

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
16 December 2004 (16.12.2004)

PCT

(10) International Publication Number
WO 2004/108651 A1

(51) International Patent Classification⁷: **C07C 67/303**,
51/36, B01J 31/18

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(21) International Application Number:
PCT/US2004/017935

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(22) International Filing Date: 7 June 2004 (07.06.2004)

(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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/476,059 5 June 2003 (05.06.2003) US

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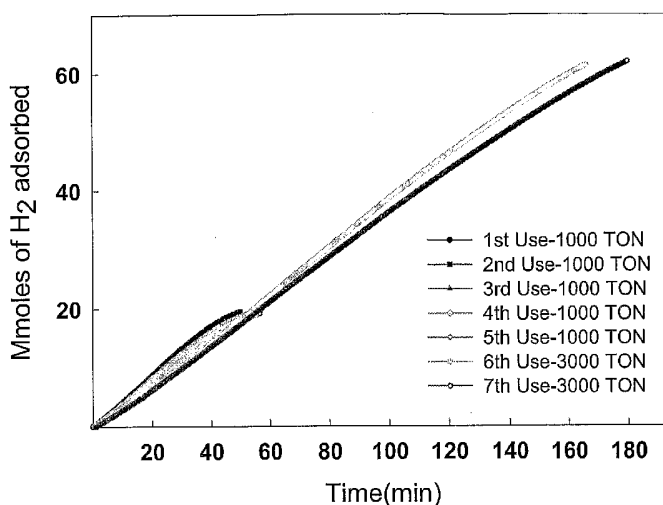
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,

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[Continued on next page]

(54) Title: SUPPORTED METAL-PHOSPHINE-AMINOPHOSPHINE CATALYSTS

Hydrogenation of DMIT
Catalyst preparation at 30°C
Reaction at rt, 50psig, 10% tol/abs. EtOH



(57) Abstract: The present invention is a re-usable and stable supported catalyst comprising a support, an anchoring agent, and a metal complex of a substantially enantiomerically pure phosphine-aminophosphine ligand. The resulting catalyst is useful for asymmetric catalytic reactions, such as asymmetric hydrogenation reactions. Also included are methods for preparing the supported catalyst and its use for asymmetric reactions.



SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

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*

SUPPORTED METAL-PHOSPHINE-AMINOPHOSPHINE CATALYSTS

Field of the Invention

5 The present invention relates to a re-usable and highly stable, supported complex which exhibits high reactivity, stability, and selectivity for asymmetric catalytic reactions. More specifically, the present invention relates to a supported metal complex of a substantially enantiomerically pure phosphine-aminophosphine ligand which comprises a support, an anchoring agent, and a metal complex of a substantially enantiomerically
10 pure phosphine-aminophosphine ligand. This invention also pertains to novel methods for the preparation of the supported catalyst complex and their use for asymmetric catalytic reactions.

Background of the Invention

15 Asymmetric catalysis is the most efficient method for generating products having high enantiomeric purity, as the asymmetry of the catalyst is multiplied many times over in the generation of the chiral product. These chiral products have found numerous applications as building blocks for single enantiomer pharmaceuticals as well as in some agrochemicals. The
20 asymmetric catalysts employed can be enzymatic or synthetic in nature. The latter types of catalyst have much greater promise than the former due to much greater latitude of applicable reaction types. Synthetic asymmetric catalysts are usually composed of a metal reaction center surrounded by an organic ligand. The ligand usually is generated in high enantiomeric purity,
25 and is the agent inducing the asymmetry. These ligands are, in general, difficult to make and therefore expensive. In addition, these ligand generally cannot be re-used due to, for example, difficulty in recovery and instability upon re-isolation.

The main strategy used to affix a homogeneous catalyst to a support (e.g., to heterogenize it) is to modify the ligand such that it can be incorporated into a polymer matrix. Unfortunately, such methods generally result in materials that exhibit significant loss of both activity and selectivity as compared to the original, soluble catalyst. Further, the activity of the heterogenized species often degrades rapidly upon attempted re-use. The supported catalysts described by Tanielyan et al. in United States Patents 6,005,148, 6,025,295 and 6,136,746 utilize a novel mode of immobilization that does not involve covalent modification of the chiral ligand. These supported species generally exhibit selectivity comparable to the homogeneous counterparts and maintain their catalytic activity over multiple re-uses.

The preparation and use of metal complexes of substantially enantiomerically pure phosphine-aminophosphine ligands for asymmetric catalysis has been described by Boaz et al. in published United States Patent application 20020065417. There has been no report of heterogenization of metal complexes of phosphine-aminophosphine ligands.

Brief Description of the Figures

Figure 1 depicts the rate of hydrogenation of dimethylitaconate using a supported metal-phosphine-aminophosphine catalyst prepared from a support, an anchoring agent, and a metal complex of a substantially enantiomerically pure phosphine-aminophosphine. This figure shows similar catalyst activity through seven uses of the same supported catalyst. Figure 1 reflects the experimental work in Example 3.

Figure 2 depicts the rate of hydrogenation of dimethyl itaconate using a supported metal-phosphine-aminophosphine prepared from a supported catalyst precursor and a substantially enantiomerically pure

phosphine-aminophosphine. This figure shows similar catalyst activity through four uses of the same supported catalyst. Figure 2 reflects the experimental work in Example 4.

5 Figure 3 depicts the rate of hydrogenation of dimethyl itaconate using a supported metal-phosphine-aminophosphine prepared from a supported catalyst precursor and a substantially enantiomerically pure phosphine-aminophosphine (e.g., hydrogenation of dimethyl itaconate using C/PTA/Rh-(R)-1 at S:C 10,000). This figure shows similar catalyst activity through five uses of the same supported catalyst. Figure 3 reflects the
10 experimental work in Example 5.

