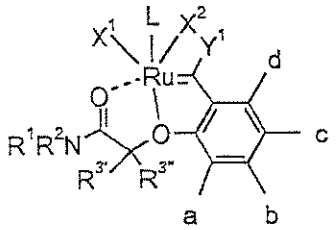
PROCESS FOR THE PREPARATION OF RUTHENIUM METATHESIS COMPLEX CATALYSTS

The invention relates to a novel process for the preparation of Ruthenium metathesis catalysts of the formula



I

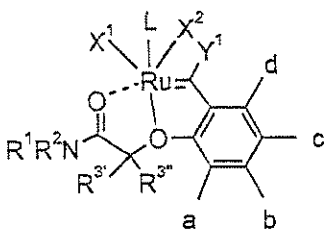
Ruthenium metathesis catalysts have been widely applied in the synthesis of macrocyclic drug compounds (see for example the PCT Publication WO 2005/037214 or PCT Publication WO 2007/015824).

It is thus important that commercially feasible pathways are available for the synthesis of these catalysts.

Object of the embodiments disclosed herein is to provide a technically feasible manufacturing process to the catalysts of general formula I.

The object has been achieved with the process of the present disclosure as outlined below.

The process for the preparation of compounds of formula I



I

wherein the dotted line either signifies the existence of a bond or no bond;

L is a neutral ligand;

X^1 and X^2 independently of each other are anionic ligands;

Y^1 is hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, C_{2-6}-alkynyloxy, aryloxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylthio, aryl, arylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulfinyl;

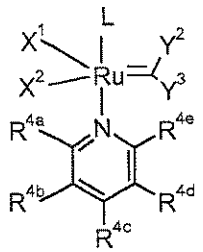
a, b, c and d independently of each other have the meaning of hydrogen, C_{1-6}-alkyl, halogen-C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, C_{2-6}-alkynyloxy, C_{1-6}-alkylcarbonyl, aryl, hydroxy, aryloxy, nitro, C_{1-6}-alkoxycarbonyl, amino, mono-C_{1-6}-alkyl-or di-C_{1-6}-alkylamino, halogen, thio, C_{1-6}-alkylthio, arylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulfinyl, arylsulfonyl, SO_3H, C_{1-6}-alkylcarbonyl amino, aryl carbonyl amino, C_{1-6}-alkyl sulfonyl amino, aryl sulfonyl amino, halogen-C_{1-6}-alkyl sulfonyl amino, SO_3-C_{1-6}-alkyl or $OSi(C_{1-6}\text{-alkyl})_3$ and SO_2-NR'R'' wherein R' and R'' independently of each other have the meaning of hydrogen, aryl or C_{1-6}-alkyl or R' and R'' together with the N atom form a cycle;

R^1 and R^2 independently of each other are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl or

R^1 and R^2 together with the N atom form a 5 to 8 member cycle which may contain nitrogen, oxygen or sulfur as additional hetero atom;

$R^{3'}$ and $R^{3''}$ independently of each other are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl,

comprises the conversion of a Ru precursor compound of the formula II

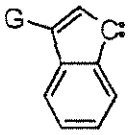


II

wherein X^1, X^2 and L are as defined above and

Y^2 and Y^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkylthio, aryl, arylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulfinyl,

or Y^2 and Y^3 taken together form a cycle of the type

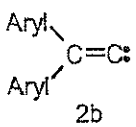


2a

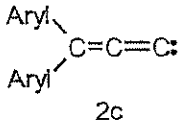
with G being hydrogen or aryl;

or

Y^2 and Y^3 together form a cumulenyl group of the type



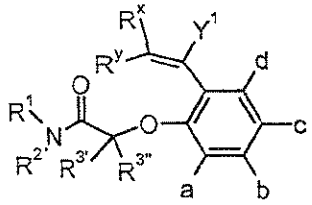
2b



2c

R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e} independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkyloxy, aryl, aryloxy, halogen, C_{1-6}-alkylcarbonyl amino or arylcarbonyl amino;

with a preligand of the formula III

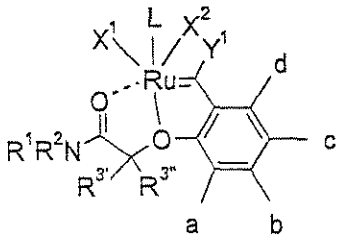


III

wherein R^1, R^2 and $R^{3'}$ and $R^{3''}$, Y^1 and a,b,c,d are as defined above;

R^x and R^y independently of each denote hydrogen, C_{1-6}-alkyl optionally substituted by one or more halogen atoms or aryl optionally substituted by one or more halogen atoms or by C_{1-6}-alkyl.

