

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 June 2006 (29.06.2006)

PCT

(10) International Publication Number
WO 2006/068879 A1

(51) International Patent Classification:
C07F 17/02 (2006.01)

(21) International Application Number:
PCT/US2005/045031

(22) International Filing Date:
12 December 2005 (12.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/018,287 21 December 2004 (21.12.2004) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG,
SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ,
VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: TETRADENTATE LIGANDS AND METAL COMPLEXES THEREOF FOR ASYMMETRIC CATALYSIS

(57) Abstract: This invention relates to novel, substantially enantiomerically pure tetradentate ligands comprised of two phosphines and two secondary amines. These species have been used as ligands for metal catalysts for asymmetric reactions and have demon-
strated good enantioselectivity, in particular as ruthenium complexes for asymmetric hydrogenation. Also disclosed are methods
for making the ligands, corresponding catalyst complexes, and processes employing the ligands and catalysts. The ligands may be
described by the general formula (1): $R_2P-L^1-NH-L^2-NH-L^3-PR^1_2$.



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Tetradentate Ligands and Metal Complexes Thereof For Asymmetric Catalysis

5 Field of the Invention

 This invention relates to novel tetradentate ligands comprised of two phosphines and two secondary amines. These species have been used as ligands for metal catalysis for asymmetric reactions and have demonstrated good enantioselectivity, in particular as ruthenium complexes for
10 asymmetric hydrogenation.

Background of the Invention

 Asymmetric catalysis is the most efficient method for generating products with high enantiomeric purity, as the asymmetry of the catalyst is
15 multiplied many times over in generating the chiral product. These chiral products have found numerous applications, such as building blocks for single enantiomer pharmaceuticals and in some agrochemicals. The asymmetric catalysts employed can be enzymatic or synthetic in nature. The latter types of catalyst have much greater promise than the former
20 because of a much greater latitude in applicable reaction types. Synthetic asymmetric catalysts are usually composed of a metal reaction center surrounded by one or more organic ligands. The ligands usually are generated in high enantiomeric purity, and are the agents inducing the asymmetry. These ligands are, in general, difficult to make and therefore
25 expensive.

 The asymmetric reduction of ketones to afford chiral alcohols is a key transformation having numerous applications in the pharmaceutical, agrochemical, and flavors and fragrances areas. A number of technologies are available for this type of reduction, including chiral oxazaborolidine-
30 catalyzed borane reductions (Itsuno, S. in *Comprehensive Asymmetric Catalysis*, Volume I, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H, eds,

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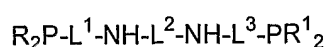
Springer-Verlag, New York, pp. 289-315) and rhodium- and ruthenium-catalyzed transfer hydrogenations (Ohkuma et al. in *Comprehensive Asymmetric Catalysis*, Volume I, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H, eds, Springer-Verlag, New York, pp. 227-246). The foregoing technologies, however, generally use relatively large amounts of catalyst (>1 mol%) and, for the latter reaction, require dilute conditions and are therefore not particularly efficient. Of particular note are the recent reports of catalysts comprised of a mixture of a chiral bis-phosphine and a chiral diamine ligated to ruthenium, which are reported to afford high enantioselectivity for the asymmetric hydrogenation of ketones at low catalyst loadings (Ohkuma, et al, *J. Am. Chem. Soc.* **1995**, *117*, 2675-2676; Doucet, et al, *Angew. Chem. Int. Ed.* **1998**, *37*, 1703-1707; Ohkuma, et al, *Organic Lett.* **2000**, *2*, 1749-1751). A particular drawback of these systems is the potential for formation of mixed complexes comprising two bis-phosphines or two bis-amines surrounding the metal. These species may afford results that are destructive compared to that of the mixed complexes. There has been a report of a ruthenium complex of a ligand system comprising two achiral phosphines linked through a chiral diamine for ketone reduction (Gao, et al, *Organometallics* **1996**, *15*, 1087-1089). This system is effective for the transfer hydrogenation of ketones but has not been reported for direct hydrogenation reactions.

As described by Richards et al. in *Tetrahedron: Asymmetry* **1998**, *9*, 2377-2407, asymmetric ferrocene derivatives have found great utility as ligands for asymmetric catalysis in reactions as varied as asymmetric hydrogenations, asymmetric Aldol reactions, asymmetric organometallic additions, and asymmetric hydrosilations. These ferrocene species usually are bidentate in nature, using a variety of ligating species.

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Brief Summary of the Invention

We have now found a series of novel, substantially enantiomerically pure, tetradentate ligands wherein the ligating groups comprise two phosphines linked by chiral backbones to two secondary amines. These
5 ligands may be described by the general formula 1:



1

In the foregoing formula 1, R and R¹ are, independently, branched- or straight-chain C₁-C₂₀ alkyl, C₃-C₈ cycloalkyl, C₆-C₂₀ carbocyclic aryl, or a
10 C₄-C₂₀ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen; L¹, L², and L³ may be the same or different, and are divalent radicals selected from branched- or straight-chain C₁-C₂₀ alkyl, C₃-C₈ cycloalkyl, C₆-C₂₀ carbocyclic aryl, a C₄-C₂₀ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen,
15 or metallocenylalkyl and wherein L¹, L³ and, optionally, L² are substantially enantiomerically pure. The foregoing moieties for each of R and R¹, and each of L¹ through L³ may be unsubstituted or substituted with groups described below.

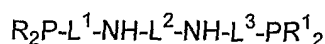
Also described herein is a method for making the novel, substantially
20 enantiomerically pure, tetradentate ligands in good yields and purity. Further, methods for making metal catalyst complexes and processes employing the ligands and the metal complexes are described herein.

Detailed Description

25 We have discovered a series of novel substantially enantiomerically pure tetradentate ligands wherein the ligating groups comprise two

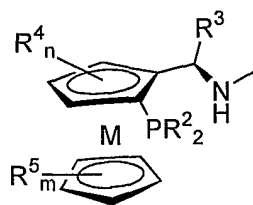
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phosphines linked by chiral backbones to two secondary amines. These ligands are described by the general formula **1**:

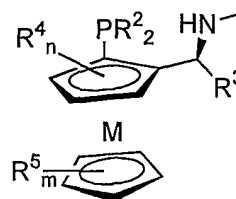
**1**

- 5 wherein R and R¹ are, independently, branched- or straight-chain C₁-C₂₀ alkyl, C₃-C₈ cycloalkyl, C₆-C₂₀ carbocyclic aryl, or a C₄-C₂₀ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen; L¹, L², and L³ may be the same or different, and are divalent radicals selected from branched- or straight-chain C₁-C₂₀ alkyl, C₃-C₈ cycloalkyl, C₆-
10 C₂₀ carbocyclic aryl, a C₄-C₂₀ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen, or metallocenylalkyl and wherein L¹, L³ and, optionally, L² are substantially enantiomerically pure. The foregoing moieties for each of R and R¹, and each of L¹ through L³ may be unsubstituted or substituted with one or more
15 groups described below. As used herein, the phrase "enantiomerically enriched" indicates that one enantiomer is present in excess of the other, the phrase "substantially enantiomerically pure" connotes a degree of excess of 90% or greater and "enantiomeric excess" (or ee) indicates the percent of the major enantiomer less the percent of the minor enantiomer.
20 Specific examples of the tetradentate ligands of the present invention include those wherein R and R¹ are identical and L¹ and L³ are identical. For example, R₂P-L¹-NH- and R¹₂P-L³-NH- may be identical species denoted by structures **2** or **3** (the enantiomer of **2**) as follows:

- 5 -



2



3

wherein

each R^2 is either of R or R^1 described above; R^3 , R^4 , and R^5 are
 5 each independently selected from hydrogen, branched- or straight-chain
 C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl
 having one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

n is 0 to 3;

m is 0 to 5; and

10 M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

L^2 is a C_1 - C_{20} alkylene, C_3 - C_8 cycloalkylene, or 1,1'-biaryl-2,2'-diyl.

The foregoing values for L^2 may be achiral, racemic, enantiomerically
 enriched, or substantially enantiomerically pure and may be unsubstituted
 or may be substituted with one or more groups below.

15 As noted above, the values for each of R_2P-L^1-NH- and $R^1_2P-L^3-NH-$
 need not be identical. Thus, for example, when general structure 2 or 3
 represents each of R_2P-L^1-NH- and $R^1_2P-L^3-NH-$, each of the individual
 groups R^2 through R^5 for each of general formula 2 or 3 may be chosen
 independently. For example, while general structure 2 may represent both
 20 R_2P-L^1-NH- and $R^1_2P-L^3-NH-$, the individual R or R^1 group on each end of
 structure 1 (e.g., R^2 in structure 2) may be chosen independently. Likewise,
 "L¹" may be represented by a first general formula 2 (or 3) and "L³" may be
 represented by a second general formula 2 (or 3); the R^2 through R^5 groups

- 6 -

on the first formula **2** (or **3**) may be chosen independently from those chosen for the second general formula **2** (or **3**).

The alkyl groups that may represent each of R, R¹, R², R³, R⁴, and R⁵ may be straight- or branched-chain aliphatic hydrocarbon radicals containing from one up to 20 carbon atoms and may be substituted, for example, with one to three groups selected from C₁-C₆-alkoxy, cyano, C₂-C₆-alkoxycarbonyl, C₂-C₆-alkanoyloxy, hydroxy, aryl and halogen. The terms "C₁-C₆-alkoxy", "C₂-C₆-alkoxycarbonyl", and "C₂-C₆-alkanoyloxy" are used to denote radicals corresponding to the structures -OR⁶, -CO₂R⁶, and -OCOR⁶, respectively, wherein R⁶ is C₁-C₆-alkyl or substituted C₁-C₆-alkyl.

The term "C₃ - C₈-cycloalkyl" is used to denote a saturated, carbocyclic hydrocarbon radical having three to eight carbon atoms. The "C₆-C₂₀ carbocyclic aryl" groups that each of R, R¹, R², R³, R⁴, and R⁵ may represent may include phenyl, naphthyl, or anthracenyl. Each of the cycloalkyl and carbocyclic aryl groups may be substituted with one to three substituents selected from C₁-C₆-alkyl, C₆-C₁₀ aryl, C₁-C₆-alkoxy, halogen, carboxy, cyano, C₁-C₆-alkanoyloxy, C₁-C₆-alkylthio, C₁-C₆-alkylsulfonyl, trifluoromethyl, hydroxy, C₂-C₆-alkoxycarbonyl, C₂-C₆-alkanoylamino, -O-R⁷, -S-R⁷, -SO₂-R⁷, -NHSO₂R⁷ and -NHCO₂R⁷, wherein R⁷ is phenyl, naphthyl, or phenyl or naphthyl substituted with one to three groups selected from C₁-C₆-alkyl, C₆-C₁₀ aryl, C₁-C₆-alkoxy and halogen.

The heteroaryl radicals contain from four to twenty carbon atoms and from one to three heteroatoms selected from sulfur, nitrogen and oxygen. Specific examples include 5- or 6- membered aromatic rings containing one to three heteroatoms selected from oxygen, sulfur and nitrogen. Examples of such heteroaryl groups are thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyrimidyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, indolyl and the like. The heteroaryl radicals may be substituted, for example, with up to three groups such as C₁-C₆-alkyl, C₁-C₆-alkoxy,

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halogen, C₁-C₆-alkylthio, aryl, arylthio, aryloxy, C₂-C₆-alkoxycarbonyl and C₂-C₆-alkanoylamino. The heteroaryl radicals also may be substituted with a fused ring system, e.g., a benzo or naphtho residue, which may be unsubstituted or substituted, for example, with up to three of the groups set forth in the preceding sentence. The term "halogen" includes fluorine, chlorine, bromine, and iodine.

The skilled artisan will understand that each of the references herein to groups or moieties having a stated range of carbon atoms, such as "C₁-C₆-alkyl," includes not only the C₁ group (methyl) and C₆ group (hexyl) end points, but also each of the corresponding individual C₂, C₃, C₄ and C₅ groups. In addition, it will be understood that each of the individual points within a stated range of carbon atoms may be further combined to describe subranges that are inherently within the stated overall range. For example, the term "C₁-C₆-alkyl" includes not only the individual moieties C₁ through C₆, but also contemplates subranges such as "C₂-C₅-alkyl."

The compounds of the invention that presently are preferred have formulas 2 or 3 wherein R² is aryl, most preferably phenyl; R³ is hydrogen or C₁ to C₆ alkyl (such as methyl); R⁴ and R⁵ are hydrogen; L² is 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-diyl; and M is iron, ruthenium, or osmium, most preferably iron.

