metall aus der Gruppe, bestehend aus $VO(OPr^i)_3$, $VO(acac)_2$, $VO(OEt)_3$ und $MoO_2(acac)_2$, ausgewählt ist.

29. Verfahren nach Anspruch 8, wobei das organische Hydroperoxid aus der Gruppe, bestehend aus tert-Butylhydroperoxid und Cumolhydroperoxid, ausgewählt ist.

30. Verfahren nach Anspruch 8, wobei das organische Hydroperoxid tert-Butylhydroperoxid ist.

31. Verfahren nach Anspruch 8, wobei das organische Hydroperoxid Cumolhydroperoxid ist.

32. Verfahren nach Anspruch 7, wobei das Oxidationsreagenz aus der Gruppe, bestehend aus tert-Butylhydroperoxid und Cumolhydroperoxid, ausgewählt ist.

33. Verfahren nach Anspruch 7, wobei das Oxidationsreagenz tert-Butylhydroperoxid ist.

34. Verfahren nach Anspruch 7, wobei das Oxidationsreagenz Cumolhydroperoxid ist.

35. Verfahren nach Anspruch 1, wobei das Oxidationsreagenz Wasserstoffperoxid ist.

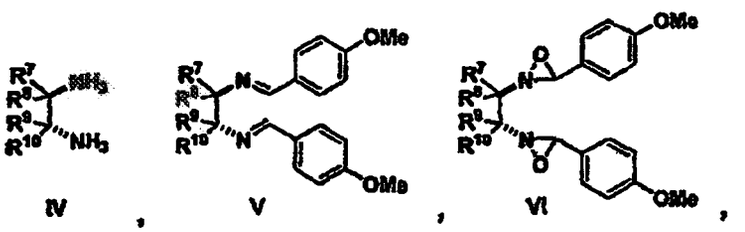
36. Verfahren nach Anspruch 7, wobei das Oxidationsreagenz Wasserstoffperoxid ist.

37. Verfahren zur Herstellung eines chiralen Bishydroxamsäureliganden, umfassend:

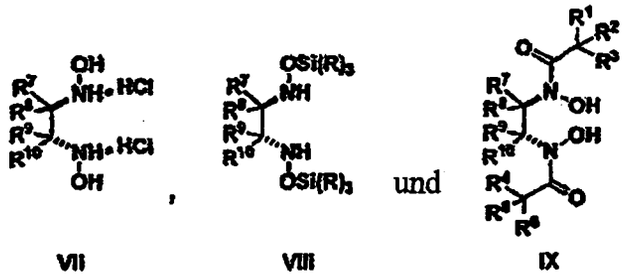
das Kondensieren eines optisch aktiven 1,2-Diammoniumtartrats mit p-Anisaldehyd,
wobei ein Diimin bereitgestellt wird;
das Oxidieren des Diimins, wobei ein Dioxaziridin hergestellt wird;
das Hydrolysieren des Dioxaziridins, wobei ein Dihydroxylamin-Hydrochlorid erzeugt wird;
das Silylieren des Dihydroxylamin-Hydrochlorids, wobei ein Silyl-geschütztes Dihydroxylamin bereitgestellt wird;
das Kondensieren des Silyl-geschützten Dihydroxylamins mit einem Säurechlorid, wobei der chirale Bishydroxamsäureligand hergestellt wird.

38. Verfahren nach Anspruch 37, wobei der chirale Bishydroxamsäureligand hergestellt wird durch ein Verfahren, umfassend:

das Kondensieren eines optisch aktiven 1,2-Diammoniumtartrats **(IV)** mit p-Anisaldehyd, wobei ein Diimin **(V)** bereitgestellt wird;
das Oxidieren des Diimins **(V),** wobei ein Dioxaziridin **(VI)** hergestellt wird;
das Hydrolysieren des Dioxaziridins **(VI),** wobei ein Dihydroxylamin-Hydrochlorid **(VII)** erzeugt wird;
das Silylieren des Dihydroxylamin-Hydrochlorids **(VII),** wobei ein Silyl-geschütztes Dihydroxylamin **(VIII)** bereitgestellt wird;
das Kondensieren des Silyl-geschützten Dihydroxylamins mit einem Säurechlorid, wobei die Bishydroxamsäure **(IX)** hergestellt wird.