Brief Summary of the Invention

15 The novel supported catalysts of our invention comprise a support, an anchoring agent, and a metal complex of a substantially enantiomerically pure phosphine-aminophosphine ligand. These species are useful for asymmetric catalytic reactions, particularly for asymmetric hydrogenation. These supported catalysts have good activity, afford high enantioselectivity, and, surprisingly, can be re-used with minimal loss of catalytic activity.

20 Detailed Description

As stated above, the present invention comprises a supported catalyst comprising a support, an anchoring agent, and a metal complex of a substantially enantiomerically pure phosphine-aminophosphine ligand. The term "substantially enantiomerically pure" is meant to indicate that the
25 ligand is characterized by a >90% enantiomeric excess [ee] of the indicated enantiomer.

The support for use in the present invention comprises an insoluble, particulate amorphous or crystalline material having a sufficient surface area to facilitate uniform distribution of the anchoring agent. Suitable

supports include those that are readily and generally commercially available or may be prepared by techniques known to those of skill in the art.

Examples of appropriate support materials include, but are not limited to: metal oxides such as alumina, silica, titania, zirconia, lanthana, zeolites, and clays, as well as carbons, resins, polymers, and the like.

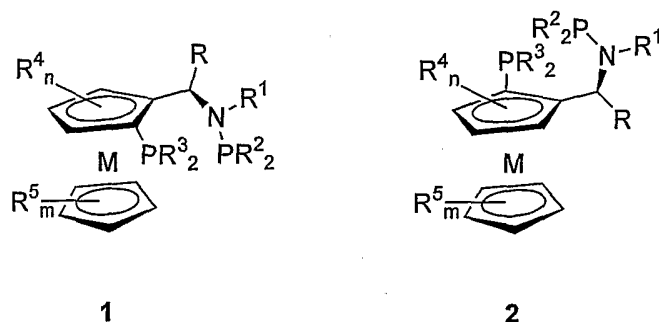
The support may be used as is (e.g., as purchased or prepared), or it may be treated prior to further use to remove unwanted species that may adversely effect the activity of the overall catalyst complex. For example, the support may be calcined either in air or in an inert atmosphere prior to use. Similarly, the support may be treated with a modifier to enhance adhesion of the anchoring agent. Suitable modifiers that may be used include, but are not limited to: metal alkoxides such as titanium alkoxide, aluminum alkoxide, silane alkoxide, vanadium alkoxide and the like; polyisocyanates, hydroxyepoxides, cyanoepoxides, and other functionalized organic materials.

The anchoring agent or anchor is a heteropoly acid or anion. The term "heteropoly acid" (or anion) as used herein denotes any polyprotic mixed oxide that is generally comprised of a central ion or ions bonded to an appropriate number of oxygen atoms and surrounded by a near spherical shell of octahedral oxometal species joined together by shared oxygen atoms. The central atom or "heteroatom" is typically a cation having a +3 to +5 oxidation state such as P(+5), As(+5), Si(+4), or Mn(+4). The metal species associated with the octahedral are usually Mo, W, or V. The octahedral in the shell of the heteropoly acid can be of uniform composition or contain different metal species. Suitable heteropoly acids include, but are not limited to: phosphotungstic acid (PTA), phosphomolybdic acid (PMA), silicotungstic acid (STA) and the like; Dawson species; Waugh species; Anderson species; Silverton species; their lacunar and other crystalline or non-crystalline forms; and anions of the preceding. When a

heteropoly anion is used, the counterions may be any species that readily affords the appropriate heteropoly anion. Suitable counterions (or cations) include, but are not limited to: alkali, alkaline earth, or quaternary ammonium ions.

5 The metal complex of the substantially enantiomerically pure phosphine-amino phosphine ligand is a complex of one or more Group IIB, IVB, VB, VIIB, VIII, IB, or IIB metals, and a substantially enantiomerically pure bis-phosphine compound comprising a substantially enantiomerically pure chiral backbone linking two phosphine residues wherein one of the
10 phosphine residues has three phosphorus-carbon bonds and the other phosphine residue has two phosphorus-carbon bonds and one phosphorus-nitrogen bond wherein the nitrogen is part of the chiral backbone. Examples of preferred metals for use with the subject ligand include Group
15 VIII metals such as rhodium, iridium or ruthenium.

15 Examples of the substantially enantiomerically pure, compounds (i.e., the subject ligand) include phosphinometalocenyl-aminophosphines having the general formulas **1** or **2** (the enantiomer of **1**):



20 wherein

R is selected from substituted and unsubstituted, branched- and straight-chain C₁-C₂₀ alkyl, substituted and unsubstituted C₃-C₈ cycloalkyl, substituted and unsubstituted C₆-C₂₀ carbocyclic aryl, and substituted and

unsubstituted C₄-C₂₀ heteroaryl wherein the heteroatoms are selected from sulfur, nitrogen, and oxygen;

R¹, R², R³, R⁴, and R⁵ are independently selected from hydrogen, substituted and unsubstituted, branched- and straight-chain C₁-C₂₀ alkyl, substituted and unsubstituted C₃-C₈ cycloalkyl, substituted and unsubstituted C₆-C₂₀ carbocyclic aryl, and substituted and unsubstituted C₄-C₂₀ heteroaryl wherein the heteroatoms are 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.

The alkyl groups which may be represented by each of R, R¹, R², R³, R⁴, and R⁵ may be straight- or branched-chain, aliphatic hydrocarbon radicals containing up to about 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 aryl groups which each of R, R¹, R², R³, R⁴, and R⁵ may represent may include phenyl, naphthyl, or anthracenyl and phenyl, naphthyl, or anthracenyl substituted with one to three substituents selected from C₁-C₆-alkyl, substituted C₁-C₆-alkyl, C₆-C₁₀ aryl, substituted 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 and -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 include a 5- or 6- membered aromatic ring containing one to three heteroatoms selected from oxygen, sulfur and
5 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-
10 alkyl, C₁-C₆-alkoxy, substituted C₁-C₆-alkyl, 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.
15 The term "halogen" is used to include fluorine, chlorine, bromine, and iodine.

