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(54) Titre : PROCÉDE POUR LA FABRICATION D'AMINES A PARTIR D'ALCOOLS ET D'AMMONIAC
(54) Title: PROCESS FOR PREPARING AMINES FROM ALCOHOLS AND AMMONIA

(57) **Abrégé/Abstract:**

The present invention provides novel ruthenium based catalysts, and a process for preparing amines, by reacting a primary alcohol and ammonia in the presence of such catalysts, to generate the amine and water. According to the process of the invention, primary alcohols react directly with ammonia to produce primary amines and water in high yields and high turnover numbers. This reaction is catalyzed by novel ruthenium complexes, which are preferably composed of quinolinylyl or acridinylyl based pincer ligands.



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(54) Title: PROCESS FOR PREPARING AMINES FROM ALCOHOLS AND AMMONIA

(57) Abstract: The present invention provides novel ruthenium based catalysts, and a process for preparing amines, by reacting a primary alcohol and ammonia in the presence of such catalysts, to generate the amine and water. According to the process of the invention, primary alcohols react directly with ammonia to produce primary amines and water in high yields and high turnover numbers. This reaction is catalyzed by novel ruthenium complexes, which are preferably composed of quinolinyl or acridinyl based pincer ligands.



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PROCESS FOR PREPARING AMINES FROM ALCOHOLS AND AMMONIA

FIELD OF THE INVENTION

The present invention relates to novel ruthenium catalysts, and to a process of
5 preparing primary amines by reacting alcohols with ammonia in the presence of such
catalysts.

BACKGROUND OF THE INVENTION

Amines are a very important family of compounds in chemistry and biology. They
10 are widely used in the production of pharmaceuticals, fine chemicals, agrochemicals,
polymers, dyestuffs, pigments, emulsifiers and plasticizing agents (1). Among the amines,
the terminal primary amines (e.g. RNH_2 wherein R is an organic radical) are the most
useful, but their selective synthesis is challenging, due to their high reactivity.

The conversion of alcohols to amines by conventional methods typically involves
15 two to three steps, each step generally requiring isolation and purification, making the
process cumbersome for even small-scale syntheses (2). Fewer classical methods are
known for the stepwise, one-pot conversion of alcohols to primary amines, although such
methods are not environmentally benign and are inappropriate for large scale production (3-
6). Existing methods for the preparation of primary amines generally utilize stoichiometric
20 amounts of toxic reagents and lead to poor selectivity and very low atom-economy (7-9).
An attractive method for the preparation of secondary and tertiary linear amines by
hydroaminomethylation of internal olefins was reported (10). Amines are also prepared by
the reduction of amides, generally under harsh conditions to result in a mixture of products
(11). Iridium and rhodium catalyzed preparation of amines from aldehydes was also
25 reported (12). Although high hydrogen pressure is required for the reductive amination of
aldehydes, and alcohols are formed as by-products, this method demonstrated the first
homogeneous catalytic reductive amination process with ammonia. Lewis acid catalyzed
reductive amination methods for the synthesis of amines are also known (13, 14).
Recently, synthesis of arylamines was achieved by palladium-catalyzed arylation of
30 ammonia in dioxane (15). Primary amines can be alkylated by alcohols to obtain secondary

amines (16). Iridium-catalyzed multialkylation of ammonium salts with alcohols was reported for the synthesis of secondary and tertiary amines, but selective synthesis of primary amines remains as a tantalizing task (17).

Among the methods utilized for commercial production of amines (1, 18), by far, the largest and most utilized are based on the reaction of alcohols with ammonia. However, the solid acid catalyzed reaction of alcohols with ammonia requires very high temperatures (300-500 °C) and forms mixtures of primary, secondary and tertiary amines, and also large amounts of alkene as a result of dehydration. The metal-oxide catalyzed reaction of alcohols and amines at high temperature and pressure also results in mixtures of amines and has to be conducted under hydrogen pressure for catalyst stability. In addition, this reaction forms alkanes as a result of CO extrusion. (18)

Catalytic coupling of ammonia with organic substrates for the direct preparation of aryl and alkyl primary amines are considered to be two of the ten greatest challenges in catalysis (19). Atom economical methods to activate alcohols (replacing the Mitsunobu protocol) for the direct nucleophilic substitution and "N"-centered chemistry that precludes azides and hydrazine are among the most required processes in pharmaceutical industries (20). Selective catalytic synthesis of primary amines is a paradoxical challenge as the primary amines are more nucleophilic than ammonia and compete with it in reaction with electrophiles such as alkyl halides or aldehydes, producing secondary amines (21), which can also react, leading to the formation of mixtures of products.

Thus, selective, catalytic synthesis of primary amines directly from alcohols and ammonia with elimination of water, under relatively mild conditions, without producing waste, is highly desirable economically and environmentally. However, such a facile process is unknown.

Pincer complexes can have outstanding catalytic properties (22, 23). The applicants of the present invention previously reported the dehydrogenation of alcohols catalyzed by PNP- and PNN-Ru(II) hydride complexes (24). Whereas secondary alcohols lead to ketones (25, 26), primary alcohols are efficiently converted into esters and dihydrogen (25-26). A dearomatized PNN pincer complex was particularly efficient (28); it catalyzed this process in high yields under neutral conditions, in the absence of acceptors or promoters. US patent application publication no. US 2009/0112005, to the applicants of the present invention,

describes methods for preparing amides, by reacting a primary amine and a primary alcohol in the presence of ruthenium catalysts, to generate the amide compound and molecular hydrogen.

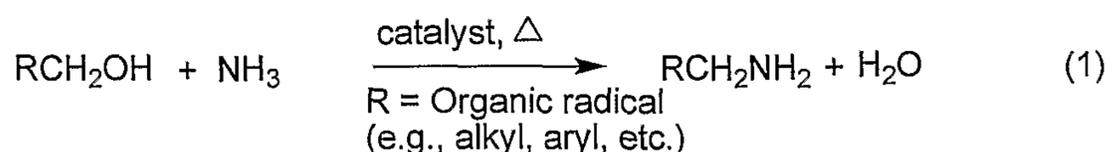
Given the widespread importance of amines in biochemical and chemical systems,
5 an efficient synthesis that avoids the shortcomings of prior art processes is highly desirable.

SUMMARY OF THE INVENTION

The present invention provides novel ruthenium based catalysts, and a process for preparing primary amines, by reacting a primary alcohol and ammonia in the presence of
10 such catalysts, to generate the primary amine compound and water. As contemplated herein, the inventors have discovered a novel process for preparing amines in which primary amines are directly prepared from primary alcohols and ammonia under mild conditions, precluding the need for stoichiometric amounts of toxic reagents, high pressure, and harsh experimental conditions. The reaction is homogeneously catalyzed by a novel, air
15 stable ruthenium pincer complex, and can proceed in water, in various organic solvents, in the absence of a solvent, or in heterogeneous or homogeneous mixtures of water and an organic solvent. The simplicity, generality and excellent atom-economy of this process make it attractive for the transformations of alcohols to amines both in small and large scale applications.

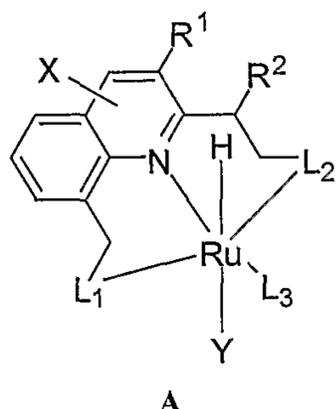
20 The process of the invention, i.e., the direct catalytic conversion of alcohols and ammonia into amines and water is illustrated in Scheme 1. This novel, environmentally benign reaction can be used to produce various amines from very simple substrates, with high atom economy and without use of any stoichiometric activating agents, thus generating no waste.

25 **Scheme 1:**



The applicants of the present invention have unexpectedly discovered that novel ruthenium complexes catalyze the reaction of primary alcohols with ammonia to form

primary amines and H₂O. In one embodiment, the ruthenium catalyst is represented by the structure of formula A:

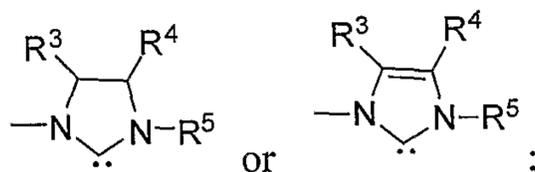


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wherein

L_1 and L_2 are each independently selected from the group consisting of phosphine (PR^aR^b), amine (NR^aR^b), imine, sulfide (SR), thiol (SH), sulfoxide ($S(=O)R$), heteroaryl containing at least one heteroatom selected from nitrogen and sulfur; arsine (AsR^aR^b), stibine (SbR^aR^b) and an N-heterocyclic carbene represented by the structures:

10



15

L_3 is a mono-dentate two-electron donor such as CO, $PR^aR^bR^c$, NO^+ , $AsR^aR^bR^c$, $SbR^aR^bR^c$, SR^aR^b , nitrile (RCN), isonitrile (RNC), N_2 , PF_3 , CS, heteroaryl (e.g., pyridine, thiophene), tetrahydrothiophene and N-heterocyclic carbene;

R^1 and R^2 are either each hydrogen or together with the carbons to which they are attached represent a phenyl ring which is fused to the quinoliny moiety of formula A so as to form an acridinyl moiety;

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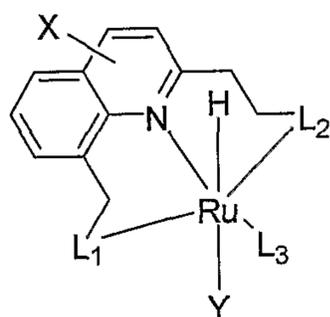
R , R^a , R^b , R^c , R^3 , R^4 and R^5 are each independently alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl;

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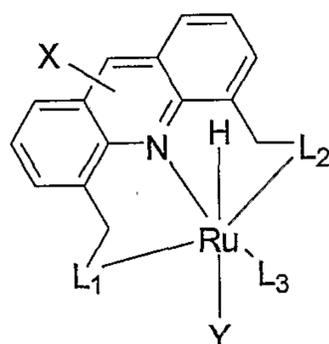
Y is a monoanionic ligand such as halogen, OCOR, $OCOCF_3$, OSO_2R , OSO_2CF_3 , CN, OH, OR, NR_2 ; a neutral solvent molecule NH_3 , NR_3 or R_2NSO_2R , wherein R is as defined above. It is noted that when Y is neutral, the whole molecule carries a positive charge.

X represents one, two, three, four, five, six or seven substituents positioned at any carbon atom on the acridinyl moiety (in the case where R^1 and R^2 together with the carbons to which they are attached represent a phenyl ring which is fused to the quinolinyl moiety of formula A); or one, two, three, four or five substituents positioned on any carbon atom on the quinolinyl moiety (in the case where R^1 and R^2 are each hydrogen), and is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, halogen, nitro, amide, ester, cyano, alkoxy, alkylamino, arylamino, an inorganic support (e.g., silica) and a polymeric moiety (e.g., polystyrene).

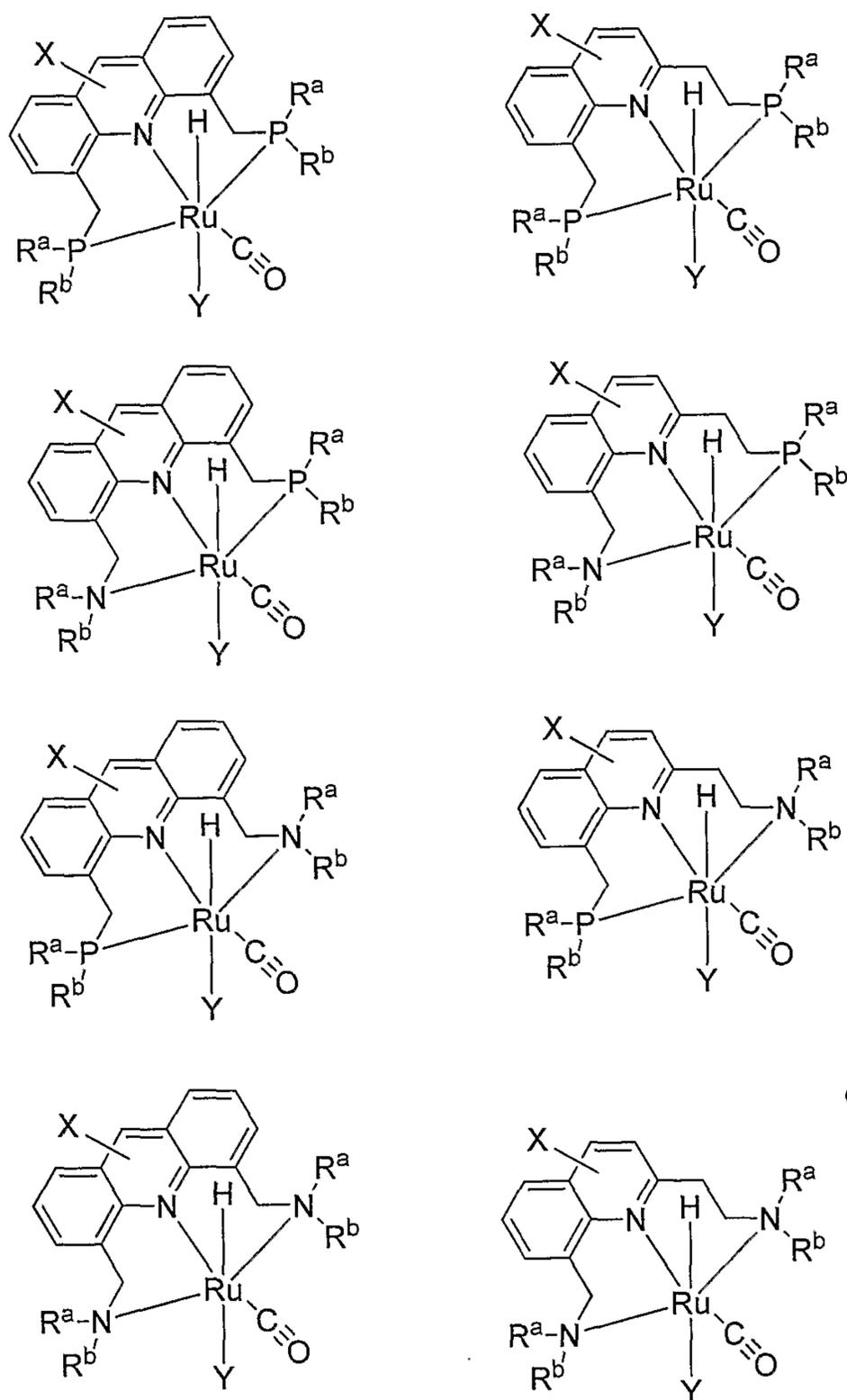
In one embodiment, R^1 and R^2 are each H, and the ruthenium catalyst is represented by the structure:



In another embodiment, R^1 and R^2 together with the carbon atoms to which they are attached form a phenyl ring which is fused to the quinolinyl moiety so as to form an acridinyl moiety, and the ruthenium catalyst is represented by the structure:



Several non-limiting embodiments of the ruthenium catalysts of the present invention are:

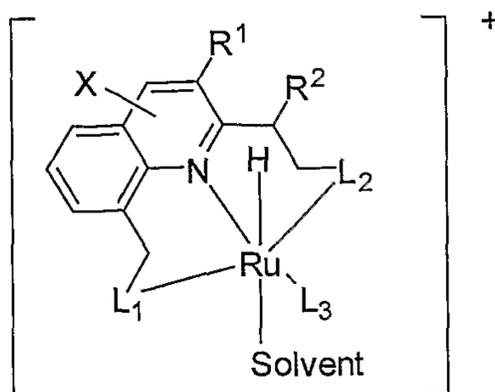


The substituents R^a and R^b are each independently alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl. Some non-limiting examples are methyl, ethyl, isopropyl, t-butyl, cyclohexyl, cyclopentyl, phenyl, mesityl and the like.

The substituent Y is a monoanionic ligand such as halogen, $OCOR$, $OCOCF_3$, OSO_2R , OSO_2CF_3 , CN , OH , OR or NR_2 wherein R is alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl. Some non-limiting examples are F , Cl , Br , I , $OCOCH_3$, $OCOCF_3$, OSO_2CF_3 and other anionic ligands.

A currently preferred Y ligand is a halogen, e.g., Cl . Y can also be a neutral solvent

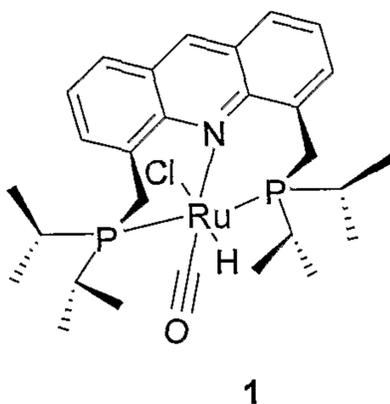
molecule, NH_3 , NR_3 , $\text{R}_2\text{NSO}_2\text{R}$ and the like. When Y is neutral, the complex is charged, as exemplified below for embodiments wherein Y is a solvent ligand:



Examples of solvent ligand molecules (i.e., $Y = \text{solvent molecule}$) include, but are not limited to, acetone, dialkyl ketones (for examples 2-butanone), cyclic ketones (for example cyclohexanone), THF, anisole, dimethyl sulfoxide, acetonitrile, CH_2Cl_2 , toluene, water, pyridine and the like.

In a currently preferred embodiment, L_3 is CO.

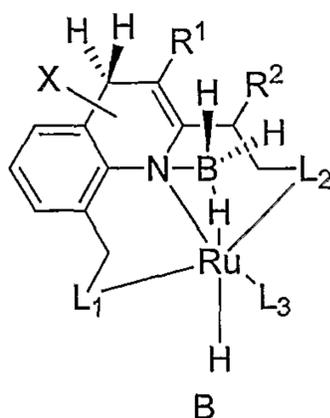
In a particular embodiment, the ruthenium catalyst is represented by the following structure of formula 1:



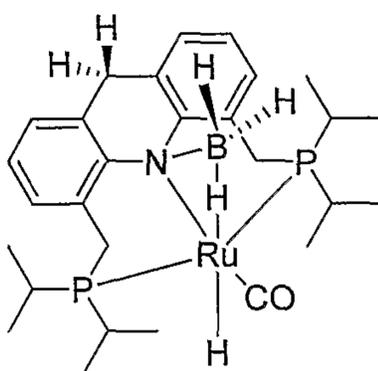
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In an alternative embodiment, the ruthenium catalyst is a borane derivative of the catalyst of formula A, which is obtained by reacting complex A with sodium borohydride (NaBH_4). The borane derivative is represented by the structure of formula B.

15



In one particular embodiment, the borane derivative is represented by the structure of formula 3. Complex 3 is sometimes designated herein as “RuH(BH₃)(A-ⁱPr-PNP)(CO)”.



3

5

The term “primary alcohol”, as used herein, refers to a compound of the formula RCH₂OH wherein R is an organic radical. A variety of primary alcohols can be used in the process of the invention. In one embodiment, the alcohol is represented by the formula R⁶CH₂OH wherein R⁶ is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, and alkoxyalkyl. In several exemplary embodiments, the alcohol is selected from the group consisting of methanol, ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, benzyl alcohol, o-, m-, or p-methoxy benzyl alcohol, o-, m-, or p-halo benzyl alcohol, pyridine-2-yl-methanol, 2-furylmethanol, 2-phenylethanol, 2-methoxyethanol, 2-methyl-1-butanol, cyclohexylmethanol, and 3-methyloxetan-3-yl)methanol.

The term “ammonia”, as used herein, refers to the compound “NH₃”. Generally, ammonia is used as a gas. In an alternative embodiment, however, when water is used as the reaction solvent, the present invention contemplates the use of a solution of ammonium hydroxide (NH₄⁺OH⁻) in water. Thus, in accordance with this embodiment, the ammonia is provided as a solution of ammonium hydroxide in water.

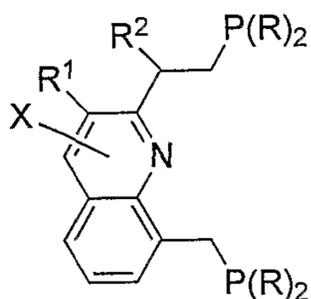
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The term "primary amine", as used herein, refers to a compound of the formula RNH_2 wherein R is an organic radical. The primary amine is generally a compound of formula RNH_2 wherein R is an organic radical. Preferably, the primary amine is a compound of formula RCH_2NH_2 wherein R is an organic radical. A variety of primary amines can be prepared in the process of the invention. In one embodiment, the primary amine obtained by the process of the invention is represented by the formula $\text{R}^6\text{CH}_2\text{NH}_2$ wherein R^6 is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, and alkoxyalkyl.

The methods of the present invention can be conducted in the absence or in the presence of a solvent. When a solvent is present, it can be aqueous (i.e., water), an organic solvent, or mixtures thereof. When mixtures of water and an organic solvent are used, the solvent system may form a homogenous solution or a heterogeneous mixture. Some non-limiting examples of organic solvents are benzene, toluene, o-, m- or p-xylene and mesitylene (1,3,5-trimethyl benzene), dioxane, THF, DME (dimethoxyethane), anisole, and cyclohexane.

The ammonia and primary alcohol can be used in equimolar amounts, however, it is preferred that ammonia is added in excess.

In another embodiment, the present invention provides precursors for preparing the ruthenium catalysts of the present invention. In one embodiment, the precursor is represented by the structure formula 2A:



2A

wherein

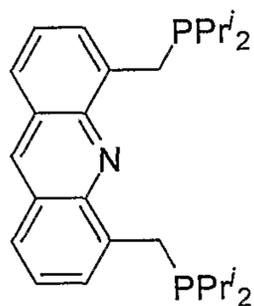
each R is independently alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl;

R^1 and R^2 are either each hydrogen, or together with the carbons to which they are attached represent a phenyl ring which is fused to the quinolinyl moiety so as to form an

acridinyl moiety; and

X represents one, two, three, four, five, six or seven substituents positioned at any carbon atom on the acridinyl moiety (in the case where **R**¹ and **R**² together with the carbons to which they are attached represent a phenyl ring which is fused to the quinolinyl moiety of formula A); or one, two, three, four or five substituents positioned on any carbon atom on the quinolinyl moiety (in the case where **R**¹ and **R**² are each hydrogen), and is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, halogen, nitro, amide, ester, cyano, alkoxy, alkylamino, arylamino, an inorganic support (e.g., silica) and a polymeric moiety (e.g., polystyrene).

One specific embodiment of formula 2A is a compound wherein each **R** is isopropyl, **R**¹ and **R**², together with the carbons to which they are attached represent a phenyl ring which is fused to the quinolinyl moiety so as to form an acridinyl moiety, and the compound has the structure of formula 2:



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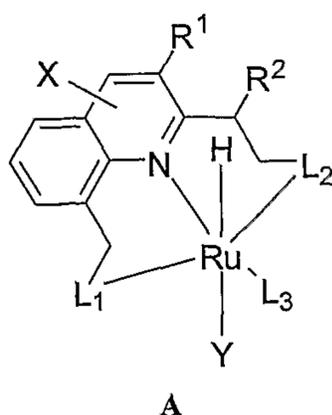
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DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to novel ruthenium catalysts, and to a process for preparing primary amines, by reacting a primary alcohol and ammonia in the presence of such catalysts, to generate the amine and water as the only products.

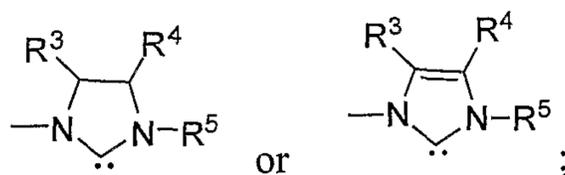
This reaction is catalyzed by novel ruthenium complexes, which are preferably based on quinolinyl or acridinyl ligands, and no base or acid promoters are required.

In one embodiment, the ruthenium catalyst is represented by the following structure:



wherein

L_1 and L_2 are each independently selected from the group consisting of phosphine (PR^aR^b), amine (NR^aR^b), imine, sulfide (SR), thiol (SH), sulfoxide ($S(=O)R$), heteroaryl containing at least one heteroatom selected from nitrogen and sulfur; arsine (AsR^aR^b), stibine (SbR^aR^b) and an N-heterocyclic carbene represented by the structure:



L_3 is a mono-dentate two-electron donor such as CO, $PR^aR^bR^c$, NO^+ , $AsR^aR^bR^c$, $SbR^aR^bR^c$, SR^aR^b , nitrile (RCN), isonitrile (RNC), N_2 , PF_3 , CS, heteroaryl (e.g., pyridine, thiophene) and tetrahydrothiophene;

R^1 and R^2 are either each hydrogen or together with the carbons to which they are attached represent a phenyl ring which is fused to the quinolinyl moiety of formula A so as to form an acridinyl moiety;

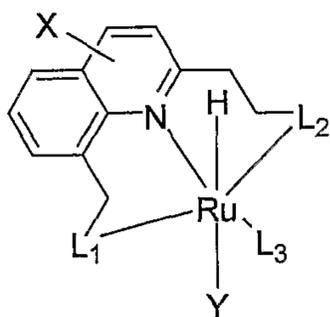
R , R^a , R^b , R^c , R^3 , R^4 and R^5 are each independently alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl;

Y is a monoanionic ligand such as halogen, OCOR, $OCOCF_3$, OSO_2R , OSO_2CF_3 , CN, OH, OR, NR_2 ; a neutral solvent molecule NH_3 , NR_3 or R_2NSO_2R , wherein R is as defined above. It is noted that when Y is neutral, the whole molecule carries a positive charge.