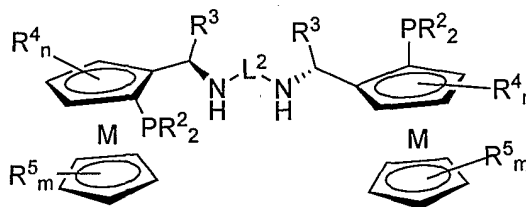
When the diamino portion represented by -NH-L²-NH- is achiral, it can be any diamino species having two NH groups, and are preferably alkane species with amino groups at each terminus such as ethylenediamino, 1,3-propanediamino, 1,4-butanediamino, and the like. When the diamino group represented by -NH-L²-NH- is chiral, it can be any chiral diamino species possessing two NH groups with one or more chiral centers. The chiral diamino groups are most preferably substantially enantiomerically pure C₂-symmetrical diamino groups such as 1,2-diphenyl-

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1,2-ethanediamino, trans-1,2-cyclohexanediamino, and 1,1'-binaphth-2,2'-yl diamino.

As stated above, certain embodiments of the compounds of our invention are those containing two substantially enantiomerically pure
 5 phosphinometallocenylalkyl groups linked together by a chiral or achiral diamine. The metallocene-based embodiments of our ligands are readily modifiable by varying R^2 according to the choice of the phosphine used, R^3 according to the backbone used, and L^2 according to the diamine used, and thus allows simple modification of the reactivity and selectivity of the
 10 catalyst prepared from such ligands.

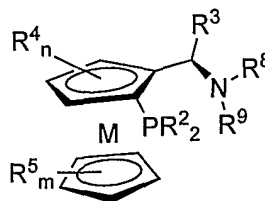
We also provide novel processes for preparing compounds of formula 1 in which the two phosphine moieties are linked by the diamine. Thus, for example, the present invention includes a process for preparing a substantially enantiomerically pure compound having formula 4:



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which comprises the steps of:

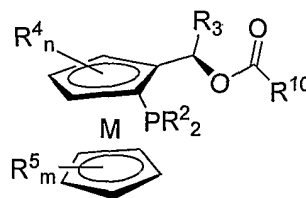
(1) contacting a dialkyl amine having formula 5:



5

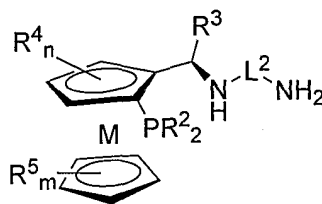
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with a carboxylic anhydride having the formula $(R^{10}CO)_2O$ to obtain an ester compound having formula 6:



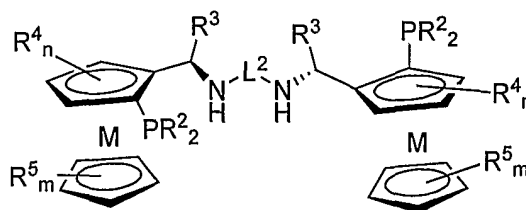
6

- (2) contacting the ester produced in step (1) with a diamine having the formula $H_2N-L^2-NH_2$ to obtain phosphine-diamine 7:



7

- (3) contacting the phosphine-diamine produced in step (2) with an ester such as that produced in step (1) to afford diphosphine-diamine 4



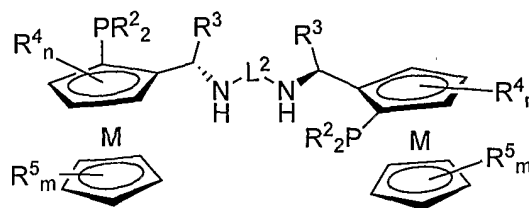
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wherein each R^2 , R^3 , R^4 , R^5 , n , m , L^2 and M are defined hereinabove, R^8 and R^9 are independently selected from branched- or straight-chain C_1 - C_{20}

- 10 -

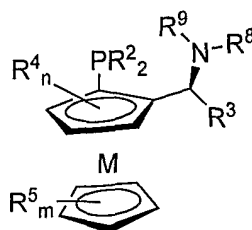
alkyl, C₃-C₈ cycloalkyl, C₆-C₂₀ carbocyclic aryl, or C₄-C₂₀ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen, and R¹⁰ is a C₁ to C₄ alkyl radical. The groups representing each of R⁸ and R⁹ may be unsubstituted or substituted with, for example, one or more groups as set forth above in relation to substituents for each of R², R³, R⁴ and R⁵.

The compounds of formula **8**:

**8**

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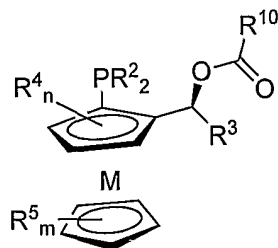
may be prepared when a dialkylamine having formula **9**:

**9**

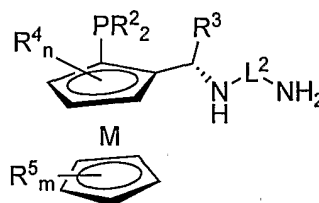
is used as the starting material affording intermediates **10** and **11** analogous to **6** and **7**, respectively.

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- 11 -

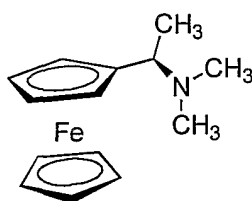


10



11

Dialkylamine reactant compounds **5** (or **9**) can be prepared in high enantiomeric purity by several known methods. For example, precursor **12** having the formula:



12

5

can be prepared in high enantiomeric purity using the procedures described by Marquarding et al., *J. Am. Chem. Soc.* **1970**, 92, 5389-5393; Armstrong et al., *Anal. Chem.* **1985**, 57, 481-484; and Boaz, N. W. *Tetrahedron Letters* **1989**, 30, 2061-2064. Precursor **12** can then be converted by known procedures to dialkylamine reactant **5**, e.g., using the procedures described in Hayashi, T. et al. *Bull Chem. Soc. Jpn.* **1980**, 53, 1130-1151; and the references mentioned in the preceding sentence. The enantiomeric species **9** can be prepared in a like manner.

In the first step of the process, dialkylamine reactant compound **5** (or **9**) is contacted with a carboxylic anhydride. The amount of anhydride used may be 1 to 100 moles, preferably 2 to 10 moles, per mole of dialkylamine reactant **5** (or **9**). Although the carboxylic anhydride may contain up to 10 carbon atoms, acetic anhydride is preferred. That is, R¹⁰ is a C₁ to C₄ alkyl,

15

- 12 -

and R¹⁰ is preferably a C₁ group. The first step of the process may be carried out at a temperature between 20°C and the boiling point of the anhydride, preferably 80°C to 120°C. While an inert solvent may be used in step (1), the carboxylic anhydride may function as both solvent and
5 reactant. At the completion of the first step, the ester intermediate may be isolated for use in the second step by conventional procedures known to those skilled in the art. For example, the product may be crystallized or isolated by removing the carboxylic anhydride and any extraneous solvent present, such as by decanting or distillation or both.

10 In the second step of the process, the ester intermediate obtained from step (1) is contacted with a diamine having the formula H₂N-L²-NH₂ in the presence of a solvent. The solvent may be water, a C₁ to C₄ alkanol such as methanol, ethanol, isopropanol, or n-butanol, a dipolar aprotic solvent such as acetonitrile, dimethylformamide, or dimethylsulfoxide, an
15 aromatic hydrocarbon such as benzene, toluene, or xylene, a halocarbon solvents such as dichloromethane, tetrachloroethylene, or chlorobenzene or a mixture of any of the foregoing. Preferred solvents include, but are not limited to, a mixture of methanol and toluene, a mixture of water, 2-propanol, and toluene, or dimethylformamide. The second step may be
20 carried out at a temperature between 20°C and the boiling point of the solvent, preferably 25°C to 50°C.

In the foregoing description of a process to make compound 4, the reaction in step (2) is conducted in a way to allow for isolation of intermediate 7 (or, in the case of starting material 9, intermediate 11). For
25 example, using an excess of diamine in step (2) predominantly results in the mono-substituted diamine exemplified by intermediate 7. Thus, the mole ratio in step (2) of the diamine:ester intermediate 6 (or 10) typically is in the range of 0.8:1 to 10:1, preferably 0.8:1 to 5:1.

30 Allowing for the isolation of intermediate 7 (or, in the case of starting material 9, intermediate 11), in turn allows one to select the ester used in

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step (3) according to the characteristics desired in the end product. In the above example, the ester of **5** (compound **6**) is used in both step (1) and step (3) to provide compound **4**; one of skill in the art will appreciate, however, that an ester of **9** (compound **10**) may be used in step (3).

5 Likewise, an ester of **5** (compound **6**) may be used in step (3) when ester of **9** (compound **10**) is produced in step (1). Further, as stated above, when the ester of **5** (compound **6**) is used in both steps (1) and (3) (as a first ester **6** and a second ester **6**, respectively), each of the variables on compound **6** used in step (3) may be chosen differently from those employed in step (1) (e.g., each R^2 , R^3 , R^4 , and R^5 on the second ester **6** are selected
10 independently of those chosen for the first ester **6**); the same applies when compound **10** is employed in both steps (1) and (3).

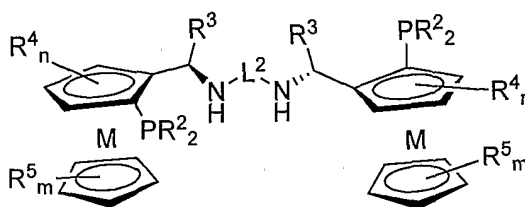
In addition, the second step of the reaction may optionally be carried out in the presence of an acid acceptor. Suitable examples include a
15 tertiary amine such as trialkylamines containing a total of 3 to 15 carbon atoms such as triethylamine, tripropylamine, and diisopropylethylamine, pyridine, substituted pyridines and the like. The amount of acid acceptor used normally is from 0 up to 10 moles of acid acceptor per mole of diamine reactant.

20 In the third step of the above process, the phosphine-diamine intermediate obtained from step (2) is contacted with an ester of formula **6** (or **10**) in the presence of a solvent, which may be chosen from among those noted above as suitable for use in the second step. The third step may be carried out at a temperature between 20°C and the boiling point of the solvent, preferably 25°C to 50°C. The mole ratio of the phosphine-
25 diamine:ester intermediate **6** (or **10**) in the third step typically is in the range of 1:1 to 1:5. As with the second step, this reaction may optionally be carried out in the presence of an acid acceptor such as those listed above as being suitable for use in the second step. The amount of acid acceptor

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used normally is from 0 up to 10 moles of acid acceptor per mole of diamine reactant.

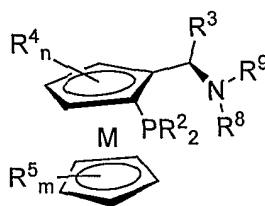
A further embodiment of the processes of the present invention involves directly producing compounds having formula 1 in a two step process. Thus, for example, the present invention relates to a process for
 5 preparing a substantially enantiomerically compound having formula 4:



4

which comprises the steps of:

10 (1) contacting a dialkyl amine having formula 5:

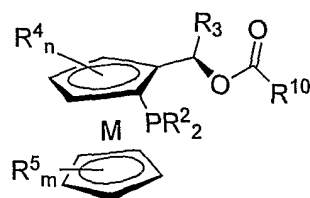


5

with a carboxylic anhydride having the formula $(R^{10}CO)_2O$ to obtain an ester compound having formula 6:

15

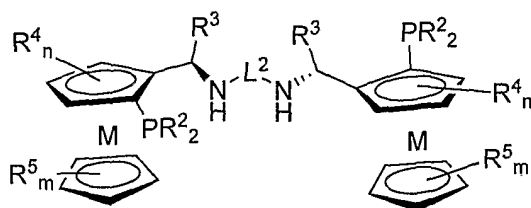
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6

and

(2) contacting the ester produced in step (1) with a diamine having the formula $H_2N-L^2-NH_2$ to obtain in simple fashion the diphosphine-diamine **4**:

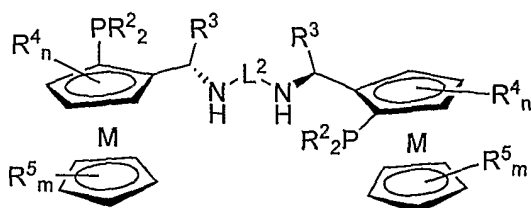


4

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wherein R^2 , R^3 , R^4 , R^5 , R^8 , R^9 , R^{10} , n , m , L^2 and M are defined above.

Likewise, the compounds of formula **8**:

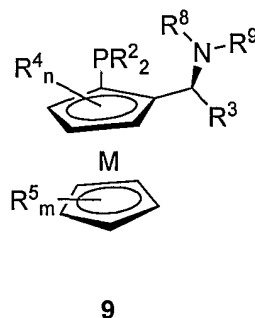


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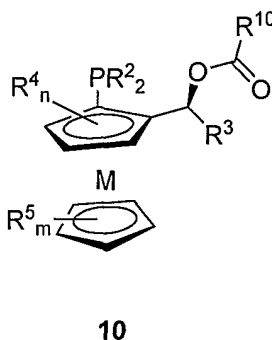
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may be prepared when dialkylamine having formula **9**:



is used as the starting material affording intermediate **10** (which is analogous to **6**).