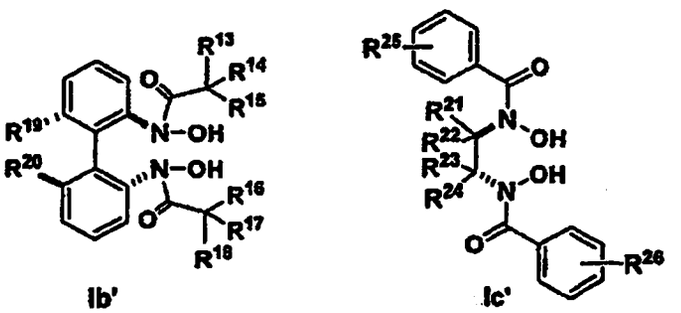


IV , V , VI ,



VII VIII und IX

39. Verfahren nach Anspruch 1, wobei der chirale Bishydroxamsäureligand (I) aus den folgenden Formeln ausgewählt ist:

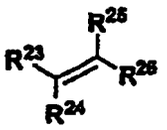


Ib' Ic'

wobei:

R^{13}, R^{14}, R^{15}, R^{16}, R^{17} und R^{18} jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Alkyl, Cycloalkyl, Alkoxy, Alkylamino, Heterocyclyl, Aryl, Heteroaryl und Arylalkyl, ausgewählt sind;
R^{19} und R^{20} jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Halogen, Alkyl, Cycloalkyl, Alkoxy, Alkylamino, Heterocyclyl, Aryl, Heteroaryl und Arylalkyl, ausgewählt sind;
R^{21}, R^{22}, R^{23} und R^{24} jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Alkyl, Cycloalkyl, Alkoxy, Alkylamino, Heterocyclyl, Aryl, Heteroaryl und Arylalkyl, ausgewählt sind;
R^{25} und R^{26} jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Halogen, Alkyl, Cycloalkyl, Alkoxy, Alkylamino, Heterocyclyl, Aryl, Heteroaryl und Arylalkyl, ausgewählt sind.

40. Verfahren nach Anspruch 7, wobei das Alken die Formel **(X)** aufweist:

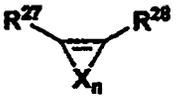


X

wobei:

R^{23}, R^{24}, R^{25} und R^{26} jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Halogen, Alkyl, Cycloalkyl, Alkoxy, Alkylamino, Heterocyclyl, Aryl, Heteroaryl und Arylalkyl, ausgewählt sind.

41. Verfahren nach Anspruch 7, wobei das Alken ein cyclisches Alken der Formel **(Xa)** ist:

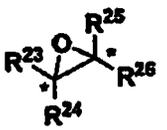


Xa

wobei:

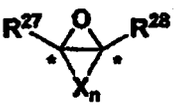
R^{27} und R^{28} jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Alkyl, Cycloalkyl, Alkoxy, Alkylamino, Heterocyclyl, Aryl, Aralkyl, Heteroaryl, Halogen und Alken, ausgewählt sind;
n für 1, 2, 3, 4, 5, 6 oder 6 steht;
jedes X unabhängig aus der Gruppe, bestehend aus -CR'R"-, -NR'- und -O-, ausgewählt ist;
R' und R'' jeweils unabhängig aus der Gruppe, bestehend aus Wasserstoff, Alkyl, Cycloalkyl, Alkoxy, Alkylamino, Heterocyclyl, Aryl, Aralkyl, Heteroaryl und Halogen, ausgewählt sind.

42. Verfahren nach Anspruch 40, wobei das chirale Oxidationsprodukt die Formel (Xb) aufweist:



Xb .

43. Verfahren nach Anspruch 41, wobei das chirale Oxidationsprodukt die Formel **(Xc)** aufweist:



Xc .

44. Verfahren nach Anspruch 1, wobei der Reaktionsschritt in einem Lösungsmittel durchgeführt wird.

45. Verfahren nach Anspruch 44, wobei der Reaktionsschritt in einem Lösungsmittel, welches aus der Gruppe, bestehend aus Methylenchlorid, Toluol, Chloroform und Ethylacetat, ausgewählt ist, durchgeführt wird.

46. Verfahren nach Anspruch 1, wobei der Reaktionsschritt bei einer Temperatur von etwa -20 bis etwa 25°C durchgeführt wird.

47. Verfahren nach Anspruch 1, wobei die Umsetzung mit etwa 0,001 bis etwa 0,1 Äquivalenten des chiralen Bishydroxamsäureliganden (I) durchgeführt wird.