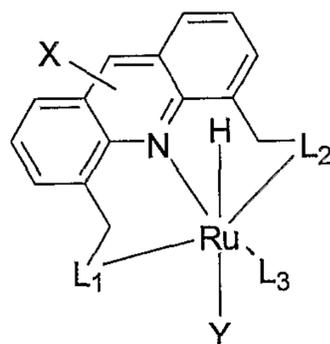
X represents one, two, three, four, five, six or seven substituents positioned at any carbon atom on the acridinyl moiety (in the case where R^1 and R^2 together with the carbons to which they are attached represent a phenyl ring

which is fused to the quinolinyl moiety of formula A); or one, two, three, four or five substituents positioned on any carbon atom on the quinolinyl moiety (in the case where R^1 and R^2 are each hydrogen), and is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, halogen, nitro, amide, ester, cyano, alkoxy, alkylamino, arylamino, an inorganic support (e.g., silica) and a polymeric moiety (e.g., polystyrene).

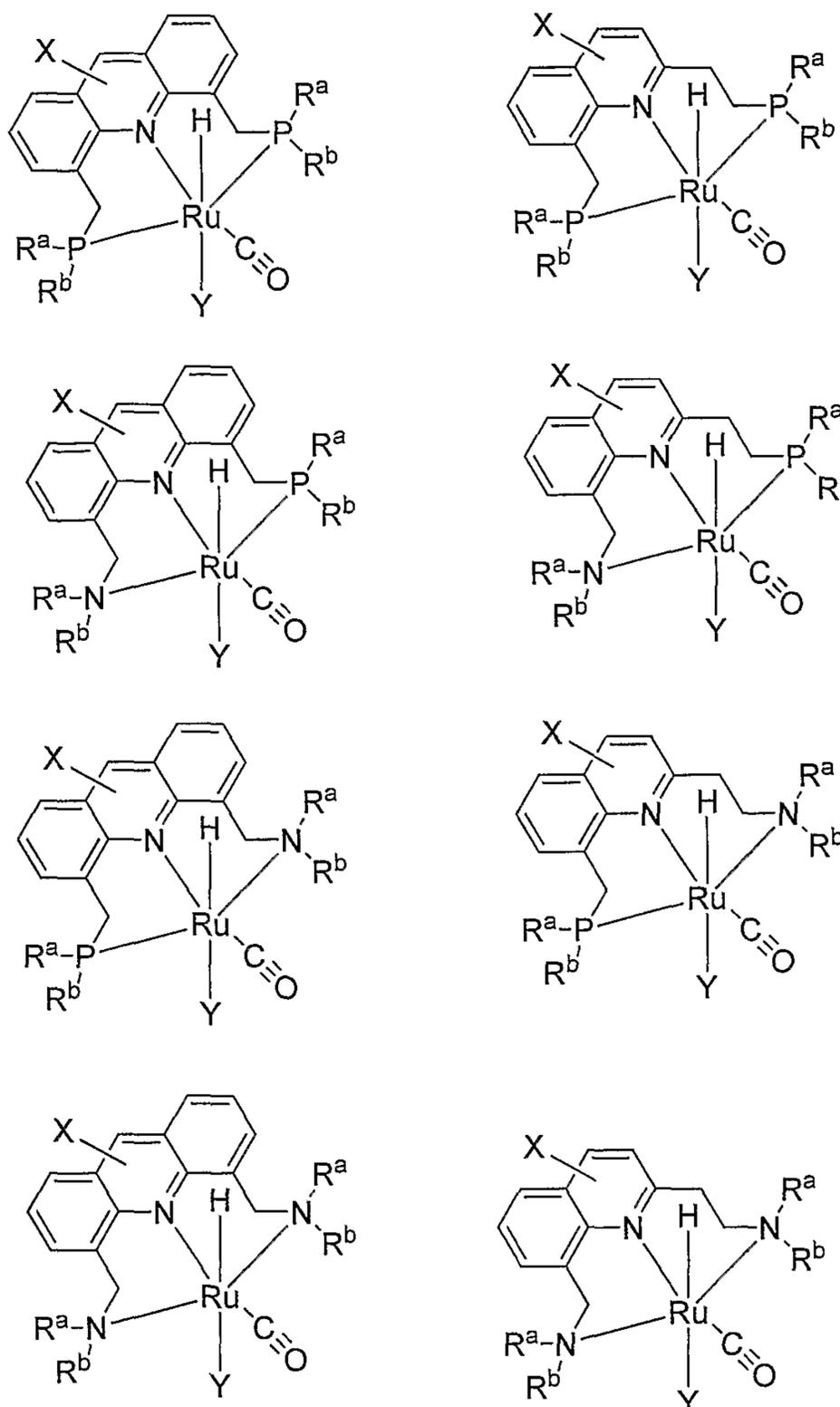
In one embodiment, R^1 and R^2 are each H, and the ruthenium catalyst is represented by the structure:



In another embodiment, R^1 and R^2 together with the carbon atoms to which they are attached form a phenyl ring which is fused to the quinolinyl moiety so as to form an acridinyl moiety, and the ruthenium catalyst is represented by the structure:



Several non-limiting embodiments of the ruthenium catalysts of the present invention are:

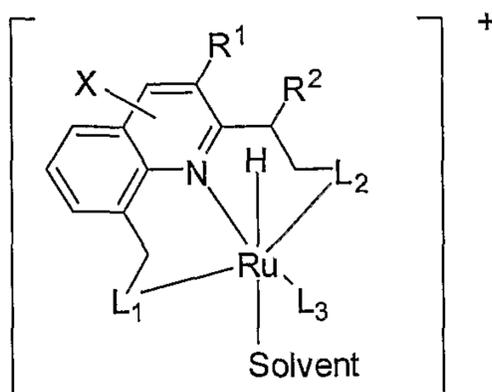


The substituents R^a and R^b are each independently alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl. Some non-limiting examples are methyl, ethyl, isopropyl, t-butyl, cyclohexyl, cyclopentyl, phenyl, mesityl and the like.

The substituent Y is a monoanionic ligand such as halogen, OCOR, OCOCF₃, OSO₂R, OSO₂CF₃, CN, OH, OR or NR₂ wherein R is alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl. Some non-limiting examples are F, Cl, Br, I, OCOCH₃, OCOCF₃, OSO₂CF₃ and other anionic ligands.

A currently preferred Y substituents is halogen, such as Cl. Y can also be a neutral solvent

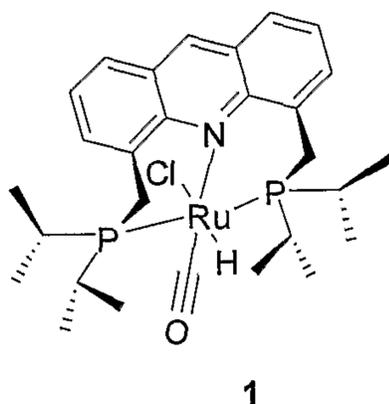
molecule, NH_3 , NR_3 , $\text{R}_2\text{NSO}_2\text{R}$ and the like. When Y is neutral, the complex is charged, as exemplified below for embodiments wherein Y is a solvent:



Examples of embodiments wherein Y is a solvent include, but are not limited to, acetone, dialkyl ketones (for examples 2-butanone), cyclic ketones (for example cyclohexanone), THF, anisole, dimethyl sulfoxide, acetonitrile, CH_2Cl_2 , toluene, water, pyridine and the like.

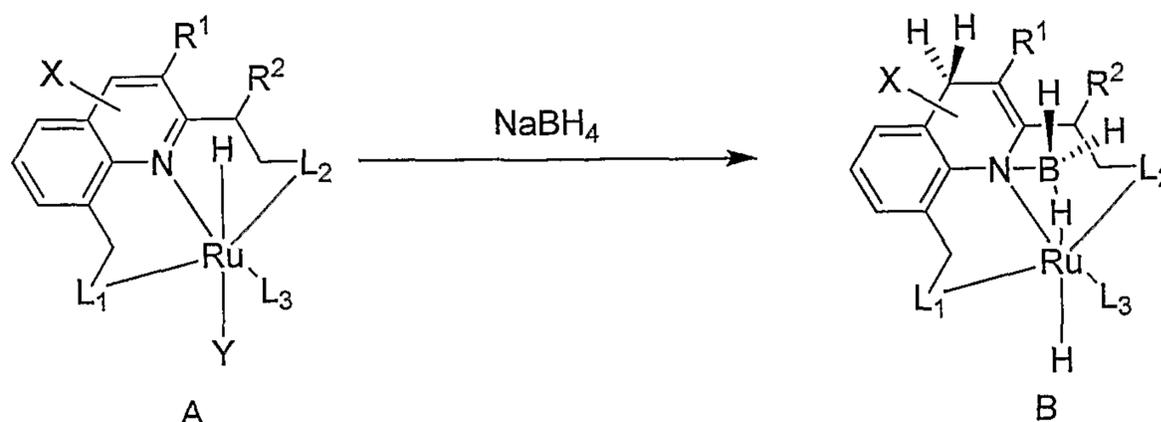
In one currently preferred embodiment, L_3 is CO.

In a particular embodiment, the ruthenium catalyst is represented by the following structure of formula 1:



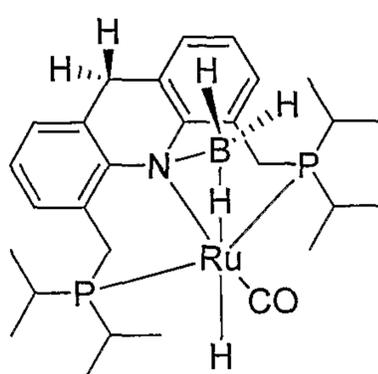
In one embodiment, the ruthenium catalyst is a borane derivative of the catalyst of formula A obtained by reacting compound A with sodium borohydride (NaBH_4), as illustrated in Scheme 2 below. The borane derivative is represented by the structure of formula B.

Scheme 2



In one embodiment, the borane derivative is represented by the structure of formula

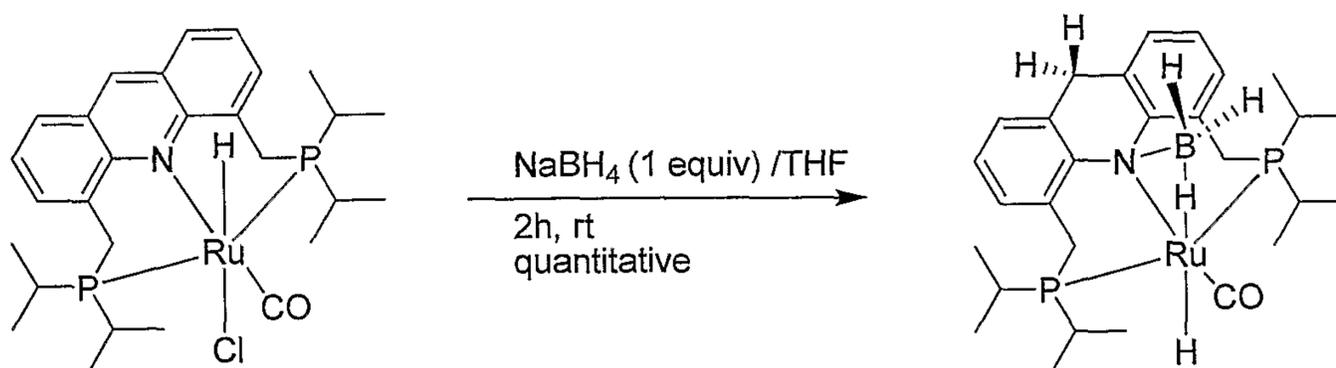
3:



3

The borane derivative of formula 3 may be obtained by the process set forth in

Scheme 3:



10 It is understood that when the catalyst includes one or more chiral centers, all stereoisomers are included in the scope of this invention.

A variety of primary alcohols can be used in the process of the invention. In one embodiment, the alcohol is represented by the formula RCH₂OH wherein R is an organic radical. In another embodiment, the alcohol is represented by the formula R⁶CH₂OH
15 wherein R⁶ is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, aryloxyalkyl and alkoxyalkyl. In several exemplary embodiments, the alcohol is selected from the group

consisting of methanol, ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, benzyl alcohol, o-, m-, or p-methoxy benzyl alcohol, o-, m-, or p-halo benzyl alcohol, (pyridine-2-yl)methanol, 2-furylmethanol, 2-phenylethanol, 2-methoxyethanol, 2-methyl-1-butanol, cyclohexylmethanol, and (3-methyloxetan-3-yl)methanol.

5 A variety of primary amines can be prepared in the process of the invention. In one embodiment, the primary amine obtained by the process of the invention is represented by the formula RNH_2 wherein R is an organic radical. In another embodiment, the primary amine obtained by the process of the invention is represented by the formula RCH_2NH_2 wherein R is an organic radical. Preferably, the primary amine obtained by the process of the invention is represented by the formula $\text{R}^6\text{CH}_2\text{NH}_2$ wherein R^6 is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, and alkoxyalkyl.