In the first step of the process, dialkylamine reactant compound **5** (or **9**) is contacted with a carboxylic anhydride. The amount of anhydride used may be 1 to 100 moles, preferably 2 to 10 moles, per mole of dialkylamine reactant **5** (or **9**). The first step of the process may be carried out at a temperature between 20°C and the boiling point of the anhydride, preferably 80°C to 120°C. While an inert solvent may be used in step (1), the carboxylic anhydride may function as both solvent and reactant. At the completion of the first step, the ester intermediate may be isolated for use in the second step by conventional procedures known to those skilled in the art. For example, the product may be crystallized or isolated by removing

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the carboxylic anhydride and any extraneous solvent present, such as by decanting or distillation or both.

In the second step of the process, the ester intermediate obtained from step (1) is contacted with a diamine having the formula $H_2N-L^2-NH_2$ in the presence of a solvent. The solvent may be water, a C_1 to C_4 alkanol such as methanol, ethanol, n-propanol, isopropanol, or n-butanol, a dipolar aprotic solvent such as acetonitrile, dimethylformamide, or dimethylsulfoxide, an aromatic hydrocarbon such as benzene, toluene, or xylene, a halocarbon solvents such as dichloromethane, tetrachloroethylene, or chlorobenzene or a mixture of any of the foregoing. Preferred solvents include, but are not limited to, a mixture of methanol and toluene, a mixture of water, isopropanol, and toluene, or dimethylformamide. The second step may be carried out at a temperature between 20°C and the boiling point of the solvent, preferably 25°C to 50°C.

In the foregoing two-step process to produce compounds of formula **1**, the same ester is attached to both amine moieties of the diamine having the formula $H_2N-L^2-NH_2$. This may be done in a simple and direct fashion by controlling the reactant ratio. Thus, the mole ratio of the diamine:ester intermediate **6** (or **10**) typically is in the range of 1:2 to 1:5. When the process is operated in this manner, it is not necessary to isolate a phosphine-diamine intermediate for further reaction with an ester. In this two-step process, one may therefore easily and simply produce **4**, in the case of starting material **5** and ester **6** (or, compound **8** in the case of starting material **9** and ester **10**).

In addition, the second step of the reaction may optionally be carried out in the presence of an acid acceptor. Suitable examples include a tertiary amine such as trialkylamines containing a total of 3 to 15 carbon atoms such as triethylamine, tripropylamine, and diisopropylethylamine, pyridine, substituted pyridines and the like. The amount of acid acceptor

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used normally is from 0 up to 10 moles of acid acceptor per mole of diamine reactant.

Also included within the scope of the present invention are catalytically-active compounds comprising one or more substantially enantiomerically pure, diphosphinodiamine compounds **1** in complex association with one or more Group VIb or Group VIII metals, preferably rhodium, iridium, or ruthenium, most preferably ruthenium. These complexes can be prepared *in situ*, but it is often preferable to prepare and isolate them. The catalyst complexes generally may be prepared by mixing the ligand and a metal precursor in an inert solvent followed by isolation of the complex by standard procedures such as solvent distillation or crystallization.

For example, ruthenium complexes of **4** may be prepared by mixing **4** with a suitable ruthenium precursor, such as arenerutheniumdichloride dimer. Examples of such precursors include benzenerutheniumdichloride dimer and p-cymeneruthenium dichloride dimer. The molar ratio of ligand to metal atoms in the metal precursor (e.g., areneruthenium dichloride dimer) is generally 0.5:1 to 2.5:1, respectively, and preferably is 0.8:1 to 1.5:1. Inert solvents used to prepare such a complex include aromatic hydrocarbons such as benzene, toluene, xylenes, and the like, lower alcohols such as methanol, ethanol, n-propanol, or isopropanol, or polar aprotic solvents such as dimethyl formamide, acetonitrile, or dimethyl sulfoxide. Preferable solvents include toluene, isopropanol or dimethyl formamide. The reactions can be performed between ambient temperature and the boiling point of the solvent, most preferably between 50°C and 120°C.

There are a large number of possible reactions of a wide variety of substrates using catalysts based on compound **1**, including but not limited to asymmetric hydrogenations, asymmetric reductions, asymmetric hydroborations, asymmetric olefin isomerizations, asymmetric

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hydrosilations, asymmetric allylations, and asymmetric organometallic additions. A further embodiment of the present invention is an asymmetric hydrogenation reaction using a metal complex of compound 1. Thus, the present invention includes a process for the asymmetric hydrogenation of a
5 suitable carbonyl compound which comprises contacting the carbonyl compound with hydrogen in the presence of a catalyst complex comprising ligand 1 in complex association with a metal. The reaction results in the formation of a chiral secondary alcohol, which is generally obtained in moderate to high enantiomeric excess.

10 For an asymmetric hydrogenation reaction, the metal complexed can be chosen from the group consisting of rhodium, ruthenium, and iridium, and is most preferably ruthenium. The ligand-metal complex can be prepared and used *in situ*, but it is often preferable to prepare and isolate the complex as described above. The amount of complex can vary
15 between 0.00005 and 0.5 equivalents based on the reactant carbonyl compound, with more complex usually providing faster reaction rates. The atmosphere is generally hydrogen or hydrogen mixed with other inert gases. The reaction can be run between 1 and 2000 psig hydrogen, and is preferably run between 50 and 500 psig. The reaction is run at a
20 temperature which affords a reasonable rate of conversion, which can be as low as -50°C, but is usually between ambient temperature and the boiling point (or apparent boiling point at elevated pressure) of the lowest boiling component of the reaction mixture. The asymmetric hydrogenation is usually performed in the presence of a suitable solvent. A solvent for use
25 herein includes: lower alcohols such as methanol, ethanol, or isopropanol; aliphatic hydrocarbons such as hexane, heptane, octane and the like; aromatic hydrocarbons such as toluene, xylenes and the like; cyclic or acyclic ethers such as tert-butyl methyl ether, diisopropyl ether, tetrahydrofuran and the like; halogenated aliphatic or aromatic
30 hydrocarbons such as dichloromethane, tetrachloroethylene, chloroform,

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chlorobenzene and the like; or polar aprotic solvents such as dimethylformamide, dimethyl sulfoxide and the like. The most preferred solvent is isopropanol.

The asymmetric hydrogenations are also run in the presence of a Bronsted base chosen from alkali metal hydroxides such as sodium hydroxide or potassium hydroxide or metal alkoxides such as sodium methoxide, potassium methoxide, sodium tert-butoxide, potassium tert-butoxide and the like. The preferred base is potassium tert-butoxide. The amount of base is generally between 1 and 100 equivalents based on the metal complex, preferably between 10 and 50 equivalents.

This invention can be further illustrated by the following examples of preferred embodiments thereof, although it will be understood that these examples are included merely for purposes of illustration and are not intended to limit the scope of the invention unless otherwise specifically indicated.

Examples

Example 1:

Preparation of (S)-1-[(R)-2-(Diphenylphosphino)ferrocenyl]ethyl acetate (S,R-10a)

(S)-N,N-Dimethyl-1-[(R)-2-(diphenylphosphino)ferrocenyl]ethylamine (S,R-9a, $R^3 = R^8 = R^9 = \text{methyl}$, $R^2 = \text{phenyl} - \text{Ph}$, $R^4 = R^5 = \text{H}$, $M = \text{Fe}$)(5.0 g; 11.3 mmol) was combined with acetic anhydride (5.0 mL; 53 mmol; 4.7 equivalents). The flask was evacuated and filled with nitrogen ten times and then heated to 90°C for 4 hours, at which point thin layer chromatography (tlc) analysis indicated no 9a present. The residual acetic anhydride was evaporated at reduced pressure, dissolved in ethyl acetate and concentrated two times to afford a crude solid. The crude product was dissolved in ethyl acetate (4 mL), diluted with heptane (20 mL) and cooled

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to 4°C. The resulting crystals were filtered, washed with heptane, and dried under nitrogen to afford 4.21 g (82%) of *S,R*-**10a**.

¹H NMR (CDCl₃) δ 7.6-7.1 (m, 10 H); 6.22 (m, 1H); 4.573 (br s, 1H); 4.36 (m, 1H); 4.049 (s, 5H); 3.804 (m, 1H); 1.632 (d, *J* = 6.32 Hz, 3H); 1.170 (s, 3H).

The enantiomer *R,S*-**6a** was prepared in a similar fashion from *R,S*-**5a**.

Example 2:

10 Preparation of *N,N'*-Bis[(*S*)-1-[(*R*)-2-Diphenylphosphino]ferrocenyl]ethyl ethylenediamine (*S*-**8a**)

Ester *S,R*-**10a** (1.0 g; 2.19 mmol; 2.1 equiv) was combined with 5 mL of isopropanol and 2 mL of water. Ethylenediamine (69 mL; 1.04 mmol) was added and the mixture was heated to 50°C. Toluene (1 mL) was added and the reaction was heated overnight at 50°C, at which time a small amount of **10a** was still present according to tlc analysis. Triethylamine (0.30 mL) was added and the mixture was heated at 50°C for 4 h to completely consume **10a** according to tlc analysis. The volatiles were distilled at reduced pressure and the residue was partitioned between 1 N sodium hydroxide and ethyl acetate. The layers were separated and the aqueous layer was extracted with additional ethyl acetate. The combined organic solution was extracted with 10% aqueous citric acid (4 x 5 mL). The aqueous extracts were made basic with 2 N sodium hydroxide (20 mL) and extracted three times with ethyl acetate. The combined extracts were dried (magnesium sulfate) and concentrated to afford 0.71 g. The crude product was filtered through a pad of flash silica gel and eluted with 1:1 ethyl acetate:heptane to remove impurities, and then with 5% triethylamine in ethyl acetate to afford 0.18 g (20%) of *S*-**8a**.

30 ¹H NMR (CDCl₃) δ 7.6-7.1 (m, 20 H); 4.44 (m, 2H); 4.28 (m, 2H); 3.972 (s, 10H); 3.88 (m, 2H); 3.78 (m, 2H); 1.9-1.8 (m, 4H); 1.4-1.3 (m, 6H).

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FDMS: m/e 852.14 (M^+).

Example 3:

Preparation of N,N'-Bis[(S)-1-[(R)-2-Diphenylphosphino]ferrocenyl]ethyl
(R,R)-1,2-cyclohexyldiamine (S,R-8b)

5 Ester S,R-10a (1.0 g; 2.19 mmol) was combined with R,R-1,2-diaminocyclohexane (1.25 g; 10.95 mmol; 5 equiv) in 5 mL of isopropanol, 2 mL of water, and 1 mL of toluene. The reaction mixture was heated overnight at 50°C to completely consume 10a according to tlc analysis.

10 The reaction mixture was diluted with ethyl acetate and 1 N sodium hydroxide (10 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic solution was dried (magnesium sulfate) and concentrated to afford 1.36 g of crude product. This material was filtered through a pad of flash silica gel and

15 eluted with ethyl acetate to remove impurities, and then with 1:1 ethyl acetate:isopropanol with 5% added triethylamine to afford 0.92 g (82%) of S,R-11b.

A portion of this phosphinodiamine (0.71 g; 1.39 mmol) was combined with ester S,R-10a (952 mg; 2.09 mmol; 1.5 equiv) in 5 mL of

20 isopropanol, 2 mL of water, and 1 mL of toluene. The mixture was heated overnight at 50°C, at which point tlc analysis indicated some 11b residual. Additional S,R-10a (630 mg; 1.39 mmol; 1.0 equiv) and triethylamine (0.48 mL; 2.5 equiv) were added and the mixture was heated overnight at 50°C to completely consume 11b according to tlc analysis. The reaction mixture

25 was diluted with ethyl acetate and 1 N sodium hydroxide (20 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic solution was dried (magnesium sulfate) and concentrated to afford 2.27 g of crude product. This material was filtered through a pad of flash silica gel and eluted with 1:1 ethyl acetate:heptane to

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remove impurities, and then with 5% triethylamine in ethyl acetate to afford 0.79 g (63%) of *S,R*-**8b** as a yellow foam.

S,R-**11b**: ^1H NMR (CDCl_3) δ 7.6-7.2 (m, 10 H); 4.512 (s, 1H); 4.33 (m, 1H); 4.13 (m, 1H); 3.942 (s, 1H); 3.910 (s, 5H); 1.9-1.8 (m, 4H); 1.849 (d, $J =$
5 8.04 Hz, 3H); 1.8-0.7 (m, 8H).

FDMS: m/e 852.14 (M^+).