Examples of preferred ligands of the invention have formulas 1 or 2 wherein R is C₁ to C₆ alkyl; R¹ is hydrogen or C₁ to C₆ alkyl; R² is aryl (preferably phenyl), ethyl, isopropyl, or cyclohexyl; R³ is aryl, most
20 preferably phenyl; R⁴ and R⁵ are hydrogen; and M is iron, ruthenium, or osmium, most preferably iron. The foregoing ligand-metal complexes may further comprise one or more achiral ligands which include, but are not limited to: species such as cyclopentadiene, carbon monoxide, cyclooctadiene, norbornadiene, and tertiary phosphines.

25 The present invention also provides for the preparation of the supported catalyst complexes described above. A method for preparing the supported catalysts may involve contacting a support with a heteropoly acid or anion anchoring agent under conditions effective to form a heteropoly acid or anion-containing support, and then contacting a metal complex of a

substantially enantiomerically pure phosphine-aminophosphine with the heteropoly acid or anion-containing support under conditions effective to form a supported catalyst.

Further, the supported catalyst of the present invention may be
5 prepared by contacting a previously prepared support and anchor combination with a metal complex of the substantially enantiomerically pure phosphine-aminophosphine ligand. The preparation of the anchor-support is as described in Tanielyan et al. in United States Patents 6,005,148, 6,025,295 and 6,136,746, the disclosures of which are hereby incorporated
10 by reference. Likewise, the preparation of the phosphine-aminophosphine ligand and its metal complex is as described in Boaz et al. in published United States Patent application 20020065417, the disclosure of which is hereby incorporated by reference.

The contacting of the ligand-metal complex and the support-anchor
15 combination typically occurs in a solvent and at a temperature from about -25°C to about 250°C for a time period from about 1 min to about 50 hrs. Preferably this contacting takes place at temperatures between about 25°C and 50°C for a time period of between about 1 hr and about 24 hrs. Generally, the ligand-metal complex is employed at a concentration such
20 that the metal complex to heteropolyacid or anion anchor material molar ratio is from about 0.1:1 to about 6:1; more preferably the ratio is from about 0.5:1 to about 1.5:1. The solvent employed is capable of dissolving the metal complexes. Preferred solvents include lower alcohols (C1-C5), ethers, esters, ketones, and aliphatic or aromatic hydrocarbons or mixtures
25 thereof.

The resulting solid, supported catalyst of the invention may then be optionally recovered using techniques known to those skilled in the art, such as decantation, filtration, or centrifugation. The solid supported catalyst may be used as is, or it optionally may be washed with one of the

5 aforementioned solvents prior to use to remove any non-supported material.

 An alternative method of preparing the solid catalysts of the invention involves first contacting the anchoring agent with the ligand-metal complex of the substantially enantiomerically pure phosphine-aminophosphine to form a mixture, and then that mixture is contacted with a support material. The foregoing mixture may take the form of either a suspension or solution.

10 The contacting between the anchoring agent and the metal complex of the substantially enantiomerically pure phosphine-aminophosphine typically occurs in a solvent and at a temperature from about -25°C to about 250°C for a time period from about 1 min to about 50 hrs. Preferably this contacting takes place at temperatures between about 25°C and about 50°C for a time period of between about 1 hr and about 24 hrs. Generally, in the present invention, the metal complex is employed at a concentration
15 such that the metal complex to heteropolyacid or anion molar ratio is from about 0.1:1 to about 6:1, more preferably from about 0.5:1 to about 1.5:1.

 The resulting mixture containing the anchoring agent and the metal complex may be contacted with the support material as is, or, alternatively, the resulting solution or suspension may be dried and then slurried in a
20 comparable solvent prior to contacting with one of the support materials set forth above. This contacting generally occurs in a solvent at a temperature of from about -25°C to about 250°C for a period of time from about 1 min to 50 hrs. Preferably, this contacting takes place at a temperature of about 25°C to about 50°C for a period of time from about 3 hrs to about 12 hrs. In
25 accordance with this aspect of the present invention, the anchoring agent and metal complex solution or suspension is present in about 0.01% to about 150% by weight of the support employed in this contacting step. Solvents that may be used in either step of this embodiment include lower

alcohols (C1-C5), ethers, esters, ketones, and aliphatic or aromatic hydrocarbons or mixtures thereof.

The solid supported catalyst of this invention may then be optionally recovered using techniques known to those skilled in the art, such as
5 decantation, filtration, or centrifugation. The solid supported catalyst may be used as is, or it optionally may be washed with one of the aforementioned solvents prior to use to remove any non-supported material.

In a further embodiment of the present invention, a supported
10 catalyst complex is prepared by contacting a supported catalyst precursor with a substantially enantiomerically pure phosphine-aminophosphine ligand. The preparation of a supported, metal-containing, catalyst precursor is described by Tanielyan et al. in the United States Patents identified above. Once prepared, the supported catalyst precursor is then contacted
15 with a substantially enantiomerically pure phosphine-aminophosphine ligand, described hereinabove, to form the supported metal complex.

The supported catalyst precursor for use herein comprises a support, an anchoring agent, and a metal salt or complex from which a catalytically active entity may be prepared. Examples of catalyst precursor materials
20 include rhodium cyclooctadiene dimer, bis(cyclooctadiene)rhodium tetrafluoroborate, bis(cyclooctadiene)rhodium trifluoromethanesulfonate, bis(norbornadiene)rhodium tetrafluoroborate, ruthenium cyclooctadiene dimer, allyl palladium chloride dimer, and rhodium chloride.