10 The methods of the present invention can be conducted in the absence or in the presence of a solvent. When a solvent is present, it can be aqueous (i.e., water), an organic solvent, or mixtures thereof. When mixtures of water and an organic solvent are used, the solvent system may form a homogenous solution or a heterogeneous mixture. Non-limiting examples of organic solvents are benzene, toluene, o-, m- or p-xylene mesitylene (1,3,5-trimethyl benzene), dioxane, THF, DME, anisole and cyclohexane. In one embodiment, when water is used as the reaction solvent the present invention contemplates the use of a solution of ammonium hydroxide (NH_4^+OH^-) in water.

15 The stoichiometric ratios of ammonia to primary alcohol can vary, and depend on the particular alcohol and solvent used for the reaction. In one embodiment, the ammonia and alcohol can be added in equimolar amounts. In preferred embodiments, however, the ammonia is used in excess. Exemplary amounts of ammonia are between 1 atm to about 25 1000 atm, for example between 5 and 500 atm, 5 and 100 atm, 5 and 20 atm, preferably between 7 and 10 atm, for example 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5 or 10 atm. Exemplary corresponding amounts of alcohols are between 1 and 100 mmoles or higher amounts such as 100-500 mmoles, preferably between 1 and 10 mmoles, more preferably between 1 and 5 mmoles.

30 The reactions of the present invention can be performed for as long as needed so as to effect transformation of the primary alcohol to the primary amine, for example 1 hr to 24 hr

or longer than 24 hr. The temperature range can vary from room temperature to heated conditions, for example up to 200 °C.

In another embodiment, the process of the present invention can be used to prepare secondary amines by reaction of a primary amine and a primary alcohol. The primary alcohol can be any of the alcohols of the formula R^6CH_2OH described above. The primary amine can be, for example, of the formula R^7NH_2 wherein R^7 is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, and alkoxyalkyl. In several exemplary embodiments, the primary amine is selected from the group consisting of methylamine, ethylamine, propylamine, butylamine, pentylamine, hexylamine, benzylamine, cyclohexylamine and the like. In accordance with this embodiment, the resulting secondary amine has the formula $R^6CH_2NR^7H$. Typically, the reaction between a primary alcohol and a primary amine to generate a secondary amine is conducted at elevated temperatures (e.g., 160-180°C), in solvents such as xylene or mesitylene, for a period of time ranging from 24 to 72 hours. It is apparent to a person of skill in the art, however, that the reaction conditions can be optimized as deemed appropriate by a person with ordinary skill in the art.

Chemical Definitions

As used herein, the term alkyl, used alone or as part of another group, refers, in one embodiment, to a "C₁ to C₁₂ alkyl" and denotes linear and branched, saturated or unsaturated (e.g, alkenyl, alkynyl) groups, the latter only when the number of carbon atoms in the alkyl chain is greater than or equal to two, and can contain mixed structures. Preferred are alkyl groups containing from 1 to 6 carbon atoms (C₁ to C₆ alkyls). More preferred are alkyl groups containing from 1 to 4 carbon atoms (C₁ to C₄ alkyls). Examples of saturated alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, and hexyl. Examples of alkenyl groups include, but are not limited to, vinyl, allyl, butenyl and the like. Examples of alkynyl groups include, but are not limited to, ethynyl, propynyl and the like. Similarly, the term "C₁ to C₁₂ alkylene" denotes a bivalent radical of 1 to 12 carbons.

The alkyl group can be unsubstituted, or substituted with one or more substituents selected from the group consisting of halogen, hydroxy, alkoxy, aryloxy, alkylaryloxy, heteroaryloxy, oxo, cycloalkyl, phenyl, heteroaryls, heterocyclyl, naphthyl, amino, alkylamino, arylamino, heteroarylamino, dialkylamino, diarylamino, alkylarylamino, alkylheteroarylamino, arylheteroarylamino, acyl, acyloxy, nitro, carboxy, carbamoyl, carboxamide, cyano, sulfonyl, sulfonylamino, sulfinyl, sulfinylamino, thiol, alkylthio, arylthio, or alkylsulfonyl groups. Any substituents can be unsubstituted or further substituted with any one of these aforementioned substituents. By way of illustration, an “alkoxyalkyl” is an alkyl that is substituted with an alkoxy group.

10 The term “cycloalkyl” used herein alone or as part of another group, refers to a “C₃ to C₈ cycloalkyl” and denotes any unsaturated or saturated (e.g., cycloalkenyl, cycloalkynyl) monocyclic or polycyclic group. Nonlimiting examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Examples of cycloalkenyl groups include cyclopentenyl, cyclohexenyl and the like. The cycloalkyl group can be unsubstituted or substituted with any one or more of the substituents defined above for alkyl. Similarly, the term “cycloalkylene” means a bivalent cycloalkyl, as defined above, where the cycloalkyl radical is bonded at two positions connecting together two separate additional groups. An alkylcycloalkyl group denotes an alkyl group bonded to a cycloalkyl group.

20 The term “aryl” used herein alone or as part of another group denotes an aromatic ring system containing from 6-14 ring carbon atoms. The aryl ring can be a monocyclic, bicyclic, tricyclic and the like. Non-limiting examples of aryl groups are phenyl, naphthyl including 1-naphthyl and 2-naphthyl, and the like. The aryl group can be unsubstituted or substituted through available carbon atoms with one or more groups defined hereinabove for alkyl. An alkylaryl group denotes an alkyl group bonded to an aryl group (e.g., benzyl).

25 The term “heteroaryl” used herein alone or as part of another group denotes a heteroaromatic system containing at least one heteroatom ring atom selected from nitrogen, sulfur and oxygen. The heteroaryl contains 5 or more ring atoms. The heteroaryl group can be monocyclic, bicyclic, tricyclic and the like. Also included in this expression are the benzoheterocyclic rings. If nitrogen is a ring atom, the present invention also contemplates 30 the N-oxides of the nitrogen containing heteroaryls. Nonlimiting examples of heteroaryls

include thienyl, benzothienyl, 1-naphthothienyl, thianthrenyl, furyl, benzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, purinyl, isoquinolinyl, quinolinyl, acridinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, piperidinyl, carbolinyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl
5 and the like. The heteroaryl group can be unsubstituted or substituted through available atoms with one or more groups defined hereinabove for alkyl. An alkylheteroaryl group denotes an alkyl group bonded to a heteroaryl group.

The term "heterocyclic ring" or "heterocyclyl" used herein alone or as part of another group denotes a five-membered to eight-membered rings that have 1 to 4
10 heteroatoms, such as oxygen, sulfur and/or nitrogen. These five-membered to eight-membered rings can be saturated, fully unsaturated or partially unsaturated. Non-limiting examples of heterocyclic rings include piperidinyl, pyrrolidinyl, pyrrolinyl, pyrazolinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl, indolinyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothiophenyl, tetrahydrothiophenyl,
15 dihydropyranyl, tetrahydropyranyl, and the like. The heterocyclyl group can be unsubstituted or substituted through available atoms with one or more groups defined hereinabove for alkyl. An alkylheterocyclyl group denotes an alkyl group bonded to a heterocyclyl group.

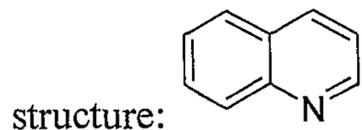
The term "alkoxy" refers to an alkyl bonded to an oxygen, e.g., methoxy, ethoxy, propoxy and the like. The term "aryloxy" refers to an aryl bonded to an oxygen, e.g., phenoxy, and the like. The term "halogen" refers to F, Cl, Br or I. The term "amide" refers to $RCONH_2$, $RCONHR$ or $RCON(R)_2$ wherein R is as defined herein. The term "ester" refers to $RCOOR$ wherein R is as defined herein. The term "cyano" refers to a CN group. The term "nitro" refers to a "NO₂" group.
20

25 The inorganic support which is attached to the pyridine ring in formula A can be, for example, silica, silica gel, glass, glass fibers, titania, zirconia, alumina and nickel oxide.

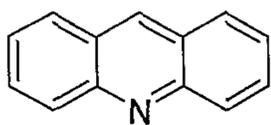
The polymer which is attached to the pyridine ring in formula A can be, for example, selected from polyolefins, polyamides, polyethylene terephthalate, polyvinylchloride, polyvinylidenechloride, polystyrene, polymethacrylate, natural rubber,
30 polyisoprene, butadiene-styrene random copolymers, butadiene acrylonitrile copolymers, polycarbonate, polyacetal, polyphenylenesulfide, cyclo-olefin copolymers, styrene-

acrylonitrile copolymers, ABS, styrene-maleic anhydride copolymers, chloroprene polymers, isobutylene copolymers, polystyrene, polyethylene, polypropylene, and the like.

The term "quinolinyl", as used herein, refers to a group represented by the



The term "acridinyl", as used herein, refers to a group represented

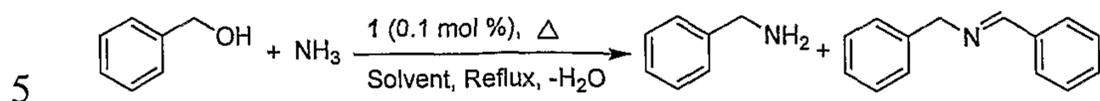


5 The quinolinyl or acridinyl functional groups can be attached to the Ruthenium catalysts of the present invention as readily understood by a person of skill in the art, and as described herein.

Exemplary Processes:

10 Benzyl alcohol was reacted with ammonia in the presence of ruthenium catalyst **1** (0.1 mol%) in refluxing mesitylene (b.p. 163 °C). As shown in Table 1 entries 1-3, 98% conversion of the alcohol was observed after 1 hr, yielding 69% of benzylamine and 28% of N-benzylidenebenzylamine. Slightly higher yields of benzylamine were observed at longer reaction times. Similar results were obtained at lower temperature in refluxing *p*-
15 xylene (b.p. 138 °C) after 3 hrs (Table 1, entry 4). When the reaction was performed for the same period in toluene (b.p. 110.5 °C) the conversion of benzyl alcohol was less efficient (Table 1, entry 5), but after 13 h 99% conversion of benzyl alcohol occurred (Table 1, entry 6) to provide benzylamine in 87% yield along with N-benzylidenebenzylamine (12%). A further drop in reaction temperature using dioxane (b.p. 100 °C) as a solvent resulted in a
20 lower conversion (Table 1, entry 7).

Table 1. Direct synthesis of benzylamine from benzyl alcohol and ammonia catalyzed by the ruthenium complex **1**. Complex **1** (0.01 mmol), benzyl alcohol (10 mmol), ammonia (7.5 atm), and solvent (3 ml) were heated at reflux in a Fischer-Porter flask. Conversion of alcohols and yield of products were analyzed by Gas Chromatography (GC).



Entry	Solvent ^a	Temp. (°C) ^b	Time (hours)	Conversion of alcohol (%)	Yield (%)	
					Benzylamine	N-Benzylidenebenzylamine
1	mesitylene	180	10	100	73	24
2	mesitylene	180	2	98	71	25
3	mesitylene	180	1	98	69	28
4	<i>p</i> -xylene	160	3	100	73	26
5	toluene	135	3	30	18	11
6	toluene	135	13	99	87	12
7	dioxane	120	15	27	20	7

^a Reactions were carried out in refluxing solvents. ^b Temperature of oil bath.

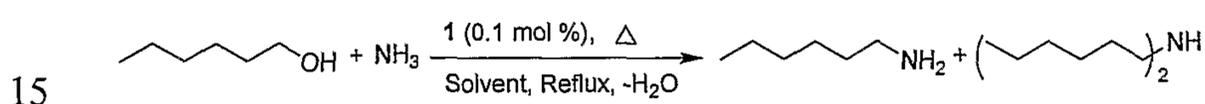
To test whether increasing the concentration of ammonia relative to the alcohol might reduce the formation of imines (for example by capturing the contemplated intermediate aldehyde and preventing its reaction with the primary amine), complex **1** (0.01 mmol), benzyl alcohol (2.5 mmol) and ammonia (8 atm) in toluene were heated under reflux in a Fischer-Porter tube for 130 min, to get benzylamine (64.6%) and N-benzylidenebenzylamine (19.3%) whereas the conversion of benzyl alcohol was 84.7%

(compare to entry 6, Table 1). Thus, increasing the concentration of ammonia did not affect the extent of formation of imine.

1-hexanol was chosen as a benchmark substrate for studying the direct amination reactions of simple aliphatic alcohols. 1-hexylamine and dihexylamine were formed, the yield of the latter increasing at higher reaction temperature and longer reaction time (Table 2). When the reaction was carried out in refluxing toluene for 15 h, 1-hexylamine was obtained in 63% yield whereas the major by-product was the corresponding imine (Table 2, entry 3). When the same reaction was prolonged to 24 h the yield of dihexylamine increased from 3 to 18% while the 1-hexylamine yield decreased to 58% (Table 2, entry 4).

10

Table 2. Direct synthesis of 1-hexylamine from 1-hexanol and ammonia catalyzed by the ruthenium complex **1**. Complex **1** (0.01 mmol), 1-hexanol (10 mmol), ammonia (7.5 atm), and solvent (3 ml) were heated at reflux in a Fischer-Porter. Conversion of alcohols and yield of products were analyzed by GC.