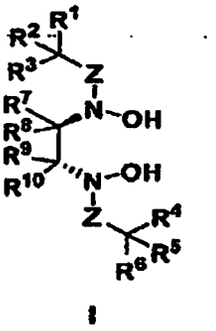
48. Verfahren nach Anspruch 1, wobei die Umsetzung mit etwa 0,005 bis etwa 0,05 Äquivalenten Metall durchgerührt wird.

Revendications

1. Procédé de conduite d'une oxydation asymétrique catalytique comprenant :

la réaction d'un substrat choisi dans le groupe consistant en un sulfure, un alcène et un alcène cyclique avec des quantités catalytiques d'un ligand acide bishydroxamique chiral et d'un métal choisi dans le groupe consistant en le vanadium et le molybdène en présence d'un réactif d'oxydation, pour produire un produit d'oxydation chiral.

2. Procédé selon la revendication 1 où le ligand acide bishydroxamique chiral a une structure I :



I

où:

R^1, R^2, R^3, R^4, R^5 et R^6 sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, alkyle, cycloalkyle, alcoxy, alkylamino, hétérocyclyle, aryle, hétéroaryle et arylalkyle ;
ou bien où R^1 et R^2, avec l'atome auquel ils sont liés, forment un cycle substitué ou non substitué choisi dans le groupe consistant en cycloalkyle, hétérocyclyle ou aryle ;
ou bien où R^4 et R^5, avec l'atome auquel ils sont liés, forment un cycle substitué ou non substitué choisi dans le groupe consistant en cycloalkyle, hétérocyclyle ou aryle ;
R^7, R^8, R^9 et R^{10} sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, alkyle, cycloalkyle, alcoxy, alkylamino, hétérocyclyle, aryle, hétéroaryle et arylalkyle ;
ou bien où R^7 et R^9, avec les atomes auxquels ils sont liés, forment un cycle substitué ou non substitué choisi dans le groupe consistant en cycloalkyle et hétérocyclyle ;
-Z- est -C(O)-.

3. Procédé selon la revendication 1 où le métal est choisi dans le groupe consistant en le vanadium (IV), le vanadium (V), le molybdène (IV), le molybdène (V) et le molybdène (VI).

4. Procédé selon la revendication 3 où le métal est choisi dans le groupe consistant en le vanadium (IV) et le vanadium (V).

5. Procédé selon la revendication 3 où le métal est choisi dans le groupe consistant en le molybdène (IV), le molybdène (V) et le molybdène (VI).

6. Procédé selon la revendication 1 où le substrat est un sulfure.

7. Procédé selon la revendication 1 où le substrat est choisi dans le groupe consistant en un alcène et un alcène cyclique.

8. Procédé selon la revendication 1 où le réactif d'oxydation est un hydroperoxyde organique ayant la formule (II) suivante :

$$R^{11}\text{-O-OH} \qquad \text{II}$$

où R^{11} est choisi dans le groupe consistant en alkyle, cycloalkyle, aryle, hétéroaryle et hétérocyclyle.

9. Procédé selon la revendication 1 où le produit d'oxydation chiral a une structure III :

III

où Y est un sulfure.

10. Procédé selon la revendication 2 où le substrat est un alcène ou un alcène cyclique.

11. Procédé selon la revendication 2 où R^1, R^2, R^3, R^4, R^5 et R^6 sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, alkyle, alcoxy et alkylamino.

12. Procédé selon la revendication 2 où R^1, R^2, R^3, R^4, R^5 et R^6 sont choisis chacun indépendamment dans le groupe consistant en cycloalkyle et hétérocyclyle.

13. Procédé selon la revendication 2 où R^1, R^2, R^3, R^4, R^5 et R^6 sont choisis chacun indépendamment dans le groupe consistant en aryle, arylalkyle, hétéroaryle et halogène.

14. Procédé selon la revendication 2 où :

R^1 et R^2, avec l'atome auquel ils sont liés, forment un cycle substitué ou non substitué ;
R^4 et R^5, avec l'atome auquel ils sont liés, forment un cycle substitué ou non substitué ; et
le cycle formé par R^1 et R^2 est identique au cycle formé par R^4 et R^5.

15. Procédé selon la revendication 2 où R^7, R^8, R^9 et R^{10} sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, alkyle, alcoxy et alkylamino.