The concentration of the substantially enantiomerically pure
25 phosphine-aminophosphine ligand that is added to the supported catalyst precursor is typically about 1 to about 6 mmol per mmol of supported catalyst precursor material. The treatment of the supported catalyst precursor with the substantially enantiomerically pure phosphine-aminophosphine ligand typically occurs in a solvent at temperatures of from

about -25°C to about 250°C, and preferably about 25° to about 50°C, for a period of time from about 1 min to about 50 hrs. Preferred solvents for this embodiment include lower alcohols (C1-C5), ethers, esters, ketones, and aliphatic or aromatic hydrocarbons or mixtures thereof.

5 The solid supported catalyst of this invention may then be optionally recovered using techniques known to those skilled in the art, such as decantation, filtration, or centrifugation. The solid supported catalyst may be used as is, or it optionally may be washed with one of the
10 aforementioned solvents prior to use to remove any non-supported material.

 These supported complexes of the present invention may be used to perform asymmetric catalytic reactions. Examples of such reactions include, but are not limited to: asymmetric hydrogenations, asymmetric reductions, asymmetric hydroborations, asymmetric olefin isomerizations,
15 asymmetric hydrosilations, asymmetric allylations, asymmetric hydroformylations, and asymmetric organometallic additions. A preferred embodiment of the present invention is the use of the supported complexes for asymmetric hydrogenation reactions, an example of which is the
20 catalytic asymmetric hydrogenation of prochiral substituted α,β -unsaturated acids or esters or other prochiral substrates to provide the saturated, chiral counterpart. The hydrogenation conditions employed in the present invention are those that are typically employed by those of skill in the art for carrying out such a reaction.

 The amount of supported catalyst complex employed may vary
25 between 0.000005 and 0.5 equivalents based on the reactant compound, with more complex usually providing faster reaction rates. The atmosphere for the reaction is hydrogen, but may also contain other gases or materials that are inert to the reaction conditions. The reaction can be run at atmospheric pressure or at elevated pressure, generally from about 0.5 to

about 200 bars gauge (barg). The reaction is run at a 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 reaction may be run in the presence of a solvent chosen from 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, lower alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol and the like, halogenated aliphatic or aromatic hydrocarbons such as dichloromethane, tetrachloroethylene, chloroform, chlorobenzene and the like, esters such as methyl acetate, ethyl acetate, methyl propionate, isopropyl acetate and the like, dialkyl ketones such as acetone, 2-butanone, 3-pentanone, methyl isopropyl ketone, methyl isobutyl ketone and the like, or polar aprotic solvents such as dimethylformamide, dimethyl sulfoxide and the like or mixtures thereof. The products of such reaction are generally obtained in high enantiomeric excess ($>85\%$ ee).

As stated previously, the supported catalysts described herein may be re-used multiple times without substantial loss of catalytic activity or enantioselectivity. The ability to re-use the supported catalysts of this invention is surprising and unexpected because the skilled artisan would expect a phosphine-aminophosphine catalyst to degrade or deactivate due to cleavage of the nitrogen-phosphorus bond of the aminophosphine over continued uses even if one were able to affix it to a support. This is particularly true when such phosphine-aminophosphine catalysts are exposed to alcoholic solvents. Clearly, cleavage of the nitrogen-phosphorus bond would result in loss of catalytic activity and enantioselectivity.

Examples

The novel compounds and processes provided by the present invention are further illustrated by the following examples.

5

Example 1

A reactor containing Al_2O_3 /PTA support (0.4221g) was evacuated and refilled with argon several times before adding 15 mL of degassed absolute ethanol via cannula. After this addition, the cannula was removed and the reactor evacuated for about 10 minutes or until no bubbling was observed. During this time, bis(norbornadiene)rhodium tetrafluoroborate (0.0075 g; 20 micromoles) and (R)-N-diphenylphosphino-1-[(S)-2-(diphenylphosphino)-ferrocenyl]ethylamine (1, $R = R^1 = \text{CH}_3$, $R^2 = R^3 = \text{Ph}$, $n = m = 0$, $M = \text{Fe}$)(0.0122 g; 20 micromoles) were weighed and transferred to a 10 mL volumetric flask. After evacuating the contents of the flask for about 5 minutes, the contents were diluted to the mark with absolute ethanol and sonicated for 25 minutes. The contents of this flask were then added to the reactor via cannula at a slow rate (~10 minutes). Upon complete addition and removal of the cannula, the reactor was evacuated, refilled with argon at least 3 times and then placed in a water bath (37°C) for overnight stirring (~550 rpm). The next day, the support was washed 3-4 times with absolute ethanol and then dried under vacuum.

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Example 2

A reactor containing Al_2O_3 /PTA support (0.4221g) was evacuated and refilled with argon several times before adding 15 mL of degassed absolute ethanol via cannula. After this addition, the cannula was removed and the reactor evacuated for about 10 minutes or until no bubbling was observed. During this time, bis(cyclooctadiene)rhodium tetrafluoroborate (0.0081g; 20 micromoles) was weighed and transferred to a 10 mL

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volumetric flask. After evacuating the contents of the flask for about 5 minutes, the contents were diluted to the mark with absolute ethanol. The contents of this flask were then added to the reactor via cannula at a slow rate (~10 minutes). Upon complete addition and removal of the cannula, 5 the reactor was evacuated, refilled with argon at least 3 times and then placed in a water bath (37°C) for overnight stirring (~550 rpm). The next day, the support was washed 2 times with absolute ethanol. At this point, the support can be dried for further use or re-suspended in 15 mL of absolute ethanol. A solution containing 20 micromoles of (R)-N- 10 diphenylphosphino-1-[(S)-2-(diphenylphosphino)-ferrocenyl]ethylamine (1, $R = R^1 = \text{CH}_3$, $R^2 = R^3 = \text{Ph}$, $n = m = 0$, $M = \text{Fe}$) (0.0122g) was added dropwise to the support and the contents stirred overnight at a temperature of 37°C. The next day, the support was washed 3-4 times with absolute ethanol and then dried under vacuum.