Entry	Solvent	Time (hours)	Conversion of 1-hexanol (%)	Yield (%)	
				1-Hexylamine	Dihexylamine
1	mesitylene	3	95	59	28.5
2	mesitylene	11	100	16.4	78.2
3*	toluene	15	87.5	63	3
4 [†]	toluene	24	98.8	58	18

Corresponding imine was the major by-product. [†]Trihexylamine is formed as by-product.

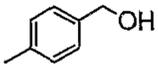
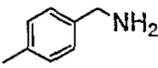
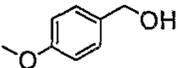
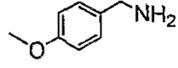
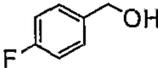
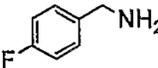
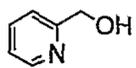
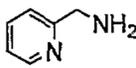
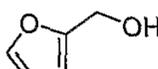
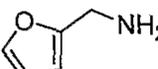
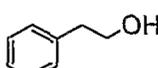
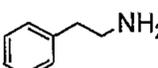
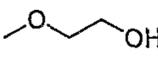
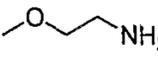
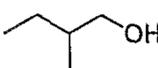
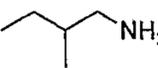
The scope of the direct amination of alcohols with ammonia catalyzed by complex **1** (0.1 mol%) in refluxing toluene was studied with respect to the alcohol (Table 3). Aryl methanols underwent facile reaction to provide benzylamines in good yields. Benzyl

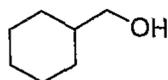
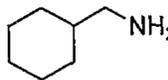
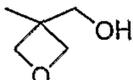
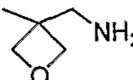
alcohols with electron donating groups on the benzene ring reacted faster (Table 3, entries 1, 2) than benzyl alcohols with an electron withdrawing group (Table 3, entry 3). The electron rich heteroaryl methanols exhibited excellent selectivity for primary amines. Pyridine-2-yl-methanol and 2-furylmethanol were converted to the corresponding primary amines in 96 and 94.8 % yields, respectively (Table 3, entries 4, 5). As with 1-hexanol, 1-pentanol also reacted to result in the formation of 1-pentylamine (61%) and dipentylamine (34.6%) (Table 3, entry 6). 2-Phenylethanol reacted similarly but the formation of secondary amines was less favored (Table 3, entry 7). 2-Methoxyethanol exhibited very good selectivity for the primary amine, providing 2-methoxyethylamine in 94.5% yield (Table 3, entry 8). Good selectivity was attained for the synthesis of aryl and heteroaryl methylamines. Increasing the steric hindrance at the β - position of alkyl alcohols diminished the formation of imines and the corresponding secondary amines and hence increased the selectivity and yields of primary amines (Table 3, entries 9-11). It is noteworthy that the strained 4-membered ring in the (3-methyloxetan-3-yl)methanol (Table 3, entry 9) remained intact, resulting in high yield of the primary amine. The reaction took place effectively also in neat alcohols, requiring no added solvent (Table 3, entries 6, 9).

Table 3. Direct synthesis of amines from alcohols and ammonia catalyzed by the ruthenium complex **1**. Complex **1** (0.01 mmol), alcohol (10 mmol), ammonia (7.5 atm), and toluene (3 ml) were heated in a Fischer-Porter. Conversion of alcohols and yield of products were analyzed by GC.

5

$$\text{RCH}_2\text{OH} + \text{NH}_3 \xrightarrow[\text{Toluene, Reflux, } -\text{H}_2\text{O}]{\text{1 (0.1 mol \%), } \Delta} \text{RCH}_2\text{NH}_2 + \text{RCH}=\text{NCH}_2\text{R}$$

Entry	RCH ₂ OH	Time (hours)	Conv. of alcohol	RCH ₂ NH ₂	Yield † (%)
1		12	100		83
2		14	100		78
3		24	100		91
4		30	100		96
5		12	100		94.8
6*		20	97		61 (34.6) ‡
7		32	100		68.8
8		12	100		94.5
9*		18	93		67.7

10		25	95.5		82
11		25	96.4		90

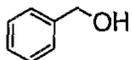
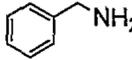
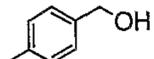
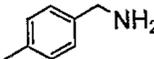
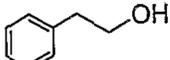
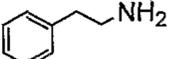
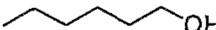
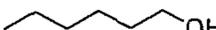
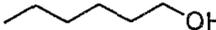
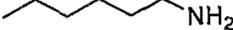
*Neat Reaction. †The corresponding imine is the major byproduct in all reactions (analyzed by GC-MS and MS(ESI)); its yield was not determined. ‡Yield of dipentylamine.

Since the generation of a stoichiometric amount of water in the reaction didn't
 5 affect the catalysis by complex **1**, the possibility of using water as a reaction medium was
 explored. Interestingly, the direct amination of alcohols with ammonia by complex **1**
 proceeded "on water" very well with excellent selectivity for primary amines. While water
 is the natural, greenest possible solvent, its current applications in catalysis are limited (28).
 The presence of water in large excess was advantageous since it may have led to the
 10 hydrolysis of imines formed from further reactions of the primary amines, and thus
 enhanced the selectivity towards primary amines (Table 4, entry 1-3). The benzyl alcohols
 and 2-phenylethyl alcohol, which are insoluble in water at room temperature, formed a
 homogeneous solution on heating and thus the reaction might be considered "in water".
 Aliphatic alcohols such as 1-hexanol were not miscible with water even on heating and the
 15 reaction took place "on water" (29) (Table 4, entry 4). Surprisingly, when water soluble
 alcohols ([pyridin-2-yl]methanol and 2-methoxyethanol) were subjected to direct amination
 reaction "in water", the reaction became very sluggish even after prolonged heating (30 h)
 and the conversions were less efficient, in sharp contrast to excellent reactions in toluene
 (Table 3, entries 4 and 8).

Table 4. Direct synthesis of amines from alcohols and ammonia catalyzed by the ruthenium complex **1** *in and on water*. Complex **1** (0.01 mmol), alcohol (10 mmol), ammonia (7.5 atm), and water (3 ml) were heated at reflux in a Fischer-Porter. Conversion of alcohols and yield of products were analyzed by GC.

5

$$\text{RCH}_2\text{OH} + \text{NH}_3 \xrightarrow[\text{Water, 135 }^\circ\text{C}]{\text{1 (0.1 mol \%), } \Delta} \text{RCH}_2\text{NH}_2 + \text{RCH=NCH}_2\text{R}$$

Entry	RCH ₂ OH	Time (h)	Conv.	RCH ₂ NH ₂	Yield (%) [†]
1		18	100		95.4
2		18	100		91.7
3		36	100		80.4 [‡]
4		24	92.4		54.8 [*]
5 [¶]		28	89.4		74.3
6 [§]		30	99		79.7
7 [§]		30	98.7		70.0

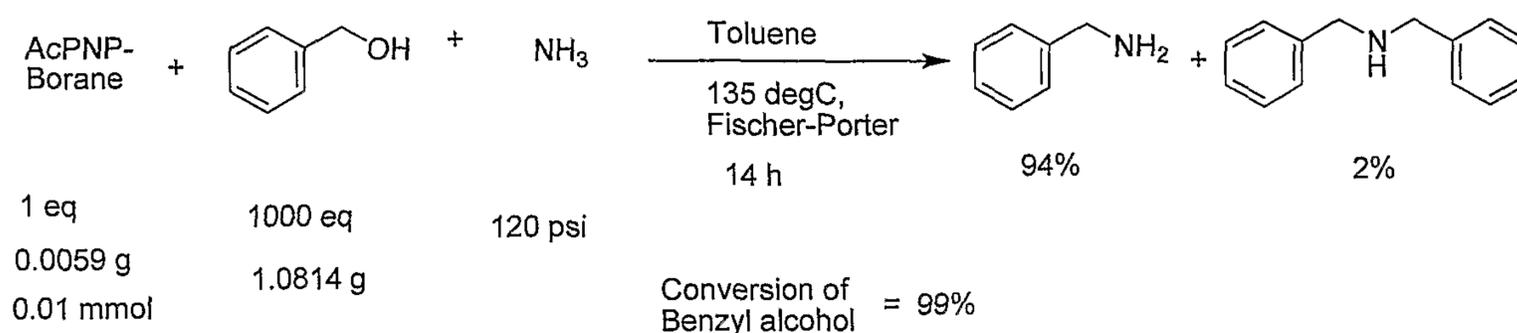
[†]Corresponding imine was the major by-product in entries 1-3; Corresponding acid was the by product in entries 6-8.

[‡]Corresponding acids were found in aqueous layer. ^{*}Hexamide was found in aqueous layer. [¶]Mixture of 2ml water and 2ml toluene is used as solvent. [§]Mixture of 1ml water and 2ml dioxane is used as solvent.

10 The inventors of the present application have further discovered that borane derivatives of the ruthenium catalysts of the present invention also act as catalysts in processes for converting primary alcohols to primary amines in accordance with the invention. Such borane derivatives are obtained by treatment of ruthenium catalysts with

sodium borohydride (NaBH_4). For example, complex **3** ($\text{RuH}(\text{BH}_3)(\text{A-}^i\text{Pr-PNP})(\text{CO})$) can be used to convert benzyl alcohol to benzylamine in excellent yields, as illustrated in Scheme 4 below:

5 **Scheme 4:**



It should be noted that instead of ammonia gas, a solution of ammonium hydroxide in water can be used. The reactions in water have several practical advantages as the aqueous and organic layers separate at the end of the reaction upon cooling and further purification of products could be carried out by vacuum distillation. The selectivity for the linear primary amines is improved by the use of co-solvents such as toluene or dioxane in water (Table 4, entries 5-7).

In addition to the selective synthesis of commercially important primary amines, the present invention also provides tools to install the amine functionality directly from alcohols in the synthesis of complex natural products and drugs without generating waste.

The disclosures of all cited references are incorporated by reference as if fully set forth herein.

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EXPERIMENTAL DETAILS SECTION

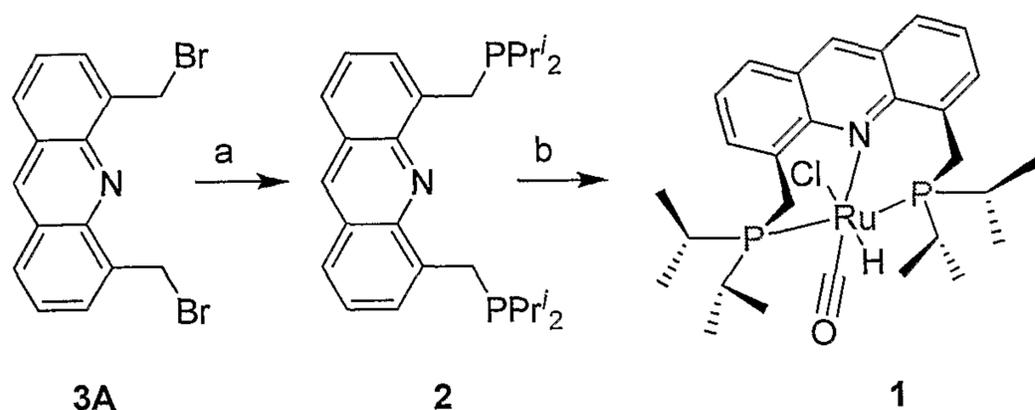
EXAMPLE 1

Preparation of Acridine-Based Pincer Complex $\text{RuHCl}(\text{A-}^i\text{Pr-PNP})(\text{CO})$ **1**

The novel, acridine-based pincer complex $\text{RuHCl}(\text{A-}^i\text{Pr-PNP})(\text{CO})$ **1** was quantitatively prepared by reaction of the new electron-rich tridentate PNP ligand **2** with $\text{RuHCl}(\text{PPh}_3)_3(\text{CO})$ in toluene at 65 °C for 2 h (Scheme 5). $^{31}\text{P}\{^1\text{H}\}$ NMR of **1** shows a singlet at 69.35 ppm. The ^1H NMR spectrum of **1** exhibits a triplet resonance at -16.09 ppm for Ru-H. The “arm” methylene protons give rise to two double triplets at 3.50 and 5.24

ppm ($^2J_{\text{HH}} = 12.8$ Hz, $^2J_{\text{PH}} = 3.7$ Hz). One singlet resonance for C9H of the acridine ring appears at 8.15 ppm, representing an up field shift of 0.46 ppm relative to the corresponding proton of the ligand **2** (8.61 ppm), suggesting diminished aromaticity of acridine on complexation with ruthenium. The structure of complex **1** was determined by a single-crystal X-ray diffraction study, which reveals a distorted octahedral geometry around the ruthenium center (30). Upon complexation acridine loses its planarity and becomes bent at the middle aryl ring to adopt a boat shape with a dihedral angle of 167.6° . Convenient to practical applications, complex **1** is stable in air for several months.