S,R-**8b**: ^1H NMR (CDCl_3) δ 7.7-7.1 (m, 20 H); 4.485 (br s, 2H); 4.32 (m, 2H); 3.92 (br s, 12H); 1.94 (br s, 2H); 1.8-0.3 (m, 14H).

FDMS: m/e 906.13 (M^+).

10

Example 4:

*Preparation of N,N'-Bis[(S)-1-[(R)-2-Diphenylphosphino]ferrocenyl]ethyl
(S,S)-1,2-cyclohexyldiamine (S,S-8b)*

Ester *S,R*-**10a** (1.0 g; 2.19 mmol) was combined with *S,S*-1,2-
15 diaminocyclohexane (500 mg; 4.38 mmol; 2 equiv) and triethylamine (0.92 mL; 6.57 mmol; 3 equiv) in 5 mL of isopropanol, 2 mL of water, and 1 mL of toluene. The reaction mixture was heated overnight at 50°C to completely consume **10a** according to tlc analysis. The reaction mixture was diluted with ethyl acetate and 2 N sodium hydroxide (10 mL). The layers were
20 separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic solution was dried (magnesium sulfate) and concentrated to afford 1.58 g of crude product. This material was filtered through a pad of flash silica gel and eluted with 1:1 ethyl acetate:heptane to remove impurities, and then with 1:1 ethyl acetate:isopropanol with 5%
25 added triethylamine to afford 0.84 g (75%) of *S,S*-**11b**.

A portion of this phosphinodiamine (0.74 g; 1.45 mmol) was combined with ester *S,R*-**10a** (0.99 g; 2.17 mmol; 1.5 equiv) in 5 mL of isopropanol, 2 mL of water, and 1 mL of toluene. Triethylamine (0.40 mL; 2.9 mmol; 2.0 equiv) was added and the mixture was heated overnight at
30 50°C, at which point tlc analysis indicated no **11b** residual according to tlc

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analysis. The reaction mixture was diluted with ethyl acetate and 1 N sodium hydroxide (20 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic solution was dried (magnesium sulfate) and concentrated to afford 2.03 g of crude product. This material was filtered through a pad of flash silica gel and eluted with 1:4 ethyl acetate:heptane to remove impurities, and then with 1:1 ethyl acetate:heptane with 5% added triethylamine to afford 0.98 g (75%) of S,S-8b as a yellow foam.

S,S-8b: ¹H NMR (CDCl₃) δ 7.6-7.1 (m, 20 H); 4.456 (br s, 2H); 4.228 (br s, 2H); 3.979 (s, 10H); 3.9 (m, 2H); 3.676 (br s, 2H); 1.69 (br s, 2H); 1.6-0.4 (m, 14H).

Example 5:

Preparation of N,N'-Bis[(R)-1-[(S)-2-Diphenylphosphino]ferrocenyl]ethyl (S,S)-1,2-cyclohexyldiamine (R,S-4b)

Ester R,S-6a (3.0 g; 6.6 mmol; 3 equiv) was combined with S,S-1,2-diaminocyclohexane tartrate salt (579 mg; 2.2 mmol) and triethylamine (1.84 mL; 13.2 mmol; 6 equiv) in 10 mL of isopropanol, 4 mL of water, and 2 mL of toluene. The reaction mixture was heated for 24 h at 50°C to consume most of 6a according to tlc analysis. The reaction mixture was diluted with ethyl acetate and 1 N sodium hydroxide (20 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic solution was dried (magnesium sulfate) and concentrated to afford 3.06 g of crude product. This material was filtered through a pad of flash silica gel and eluted with 1:1 ethyl acetate:heptane to remove impurities, and then with ethyl acetate to afford 1.60 g (80%) of R,S-4b.

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Example 6:Preparation of N,N'-Bis[(S)-1-[(R)-2-Diphenylphosphino]ferrocenyl]ethyl
(S,S)-1,2-diphenylethylenediamine (S,S-8c)

5 Ester S,R-10a (1.07 g; 2.36 mmol; 1.25 equiv) was combined with S,S-1,2-diphenylethylenediamine (400 mg; 1.88 mmol) and triethylamine (0.53 mL; 3.76 mmol; 2 equiv) in 5 mL of isopropanol, 2 mL of water, and 1 mL of toluene. The reaction mixture was heated overnight at 50°C to completely consume 10a according to tlc analysis. The reaction mixture was diluted with ethyl acetate, water (10 mL), and 2 N sodium hydroxide (10 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic solution was dried (magnesium sulfate) and concentrated to afford 1.58 g of crude product. This material was filtered through a pad of flash silica gel and eluted with 1:4 ethyl acetate:heptane to remove impurities, and then with 1:1 ethyl acetate:heptane with 5% added triethylamine to afford 0.67 g (58%) of S,S-11c.

20 A portion of this phosphinodiamine (0.57 g; 0.94 mmol) was combined with ester S,R-10a (534 mg; 1.17 mmol; 1.25 equiv) and triethylamine (0.20 mL; 1.41 mmol; 1.5 equiv) in 5 mL of isopropanol, 2 mL of water, and 1 mL of toluene, and the mixture was heated for 24 h at 50°C, at which point tlc analysis indicated no 10a but still some 11c residual. Additional S,R-10a (107 mg; 0.24 mmol; 0.25 equiv) and triethylamine (33 µL; 0.24 mmol; 0.25 equiv) were added and the mixture was stirred overnight at 50°C to completely consume 11c. The reaction mixture was diluted with ethyl acetate and 1 N sodium hydroxide (20 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic solution was dried (magnesium sulfate) and concentrated to afford 1.07 g of crude product. This material was flash-chromatographed and eluted with 1:9 ethyl acetate:heptane to afford 0.70 g (74%) of S,S-8c.

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S,S-**11c**: ^1H NMR (CDCl_3) δ 7.8-7.2 (m, 10 H); 7.2-6.75 (m, 10H); 4.384 (br s, 1H); 4.27 (m, 1H); 3.910 (s, 5H); 3.82 (m, 1H); 3.714 (m, 1H); 3.482 (d, J = 7.42 Hz, 1H); 2.05 (br s, 3H); 1.275 (d, J = 6.59 Hz, 3H).

FDMS: m/e 608.09 (M^+)

5 S,S-**8c**: ^1H NMR ($\text{DMSO}-d_6$) δ 7.6-6.5 (m, 30 H); 4.420 (m, 2H); 4.272 (m, 2H); 3.885 (s, 10H); 3.558 (m, 2H); 3.257 (m, 2H); 2.05 (m, 2H); 1.141 (d, J = 7.14 Hz, 3H).

FDMS: m/e 1005.22 (M^+)

10 Example 7:

Preparation of N,N'-Bis[(S)-1-[(R)-2-Diphenylphosphino]ferrocenyl]ethyl
(R,R)-1,2-diphenylethylenediamine (S,R-**8c**)

Ester S,R-**10a** (1.61 g; 3.5 mmol; 2.5 equiv) was combined with R,R-1,2-diphenylethylenediamine (300 mg; 1.41 mmol) and triethylamine (0.49 mL; 3.5 mmol; 2.5 equiv) in 5 mL of isopropanol, 2 mL of water, and 1 mL of
15 toluene. The reaction mixture was heated overnight at 50°C to afford incomplete formation of **8c** (but complete consumption of **10a**) according to tlc analysis. Additional S,R-**10a** (161 mg; 0.35 mmol; 0.25 equiv) and triethylamine (49 μL ; 0.35 mmol; 0.25 equiv) were added and the reaction
20 mixture was heated at 50°C overnight to complete the formation of **8c** according to tlc analysis. The reaction mixture was diluted with ethyl acetate, water (10 mL), and 2 N sodium hydroxide (2 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic solution was dried (magnesium sulfate) and
25 concentrated. The crude product was flash-chromatographed and eluted with 1:9 ethyl acetate:heptane to afford 0.79 g of S,R-**8c** which still contained some impurities. This material was recrystallized from 1:9 ethyl acetate:heptane to afford 456 mg (52%) of S,R-**8c**.

30 S,R-**8c**: ^1H NMR ($\text{DMSO}-d_6$) δ 7.6-7.0 (m, 20 H); 6.83 (m, 2H); 6.783 (t, J = 6.59 Hz, 4H); 6.373 (d, J = 7.14 Hz, 4H); 4.557 (br s, 2H); 4.371 (m, 2H);

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3.951 (s, 10H); 3.784 (br s, 2H); 3.27 (m, 2H); 2.28 (m, 2H); 1.095 (d, $J = 6.59$ Hz, 6H).

FDMS: m/e 1005.21 (M^+)

5 Example 8:

Preparation of (R)-1-[(S)-2-(Bis[3,5-dimethylphenyl]phosphino)ferrocenyl]ethyl acetate (R,S-6b)

(S)-N,N-Dimethyl-1-[(R)-2-(bis[3,5-dimethylphenyl]phosphino)ferrocenyl]-ethylamine (*R,S*-**5b**, $R^3 = R^8 = R^9 = \text{methyl}$, $R^2 = 3,5\text{-dimethylphenyl}$, $R^4 = R^5 = \text{H}$, $M = \text{Fe}$)(1.00 g; 2.01 mmol) was combined
10 with acetic anhydride (3 mL; 32 mmol; 15.8 equivalents). The flask was evacuated and filled with nitrogen ten times and then heated to 70°C for 4 hours, at which point thin layer chromatography (tlc) analysis indicated no **5b** present. The residual acetic anhydride was evaporated at reduced
15 pressure to afford 1.08 g (99%) of *R,S*-**6b**.

Example 9:

Preparation of N,N'-Bis[(R)-1-[(S)-2-[(3,5-dimethylphenyl]phosphino)ferrocenyl]ethyl (S,S)-1,2-cyclohexyldiamine (R,S-4d)

Ester *R,S*-**6b** (961 mg; 1.88 mmol; 2.75 equiv) was combined with
S,S-1,2-diaminocyclohexane tartrate salt (181 mg; 0.68 mmol) and
triethylamine (0.57 mL; 4.1 mmol; 6 equiv) in 3.5 mL of isopropanol, 1.4 mL
of water, and 0.7 mL of toluene. The reaction mixture was heated for 24 h
25 at 50°C to consume most of **6b** according to TLC analysis. The reaction mixture was diluted with ethyl acetate and 1 N sodium hydroxide (15 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic solution was dried (magnesium sulfate) and concentrated to afford 0.93 g of crude product. This material
30 was filtered through a pad of flash silica gel and eluted with 1:1 ethyl

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acetate:heptane to remove impurities, and then with ethyl acetate to afford 405 mg (58%) of *R,S*-**4d**.

¹H NMR (CDCl₃) δ 7.207 (s, 2H); 7.179 (s, 2H); 7.003 (s, 2H); 6.820 (s, 2H); 6.793 (s, 4H); 4.485 (br s, 2H); 4.288 (m, 2H); 3.983 (s, 12H); 3.881 (br s, 2H); 2.320 (s, 6H); 2.172 (s, 6H); 2.4-0.4 (m, 10H); 1.531 (d, *J* = 6.32 Hz, 6H).

FDMS: *m/e* 1018 (*M*⁺)

Example 10:

10 Preparation of *N,N'*-Bis[(*S*)-1-[(*R*)-2-Diphenylphosphino]ferrocenyl]ethyl ethylenediamineruthenium(II) dichloride (*S*-**13a**)

Ligand *S*-**8a** (100 mg; 0.12 mmol) and *p*-cymeneruthenium dichloride dimer (36 mg; 0.06 mmol; 0.5 molar equiv) were combined. *N,N*-Dimethylformamide (3 mL) was added and the reaction mixture was
15 evacuated and filled with nitrogen five times. The mixture was heated to 100°C for 10 min to afford a homogeneous solution and then cooled. The volatiles were stripped *in vacuo* and the residue was dissolved in dichloromethane (1 mL) and diluted with tert-butyl methyl ether (20 mL) to afford *S*-**13a** as a precipitate. The solid was collected, washed with tert-
20 butyl methyl ether, and dried *in vacuo* to afford 57 mg (46%) of *S*-**13a**.
FDMS: *m/e* 1024 (*M*⁺).

Example 11:

25 Preparation of *N,N'*-Bis[(*S*)-1-[(*R*)-2-Diphenylphosphino]ferrocenyl]ethyl (*R,R*)-1,2-cyclohexyldiamineruthenium(II) dichloride (*S,R*-**13b**)

Ligand *S,R*-**8b** (200 mg; 0.22 mmol) and *p*-cymeneruthenium dichloride dimer (67.5 mg; 0.11 mmol; 0.5 molar equiv) were combined. *N,N*-Dimethylformamide (4 mL) was added and the reaction mixture was
30 evacuated and filled with nitrogen five times. The mixture was heated to 100°C for 10 min to afford a homogeneous solution and then cooled. The

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volatiles were stripped *in vacuo* and the residue was dissolved in dichloromethane (1 mL) and diluted with tert-butyl methyl ether to afford *S,R*-**13b** as a precipitate. The solid was collected, washed with tert-butyl methyl ether, and dried *in vacuo* to afford 108 mg (45%) of *S,R*-**13b**.