15

Example 3

The supported complex described in Example 1 was connected to a hydrogen line and the entire system was evacuated 8 times before exposing the support to hydrogen. A color change was observed as soon 20 as the support was exposed to hydrogen (from orange to red-orange). At this point 15 mL of 15%toluene/abs. ethanol was added via syringe followed by the desired amount of dimethyl itaconate (8.5mL for a 3000 turnover number reaction). The hydrogenation was performed at ambient temperature under 50 psig of hydrogen and followed by hydrogen uptake. 25 Upon completion of the reaction, the supernatant was removed and the reactor was charged with a second batch of solvent and substrate as described above. The supported complex was used for a total of seven runs. The rate data from these runs is graphed in Figure 1 and the

turnover frequencies and enantiomeric excesses of the product is shown in Table 1.

Use No.	TON	TOF (Hr^{-1})	% e.e.
1	1000	1140	91%
2	1000	1260	92%
3	1000	1200	92%
4	1000	1140	92%
5	1000	1080	92%
6	3000	1050	92%
7	3000	1050	92%

- 5 Table 1. TON is total supported catalyst turnover number. TOF is the catalyst turnover frequency per hour at the initial stages of the reaction.

Example 4

- 10 The supported complex described in Example 2 was connected to a hydrogen line and the entire system was evacuated 8 times before exposing the support to hydrogen. A color change was observed as soon as the support was exposed to hydrogen (from orange to red-orange). At this point 15 mL of 15%toluene/abs. ethanol were added via syringe followed by the desired amount of dimethyl itaconate (8.5mL for a 3000
- 15 turnover number reaction). The hydrogenation was performed at ambient temperature under 50 psig of hydrogen and followed by hydrogen uptake. Upon completion of the reaction, the supernatant was removed and the reactor was charged with a second batch of solvent and substrate as described above. The supported complex was used for a total of four runs.
- 20 The rate data from these runs is graphed in Figure 2 and the turnover frequencies and enantiomeric excesses of the product is shown in Table 2.

Use No.	TON	TOF (Hr^{-1})	% e.e.
1	3000	1920	90.6%
2	3000	1890	91.3%
3	3000	1770	90.8%
4	3000	1710	91.6%

Table 2. TON is total supported catalyst turnover number. TOF is the catalyst turnover frequency per hour at the initial stages of the reaction.

Example 5

Phosphotungstic acid on carbon (0.164 g; contains 10 μmol of phosphotungstic acid) and 1,5-cyclooctadienerrhodium-(R)-N-diphenylphosphino-1-[(S)-2-(diphenylphosphino)-ferrocenyl]ethylamine (10 μmol) were combined in 15 mL of 5% toluene in methanol under argon. The mixture was stirred overnight to afford a suspension of the supported catalyst. The supernatant was removed via cannula, and the solid was washed until the washings were colorless. To this was added 40 mL of argon-degassed 3% toluene in methanol. The suspension was stirred and freshly purified dimethyl itaconate (14.1 mL; 100 mmol; S:C 10,000) was added. The reaction mixture was heated to 40°C and the argon atmosphere was replaced with 75 psig hydrogen. The reaction mixture was stirred and followed by hydrogen uptake. Upon completion of the reaction, the supernatant was removed and the reactor was charged with a second batch of solvent and substrate as described above. The supported complex was used for a total of five runs. The rate data from these runs is graphed in Figure 3 and the turnover frequencies and enantiomeric excesses of the product is shown in Table 3.

Use No.	TON	TOF (Hr ⁻¹)	% e.e.
1	10000	10,400	92%
2	10000	10,500	92%
3	10000	10,500	92%
4	10000	10,600	91%
5	10000	9,200	92%

Table 3. TON is total supported catalyst turnover number. TOF is the catalyst turnover frequency per hour at the initial stages of the reaction.

5 Example 6

Phosphotungstic acid on carbon (0.082 g; contains 5 μ mol of phosphotungstic acid) and 1,5-cyclooctadienerhodium-(R)-N-diphenylphosphino-1-[(S)-2-(diphenylphosphino)-ferrocenyl]ethylamine (5 μ mol) were combined in 15 mL of 5% toluene in methanol under argon.

10 The mixture was stirred overnight to afford a suspension of the supported catalyst. The supernatant was removed via cannula, and the solid was washed until the washings were colorless. To this was added 120 mL of argon-degassed methanol. The suspension was stirred and freshly purified dimethyl itaconate (100 mL; 708 mmol; S:C 141,600) was added. The
15 reaction mixture was heated to 50°C and the argon atmosphere was replaced with 75 psig hydrogen. The reaction mixture was stirred for about 15 hours to completely consume the dimethyl itaconate, affording dimethyl (R)-2-methylsuccinate with 88% ee and a catalytic activity of 12,500 turnovers per hour.

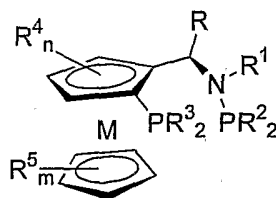
20 The invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

CLAIMS

We claim:

1. A supported catalyst comprising a support, an anchoring agent, and a metal complex of a substantially enantiomerically pure phosphine-aminophosphine ligand.
- 5 2. The supported catalyst of Claim 1 wherein said support is selected from the groups consisting of metal oxides, carbon, resins, and polymers.
3. The supported catalyst of Claim 2 wherein the metal oxide is selected from the group consisting of alumina, silica, titania, lanthana, zeolites, and clays.
- 10 4. The supported catalyst of Claim 2 wherein the support is treated by calcination or contacted with a modifier.
5. The supported catalyst of Claim 4 where the modifier is a metal alkoxide chosen from titanium alkoxide, aluminum alkoxide, silane alkoxide, or vanadium alkoxide.
- 15 6. The supported catalyst of Claim 1 wherein the anchoring agent is a heteropoly acid or anion selected from a Keggin type, a Dawson type, an Anderson type, or a Silverton type or mixtures thereof.
7. The supported catalyst of Claim 6 wherein the heteropoly acid is phosphotungstic acid, phosphomolybdic acid, silicotungstic acid, or the anions thereof.
- 20 8. The supported catalyst of Claim 1 wherein the metal complex comprises a metal from Groups IIIB, IVb, VB, VIIB, IB, or IIB .
9. The supported catalyst of Claim 8 wherein said metal is a Group VIII metal.
- 25