10 **Scheme 5.** Synthesis of ligand **2** and complex **1**.



Key: a) i. Di-*iso*-propylphosphine/MeOH, 50 °C, 48 h; ii. Triethylamine, r.t, 1h, 83%. b) RuHCl(PPh₃)₃(CO)/toluene, 65 °C, 2 h, quantitative or RuHCl(PPh₃)₃(CO)/THF, r.t, 9 h, 82 %.

15

EXAMPLE 2. - SYNTHETIC METHODS

General Experimental

All experiments with metal complexes and phosphine ligands were carried out under an atmosphere of purified nitrogen in a Vacuum Atmospheres glovebox equipped with a MO 40-2 inert gas purifier or using standard Schlenk techniques. All solvents were reagent grade or better. All non-deuterated solvents were refluxed over sodium/benzophenone ketyl and distilled under argon atmosphere. Deuterated solvents were used as received. All solvents were degassed with argon and kept in the glove box over 4Å molecular sieves. Most of the chemicals used in catalysis reactions were purified by vacuum distillation. However when commercial grade reagents were used comparable

25

yield of products were obtained. Ultrapure water obtained from Barnstead NANOpure Diamond™ water purification system was used for catalysis reactions in water. 4,5-bis(bromomethyl)acridine (31) and RuHCl(CO)(PPh₃)₃ (32) were prepared according to literature procedures.

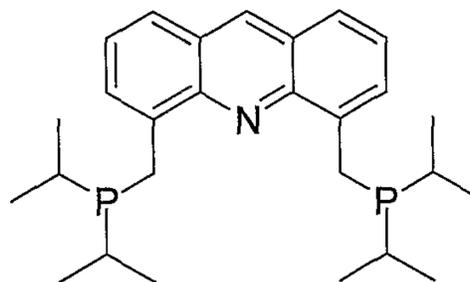
5 ¹H, ¹³C and ³¹P NMR spectra were recorded at 500, 100, and 162 MHz, respectively, using a Bruker AMX-500 NMR spectrometers. ¹H and ¹³C{¹H} NMR chemical shifts are reported in ppm downfield from tetramethylsilane. ³¹P NMR chemical shifts are reported in parts per million downfield from H₃PO₄ and referenced to an external 85% solution of phosphoric acid in D₂O. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, v, virtual.

15 **4,5-Bis(bromomethyl)acridine (3A)**³⁴: ¹H NMR (CDCl₃): 5.31 (s, 4H, ArCH₂), 7.39 (dd, ³J_{H,H} = 8.5 Hz, ⁴J_{H,H} = 7.9 Hz, 2H, ArH), 7.82 (d, ³J_{H,H} = 6.7 Hz, 2H, ArH), 7.86 (d, ³J_{H,H} = 8.5 Hz, 2H, ArH), 8.65 (s, 1H, ArH).

15

4,5-bis-(di-*iso*-propylphosphinomethyl)acridine (2): To an oven dried 100 mL Schlenk flask equipped with magnetic bar was added 4,5-bis(bromomethyl)acridine (3, 2 g, 5.48 mmol), diisopropyl phosphine (1.71g, 14.52 mmol), and 25 mL MeOH. The flask was sealed and heated at

20 50 °C for 48 h with stirring. After cooling the reaction mixture, triethylamine (2.20 g, 21.78 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The solvents were removed under



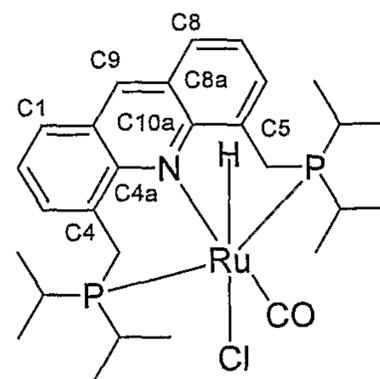
25 reduced pressure to obtain a yellow solid. The residue was washed with ether (4 × 15 mL) and the ether was removed under reduced pressure to yield a bright yellow solid. It was recrystallized from pentane/acetone mixture to yield 2.0 g (83%) of 4,5-bis[(diisopropylphosphanyl) methyl] acridine (2). ³¹P{¹H}NMR (C₆D₆): 12.35 (s). ¹H NMR (CDCl₃): 1.03 (m, 24H, 2 × P(CH(CH₃)₂)₂), 1.82 (m, 4H, (P-CH(CH₃)₂)₂), 3.72 (d, ²J_{P,H} = 2.4 Hz, 4H, 2 × P-CH₂), 7.39 (dd, ³J_{H,H} = 7.9 Hz, ⁴J_{H,H} = 6.7 Hz, 2H, ArH), 7.73 (d, ³J_{H,H} = 7.9 Hz, 2H, ArH), 7.81 (d, ³J_{H,H} = 6.7 Hz, 2H, ArH), 8.61 (s, 1H, ArH). ¹³C{¹H}NMR (CDCl₃): 19.45 (d, ²J_{PC} = 11.5 Hz, P(CH(CH₃)₂)₂), 19.74 (d, ²J_{PC} = 13.5 Hz, P(CH(CH₃)₂)₂),

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23.32 (d, $^1J_{PC} = 18.1$ Hz, $2 \times \text{P-CH}_2$), 23.75 (d, $^1J_{PC} = 14.3$ Hz, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 125.38 (s, C_1 , C_8 , A-PNP), 125.58 (d, $^4J_{PC} = 2.0$ Hz, C_2 , C_7 , A-PNP), 126.59 (s, C_{8a} , C_{9a} , A-PNP), 129.80 (d, $^3J_{PC} = 12.3$ Hz, C_3 , C_6 , A-PNP), 136.32 (s, C_9 , A-PNP), 139.44 (d, $^2J_{PC} = 7.5$ Hz, C_4 , C_5 , A-PNP), 148.82 (d, $^3J_{PC} = 2.9$ Hz, C_{4a} , C_{10a} , A-PNP). Assignment of signals was confirmed by DEPT 135.

Synthesis of RuH(Cl)(A-ⁱPr-PNP)(CO) 1: RuHCl(PPh₃)₃(CO) (301 mg, 0.32 mmol), ligand 2 (A-ⁱPr-PNP; 153 mg, 0.35 mmol), and toluene (20 mL) were charged in a Schlenk flask sealed under the nitrogen atmosphere. The reaction mixture was heated at 65 °C for 2 hrs. The solvent was evaporated and the orange solid was washed with pentane and dried under vacuum overnight, resulting in pure complex 1 in a quantitative yield (191 mg).

$^{31}\text{P}\{^1\text{H}\}$ NMR (C₆D₆): 69.35 (s). ^1H NMR (C₆D₆): -16.09 (vt, $^2J_{\text{PH}} = 19.2$ Hz, 1H, Ru-H), 0.88 (q, $^3J_{\text{PH}} = 15.6$ Hz, $^3J_{\text{HH}} = 7.3$ Hz, 6H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 1.03 (q, $^3J_{\text{PH}} = 12.8$ Hz, $^3J_{\text{HH}} = 6.4$ Hz, 6H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 1.53 (overlapping m, 2H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 1.54 (q, $^3J_{\text{PH}} = 13.7$ Hz, $^3J_{\text{HH}} = 7.3$ Hz, 6H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 1.79 (q, $^3J_{\text{PH}} = 14.7$ Hz, $^3J_{\text{HH}} = 7.3$ Hz, 6H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 2.17 (m, 2H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 3.50 (dt, $^2J_{\text{HH}} = 12.8$ Hz, $^2J_{\text{PH}} = 3.7$ Hz, 2H, -



CHHP), 5.24 (dt, $^2J_{\text{HH}} = 12.8$ Hz, $^2J_{\text{PH}} = 3.7$ Hz, 2H, -CHHP), 7.06 (t, $^3J_{\text{HH}} = 7.3$ Hz, 2H, ArH), 7.33 (d, $^3J_{\text{HH}} = 7.3$ Hz, 2H, ArH), 7.48 (d, $^3J_{\text{HH}} = 8.2$ Hz, 2H, ArH), 8.15 (s, 1H, ArH). $^{13}\text{C}\{^1\text{H}\}$ NMR (C₆D₆): 18.60 (s, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 19.42 (t, $^2J_{PC} = 2.9$ Hz, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 20.86 (s, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 21.94 (s, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 24.07 (t, $^1J_{PC} = 12.6$ Hz, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 25.83 (t, $^1J_{PC} = 10.3$ Hz, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 31.98 (t, $^1J_{PC} = 6.0$ Hz, $2 \times \text{CH}_2\text{P}$), 124.66 (s, C_1 , C_8 , A-PNP), 129.1 (s, C_2 , C_7 , A-PNP), 134.15 (d, $^2J_{PC} = 20.12$ Hz, C_4 , C_5 , A-PNP), 135.03 (t, $^3J_{PC} = 3.4$ Hz, C_3 , C_6 , A-PNP), 135.70 (s, C_{8a} , C_{9a} , A-PNP), 142.13 (s, C_9 , A-PNP), 151.37 (t, $^3J_{PC} = 2.0$ Hz, C_{4a} , C_{10a} , A-PNP), 203.40 (t, $^2J_{PC} = 11.4$ Hz, Ru-CO). Assignment of signals was confirmed by DEPT 135. IR (KBr, pellet): 2048.7 (ν_{RuH}), 1881.9 (ν_{CO}) cm^{-1} . MS (ESI, MeOH): 569 (100%, (M-Cl)⁺); MS (ESI, CH₃CN): 569 (42%, M-Cl)⁺, 610 (100%, [(M-Cl)(CH₃CN)]⁺).

Alternative method for the preparation of 1: To a suspension of RuHCl(PPh₃)₃(CO) (95.3 mg, 0.1 mmol) in THF (5 ml) was added ligand 2 (48 mg, 0.11 mmol), and the

mixture was stirred at room temperature for 9 hrs. The orange solution was filtered and the filtrate was evaporated to dryness under vacuum. The orange residue was dissolved in minimum THF (0.5 mL) and slowly added to pentane (5 mL) to precipitate an orange solid, which was filtered and dried under vacuum (50 mg, 82%).

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Synthesis of $\text{RuH}(\text{BH}_3)(\text{A-}^i\text{Pr-PNP})(\text{CO})$ (Compound 3):

To a suspension of complex **1** (121 mg, 0.2 mmol) in THF (3 ml) was added a NaBH_4 (0.21 mmol) in THF (2 ml) under nitrogen atmosphere. The mixture was stirred at room temperature for 2 hours. The colorless solution was filtered and the solvents
 10 evaporated. The complex was dried under vacuum overnight, resulting in AcPNP-Borane ruthenium complex ($\text{RuH}(\text{BH}_3)(\text{A-}^i\text{Pr-PNP})(\text{CO})$ of formula **3**) in quantitative yield (117 mg). This complex was fully characterized by NMR and by single-crystal X-ray crystallography. $^{31}\text{P}\{^1\text{H}\}$ NMR (Benzene- d_6): 51.57 (s). ^1H NMR (Toluene- D_8 , 291K): -9.27 (td, $^2J_{\text{PH}} = 22.0$ Hz, $^2J_{\text{HH}} = 2.7$ Hz, 1H, Ru-H), -5.40 (br s, 1H, BH_3), 0.78 (q, $^3J_{\text{PH}} =$
 15 11.0 Hz, $^3J_{\text{HH}} = 6.4$ Hz, 6H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 1.22-1.32 (Overlapping 3 q, 18H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 1.51 (m, 2H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 2.04 (m, 2H, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 2.35 (dt, $^2J_{\text{HH}} =$
 13.7 Hz, $^2J_{\text{PH}} = 2.7$ Hz, 2H, -CHHP), 3.47 (d, $^2J_{\text{HH}} = 15.6$ Hz, 1H, Ar-CHH-Ar), 3.63 (d, $^2J_{\text{HH}} = 13.7$ Hz, 2H, -CHHP), 4.85 (d, $^2J_{\text{HH}} = 15.6$ Hz, 1H, Ar-CHH-Ar), 6.53 (d, $^3J_{\text{HH}} = 7.3$
 Hz, 2H, ArH), 6.81 (t, $^3J_{\text{H,H}} = 7.3$ Hz, 2H, ArH), 7.01 (d, $^3J_{\text{H,H}} = 7.3$ Hz, 2H, ArH). $^{13}\text{C}\{^1\text{H}\}$
 20 NMR (C_6D_6): 15.13 (t, $^2J_{\text{PC}} = 2.3$ Hz, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 19.80 (t, $^2J_{\text{PC}} = 2.0$ Hz, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 19.84 (s, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 20.22 (s, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 21.19 (t, $^1J_{\text{PC}} = 8.6$ Hz, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 26.75 (t, $^1J_{\text{PC}} = 14.3$ Hz, $\text{P}(\text{CH}(\text{CH}_3)_2)_2$), 32.28 (t, $^1J_{\text{PC}} = 11.5$ Hz, $2 \times \text{CH}_2\text{P}$), 38.66 (s, C_9 , ArCH_2Ar), 124.40 (s, C_2 , C_7 , A-PNP), 127.27 (s, C_4 , C_5 , A-PNP), 127.58 (s, C_1 , C_8 , A-PNP), 129.39 (t, $^3J_{\text{PC}} = 2.9$ Hz, C_3 , C_6 , A-PNP), 141.12 (s, C_{8a} , C_{9a} , A-PNP), 152.18 (t, $^3J_{\text{PC}} = 3.4$ Hz, C_{4a} , C_{10a} , A-PNP), 207.7 (t, $^2J_{\text{PC}} = 14.3$ Hz, Ru-CO). IR (KBR pellets): 2413, 2357, 2333, 1913, 1462, 1437, 1036 cm^{-1} . Anal. Calcd. for $\text{C}_{28}\text{H}_{44}\text{BNOP}_2\text{Ru}$: C, 57.54; H, 7.59. Found: C57.49; H, 7.56.