16. Procédé selon la revendication 2 où R^7, R^8, R^9 et R^{10} sont choisis chacun indépendamment dans le groupe consistant en cycloalkyle et hétérocyclyle.

17. Procédé selon la revendication 2 où R^7, R^8, R^9 et R^{10} sont choisis chacun indépendamment dans le groupe consistant en aryle, arylalkyle et hétéroaryle.

18. Procédé selon la revendication 2 où R^7 et R^9, avec les atomes auxquels ils sont liés, forment un cycle.

19. Procédé selon la revendication 18 où R^8 et R^{10} sont identiques.

20. Procédé selon la revendication 16 où R^7 et R^9, avec les atomes auxquels ils sont liés, forment un cycle.

21. Procédé selon la revendication 20 où R^8 et R^{10} sont identiques.

22. Procédé selon la revendication 2 où :

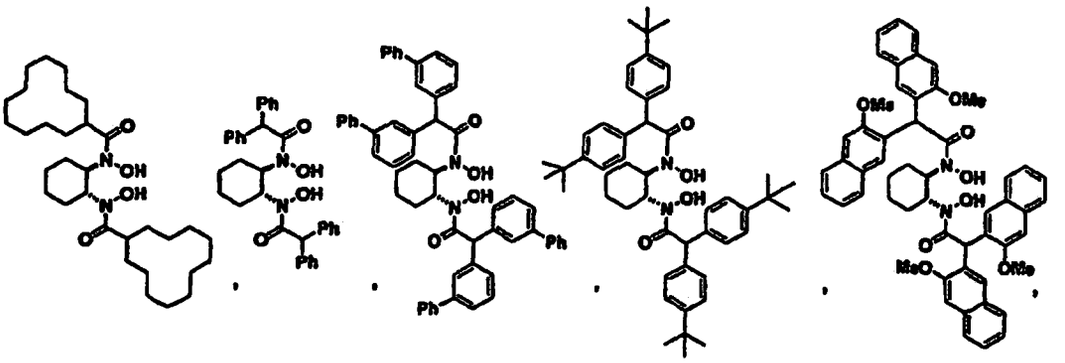
R^1 et R^2 sont des groupes aryle ;
R^3 est l'hydrogène ;
R^4 et R^5 sont des groupes aryle ; et
R^6 est l'hydrogène.

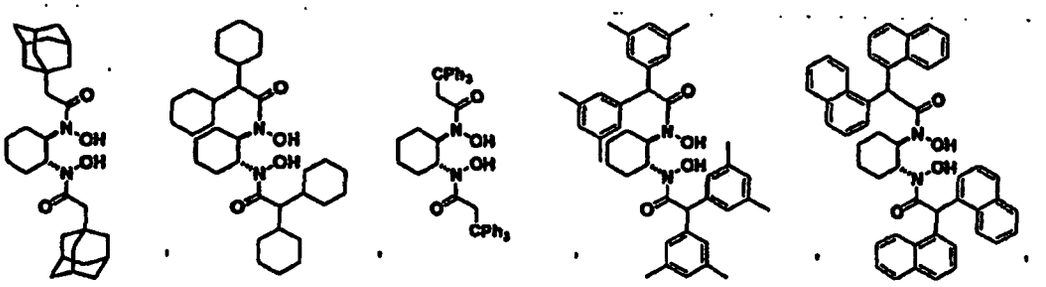
23. Procédé selon la revendication 22 où :

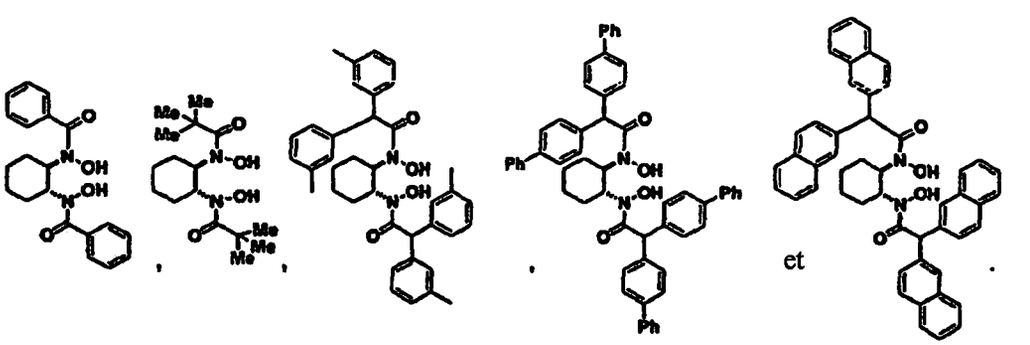
R^1 et R^2 sont identiques ; et
R^4 et R^5 sont identiques.