In one aspect, there is provided a process for the preparation of compounds of formula I



I

wherein the dotted line either signifies the existence of a bond or no bond;

X^1 and X^2 independently of each other are anionic ligands;

Y^1 is hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, C_{2-6}-alkynyloxy, aryloxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylthio, aryl, arylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulfinyl;

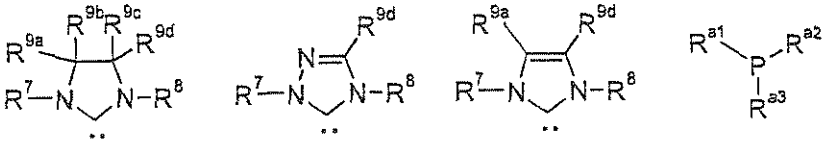
a, b, c and d independently of each other have the meaning of hydrogen, C_{1-6}-alkyl, halogen-C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, C_{2-6}-alkynyloxy, C_{1-6}-alkylcarbonyl, aryl, hydroxy, aryloxy, nitro, C_{1-6}-alkoxycarbonyl, amino, mono-C_{1-6}-alkyl-or di-C_{1-6}-alkylamino, halogen, thio, C_{1-6}-alkylthio, arylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulfinyl, arylsulfonyl, SO_3H, C_{1-6}-alkylcarbonyl amino, aryl carbonyl amino, C_{1-6}-alkyl sulfonyl amino, aryl sulfonyl amino, halogen-C_{1-6}-alkyl sulfonyl amino, SO_3-C_{1-6}-alkyl or $OSi(C_{1-6}\text{-alkyl})_3$ and SO_2-$NR'R''$ wherein R' and R'' independently of each other have the meaning of hydrogen, aryl or C_{1-6}-alkyl or R' and R'' together with the N atom form a cycle;

R^1 and R^2 independently of each other are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl or

R^1 and R^2 together with the N atom form a 5 to 8 member cycle which may contain nitrogen, oxygen or sulfur as additional hetero atom;

$R^{3'}$ and $R^{3''}$ independently of each other are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl;

L is a neutral ligand selected from



2q 2r 2s 2t

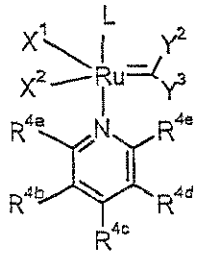
wherein R^7 and R^8 independently of each other are C_{1-6}-alkyl, aryl, C_{2-6}- alkenyl or 1-adamantyl and

R^{9a-d} are independently of each other hydrogen, C_{1-6}-alkyl, C_{2-6}- alkenyl or aryl, or R^{9b} and R^{9c} or R^{9a} and R^{9d} taken together form a-$(CH_2)_4$-bridge;

or R^{9a} and R^{9d} in formula 2s both have the meaning of halogen;

R^{a1}, R^{a2} and R^{a3} independently of each other are C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl, heteroaryl or R^{a1} and R^{a2} or R^{a2} and R^{a3} or R^{a1} and R^{a3} taken together form a 1,5-bridged cyclooctyl group,

comprising the conversion of a Ru precursor compound of the formula II

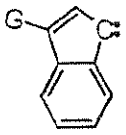


II

wherein X^1, X^2 and L are as defined above and

Y^2 and Y^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkylthio, aryl, arylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulfinyl,

or Y^2 and Y^3 taken together form a cycle of the type

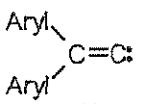


2a

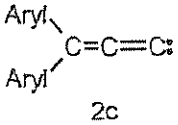
with G being hydrogen or aryl;

or

Y^2 and Y^3 together form a cumulenyl group of the type



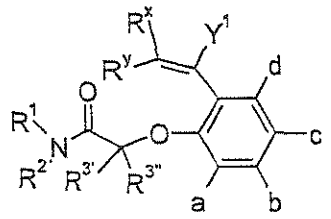
2b



2c ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e} independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkyloxy, aryl, aryloxy, halogen, C_{1-6}-alkylcarbonyl amino or arylcarbonyl amino;

with a preligand of the formula III



III

wherein R^1, R^2, $R^{3'}$, $R^{3''}$, Y^1 and a,b,c,d are as defined above;

R^x and R^y independently of each other denote hydrogen, C_{1-6}-alkyl optionally substituted by one or more halogen atoms or aryl optionally substituted by one or more halogen atoms or by C_{1-6}-alkyl.