General procedure for the catalytic direct amination of alcohols to amines: Complex **1**
 30 (0.01 mmol), alcohol (10 mmol), and a solvent (3 mL, if applicable) were added to a 90 mL Fischer-Porter tube under an atmosphere of purified nitrogen in a Vacuum

Atmospheres glovebox. The tube was taken out of the box and ammonia (7.5 atm) was charged into the Fischer-Porter tube and the reaction mixture was refluxed in an oil bath covered by a protective shield for the specified time (Tables 1-3 in the reports). After cooling to room temperature, the products were analyzed by GC with toluene or mesitylene
5 as an internal standard, using a HP-5 cross linked 5% PH ME Siloxane column (30m × 0.32mm × 0.25 μm film thickness) on a HP 6890 series GC system.

General procedure for the catalytic direct amination of alcohols to amines in water:
Complex **1** (0.01 mmol), and alcohol (10 mmol) were taken in a 90 mL volume Fischer-
10 Porter under an atmosphere of purified nitrogen in a Vacuum Atmospheres glovebox. The Fischer-Porter tube was taken out of glovebox and degassed water (3 ml) was added under an atmosphere of argon. Ammonia (7.5 atm) was charged into Fischer-Porter and the reaction mixture refluxed in an oil bath covered by a protective shield for the specified time (Table 4 in the reports). After cooling to room temperature, the products were analyzed by
15 GC with mesitylene as an internal standard, using a HP-5 cross linked 5% PH ME Siloxane column (30m × 0.32mm × 0.25 μm film thickness) on a HP 6890 series GC system.

While certain embodiments of the invention have been illustrated and described, it will be clear that the invention is not limited to the embodiments described herein. Numerous modifications, changes, variations, substitutions and equivalents will be
20 apparent to those skilled in the art without departing from the spirit and scope of the present invention as described by the claims, which follow.

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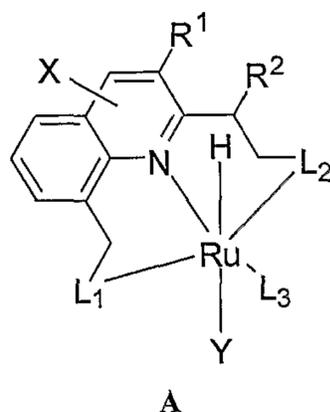
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CLAIMS

What is claimed is:

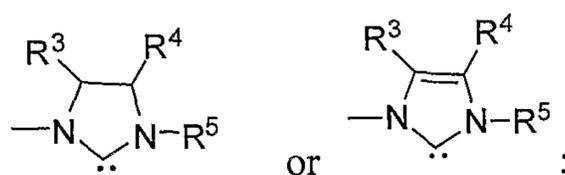
1. A ruthenium catalyst represented by the structure of formula A:



wherein

L_1 and L_2 are each independently selected from the group consisting of phosphine (PR^aR^b), amine (NR^aR^b), imine, sulfide (SR), thiol (SH), sulfoxide ($S(=O)R$), heteroaryl containing at least one heteroatom selected from nitrogen and sulfur; arsine (AsR^aR^b), stibine (SbR^aR^b) and a N-heterocyclic carbene represented by the structures:

10



L_3 is a mono-dentate two-electron donor selected from the group consisting of CO, $PR^aR^bR^c$, NO^+ , $AsR^aR^bR^c$, $SbR^aR^bR^c$, SR^aR^b , nitrile (RCN), isonitrile (RNC), N_2 , PF_3 , CS, heteroaryl and tetrahydrothiophene;

15

R^1 and R^2 are either each hydrogen or together with the carbons to which they are attached represent a phenyl ring which is fused to the quinoliny moiety so as to form an acridinyl moiety;

20

R , R^a , R^b , R^c , R^3 , R^4 and R^5 are each independently alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl;

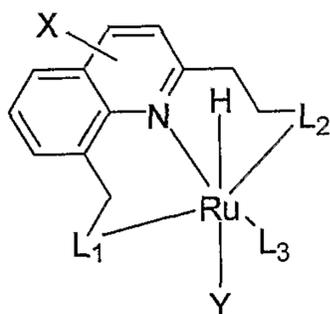
Y is halogen, OCOR, $OCOFC_3$, OSO_2R , OSO_2CF_3 , CN, OH, OR, NR_2 , NH_3 , NR_3 , R_2NSO_2R , or a neutral solvent molecule, wherein R is as defined above;

25

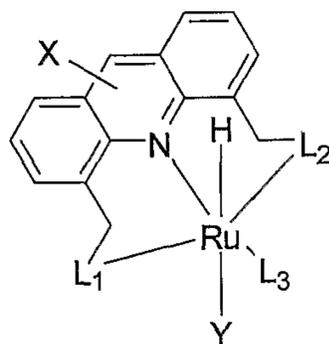
X represents one, two, three, four, five, six or seven substituents positioned

at any carbon atom on the acridinyl moiety; or one, two, three, four or five substituents positioned on any carbon atom on the quinolinyl moiety, and is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, halogen, nitro, amide, ester, cyano, alkoxy, alkylamino, arylamino, an inorganic support and a polymeric moiety, or a borane derivative of said catalyst obtained by reacting said catalyst with sodium borohydride (NaBH₄).

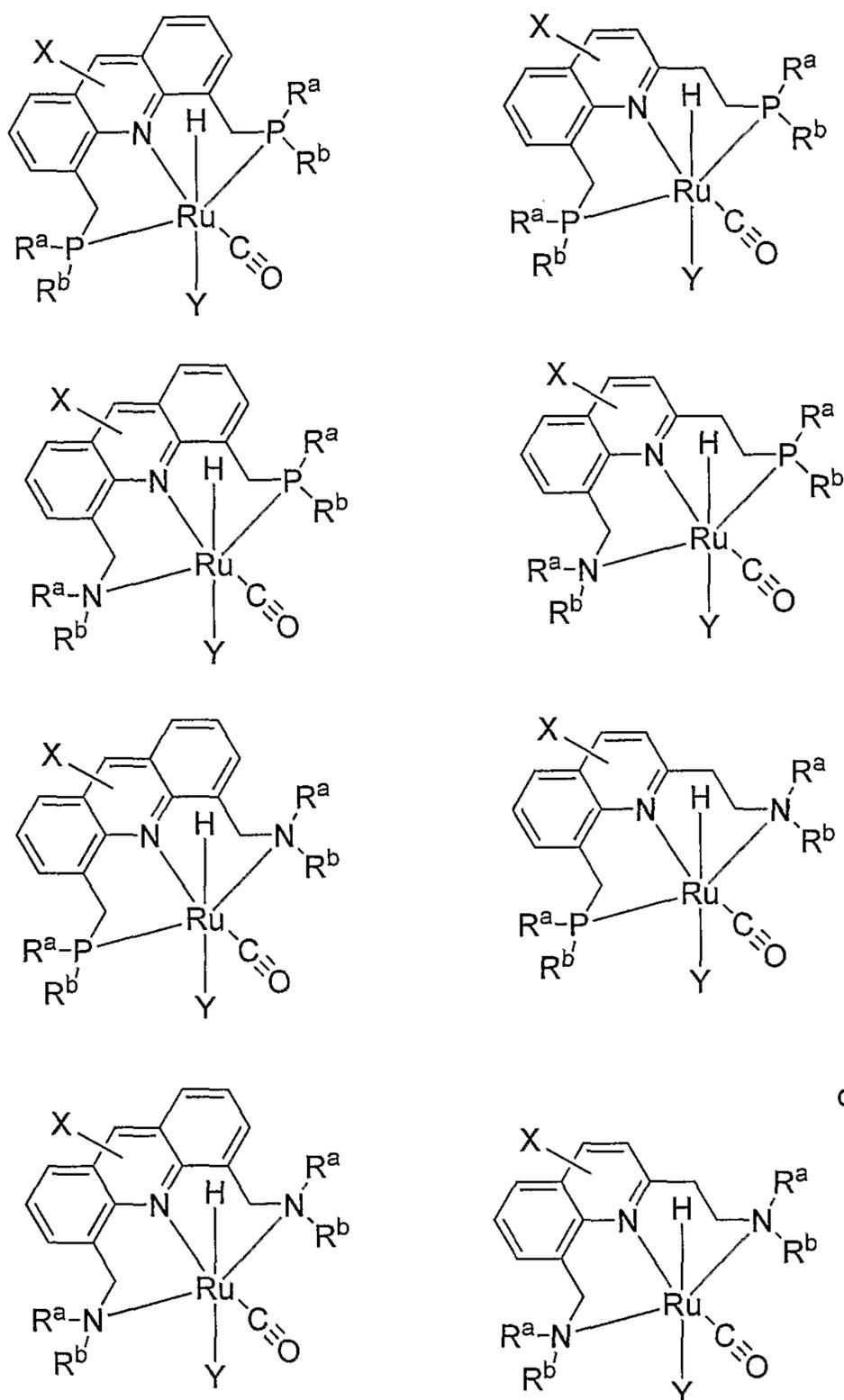
10 2. The ruthenium catalyst according to claim 1, wherein R¹ and R² are each H, and the ruthenium catalyst is represented by the structure:



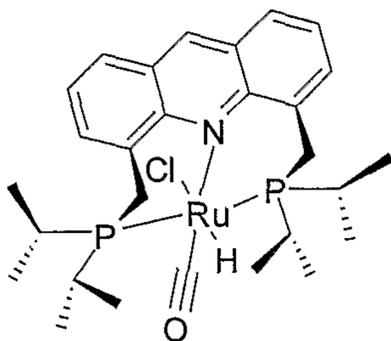
15 3. The ruthenium catalyst according to claim 1, wherein R¹ and R² together with the carbon atoms to which they are attached form a phenyl ring, and the ruthenium catalyst is represented by the structure:



4. The ruthenium catalyst according to claim 1, which is represented by any of the following structures:

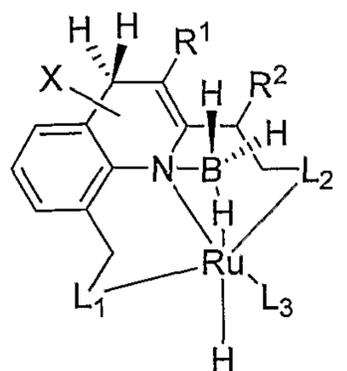


5. The ruthenium catalyst according to claim 1, which is represented by the structure of formula 1:



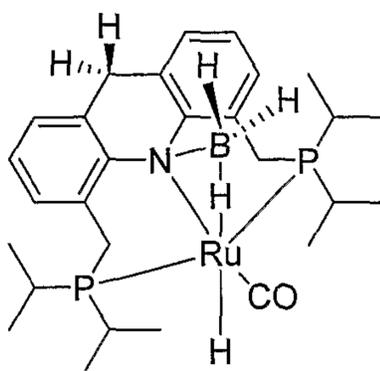
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6. A borane derivative of the ruthenium catalyst according to claim 1, represented by the structure of formula B:



B

5 7. The borane derivative of claim 6, which is represented by the structure of formula 3:



3

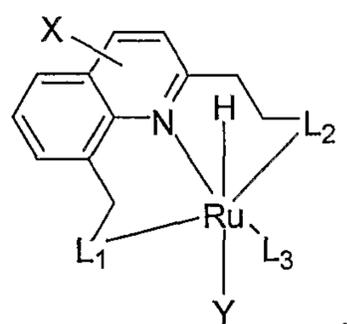
8. The ruthenium catalyst of claim 1, wherein Y is halogen.

10 9. The ruthenium catalyst of claim 1 wherein L₃ is CO.

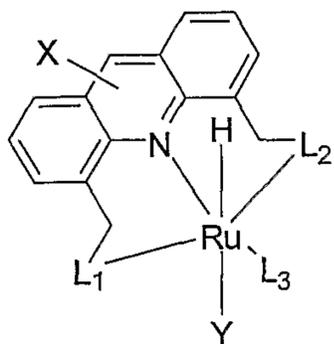
10. A process for preparing a primary amine, comprising the step of reacting a primary alcohol and ammonia in the presence of the ruthenium catalyst according to claim 1, or a borane derivative thereof, thereby generating the primary amine.