24. Procédé selon la revendication 23 où R^1, R^2, R^4 et R^5 sont identiques.

25. Procédé selon la revendication 2 où le ligand acide bishydroxamique chiral (I) est choisi dans le groupe consistant en :







et

26. Procédé selon la revendication 7 où le métal est choisi dans le groupe consistant en le molybdène (IV), le molybdène (V) et le molybdène (VI).

27. Procédé selon la revendication 3 où le métal est choisi dans le groupe consistant en $VO(OPr^i)_3$, $VO(acac)_2$, $VO(OEt)_3$ et $MoO_2(acac)_2$.

28. Procédé selon la revendication 7 où le métal est choisi dans le groupe consistant en $VO(OPr^i)_3$, $VO(acac)_2$, $VO(OEt)_3$ et $MoO_2(acac)_2$.

29. Procédé selon la revendication 8 où l'hydroperoxyde organique est choisi dans le groupe consistant en l'hydroperoxyde de tert-butyle et l'hydroperoxyde de cumène.

30. Procédé selon la revendication 8 où l'hydroperoxyde organique est l'hydroperoxyde de tert-butyle.

31. Procédé selon la revendication 8 où l'hydroperoxyde organique est l'hydroperoxyde de cumène.

32. Procédé selon la revendication 7 où le réactif d'oxydation est choisi dans le groupe consistant en l'hydroperoxyde de tert-butyle et l'hydroperoxyde de cumène.

33. Procédé selon la revendication 7 où le réactif d'oxydation est l'hydroperoxyde de tert-butyle.

34. Procédé selon la revendication 7 où le réactif d'oxydation est l'hydroperoxyde de cumène.

35. Procédé selon la revendication 1 où le réactif d'oxydation est le peroxyde d'hydrogène.

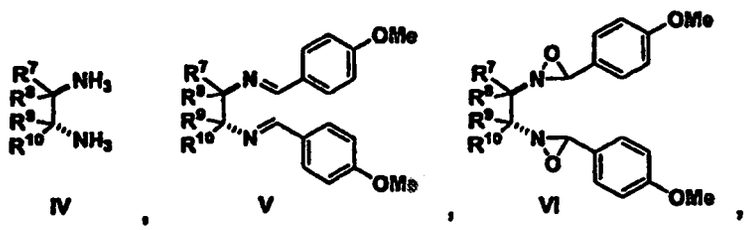
36. Procédé selon la revendication 7 où le réactif d'oxydation est le peroxyde d'hydrogène.

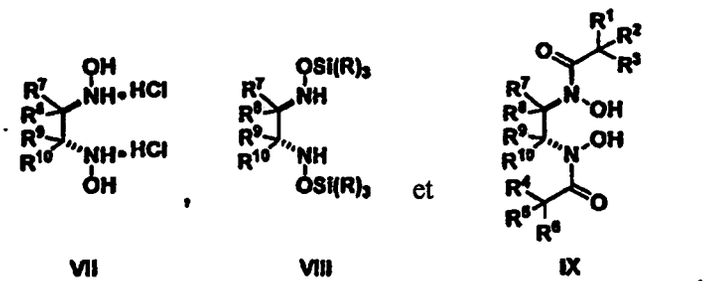
37. Procédé de préparation d'un ligand acide bishydroxamique chiral comprenant :

la condensation d'un tartrate de 1,2-diammonium optiquement actif avec le p-anisaldéhyde pour produire une di-imine ;
l'oxydation de la di-imine pour produire une dioxaziridine ;
l'hydrolyse de la dioxaziridine pour produire un chlorhydrate de dihydroxylamine ;
la silylation du chlorhydrate de dihydroxylamine pour produire une dihydroxylamine protégée par silyle ;
la condensation de la dihydroxylamine protégée par silyle avec un chlorure d'acide pour produire le ligand acide bishydroxamique chiral.