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "C_{1-6}-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to six carbon atoms, preferably one to four carbon atoms. This term is further exemplified by radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and pentyl or hexyl and its isomers.

The term "C_{2-6}-alkenyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent unsaturated aliphatic hydrocarbon radical of two to six carbon atoms, preferably two to four carbon atoms. This term is further exemplified by radicals as vinyl, propenyl, butenyl, pentenyl and hexenyl and their isomers. Preferred alkenyl radical is vinyl.

The term "C_{2-6}-alkynyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent unsaturated aliphatic hydrocarbon radical of two to six carbon atoms, preferably two to four carbon atoms. This term is further exemplified by radicals as ethynyl, propynyl, butynyl, pentynyl or hexynyl their isomers.

The term "C_{3-8}-cycloalkyl" group refres to a cycloalkyl group containing from 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

The term "halogen-C_{1-6}-alkyl" refers to a halogen substituted C_{1-6}-alkyl radical wherein halogen has the meaning as above. Preferred "halogen-C_{1-6}-alkyl" radicals are the fluorinated C_{1-6}-alkyl radicals such as CF_3, CH_2CF_3, $CH(CF_3)_2$, $CH(CH_3)(CF_3)$ or C_4F_9.

The term "C_{1-6}-alkoxy" refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to six carbon atoms, preferably 1 to 4 carbon atoms attached to an oxygen atom. Examples of "alkoxy" are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and hexyloxy. Preferred are the alkoxy groups specifically exemplified herein.

The alkyl chain of the alkoxy group can optionally be substituted, particularly mono-, di- or tri-substituted by alkoxy groups as defined above, preferably methoxy, or ethoxy or by aryl groups, preferably phenyl. Preferred substituted alkoxy group is the benzyloxy group.

The term "C_{1-6}-alkyl carbonyl" refers to C_{1-6}-alkyl substituted carbonyl group, preferably to a C_{1-4}-alkycarbonyl group. It includes for example acetyl, propanoyl, butanoyl or pivaloyl. Preferred alkyl carbonyl group is acetyl.

The term "C_{1-6}-alkylthio" refers to the group C_{1-6}-alkyl-S-, preferably C_{1-4}-alkyl-S-, e.g. methylthio or ethylthio. Preferred are the alkylthio groups specifically exemplified herein.

The term "arylthio" refers to a group aryl-S-, preferably to phenylthio.

The term "C_{1-6}-alkylsulfonyl" refers to a C_{1-6}-alkyl substituted sulfonyl group, preferably to methylsulfonyl.

The term "C_{1-6}-alkylsulfinyl" refers to a C_{1-6}-alkyl substituted sulfinyl group, preferably to methylsulfinyl.

The term "SO_2- aryl" refers to a sulfonyl substituted aryl radical. Preferred SO_2-aryl radical is SO_2-phenyl.

The term "SO_2-NR'R'' " refers to a sulfonyl group substituted with an amino group NR'R'' wherein R' and R'' independently of each other have the meaning of hydrogen or C_{1-6}-alkyl or R' and R'' together with the N atom form a cycle, e.g. $-(CH_2)_4-$ or $-(CH)_4-$. Preferred SO_2-NR'R'' radical is SO_2-$N(CH_3)_2$.

The term "mono- or di-C_{1-6}-alkyl-amino" refers to an amino group, which is mono- or disubstituted with C_{1-6}-alkyl, preferably C_{1-4}-alkyl. A mono-C_{1-6}-alkyl-amino group includes for example methylamino or ethylamino. The term "di-C_{1-6}-alkyl-amino" includes for example dimethylamino, diethylamino or ethylmethylamino. Preferred are the mono- or di-C_{1-4}-alkylamino groups specifically exemplified herein. It is hereby understood that the term "di-C_{1-6}-alkyl-amino" includes ring systems wherein the two alkyl groups together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocycle which also may carry one further hetero atom selected from nitrogen, oxygen or sulfur.