15

11. The process of claim 10, wherein R¹ and R² are each H, and the ruthenium catalyst is represented by the structure:

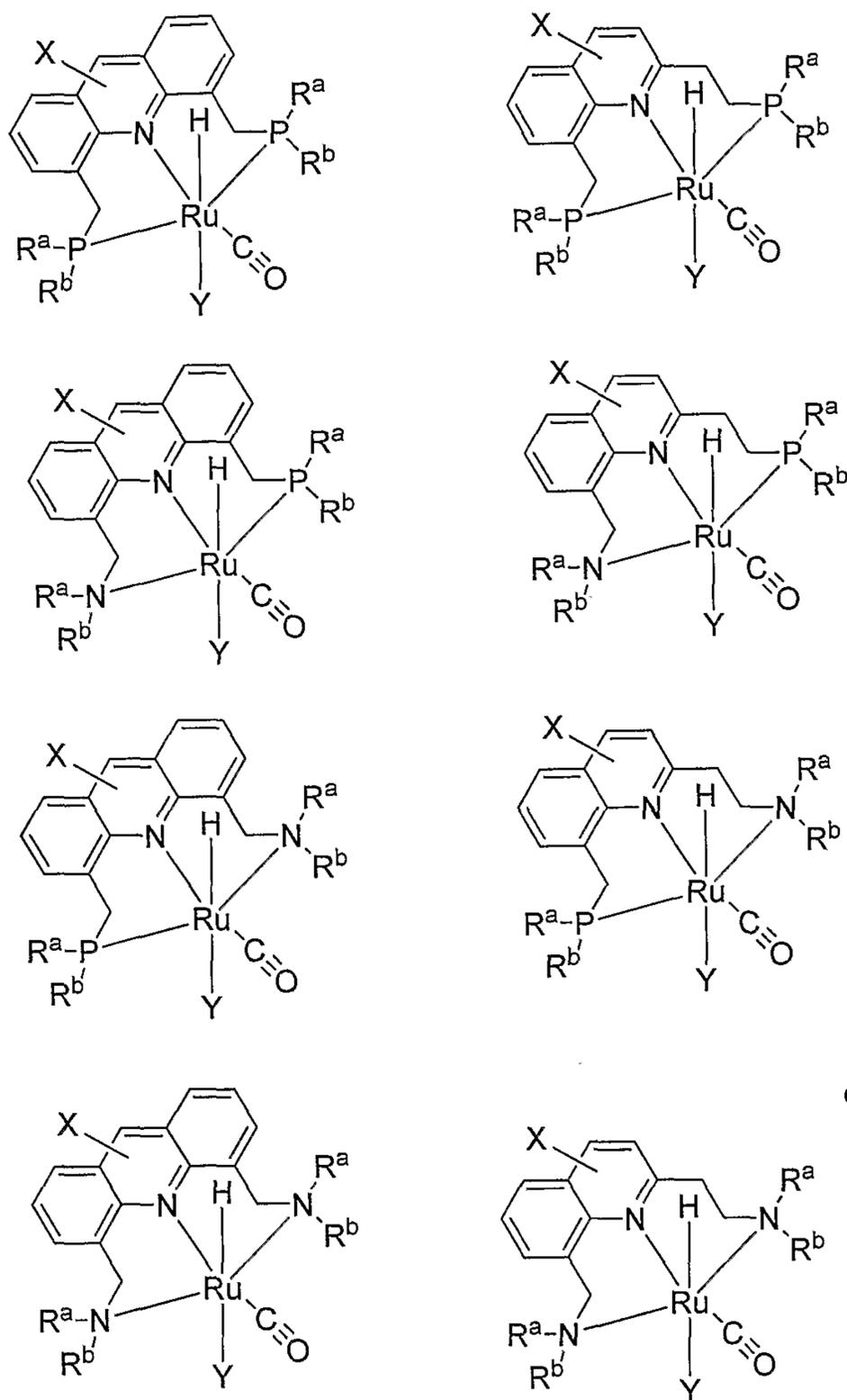


12. The process of claim 10, wherein R^1 and R^2 together with the carbon atoms to which they are attached form a phenyl ring, and the ruthenium catalyst is represented by the structure:

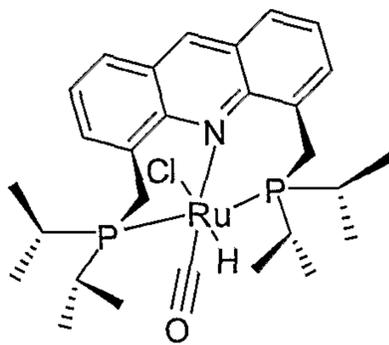


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13. The process of claim 10, wherein the ruthenium catalyst is represented by any of the following structures:



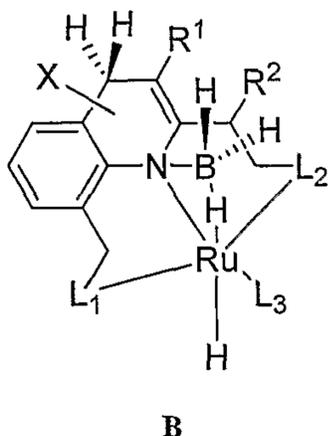
14. The process of claim 10, wherein the ruthenium catalyst is represented by the structure of formula 1:



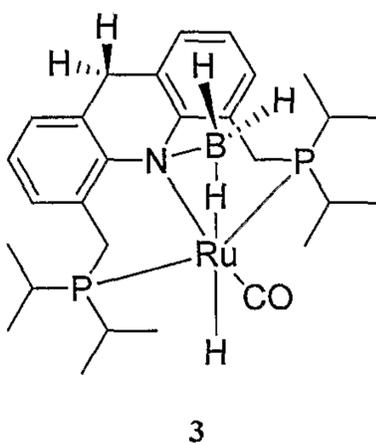
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15. The process of claim 10, wherein the borane derivative is represented by the structure of formula B:



16. The process of claim 15, wherein the borane derivative is represented by the structure of formula 3:



17. The process of claim 10, wherein the primary alcohol is represented by the formula R^6CH_2OH wherein R^6 is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl and alkoxyalkyl.

18. The process of claim 17, wherein the alcohol is selected from the group consisting of methanol, ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, benzyl alcohol, o-, m-, or p-methoxy benzyl alcohol, o-, m-, or p-halo benzyl alcohol, pyridine-2-yl-methanol, 2-furylmethanol, 2-phenylethanol, 2-methoxyethanol, 2-methyl-1-butanol, cyclohexylmethanol and (3-methyloxetan-3-yl)methanol.

19. The process of claim 10, wherein the reaction is conducted in the presence of a

solvent.

20. The process of claim 19, wherein the solvent is water or an organic solvent selected from the group consisting of benzene, toluene, o-, m- or p-xylene mesitylene (1,3,5-
5 trimethyl benzene, dioxane, THF, DME, anisole and cyclohexane.

21. The process of claim 20, wherein the solvent is water, and the ammonia is provided as a solution of ammonium hydroxide in water.

10 22. The process of claim 19, wherein the solvent is a mixture of water and an organic solvent.

23. The process of claim 22, wherein the water and organic solvent form a homogenous solution.

15 24. The process of claim 22, wherein the water and organic solvent form a heterogeneous mixture.

20 25. The process of claim 10, wherein the reaction is conducted in the absence of a solvent.

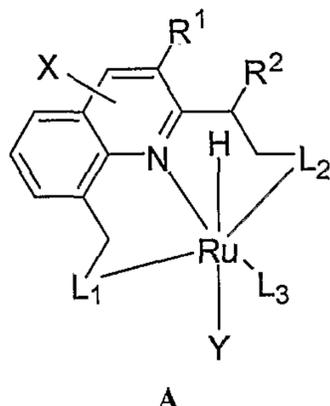
26. The process of claim 10, wherein said process is conducted under heat or under inert gas.

25 27. The process of claim 10, wherein excess ammonia is used.

28. Use of a ruthenium catalyst of formula A according to claim 1, or a borane derivative thereof, to prepare an amine by reacting a primary alcohol and ammonia in the presence of said catalyst.

30 29. A process for preparing a primary amine, comprising the step of reacting a primary

alcohol and ammonia in the presence of a ruthenium catalyst represented by the structure of formula A or a borane derivative of said catalyst obtained by reacting said catalyst with sodium borohydride (NaBH₄), thereby forming the primary amine,

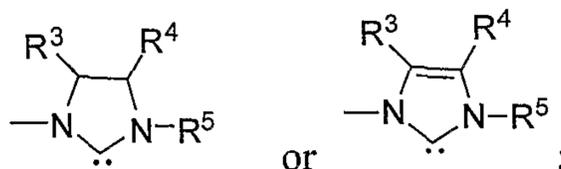


5

wherein

L_1 and L_2 are each independently selected from the group consisting of phosphine (PR^aR^b), amine (NR^aR^b), imine, sulfide (SR), thiol (SH), sulfoxide ($S(=O)R$), a heteroaryl containing at least one heteroatom selected from nitrogen and sulfur, arsine (AsR^aR^b), stibine (SbR^aR^b) and a N-heterocyclic carbene represented by the structures:

10



15

L_3 is a mono-dentate two-electron donor selected from the group consisting of CO, $PR^aR^bR^c$, NO^+ , $AsR^aR^bR^c$, $SbR^aR^bR^c$, SR^aR^b , nitrile (RCN), isonitrile (RNC), N_2 , PF_3 , CS, heteroaryl and tetrahydrothiophene;

R^1 and R^2 are either each hydrogen or together with the carbons to which they are attached represent a phenyl ring which is fused to the quinolonyl moiety so as to form an acridinyl moiety;

20

R , R^a , R^b , R^c , R^3 , R^4 and R^5 are each independently alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl;

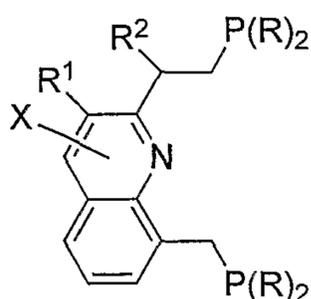
Y is halogen, OCOR, OCOCF₃, OSO₂R, OSO₂CF₃, CN, OH, OR, NR₂, NH₃, NR₃, R₂NSO₂R, or a neutral solvent molecule, wherein R is as defined above;

25

X represents one, two, three, four, five, six or seven substituents positioned at any carbon atom on the acridinyl moiety; or one, two, three, four or five

substituents positioned on any carbon atom on the quinolinyl moiety, and is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, halogen, nitro, amide, ester, cyano, alkoxy, alkylamino, arylamino, an inorganic support and a polymeric moiety.

30. A compound represented by the structure of formula 2A:



2A

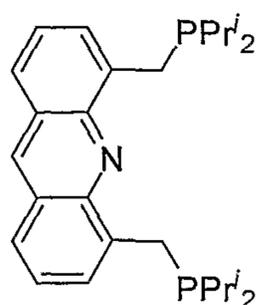
wherein

each **R** is independently alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl;

R¹ and **R**² are either each hydrogen, or together with the carbons to which they are attached represent a phenyl ring which is fused to the quinolinyl moiety so as to form an acridinyl moiety; and

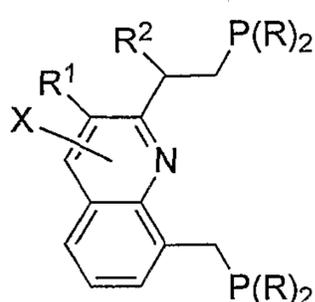
X represents one, two, three, four, five, six or seven substituents positioned at any carbon atom on the acridinyl moiety; or one, two, three, four or five substituents positioned on any carbon atom on the quinolinyl moiety, and is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, halogen, nitro, amide, ester, cyano, alkoxy, alkylamino, arylamino, an inorganic support (e.g., silica) and a polymeric moiety (e.g., polystyrene).

31. The compound according to claim 30, which is represented by the structure of formula 2:



2

32. Use of a compound represented by the structure of formula 2A:



2A

wherein

5 each **R** is independently alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl or alkylheteroaryl;

R¹ and **R**² are either each hydrogen, or together with the carbons to which they are attached represent a phenyl ring which is fused to the quinolinylnyl moiety so as to form an acridinylnyl moiety; and

10 **X** represents one, two, three, four, five, six or seven substituents positioned at any carbon atom on the acridinylnyl moiety; or one, two, three, four or five substituents positioned on any carbon atom on the quinolinylnyl moiety, and is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylcycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, halogen, nitro, amide, ester, cyano, alkoxy, alkylamino, arylamino, an inorganic support (e.g., silica) and a polymeric moiety (e.g., polystyrene);
 15 for the preparation of a ruthenium catalyst according to claim 1.

33. A process for preparing a ruthenium catalyst represented by the structure of formula B, comprising the step of reacting a ruthenium catalyst of formula A as claimed in claim 1,
 20 with sodium borohydride (NaBH₄)