10. The supported catalyst of Claim 1 wherein the substantially enantiomerically pure phosphine-aminophosphine has formula 1:



1

5 wherein

R is selected from substituted and unsubstituted, branched- and straight-chain C₁-C₂₀ alkyl, substituted and unsubstituted C₃-C₈ cycloalkyl, substituted and unsubstituted C₆-C₂₀ carbocyclic aryl, and substituted and unsubstituted C₄-C₂₀ heteroaryl wherein the heteroatoms are selected from sulfur, nitrogen, and oxygen;

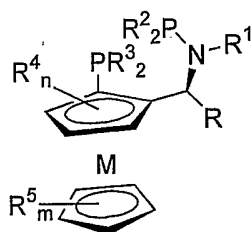
R¹, R², R³, R⁴, and R⁵ are independently selected from hydrogen, substituted and unsubstituted, branched- and straight-chain C₁-C₂₀ alkyl, substituted and unsubstituted C₃-C₈ cycloalkyl, substituted and unsubstituted C₆-C₂₀ carbocyclic aryl, and substituted and unsubstituted C₄-C₂₀ heteroaryl wherein the heteroatoms are 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.

11. The supported catalyst of Claim 1 wherein the substantially enantiomerically pure phosphine-aminophosphine has formula 2:



2

5 wherein

R is selected from substituted and unsubstituted, branched- and straight-chain C₁-C₂₀ alkyl, substituted and unsubstituted C₃-C₈ cycloalkyl, substituted and unsubstituted C₆-C₂₀ carbocyclic aryl, and substituted and unsubstituted C₄-C₂₀ heteroaryl wherein the heteroatoms are selected from sulfur, nitrogen, and oxygen;

R¹, R², R³, R⁴, and R⁵ are independently selected from hydrogen, substituted and unsubstituted, branched- and straight-chain C₁-C₂₀ alkyl, substituted and unsubstituted C₃-C₈ cycloalkyl, substituted and unsubstituted C₆-C₂₀ carbocyclic aryl, and substituted and unsubstituted C₄-C₂₀ heteroaryl wherein the heteroatoms are 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.

12. A method for preparing the supported catalyst of Claim 1 comprising:
 (a) contacting a support with a heteropoly acid or anion anchoring agent under conditions effective to form a heteropoly acid or anion-containing support; and

(b) contacting a metal complex of a substantially enantiomerically pure phosphine-aminophosphine with the heteropoly acid or anion-containing support under conditions effective to form a supported catalyst.

5 13. The method of Claim 12 wherein step (a) occurs in a solvent at a temperature of from about -25°C to about 250°C for a period of time of from about 1 min to about 50 hrs.

14. The method of Claim 12 wherein step (b) occurs in a solvent at a temperature of from about -25°C to about 250°C for a period of time of
10 from about 1 min to about 50 hrs.

15. The method of Claim 13 where the metal complex is contacted with the heteropoly acid or anion-containing support at a concentration to provide a molar ratio of metal complex to heteropoly acid or anion of from about 0.1:1 to about 6:1.

15 16. A method for the preparation of the supported catalyst of Claim 1 comprising:

(a) contacting a heteropoly acid or anion with a metal complex of a substantially enantiomerically pure phosphine-aminophosphine under conditions effective to form a mixture containing the heteropoly
20 acid or anion and the metal complex; and

(b) contacting a support with the mixture formed in step (a) under conditions effective to form a supported catalyst.

17. The method of Claim 16 wherein step (a) occurs in a solvent at a temperature of from about -25°C to about 250°C for a period of time of
25 from about 1 min to about 50 hrs.

18. The method of Claim 16 wherein the metal complex is contacted with the heteropoly acid or anion at a concentration to provide a molar ratio of metal complex to heteropoly acid or anion of from about 0.1:1 to about 6:1.

19. The method of Claim 16 wherein step (b) occurs in a solvent at a temperature of from about -25°C to about 250°C for a period of time of from about 1 min to about 50 hrs.
20. The method of Claim 16 where the heteropoly acid or anion and metal complex are present in a weight ratio of about 0.1:1 to about 20:1 as compared to the support employed in step (b).
21. A method of preparing the supported catalyst of Claim 1 comprising:
- (a) contacting a support with a heteropoly acid or anion under conditions effective to form a heteropoly acid or anion-containing support;
 - (b) contacting said heteropoly acid or anion-containing support with a catalyst precursor material under conditions effective to form a supported catalyst precursor; and
 - (c) contacting said supported catalyst precursor with a substantially enantiomerically pure phosphine-aminophosphine ligand to provide a supported catalyst.
22. The method of Claim 21 wherein the support employed in step (a) is calcined or treated with a metal alkoxide prior to use.
23. The method of Claim 22 where the metal alkoxide is selected from the group consisting of titanium alkoxide, aluminum alkoxide, silane alkoxide, and vanadium alkoxide.
24. The method of Claim 21 wherein step (a) occurs in a solvent at a temperature of from about -25°C to about 250°C for a period of time of from about 1 min to about 50 hrs.
25. The method of Claim 21 where said catalyst precursor material is a metal salt or complex from which a catalytically active entity can be prepared.
26. The method of claim 25 where the metal salt or complex of said catalyst precursor is selected from the group consisting of rhodium

cyclooctadiene dimer, bis(cyclooctadiene)rhodium tetrafluoroborate, bis(cyclooctadiene)rhodium trifluoromethanesulfonate, bis(norbornadiene)rhodium tetrafluoroborate, ruthenium cyclooctadiene dimer, allyl palladium chloride dimer, and rhodium chloride.