The term "aryl", alone or in combination with other groups, relates to a phenyl or naphthyl group, which can optionally be mono-, di-, tri- or multiply-substituted by halogen, hydroxy, CN, halogen-C_{1-6}-alkyl, NO_2, NH_2, N(H,alkyl), $N(alkyl)_2$, carboxy, aminocarbonyl, alkyl, alkoxy, alkylcarbonyl, C_{1-6}-alkylsulfonyl, SO_2-aryl, SO_3H, SO_3-alkyl, SO_2-NR'R'', aryl and/or aryloxy. Preferred aryl group usually is phenyl, however the preference for aryl may differ as indicated hereinafter for certain substituents.

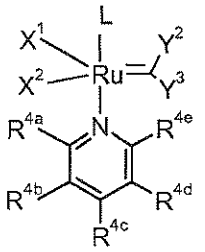
The term "aryloxy" relates to an aryl radical attached to an oxygen atom. The term "aryl" has the meaning as defined above. Preferred aryloxy group is phenyloxy.

The term "arylalkyl" relates to an aryl radical attached to an alkyl group. The term "aryl" has the meaning as defined above. Preferred arylalkyl group is benzyl.

The term "aryl carbonyl " refers to an aryl radical attached to a carbonyl group, whereas the term "aryl carbonyl amino" refers to an aryl carbonyl radical attached to an amino group.

The term "halogen" refers to a fluorine, chlorine, bromine or iodine atom, preferably to a chlorine atom.

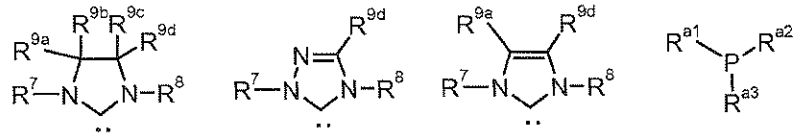
Starting compound for the process of the present invention is the Ru precursor compound of formula II



II

wherein X^1, X^2, Y^2, Y^3, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e} and L are as defined above.

The ligand L is a neutral ligand preferably selected from



2q 2r 2s 2t

wherein R^7 and R^8 independently of each other are C_{1-6}-alkyl, aryl, C_{2-6}- alkenyl or 1-adamantyl and

R^{9a-d} are independently of each other hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl or aryl, or R^{9b} and R^{9c} or R^{9a} and R^{9d} taken together form a-$(CH_2)_4$-bridge;

or R^{9a} and R^{9d} in formula 2s both have the meaning of halogen, preferably of chlorine;

R^{a1}, R^{a2} and R^{a3} independently of each other are C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl, heteroaryl or R^{a1} and R^{a2} or R^{a2} and R^{a3} or R^{a1} and R^{a3} taken together form a 1,5-bridged cyclooctyl group.

In a preferred embodiment R^7 and R^8 are C_{1-6}-alkyl, 1-adamantyl, a phenyl group which is di- or tri-substituted with C_{1-6}-alkyl or naphthyl which is di- or tri-substituted with C_{1-6}-alkyl.

R^7 and R^8 more preferably have the meaning of t-butyl, 1-adamantyl, isopropyl, 2,6-diisopropylphenyl, 2,7-diisopropylnaphthyl or 2,4,6-trimethylphenyl, most preferably 2,4,6-trimethylphenyl or 2,7-diisopropylnaphthyl.

In a preferred embodiment R^{9a} and R^{9c} are methyl or phenyl and R^{9b} and R^{9d} are hydrogen, or R^{9a} and R^{9c} or R^{9b} and R^{9d} are taken together to form a -$(CH_2)_n$- bridge with n having the meaning of 5 or 6. It is hereby understood that if chiral carbon atoms are present, both the racemic and the enantiomerically pure form are comprised.

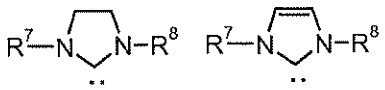
In a further preferred embodiment R^{9a-d} are hydrogen.

In a preferred embodiment R^{a1}, R^{a2} and R^{a3} independently of each other are C_{1-6}-alkyl, C_{3-8}-cycloalkyl or phenyl.

In a more preferred embodiment R^{a1}, R^{a2} and R^{a3} independently of each other stand for cyclohexyl, cyclopentyl, isopropyl and phenyl.