5 FDMS: *m/e* 1079 (*M*⁺).

Example 12:

Preparation of *N,N'*-Bis[(*S*)-1-[(*R*)-2-Diphenylphosphino]ferrocenyl]ethyl
(*S,S*)-1,2-cyclohexyldiamineruthenium(II) dichloride (*S,S*-**13b**)

10 Ligand *S,S*-**8b** (200 mg; 0.22 mmol) and *p*-cymeneruthenium dichloride dimer (67.5 mg; 0.11 mmol; 0.5 molar equiv) were combined. *N,N*-Dimethylformamide (4 mL) was added and the reaction mixture was evacuated and filled with nitrogen five times. The mixture was heated to 100°C for 10 min to afford a homogeneous solution and then cooled. The
15 volatiles were stripped *in vacuo* and the residue was dissolved in dichloromethane (1 mL) and diluted with tert-butyl methyl ether (20 mL) to afford *S,S*-**13b** as a precipitate. The solid was collected, washed with tert-butyl methyl ether, and dried *in vacuo* to afford 66 mg (28%) of *S,S*-**13b**.

20 Example 13:

Preparation of *N,N'*-Bis[(*R*)-1-[(*S*)-2-Diphenylphosphino]ferrocenyl]ethyl
(*S,S*)-1,2-cyclohexyldiamineruthenium(II) dichloride (*R,S*-**13b**)

Ligand *R,S*-**4b** (100 mg; 0.11 mmol) and *p*-cymeneruthenium dichloride dimer (33.8 mg; 0.055 mmol; 0.5 molar equiv) were combined.
25 *N,N*-Dimethylformamide (2 mL) was added and the reaction mixture was evacuated and filled with nitrogen five times. The mixture was heated to 100°C for 3 h to afford a homogeneous solution and then cooled to ambient temperature and stirred overnight. The volatiles were stripped *in vacuo* and the residue was dissolved in toluene (2 mL) and diluted with heptane (10
30 mL)

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to afford *R,S*-**13b** as a precipitate. The solid was collected, washed with heptane, and dried *in vacuo* to afford 56 mg (47%) of *S,S*-**13b** as a green solid.

5 Example 14:

Preparation of *N,N'*-Bis[(*S*)-1-[(*R*)-2-Diphenylphosphino]ferrocenyl]ethyl
(*R,R*)-1,2-diphenylethylenediamine ruthenium(II) dichloride (*S,R*-**13c**)

Ligand *S,R*-**8c** (200 mg; 0.20 mmol; 1.2 equiv) and *p*-
cymeneruthenium dichloride dimer (51 mg; 0.083 mmol) were combined.
10 *N,N*-Dimethylformamide (5 mL) was added and the reaction mixture was
evacuated and filled with nitrogen five times. The mixture was heated to
100°C for 10 min to afford a homogeneous red solution and then cooled to
50°C. The volatiles were stripped *in vacuo* and the residue was dissolved
in dichloromethane (1 mL) and diluted with tert-butyl methyl ether (10 mL)
15 and heptane (10 mL) to afford *S,R*-**13c** as a precipitate. The solid was
collected, washed with heptane, and dried *in vacuo* to afford 95 mg (49%)
of *S,R*-**13c**.

Example 15:

20 Preparation of *N,N'*-Bis[(*S*)-1-[(*R*)-2-Diphenylphosphino]ferrocenyl]ethyl
(*S,S*)-1,2-diphenylethylenediamine ruthenium(II) dichloride (*S,S*-**13c**)

Ligand *S,S*-**8c** (200 mg; 0.20 mmol; 1.2 equiv) and *p*-
cymeneruthenium dichloride dimer (51 mg; 0.083 mmol) were combined.
N,N-Dimethylformamide (5 mL) was added and the reaction mixture was
25 evacuated and filled with nitrogen five times. The mixture was heated to
100°C for 10 min to afford a homogeneous red solution and then cooled to
50°C. The volatiles were stripped *in vacuo* and the residue was dissolved
in dichloromethane (1 mL) and diluted with tert-butyl methyl ether (10 mL)
and heptane (10 mL) to afford *S,S*-**13c** as a precipitate. The solid was

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collected, washed with heptane, and dried *in vacuo* to afford 113 mg (58%) of **S,S-13c**.

Example 16:

5 Preparation of *N,N'*-Bis[(*R*)-1-[(*S*)-2-(Bis[3,5-dimethylphenyl]phosphino)-ferrocenyl]ethyl (*S,S*)-1,2-cyclohexyldiamineruthenium(II) dichloride (*R,S*-**13d**)

 Ligand **R,S-4d** (100 mg; 0.098 mmol) and p-cymeneruthenium dichloride dimer (30.0 mg; 0.049 mmol; 0.5 molar equiv) were combined. 10 *N,N*-Dimethylformamide (2 mL) was added and the reaction mixture was evacuated and filled with nitrogen five times. The mixture was heated to 100°C for 1 h to afford a homogeneous solution and then cooled to ambient temperature and stirred overnight. The volatiles were stripped *in vacuo* and the residue was dissolved in toluene (2 mL) and diluted with heptane (10 15 mL) to afford **R,S-13d** as a precipitate. The solid was collected, washed with heptane, and dried *in vacuo* to afford 44 mg (38%) of **R,S-13d** as a green solid.

Example 17:

20 Hydrogenation of Acetophenone to (*R*)-1-Phenylethanol using Complex (*S*)-**13a**

 Complex **S-13a** (2.6 mg; 0.0025 mmol; 0.005 equiv) was placed in a reaction vessel, which was pressurized with argon and vented five times. Argon-degassed isopropanol (2 mL) was added and the mixture was stirred 25 for 15 min. Acetophenone (58 µL; 0.5 mmol) dissolved in 1 mL of argon-degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of isopropanol. The reaction mixture 30 was pressurized with argon and vented five times and then pressurized to

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300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to indicate 100% conversion to *R*-1-phenylethanol with 58.6% ee.

- 5 Chiral GC [Cyclosil-B (J&W Scientific), 40°C to 100°C at 70°C/min, hold at 100°C for 15 minutes, 100°C to 170°C at 15°C/min, hold at 170°C for 7 min]: $t_R = 15.3$ min (acetophenone), $t_R = 19.6$ min (*R*-1-phenylethanol), $t_R = 19.8$ min (*S*-1-phenylethanol).

10 Example 18:

Hydrogenation of Acetylferrocene to (*R*)-1-Ferrocenylethanol using
Complex (*S*)-13a

- Complex **S-13a** (2.6 mg; 0.0025 mmol; 0.005 equiv) and acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The vessel was pressurized with argon and vented five times and 4 mL of argon-degassed isopropanol was added. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized and vented with argon five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by ^1H NMR to indicate >98% conversion to *R*-1-ferrocenylethanol which was 22.4% ee by chiral HPLC analysis.
- 25 Chiral HPLC [250 x 4.6 mm Chiralpak AS (Chiral Technologies), 90:10 hexane:isopropanol, 1 mL/min, $\lambda = 254$ nm]: $t_R = 10.6$ min (*S*-1-ferrocenylethanol), $t_R = 17.0$ min (*S*-1-ferrocenylethanol).

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Example 19:Hydrogenation of Cyclopropyl Methyl Ketone using Complex (S)-13a

Complex S-13a (2.6 mg; 0.0025 mmol; 0.005 equiv) was placed in a reaction vessel, which was pressurized with argon and vented five times.

5 Argon-degassed isopropanol (2 mL) was added and the mixture was stirred for 15 min. Cyclopropyl methyl ketone (50 μ L; 0.5 mmol) dissolved in 1.0 mL of argon-degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed
10 isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to
15 indicate 99.0% conversion to 1-cyclopropylethanol with 26.6% ee.

Chiral GC [Cyclosil-B (J&W Scientific), 55°C isothermal]: t_R = 7.3 (cyclopropyl methyl ketone), t_R = 12.8 (1-cyclopropylethanol, enantiomer 1), t_R = 13.4 (1-cyclopropylethanol, enantiomer 2).

20 Example 20:

Hydrogenation of Acetophenone to (S)-1-Phenylethanol using Complex (S,R)-13b

Complex S,R-13b (2.7 mg; 0.0025 mmol; 0.005 equiv) was placed in a reaction vessel, which was pressurized with argon and vented five times.

25 Argon-degassed isopropanol (2 mL) was added and the mixture was stirred for 15 min. Acetophenone (58 μ L; 0.5 mmol) dissolved in 1 mL of argon-degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was
30 added and was washed in with 0.5 mL of argon-degassed isopropanol. The

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reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to indicate 98.5% conversion to S-1-phenylethanol with 67.0% ee.

Example 21:

Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using
Complex (S,R)-13b

Complex S,R-13b (2.7 mg; 0.0025 mmol; 0.005 equiv) and acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The vessel was pressurized with argon and vented five times and 4 mL of argon-degassed isopropanol was added. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 500 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by ¹H NMR to indicate 98.5% conversion to S-1-ferrocenylethanol which was 78% ee by chiral HPLC analysis.

Example 22:

Hydrogenation of Acetophenone to (S)-1-Phenylethanol using in situ
prepared Complex (S,R)-13b

Ligand S,R-8b (2.7 mg; 0.003 mmol; 0.006 equiv) and p-cymeneruthenium chloride dimer (0.8 mg; 0.0013 mmol; 0.0025 molar equiv) were placed in a reaction vessel, which was pressurized with argon and vented five times. Argon-degassed isopropanol (2 mL) was added and the mixture was stirred for 15 min. Acetophenone (58 μ L; 0.5 mmol)

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dissolved in 1 mL of argon-degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to indicate 99.9% conversion to S-1-phenylethanol with 54.4% ee.

Example 23:

Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using in situ prepared Complex (S,R)-13b

Ligand S,R-8b (2.7 mg; 0.003 mmol; 0.006 equiv), p-cymeneruthenium chloride dimer (0.8 mg; 0.0013 mmol; 0.0025 molar equiv), and acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The vessel was pressurized with argon and vented five times and 4 mL of argon-degassed isopropanol was added. The mixture was stirred for 15 min. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by ¹H NMR to indicate 79% conversion to S-1-ferrocenylethanol which was 70% ee by chiral HPLC analysis.

Example 24:Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using
Complex (S,R)-13b in Tetrahydrofuran (THF)

Complex S,R-13b (2.7 mg; 0.0025 mmol; 0.005 equiv) and
5 acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The
vessel was pressurized and vented with argon five times and 4 mL of
argon-degassed THF was added. Potassium *tert*-butoxide in *tert*-butanol
(1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed THF was
added and was washed in with 0.5 mL of argon-degassed THF. The
10 reaction mixture was pressurized with argon and vented five times and then
pressurized to 300 psig with hydrogen and stirred at ambient temperature
for 6 h. The vessel was vented, then pressurized with argon and vented
five times, and the solution was assayed by ¹H NMR to indicate 12%
conversion to S-1-ferrocenylethanol which was 72% ee by chiral HPLC
15 analysis.

Example 25:Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using
Complex (S,R)-13b in Toluene

20 Complex S,R-13b (2.7 mg; 0.0025 mmol; 0.005 equiv) and
acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The
vessel was pressurized with argon and vented five times and 4 mL of
argon-degassed toluene was added. Potassium *tert*-butoxide in *tert*-
butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed
25 toluene was added and was washed in with 0.5 mL of argon-degassed
toluene. The reaction mixture was pressurized with argon and vented five
times and then pressurized to 300 psig with hydrogen and stirred at
ambient temperature for 6 h. The vessel was vented, then pressurized with
argon and vented five times, and the solution was assayed by ¹H NMR to

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indicate 87% conversion to S-1-ferrocenylethanol which was 13% ee by chiral HPLC analysis.

Example 26:

5 Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using
 Complex (S,R)-13b at Substrate:Catalyst Ratio of 500:1

Complex S,R-13b (2.2 mg; 0.002 mmol; 0.002 equiv) and acetylferrocene (228 mg; 1.0 mmol) were placed in a reaction vessel. The vessel was pressurized with argon and vented five times and 4 mL of
10 argon-degassed isopropanol was added. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.10 mL; 0.10 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at
15 ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by ¹H NMR to indicate 67% conversion to S-1-ferrocenylethanol which was 80% ee by chiral HPLC analysis.