- 5 27. The method of Claim 21 wherein step (b) occurs in a solvent at a temperature of from about -25°C to about 250°C for a period of time of from about 1 min to about 50 hrs.
28. The method of Claim 21 wherein step (c) occurs in a solvent at a temperature of from about -25°C to about 250°C for a period of time of
- 10 from about 1 min to about 50 hrs.
29. The method of Claim 21 wherein from about 1 mmol to about 6 mmol of ligand per mmol of supported catalyst precursor material is employed in step (c).
30. A process for the hydrogenation of an α,β —unsaturated acid or
- 15 ester, which comprises contacting a prochiral α,β -unsaturated acid or ester with the supported catalyst of Claim 1 and hydrogen under conditions of hydrogenation temperature and pressure.

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Hydrogenation of DMIT
Catalyst preparation at 30°C
Reaction at rt, 50psig, 10% tol/abs. EtOH

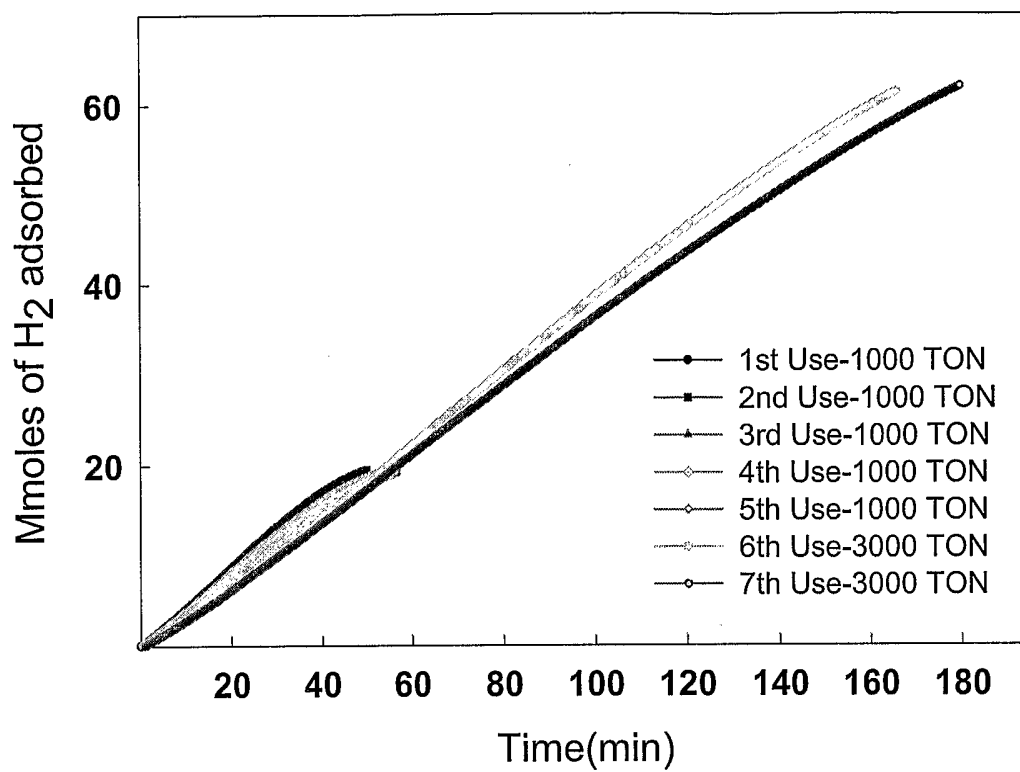


Figure 1

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Hydrogenation of DMIT 3000 TON
Ligand exchange procedure 37°C
Reaction at rt, 50psig 15% tol/abs EtOH