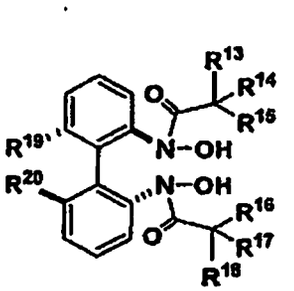
38. Procédé selon la revendication 37 où le ligand acide bishydroxamique chiral est préparé par un procédé comprenant :

la condensation d'un tartrate de 1,2-diammonium optiquement actif (IV) avec le p-anisaldéhyde pour produire une di-imine (V) ;
l'oxydation de la di-imine (V) pour produire une dioxaziridine (VI) ;
l'hydrolyse de la dioxaziridine (VI) pour produire un chlorhydrate de dihydroxylamine (VII) ;
la silylation du chlorhydrate de dihydroxylamine (VII) pour produire une dihydroxylamine protégée par silyle (VIII) ;
la condensation de la dihydroxylamine protégée par silyle avec un chlorure d'acide pour produire l'acide bis-hydroxamine (IX)

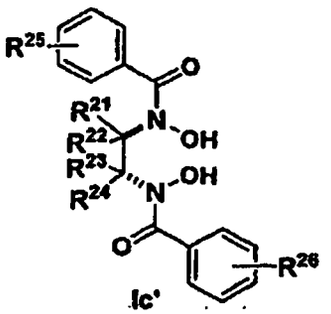




39. Procédé selon la revendication 1 où le ligand acide bishydroxamique chiral (I) est choisi parmi les formules suivantes :



Ib'

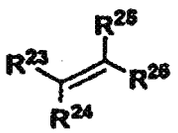


Ic'

où:

R^{13}, R^{14}, R^{15}, R^{16}, R^{17} et R^{18} sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, alkyle, cycloalkyle, alcoxy, alkylamino, hétérocyclyle, aryle, hétéroaryle et arylalkyle ;
R^{19} et R^{20} sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, halogène, alkyle, cycloalkyle, alcoxy, alkylamino, hétérocyclyle, aryle, hétéroaryle et arylalkyle ;
R^{21}, R^{22}, R^{23} et R^{24} sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, alkyle, cycloalkyle, alcoxy, alkylamino, hétérocyclyle, aryle, hétéroaryle et arylalkyle ;
R^{25} et R^{26} sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, halogène, alkyle, cycloalkyle, alcoxy, alkylamino, hétérocyclyle, aryle, hétéroaryle et arylalkyle.

40. Procédé selon la revendication 7 où l'alcène est de formule (X) :

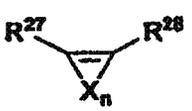


X

où :

R^{23}, R^{24}, R^{25} et R^{26} sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, halogène, alkyle, cycloalkyle, alcoxy, alkylamino, hétérocyclyle, aryle, hétéroaryle et arylalkyle.

41. Procédé selon la revendication 7 où l'alcène est un alcène cyclique de formule (Xa) :



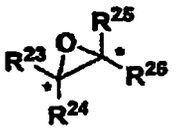
Xa

où :

R^{27} et R^{28} sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, alkyle, cycloalkyle, alcoxy, alkylamino, hétérocyclyle, aryle, aralkyle, hétéroaryle, halogène et alcène ;
n est 1, 2, 3, 4, 5, 6 ou 6 ;
chaque X est choisi indépendamment dans le groupe consistant en -CR'R'', -NR'- et -O- ;
R' et R'' sont choisis chacun indépendamment dans le groupe consistant en l'hydrogène, alkyle, cycloalkyle,

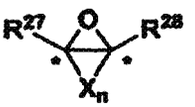
alcoxy, alkylamino, hétérocyclyle, aryle, aralkyle, hétéroaryle et halogène.

42. Procédé selon la revendication 40 où le produit d'oxydation chiral est de formule (Xb) :



Xb

43. Procédé selon la revendication 41 où le produit d'oxydation chiral est de formule (Xc) :



Xc

44. Procédé selon la revendication 1 où l'étape de réaction est conduite dans un solvant.

45. Procédé selon la revendication 44 où l'étape de réaction est conduite dans un solvant choisi dans le groupe consistant en le chlorure de méthylène, le toluène, le chloroforme et l'acétate d'éthyle.

46. Procédé selon la revendication 1 où l'étape de réaction est conduite à une température d'environ -20 à environ 25˚C.

47. Procédé selon la revendication 1 où la réaction est conduite avec environ 0,001 à environ 0,1 équivalent de ligand acide bishydroxamique chiral (I).

48. Procédé selon la revendication 1 où la réaction est conduite avec environ 0,005 à environ 0,05 équivalent de métal.