20 Example 27:

Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using
 Complex (S,R)-13b at Substrate:Catalyst Ratio of 500:1 and at 100 psig
 Hydrogen

Complex S,R-13b (2.2 mg; 0.002 mmol; 0.002 equiv) and
25 acetylferrocene (228 mg; 1.0 mmol) were placed in a reaction vessel. The vessel was pressurized with argon and vented five times and 4 mL of argon-degassed isopropanol was added. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.10 mL; 0.10 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed
30 isopropanol. The reaction mixture was pressurized with argon and vented

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five times and then pressurized to 100 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by ^1H NMR to indicate 20% conversion to S-1-ferrocenylethanol which was 70% ee by chiral HPLC analysis.

Example 28:

Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using Complex (S,R)-13b at Substrate:Catalyst Ratio of 500:1 and at 200 psig

Hydrogen

Complex S,R-13b (2.2 mg; 0.002 mmol; 0.002 equiv) and acetylferrocene (228 mg; 1.0 mmol) were placed in a reaction vessel. The vessel was pressurized with argon and vented five times and 4 mL of argon-degassed isopropanol was added. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.10 mL; 0.10 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 200 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by ^1H NMR to indicate 45% conversion to S-1-ferrocenylethanol which was 77% ee by chiral HPLC analysis.

Example 29:

Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using Complex (S,R)-13b at Substrate:Catalyst Ratio of 1000:1

Complex S,R-13b (2.7 mg; 0.0025 mmol; 0.001 equiv) and acetylferrocene (570 mg; 2.5 mmol) were placed in a reaction vessel. The vessel was pressurized with argon and vented five times and 4 mL of argon-degassed isopropanol was added. Potassium *tert*-butoxide in *tert*-

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butanol (1M; 0.125 mL; 0.125 mmol; 0.05 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by ¹H-NMR to indicate 78% conversion to *S*-1-ferrocenylethanol which was 73% ee by chiral HPLC analysis.

10 Example 30:

Hydrogenation of Acetophenone to (*R*)-1-Phenylethanol using Complex (*S,S*)-13b

Complex *S,S*-13b (2.7 mg; 0.0025 mmol; 0.005 equiv) was placed in a reaction vessel, which was pressurized with argon and vented five times. Argon-degassed isopropanol (2 mL) was added and the mixture was stirred for 15 min. Acetophenone (58 μL; 0.5 mmol) dissolved in 1 mL of argon-degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to indicate 99.1% conversion to *R*-1-phenylethanol with 57.2% ee.

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Example 31:Hydrogenation of Acetylferrocene to (R)-1-Ferrocenylethanol using
Complex (S,S)-13b

Complex S,S-**13b** (2.7 mg; 0.0025 mmol; 0.005 equiv) and
5 acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The
vessel was pressurized with argon and vented five times and 4 mL of
argon-degassed isopropanol was added. Potassium *tert*-butoxide in *tert*-
butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed
isopropanol was added and was washed in with 0.5 mL of argon-degassed
10 isopropanol. The reaction mixture was pressurized with argon and vented
five times and then pressurized to 300 psig with hydrogen and stirred at
ambient temperature for 6 h. The vessel was vented, then pressurized with
argon and vented five times, and the solution was assayed by ¹H NMR to
indicate 99% conversion to *R*-1-ferrocenylethanol which was 47% ee by
15 chiral HPLC analysis.

Example 32:Hydrogenation of Acetophenone to (R)-1-Phenylethanol using in situ
prepared Complex (S,S)-13b

20 Ligand S,S-**8b** (2.7 mg; 0.003 mmol; 0.006 equiv) and p-
cymeneruthenium chloride dimer (0.8 mg; 0.0013 mmol; 0.0025 molar
equiv) were placed in a reaction vessel, which was pressurized with argon
and vented five times. Argon-degassed isopropanol (2 mL) was added and
the mixture was stirred for 15 min. Acetophenone (58 μ L; 0.5 mmol)
25 dissolved in 1 mL of argon-degassed isopropanol was added and was
washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-
butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of
argon-degassed isopropanol was added and was washed in with 0.5 mL of
argon-degassed isopropanol. The reaction mixture was pressurized with
30 argon and vented five times and then pressurized to 300 psig with hydrogen

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and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to indicate 99.1% conversion to *R*-1-phenylethanol with 66.0% ee.

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Example 33:

Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using in situ prepared Complex (S,S)-13b

Ligand *S,S*-**8b** (2.7 mg; 0.003 mmol; 0.006 equiv), p-cymeneruthenium chloride dimer (0.8 mg; 0.0013 mmol; 0.0025 molar equiv), and acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The vessel was pressurized with argon and vented five times and 4 mL of argon-degassed isopropanol was added. The mixture was stirred for 15 min. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by ¹H NMR to indicate 55% conversion to *R*-1-ferrocenylethanol which was 58% ee by chiral HPLC analysis.

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Example 34:

Hydrogenation of Acetophenone to (S)-1-Phenylethanol using Complex (S,R)-13c

Complex *S,R*-**13c** (2.9 mg; 0.0025 mmol; 0.005 equiv) was placed in a reaction vessel, which was pressurized with argon and vented five times. Argon-degassed isopropanol (2 mL) was added and the mixture was stirred for 15 min. Acetophenone (58 μ L; 0.5 mmol) dissolved in 1 mL of argon-

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degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to indicate 72.5% conversion to S-1-phenylethanol with 2% ee.

Example 35:

Hydrogenation of Acetylferrocene to (S)-1-Ferrocenylethanol using Complex (S,R)-13c

Complex S,R-13c (2.9 mg; 0.0025 mmol; 0.005 equiv) and acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The vessel was pressurized with argon and vented five times and 4 mL of argon-degassed isopropanol was added. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by ¹H NMR to indicate 9% conversion to S-1-ferrocenylethanol which was 24% ee by chiral HPLC analysis.

Example 36:Hydrogenation of Acetophenone to (R)-1-Phenylethanol using Complex (S,S)-13c

Complex S,S-13c (2.9 mg; 0.0025 mmol; 0.005 equiv) was placed in
5 a reaction vessel, which was pressurized with argon and vented five times.
Argon-degassed isopropanol (2 mL) was added and the mixture was stirred
for 15 min. Acetophenone (58 μ L; 0.5 mmol) dissolved in 1 mL of argon-
degassed isopropanol was added and was washed in with 1.0 mL of argon-
degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05
10 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was
added and was washed in with 0.5 mL of argon-degassed isopropanol. The
reaction mixture was pressurized with argon and vented five times and then
pressurized to 300 psig with hydrogen and stirred at ambient temperature
for 6 h. The vessel was vented, then pressurized with argon and vented
15 five times, and the solution was assayed by chiral GC to indicate 74.5%
conversion to *R*-1-phenylethanol with 51.2% ee.

Example 37:Hydrogenation of Acetylferrocene to (R)-1-Ferrocenylethanol using Complex (S,S)-13c

Complex S,S-13c (2.9 mg; 0.0025 mmol; 0.005 equiv) and
20 acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The
vessel was pressurized with argon and vented five times and 4 mL of
argon-degassed isopropanol was added. Potassium *tert*-butoxide in *tert*-
25 butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed
isopropanol was added and was washed in with 0.5 mL of argon-degassed
isopropanol. The reaction mixture was pressurized with argon and vented
five times and then pressurized to 300 psig with hydrogen and stirred at
ambient temperature for 6 h. The vessel was vented, then pressurized with
30 argon and vented five times, and the solution was assayed by ^1H NMR to

indicate 56% conversion to *R*-1-ferrocenylethanol which was 40% ee by chiral HPLC analysis.

Example 38:

5 Hydrogenation of Acetophenone to (R)-1-Phenylethanol using Complex
(R,S)-13d

Complex *R,S*-**13d** (3.0 mg; 0.0025 mmol; 0.005 equiv) was placed in a reaction vessel, which was pressurized with argon and vented five times. Argon-degassed isopropanol (2 mL) was added and the mixture was stirred for 15 min. Acetophenone (58 μ L; 0.5 mmol) dissolved in 1 mL of argon-degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to indicate 99.0% conversion to *R*-1-phenylethanol with 60.0% ee.

Example 39:

Hydrogenation of Acetylferrocene to (R)-1-Ferrocenylethanol using
Complex (R,S)-13d

Complex *R,S*-**13d** (3.0 mg; 0.0025 mmol; 0.005 equiv) and
25 acetylferrocene (114 mg; 0.5 mmol) were placed in a reaction vessel. The
vessel was pressurized with argon and vented five times and 4 mL of
argon-degassed isopropanol was added. The reaction mixture was stirred
for 15 min and potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05
mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and
30 was washed in with 0.5 mL of argon-degassed isopropanol. The reaction

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5 mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral HPLC to indicate 44% ee for *R*-1-ferrocenylethanol.

Example 40:

Hydrogenation of 4-Trifluoromethylacetophenone using Complex(*R,S*)-**13d**

10 Complex *R,S*-**13d** (3.0 mg; 0.0025 mmol; 0.005 equiv) was placed in a reaction vessel, which was pressurized with argon and vented five times. Argon-degassed isopropanol (2 mL) was added and the mixture was stirred for 15 min. 4-Trifluoromethylacetophenone (94 mg; 0.5 mmol) dissolved in 1 mL of argon-degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-
15 butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with
20 argon and vented five times, and the solution was assayed by chiral GC to indicate 99.8% conversion to 1-(4-trifluoromethylphenyl)ethanol with 60.0% ee.

Chiral GC [Cyclosil-B (J&W Scientific), 40°C to 100°C at 70°C/min, hold at 100°C for 15 minutes, 100°C to 170°C at 15°C/min, hold at 170°C for 7
25 min]: t_R = 16.7 min (4-trifluoromethylacetophenone), t_R = 20.7 min [1-(4-trifluoromethylphenyl)ethanol, enantiomer 1], t_R = 20.9 min [1-(4-trifluoromethylphenyl)ethanol, enantiomer 2].

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Example 41:Hydrogenation of 4-Methoxyacetophenone using Complex (R,S)-13d

Complex *R,S*-**13d** (3.0 mg; 0.0025 mmol; 0.005 equiv) was placed in a reaction vessel, which was pressurized with argon and vented five times.

5 Argon-degassed isopropanol (2 mL) was added and the mixture was stirred for 15 min. 4-Methoxyacetophenone (75 mg; 0.5 mmol) dissolved in 1 mL of argon-degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M; 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed

10 isopropanol was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to

15 indicate 99.7% conversion to 1-(4-methoxyphenyl)ethanol with 55.0% ee. Chiral GC [Cyclosil-B (J&W Scientific), 40°C to 100°C at 70°C/min, hold at 100°C for 15 minutes, 100°C to 170°C at 15°C/min, hold at 170°C for 7 min]: t_R = 23.2 min (4-methoxyacetophenone), t_R = 23.7 min [1-(4-methoxyphenyl)ethanol, enantiomer 1], t_R = 23.8 min [1-(4-

20 methoxyphenyl)ethanol, enantiomer 2].

Example 42:Hydrogenation of 2'-Acetonaphthone using Complex (R,S)-13d

Complex *R,S*-**13d** (3.0 mg; 0.0025 mmol; 0.005 equiv) was placed in

25 a reaction vessel, which was pressurized with argon and vented five times. Argon-degassed isopropanol (2 mL) was added and the mixture was stirred for 15 min. 2'-Acetonaphthone (85 mg; 0.5 mmol) dissolved in 1 mL of argon-degassed isopropanol was added and was washed in with 1.0 mL of argon-degassed isopropanol. Potassium *tert*-butoxide in *tert*-butanol (1M;

30 0.05 mL; 0.05 mmol; 0.1 equiv) in 0.5 mL of argon-degassed isopropanol

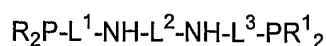
- 47 -

was added and was washed in with 0.5 mL of argon-degassed isopropanol. The reaction mixture was pressurized with argon and vented five times and then pressurized to 300 psig with hydrogen and stirred at ambient temperature for 6 h. The vessel was vented, then pressurized with argon and vented five times, and the solution was assayed by chiral GC to indicate 99.8% conversion to 1-(2-naphthyl)ethanol with 63.2% ee. Chiral GC [Cyclosil-B (J&W Scientific), 165°C for 15 minutes, 165°C to 200°C at 15°C/min, hold at 200°C for 15 min]: t_R = 17.7 min (2'-acetoneaphthone), t_R = 19.26 min [1-(2-naphthyl)ethanol, enantiomer 1], t_R = 19.35 min [1-(2-naphthyl)ethanol, enantiomer 2].