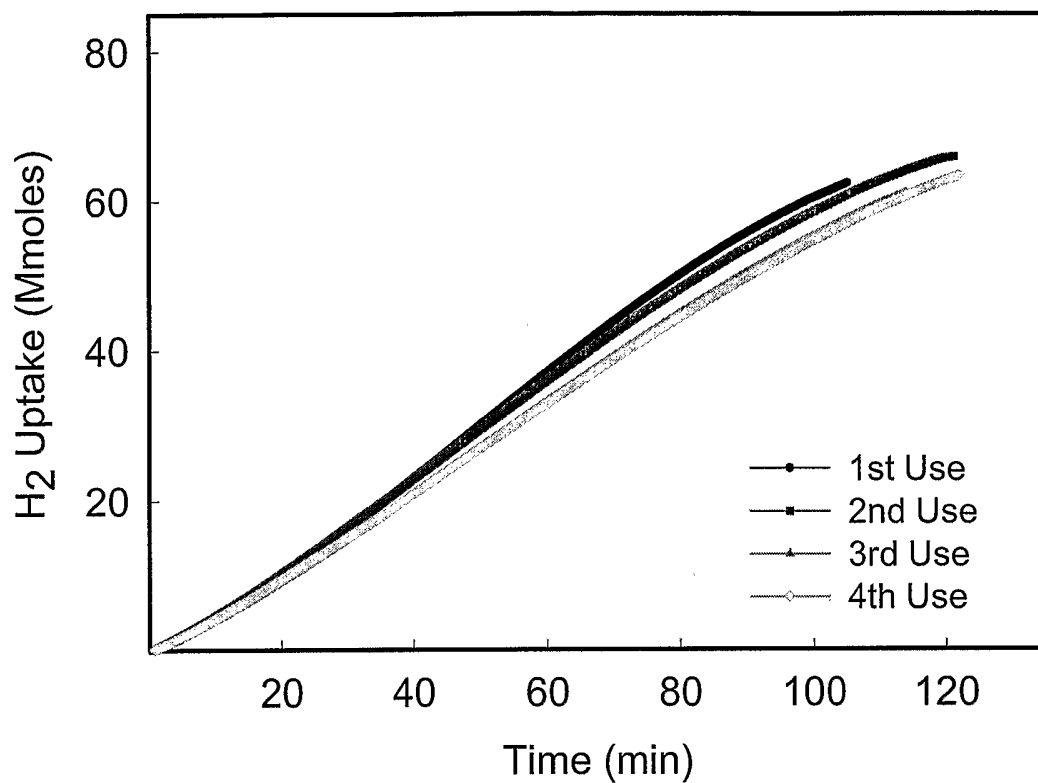


Figure 2

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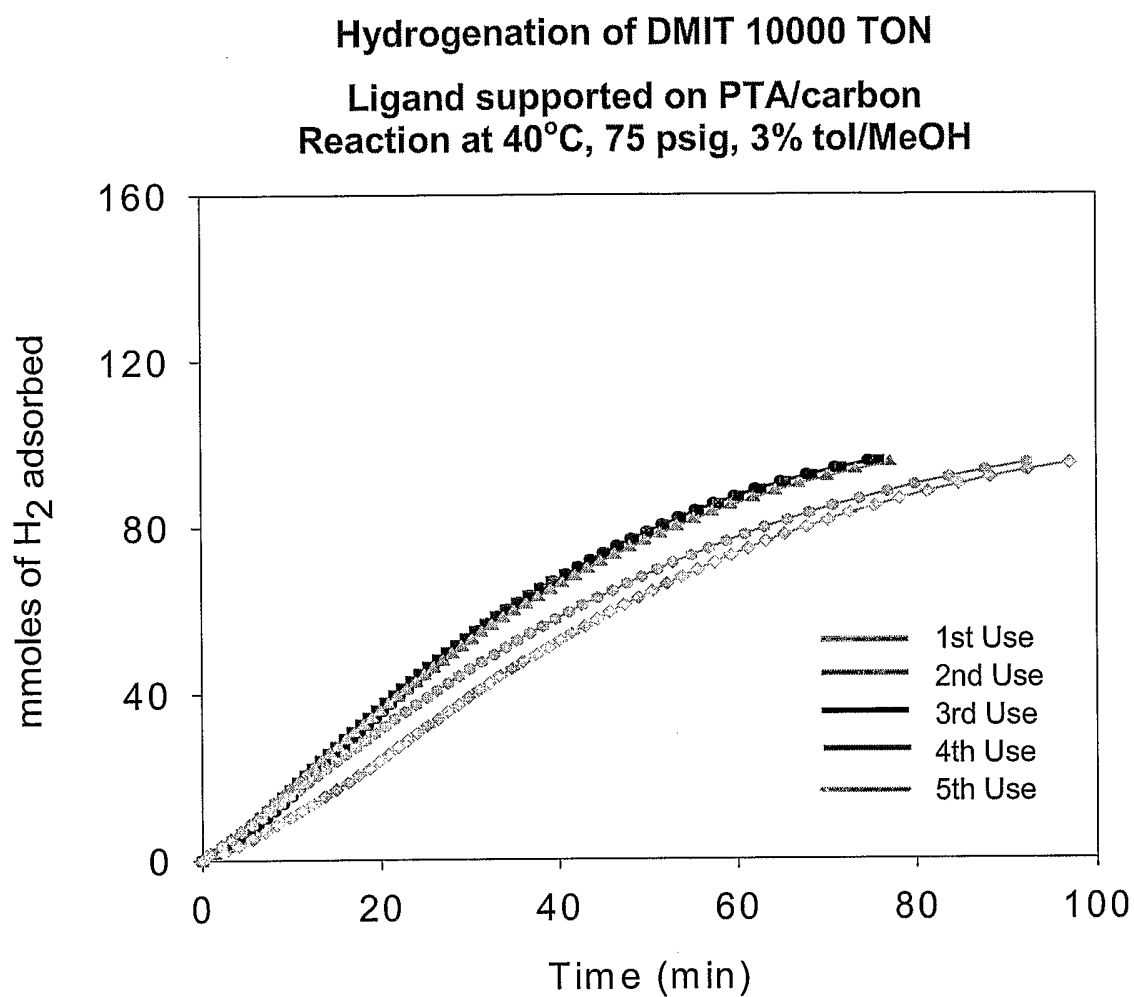


Figure 3

INTERNATIONAL SEARCH REPORT

tional Application No

.../US2004/017935

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C67/303 C07C51/36 B01J31/18

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)

IPC 7 C07C B01J

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.
A	BOAZ, NEIL W. ET AL: "Phosphinoferrocenylaminophosphines as Novel and Practical Ligands for Asymmetric Catalysis" ORGANIC LETTERS , 4(14), 2421-2424 CODEN: ORLEF7; ISSN: 1523-7060, 2002, XP002297176 scheme 1, tables 1,2; compound 2 -----	1-30
A	US 2002/065417 A1 (DEBENHAM SHERYL DAVIS ET AL) 30 May 2002 (2002-05-30) cited in the application examples page 2, column 2, paragraph 2 -----	1-30
A	US 6 025 295 A (AUGUSTINE ROBERT L ET AL) 15 February 2000 (2000-02-15) abstract ----- -/--	1-30

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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O document referring to an oral disclosure, use, exhibition or other means

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

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

21 September 2004

Date of mailing of the international search report

13/10/2004

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Klaes, D

INTERNATIONAL SEARCH REPORT

International Application No

t/US2004/017935

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	CARPENTIER, JEAN-FRANCOIS ET AL: "Catalytic asymmetric hydrogenation of activated keto compounds by some homogeneous and silica- supported di(.mu.-carboxylato)bis(aminophosphinephosphinite)dirhodium complexes" TETRAHEDRON: ASYMMETRY , 6(1), 39-42 CODEN: TASYE3; ISSN: 0957-4166, 1995, XP002297177 scheme 1, table 2 -----	1-29

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Information on patent family members

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