Suitable representatives of ligands L of formula 2t are Cy_3P, iPr_3P, Cyp_3P or Ph_3P wherein Cy stands for cyclohexyl, Cyp for cyclopentyl and iPr for isopropyl.

In a further preferred embodiment L is

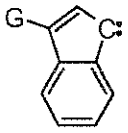


2u 2v

wherein R^7 and R^8 are as described above.

As anionic ligand X^1 and X^2 a halogenide or a pseudo halogenide such as cyanide, a rhodanide, a cyanate, an isocycanate, acetate or trifluoroacetate may be selected. Preferred anionic ligand for X^1 and X^2 is a halogenide, whereas chloro is the most preferred anionic ligand.

Y^2 and Y^3 are preferably taken together to form a cycle of the type



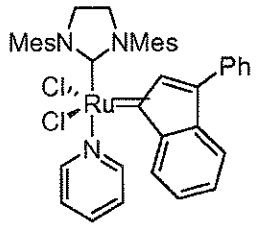
2a

with G being hydrogen or aryl, preferably phenyl.

Preferably R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e} independently of each other, have the meaning of hydrogen, C_{1-6}-alkyl, and halogen, whereas hydrogen and methyl, particularly hydrogen are even more preferred.

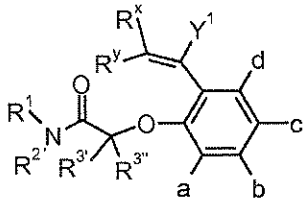
The compounds of formula II can be prepared in accordance with the disclosure of D. Burtscher, C. Lexer, K. Mereiter, R. Winde, R. Karch, C. Slugovc, *Journal of Polymer Sciences, Part A: Polymer Chemistry*, **2008**, *46*, 4630-4635).

The most preferred compound of formula II, the compound of the formula



is commercially available as Neolyst M31 from Umicore AG & Co. KG, Rodenbacher Chaussee 4, 63457 Hanau-Wolfgang, Germany.

The preligands of the formula III



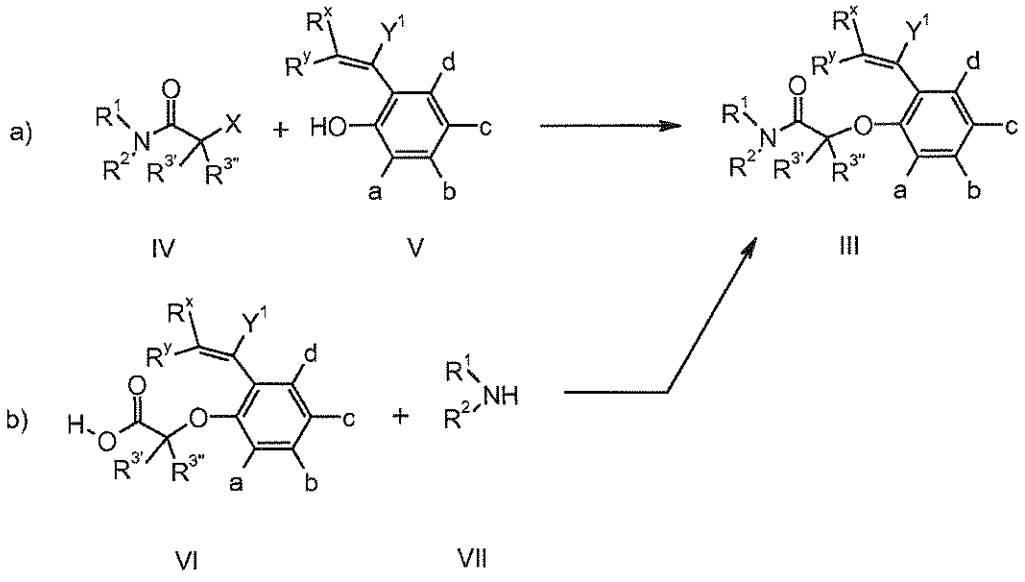
III

wherein R^1, R^2, $R^{3'}$, $R^{3''}$, Y^1 and a,b,c,d are as defined above and wherein

R^x and R^y independently of each other denote hydrogen, C_{1-6}-alkyl optionally substituted by one or more halogen atoms or aryl optionally substituted by one or more halogen atoms or by C_{1-6}-alkyl

can be prepared following the scheme below:

Scheme 1:



According to the pathway a) of scheme 1, the preligands of formula III can be prepared by standard methods of the organic synthesis, e.g. by treatment of the phenol building block with the 2-halo amide in DMF with potassium carbonate and cesium carbonate as bases (as reported in M. Bieniek et al, *Journal of Organometallic Chemistry*, 2006, *691*, 5289) or in the presence of sodium hydroxide and a phase transfer agent (as reported in M. Halpern et al, *Synthesis*, 1979, 177).