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Claims:

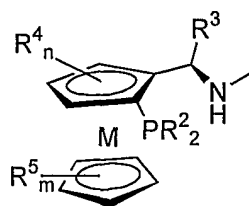
1. A substantially enantiomerically pure compound having the general
 5 formula 1:



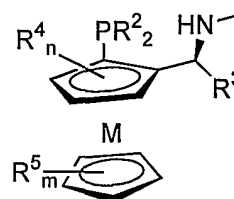
1

wherein R and R¹ are, independently, branched- or straight-chain C₁-C₂₀
 alkyl, C₃-C₈ cycloalkyl, C₆-C₂₀ carbocyclic aryl, or a C₄-C₂₀ heteroaryl having
 10 from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;
 L¹, L², and L³ may be the same or different, and are divalent radicals
 selected from branched- or straight-chain C₁-C₂₀ alkyl, C₃-C₈ cycloalkyl, C₆-
 C₂₀ carbocyclic aryl, a C₄-C₂₀ heteroaryl having from one to three
 heteroatoms selected from sulfur, nitrogen, and oxygen, or
 15 metallocenylalkyl and wherein L¹, L³ and, optionally, L² are substantially
 enantiomerically pure.

2. A compound as claimed in claim 1, wherein R₂P-L¹-NH- and R¹₂P-L³-
 20 NH- are the same or different and are selected from the structure in formula
 2 or formula 3



2



3

- 49 -

wherein

each R^2 is independently a branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or a C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

each R^3 , R^4 , and R^5 is independently selected from hydrogen, branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

n is 0 to 3;

m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

3. A compound as claimed in claim 2 wherein wherein R_2P-L^1-NH- and $R^1_2P-L^3-NH-$ are according to the structure of formula 2.

4. A compound as claimed in claim 2 wherein wherein R_2P-L^1-NH- and $R^1_2P-L^3-NH-$ are according to the structure of formula 3.

5. A compound as claimed in claim 2 wherein R^2 is aryl; R^3 is hydrogen or C_1 to C_6 alkyl; R^4 and R^5 are hydrogen; and M is iron, ruthenium, or osmium.

6. A compound as claimed in claim 5 wherein R^2 is phenyl or 3,5-dimethylphenyl; R^3 is hydrogen or methyl; and M is iron.

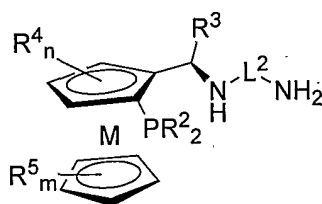
7. A compound according to claim 2 wherein L^2 is an achiral, racemic, enantiomerically enriched or substantially enantiomerically pure substituted or unsubstituted C_1 - C_{20} alkylene, C_3 - C_8 cycloalkylene, or 1,1'-biaryl-2,2'-diyl.

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8. A compound comprising a substantially enantiomerically pure compound defined in Claim 2 in complex association with a Group VIII metal.

5

9. A compound having formula 7



7

wherein

10 R^2 is a branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or a C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

15 R^3 , R^4 , and R^5 are independently hydrogen, branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having one to three heteroatoms wherein the heteroatoms are selected from sulfur, nitrogen, and oxygen;

L^2 is an achiral, racemic, enantiomerically enriched or substantially enantiomerically pure C_1 - C_{20} alkylene, C_3 - C_8 cycloalkylene, or 1,1'-biaryl-2,2'-diyl;

n is 0 to 3;

20 m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

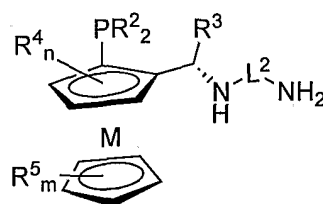
10. A compound as claimed in claim 9 wherein R^2 is aryl; R^3 is hydrogen or C_1 to C_6 alkyl; R^4 and R^5 are hydrogen, L^2 is 1,2-ethanediyl, 1,3-

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propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-diyl, and M is iron.

5

11. A compound having formula 11



11

wherein

10 R^2 is a branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or a C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

15 R^3 , R^4 , and R^5 are independently hydrogen, branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having one to three heteroatoms wherein the heteroatoms are selected from sulfur, nitrogen, and oxygen;

L^2 is an achiral, racemic, enantiomerically enriched or substantially enantiomerically pure C_1 - C_{20} alkylene, C_3 - C_8 cycloalkylene, or 1,1'-biaryl-2,2'-diyl;

n is 0 to 3;

20 m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

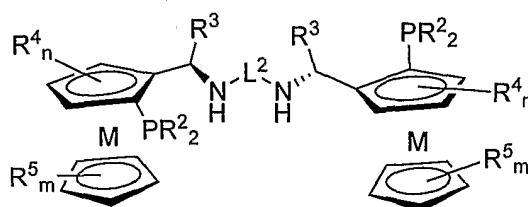
12. A compound as claimed in claim 11 wherein R^2 is aryl; R^3 is hydrogen or C_1 to C_6 alkyl; R^4 and R^5 are hydrogen, L^2 is 1,2-ethanediyl,

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1,3-propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-diyl, and M is iron.

5

13. A compound according to claim 1 having formula 4



4

10 wherein

each R² is independently a branched- or straight-chain C₁-C₂₀ alkyl, C₃-C₈ cycloalkyl, C₆-C₂₀ carbocyclic aryl, or a C₄-C₂₀ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

15 each R³, R⁴, and R⁵ is, independently, hydrogen, branched- or straight-chain C₁-C₂₀ alkyl, C₃-C₈ cycloalkyl, C₆-C₂₀ carbocyclic aryl, or C₄-C₂₀ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

20 L² is an achiral, racemic, enantiomerically enriched or substantially enantiomerically pure C₁-C₂₀ alkylene, C₃-C₈ cycloalkylene, or 1,1'-biaryl-2,2'-diyl;

n is 0 to 3;

m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

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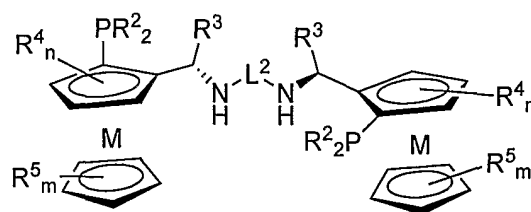
14. A compound as claimed in claim 13 wherein each R^2 is aryl; each R^3 is hydrogen or C_1 to C_6 alkyl; each R^4 and R^5 is hydrogen; and M is iron, ruthenium, or osmium.

5 15. A compound as claimed in claim 14 wherein each R^2 is phenyl or 3,5-dimethylphenyl; each R^3 is hydrogen or methyl; L^2 is 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl 1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-
10 diyl and M is iron.

16. A compound comprising a substantially enantiomerically pure compound defined in Claim 13 in complex association with a Group VIII metal.

15 17. A compound as claimed in claim 16 wherein the Group VIII metal is ruthenium, iridium or rhodium.

18. A compound according to claim 1 having formula 8



8

20

wherein

each R^2 is independently a branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or a C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

25 each R^3 , R^4 , and R^5 is independently selected from hydrogen, branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20}

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carbocyclic aryl, or C₄-C₂₀ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

L² is an achiral, racemic, enantiomerically enriched or substantially enantiomerically pure C₁-C₂₀ alkylene, C₃-C₈ cycloalkylene, or 1,1'-biaryl-2,2'-diyl;

n is 0 to 3;

m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

19. A compound as claimed in claim 18 wherein each R² is aryl; each R³ is hydrogen or C₁ to C₆ alkyl; each R⁴ and R⁵ is hydrogen; and M is iron, ruthenium, or osmium.

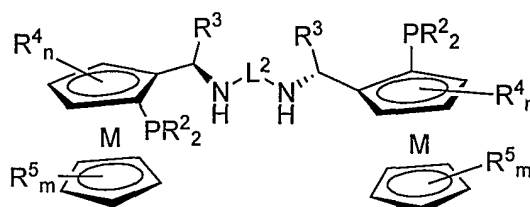
20. A compound as claimed in claim 19 wherein each R² is phenyl or 3,5-dimethylphenyl; each R³ is hydrogen or methyl; L² is 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-diyl and M is iron.

21. A compound comprising a substantially enantiomerically pure compound defined in Claim 18 in complex association with a Group VIII metal.

22. A compound as claimed in claim 21 wherein the Group VIII metal is ruthenium, iridium or rhodium.

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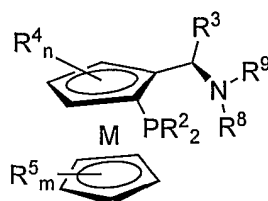
23. A process for preparing a compound having formula 4



4

which comprises the steps of:

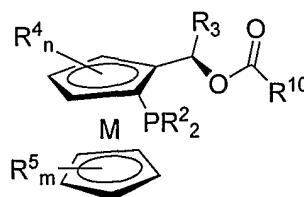
(1) contacting a dialkyl amine having formula 5:



5

5

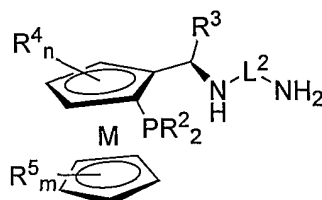
with a carboxylic anhydride having the formula $(R^{10}CO)_2O$ to obtain a first ester having formula 6:



6

- 56 -

(2) contacting the ester produced in step (1) with a diamine having the formula $H_2N-L^2-NH_2$ to obtain a phosphine-diamine **7**

**7**

5 and (3) contacting the phosphine-diamine produced in step (2) with a second ester having formula **6** to afford diphosphine-diamine **4**,

wherein each R^2 is independently a branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or a C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

each R^3 , R^4 , and R^5 is independently selected from hydrogen, branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

R^8 and R^9 are independently branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

each R^{10} is independently a C_1 to C_4 alkyl radical;

L^2 is an achiral, racemic, or enantiomerically enriched C_1 - C_{20} alkylene, C_3 - C_8 cycloalkylene, or 1,1'-biaryl-2,2'-diyl;

n is 0 to 3;

m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

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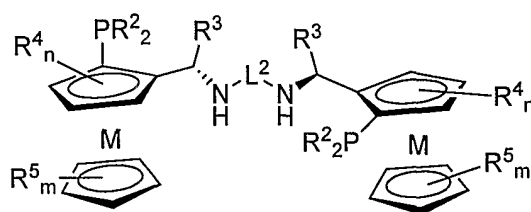
24. A process according to claim 23, which further comprises the step of isolating phosphine-diamine **7** prior to step (3).

25. A process according to claim 24 wherein each R^2 is phenyl or 3,5-dimethylphenyl; each R^3 is hydrogen or methyl; L^2 is 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-diyl and M is iron.

26. A process according to claim 23 or 24 which further comprises the step of contacting the compound of formula **4** with a ruthenium metal precursor, a rhodium metal precursor or an iridium metal precursor.

27. A process according to claim 26 wherein the ratio of the compound of formula **4** to the metal of the metal precursor is 0.8:1 to 1.5:1.

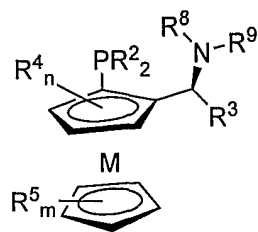
28. A process for preparing a compound having formula **8**

**8**

which comprises the steps of:

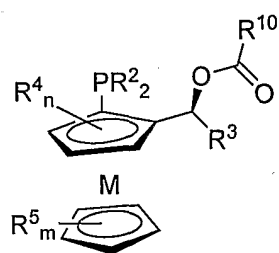
(1) contacting a dialkyl amine having formula **9**:

- 58 -



9

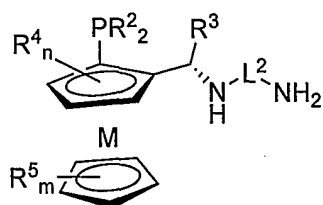
with a carboxylic anhydride having the formula $(R^{10}CO)_2O$ to obtain a first ester having formula **10**:



10

5

(2) contacting the ester produced in step (1) with a diamine having the formula $H_2N-L^2-NH_2$ to obtain a phosphine-diamine **11**



11

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and (3) contacting the phosphine-diamine produced in step (2) with a second ester having formula **10** to afford diphosphine-diamine **8**,

5 wherein each R^2 is independently a branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or a C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

10 each R^3 , R^4 , and R^5 is independently selected from hydrogen, branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

R^8 and R^9 are independently branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

15 each R^{10} is independently a C_1 to C_4 alkyl radical:

L^2 is an achiral, racemic, or enantiomerically enriched C_1 - C_{20} alkylene, C_3 - C_8 cycloalkylene, or 1,1'-biaryl-2,2'-diyl;

 n is 0 to 3;

 m is 0 to 5; and

20 M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

29. A process according to claim 28 which further comprises the step of isolating the phosphine-diamine **11** prior to step (3).

25 30. A process according to claim 29 wherein each R^2 is phenyl or 3,5-dimethylphenyl; each R^3 is hydrogen or methyl; L^2 is 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-diyl and M is iron.

30

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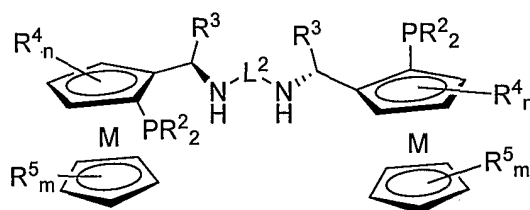
31. A process according to claim 28 or 29 which further comprises the step of contacting the compound of formula **8** with a ruthenium metal precursor, a rhodium metal precursor or an iridium metal precursor.

5

32. A process according to claim 31 wherein the ratio of the compound of formula **8** to the metal of the metal precursor is 0.8:1 to 1.5:1.

33. A process for preparing a compound having formula **4**

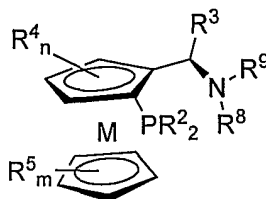
10



4

which comprises the steps of:

(1) contacting a dialkyl amine having formula **5**:

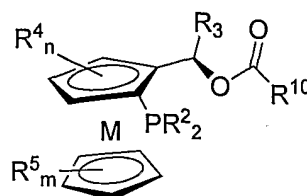


5

with a carboxylic anhydride having the formula $(R^{10}CO)_2O$ to obtain an ester having formula **6**:

15

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6

and (2) contacting the ester produced in step (1) with a diamine having the formula $H_2N-L^2-NH_2$ to obtain diphosphine-diamine **4**,

wherein R^2 is a branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or a C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

R^3 , R^4 , and R^5 are independently selected from hydrogen, branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

R^8 and R^9 are independently branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

R^{10} is a C_1 to C_4 alkyl radical:

L^2 is an achiral, racemic, enantiomerically enriched or substantially enantiomerically pure C_1 - C_{20} alkylene, C_3 - C_8 cycloalkylene, or 1,1'-biaryl-2,2'-diyl;

n is 0 to 3;

m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

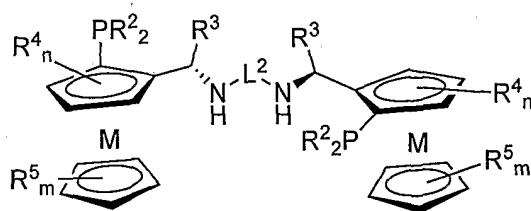
34. A process according to claim 33 which further comprises the step of contacting the compound of formula **4** with a ruthenium metal precursor, a rhodium metal precursor or an iridium metal precursor.

- 62 -

35. A process according to claim 34 wherein the ratio of the compound of formula 4 to the metal of the metal precursor is 0.8:1 to 1.5:1.

5 36. A process according to claim 34 wherein each R^2 is phenyl or 3,5-dimethylphenyl; each R^3 is hydrogen or methyl; L^2 is 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-
10 diyl and M is iron

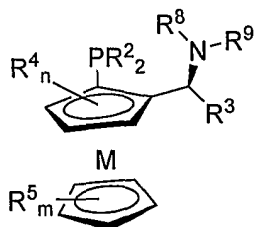
37. A process for preparing a compound having formula 8



8

which comprises the steps of:

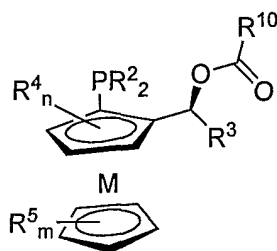
15 (1) contacting a dialkyl amine having formula 9:



9

- 63 -

with a carboxylic anhydride having the formula $(R^{10}CO)_2O$ to obtain an ester having formula **10**:

**10**

5 and (2) contacting the ester produced in step (1) with a diamine having the formula $H_2N-L^2-NH_2$ to obtain diphosphine-diamine **8**,

wherein R^2 is a branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or a C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

10 R^3 , R^4 , and R^5 are independently selected from hydrogen, branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

R^8 and R^9 are independently branched- or straight-chain C_1 - C_{20} alkyl, 15 C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

R^{10} is a C_1 to C_4 alkyl radical:

L^2 is an achiral, racemic, enantiomerically enriched or substantially enantiomerically pure C_1 - C_{20} alkylene, C_3 - C_8 cycloalkylene, or 1,1'-biaryl- 20 2,2'-diyl;

n is 0 to 3;

m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

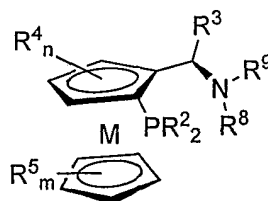
- 64 -

38. A process according to claim 37 which further comprises the step of contacting the compound of formula 8 with a ruthenium metal precursor, a rhodium metal precursor or an iridium metal precursor.

5 39. A process according to claim 38 wherein the ratio of the compound of formula 8 to the metal of the metal precursor is 0.8:1 to 1.5:1.

10 40. A process according to claim 38 wherein each R^2 is phenyl or 3,5-dimethylphenyl; each R^3 is hydrogen or methyl; L^2 is 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-diyl and M is iron.

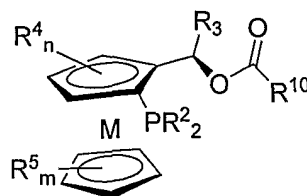
15 41. A process which comprises contacting a dialkyl amine having formula 5:



5

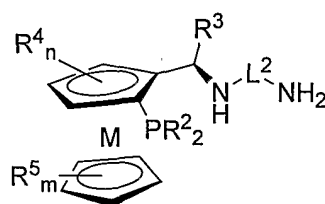
with a carboxylic anhydride having the formula $(R^{10}CO)_2O$ to obtain an ester having formula 6:

- 65 -



6

and contacting the ester **6** with a diamine having the formula $\text{H}_2\text{N}-\text{L}^2-\text{NH}_2$ to obtain a phosphine-diamine **7**



7

5

wherein R^2 is a branched- or straight-chain $\text{C}_1\text{-C}_{20}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_6\text{-C}_{20}$ carbocyclic aryl, or a $\text{C}_4\text{-C}_{20}$ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

10 R^3 , R^4 , and R^5 are independently selected from hydrogen, branched- or straight-chain $\text{C}_1\text{-C}_{20}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_6\text{-C}_{20}$ carbocyclic aryl, or $\text{C}_4\text{-C}_{20}$ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

15 R^8 and R^9 are independently branched- or straight-chain $\text{C}_1\text{-C}_{20}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_6\text{-C}_{20}$ carbocyclic aryl, or $\text{C}_4\text{-C}_{20}$ heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

R^{10} is a C_1 to C_4 alkyl radical:

L^2 is an achiral, racemic, enantiomerically enriched or substantially enantiomerically pure $\text{C}_1\text{-C}_{20}$ alkylene, $\text{C}_3\text{-C}_8$ cycloalkylene, or 1,1'-biaryl-2,2'-diyl;

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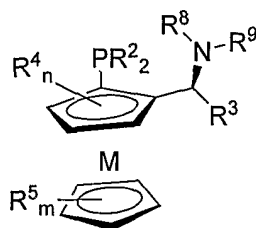
n is 0 to 3;

m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

- 5 42. A process according to claim 41 wherein R^2 is aryl; R^3 is hydrogen or C_1 to C_6 alkyl; R^4 and R^5 are hydrogen, L^2 is 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-diyl, and M is iron.
- 10

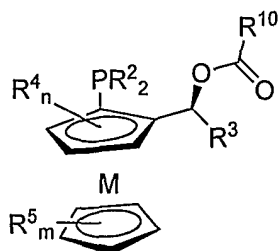
43. A process which comprises contacting a dialkyl amine having formula 9



9

15

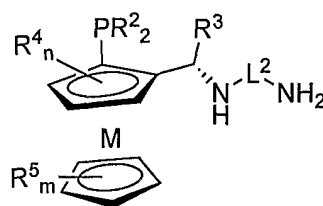
with a carboxylic anhydride having the formula $(R^{10}CO)_2O$ to obtain an ester having formula 10



10

- 67 -

and contacting ester **10** with a diamine having the formula $H_2N-L^2-NH_2$ to obtain a phosphine-diamine **11**

**11**

5 wherein R^2 is a branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or a C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, or oxygen;

R^3 , R^4 , and R^5 are independently selected from hydrogen, branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or
10 C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

R^8 and R^9 are independently branched- or straight-chain C_1 - C_{20} alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{20} carbocyclic aryl, or C_4 - C_{20} heteroaryl having from one to three heteroatoms selected from sulfur, nitrogen, and oxygen;

15 R^{10} is a C_1 to C_4 alkyl radical:

L^2 is an achiral, racemic, enantiomerically enriched or substantially enantiomerically pure C_1 - C_{20} alkylene, C_3 - C_8 cycloalkylene, or 1,1'-biaryl-2,2'-diyl;

 n is 0 to 3;

20 m is 0 to 5; and

M is selected from the metals of Groups IVB, VB, VIB, VIIB and VIII.

44. A process according to claim 43 wherein R^2 is aryl; R^3 is hydrogen or C_1 to C_6 alkyl; R^4 and R^5 are hydrogen, L^2 is 1,2-ethanediyl, 1,3-

- 68 -

propanediyl, 1,4-butanediyl, substantially enantiomerically pure 1,2-diphenyl-1,2-ethanediyl, substantially enantiomerically pure trans-1,2-cyclohexanediyl, or substantially enantiomerically pure 1,1'-binaphth-2,2'-diyl, and M is iron.

5

45. A process for the enantioselective hydrogenation of a hydrogenatable compound which comprises contacting the hydrogenatable compound with hydrogen in the presence of a catalyst complex defined in claim 8, 16 or 21.

10

46. A process according to claim 45 wherein the hydrogenatable compound is a non-symmetrical ketone such that the product of the process is a chiral secondary alcohol.

15

47. A process according to claim 46 wherein the enantioselective hydrogenation is carried out in the presence of a Bronsted base chosen from metal hydroxides or metal alkoxides.

20

48. A process according to claim 47 wherein the Bronsted base is sodium hydroxide, potassium hydroxide, sodium methoxide, potassium methoxide, sodium tert-butoxide, or potassium tert-butoxide.

25

49. A process for the enantioselective hydrogenation of a hydrogenatable compound which comprises contacting the hydrogenatable compound with hydrogen in the presence of a complex of a compound of formula 1 as set forth in claim 1 and a ruthenium metal precursor, a rhodium metal precursor or an iridium metal precursor.

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50. A process according to claim 49 wherein the hydrogenatable compound is a non-symmetrical ketone such that the product of the process is a chiral secondary alcohol.
- 5 51. A process according to claim 50 wherein the enantioselective hydrogenation is carried out in the presence of a Bronsted base chosen from metal hydroxides or metal alkoxides.
- 10 52. A process according to claim 51 wherein the Bronsted base is sodium hydroxide, potassium hydroxide, sodium methoxide, potassium methoxide, sodium tert-butoxide, or potassium tert-butoxide.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/045031A. CLASSIFICATION OF SUBJECT MATTER
INV. C07F17/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2005/068477 A (STYLACATS LIMITED; CHEN, WEI-PING; WHITTALL, JOHN) 28 July 2005 (2005-07-28) page 13 - page 24; compounds XXI, XXII, XXX-XXXVII ----- -/--	1-5, 7

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

8 May 2006

Date of mailing of the international search report

18/05/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Richter, H

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/045031

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ZHOU, ZHI-MING ET AL: "Efficient Diastereoselective Synthesis of Chiral Diferrocenylphosphine-diamines: X-ray Crystal Structure of [(η-5-C₅H₅)Fe(η-5-C₅H₃)PPh₂CHMeN(CH 2)2(CH₂)2NCHMePPh₂(η-5-C₅H₃))Fe(η-5-C₅H₅)]" XP002379956 retrieved from STN Database accession no. 2005:1007171 abstract & SYNTHETIC COMMUNICATIONS, 35(18), 2401-2408 CODEN: SYNCAV; ISSN: 0039-7911, 2005,	2-7, 9, 11
X	WO 01/58588 A1 (THE PENN STATE RESEARCH FOUNDATION, USA) 16 August 2001 (2001-08-16) Page 25, formulas 3 and 4 page 70; compounds B1, B2, E example 18	2-7, 13-15, 18-20
X		8, 16, 17, 21, 22, 45-48
A	BARBARO P ET AL: "Progress in stereoselective catalysis by metal complexes with chiral ferrocenyl phosphines" COORDINATION CHEMISTRY REVIEWS, ELSEVIER SCIENCE, AMSTERDAM, NL, vol. 248, no. 21-24, December 2004 (2004-12), pages 2131-2150, XP004917423 ISSN: 0010-8545 figure 20	2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/045031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005068477 A	28-07-2005	GB 2410950 A GB 2410951 A WO 2005068478 A1	17-08-2005 17-08-2005 28-07-2005
WO 0158588 A1	16-08-2001	AU 3691201 A CA 2400183 A1 EP 1257360 A1 JP 2003522162 T	20-08-2001 16-08-2001 20-11-2002 22-07-2003