Alternatively, according to the pathway b) of scheme 1, the preligands of formula III can be prepared by coupling of a carboxylic acid building block with an amine in the presence of a substituted tetramethyluronium salt such as TBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium tetrafluoroborate) (G.R. Pettit et al, *J. Nat. Prod.* 1999, *62*, 409) or HBTU (O-(1-Benzotriazolyl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (A. Speicher et al, *J. Prakt. Chem.* 1998, *340*, 581).

Preferred substituent definitions in the preligand of formula III are outlined below.

Y^1 is preferably hydrogen.

The preferred meaning of a, b and d is hydrogen.

The preferred meaning for c is hydrogen, halogen, nitro, C_{1-6}-alkylcarbonyl amino, aryl carbonyl amino, aryl sulfonyl amino, alkyl sulfonyl amino, halogen-C_{1-6}-alkyl sulfonyl amino, SO_2-NR'R'' wherein R' and R'' independently of each other have the meaning of hydrogen, C_{1-6}-alkyl, aryl or R' and R'' together with the N atom form a cycle.

More preferably c means hydrogen, Cl, nitro or SO_2-NR'R''.

In a preferred embodiment R^1 and R^2 independently of each other are hydrogen, C_{1-6}-alkyl or

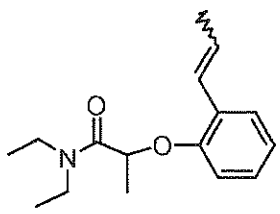
R^1 and R^2 together with the N atom form a 6 member cycle which contains oxygen as additional hetero atom.

Still more preferred R^1 and R^2 independently of each other are hydrogen or C_{1-6}-alkyl.

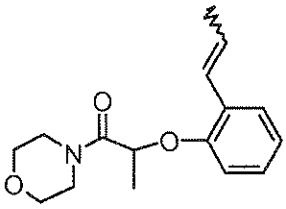
$R^{3'}$ and $R^{3''}$ independently of each other preferably are hydrogen or C_{1-6}-alkyl, more preferably hydrogen or methyl.

R^x and R^y independently of each other preferably are hydrogen or C_{1-6}-alkyl, more preferably hydrogen or methyl.

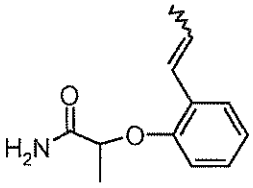
Preferred preligands of formula III are selected from



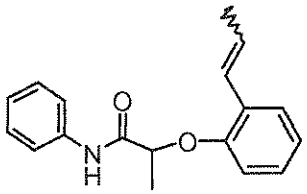
IIIa ;



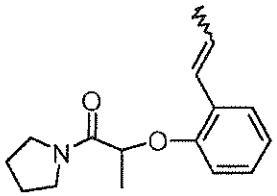
IIIb ;



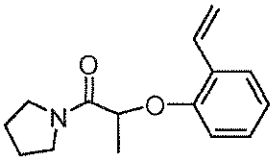
IIIc ;



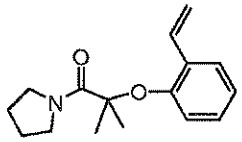
IIId ;



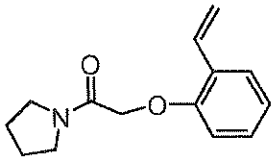
IIIe ;



IIIf ;



IIIg ;



IIIh .

Even more preferred are the preligands of formula IIIe or IIIf.

The conversion is usually performed in an inert organic solvent such as in an aromatic solvent, a halogenated aromatic solvent, a halogenated hydrocarbon and mixtures thereof or in a mixture of said solvents with an aliphatic hydrocarbon.

Suitable aromatic organic solvents are benzene, toluene or mesitylene and suitable halogenated aromatic solvents are polyfluorinated benzenes or toluenes. Useful halogenated hydrocarbons are for example dichloromethane or dichloroethane. The solvents may be used as single solvent or as a mixture of different solvents.

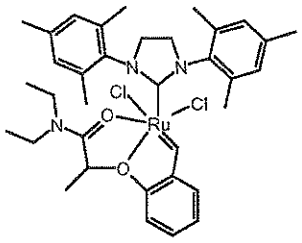
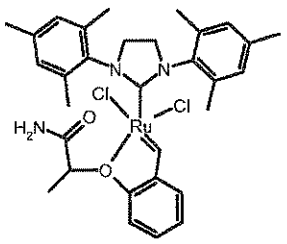
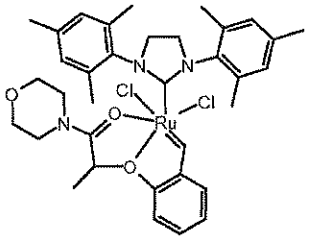
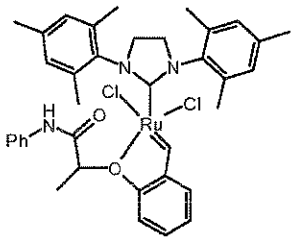
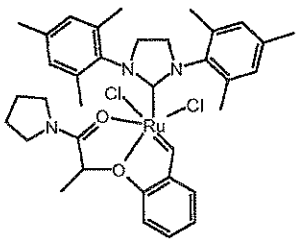
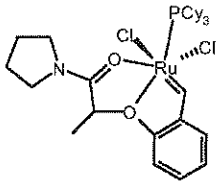
Suitable aliphatic hydrocarbon co-solvents can be selected from pentane, hexane or heptane.

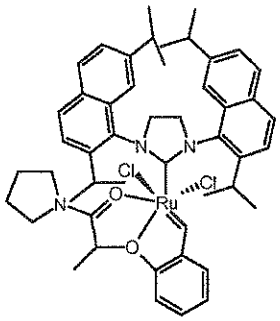
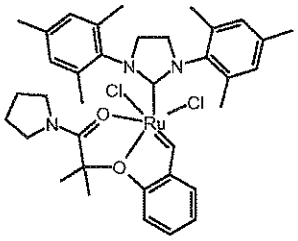
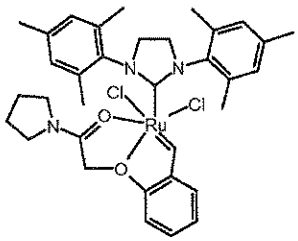
Preferred inert organic solvent is toluene.

The reaction can as a rule be performed at a reaction temperature of 0°C to 100°C, preferably at 40°C to 80°C, ideally under inert gas atmosphere.

The desired compound of formula I can be isolated from the reaction mixture applying methods known to the skilled in the art, usually by filtering off the product and by washing the precipitate with a suitable organic solvent such as with toluene, hexane, pentane and diethyl ether or with mixtures thereof.

The following compounds of formula I are preferred representatives of Ruthenium Metathesis Complex Catalysts which can be prepared in accordance with the present invention.

D		[$RuCl_2$(=CH(o-OCH(Me)$CONEt_2$)Ph)(ImH_2Mes)]
E		[$RuCl_2$(=CH(o-OCH(Me)$CONH_2$)Ph)(ImH_2Mes)]
F		[$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Morpholine)Ph)(ImH_2Mes)]
G		[$RuCl_2$(=CH(o-OCH(Me)CONHPh)Ph)(ImH_2Mes)]
J		[$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Pyrrolidine)Ph)(ImH_2Mes)]
K		[$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Pyrrolidine)Ph)(PCy_3)]

L		[$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Pyrrolidine)Ph)(SIPrNap)]
M		[$RuCl_2$(=CH(o-$OCMe_2$CO-*N*-Pyrrolidine)Ph)(ImH_2Mes)]
N		[$RuCl_2$(=CH(o-OCH_2CO-*N*-Pyrrolidine)Ph)(ImH_2Mes)]

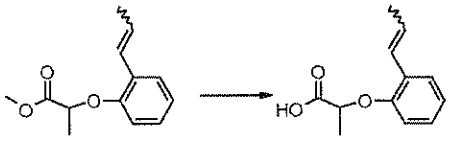
Examples

Abbreviations:

r.t. = room temperature
ImH_2Mes = 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene
RP column = reverse phase column
Mes = 2,4,6-trimethylphenyl

Preligand Example A1

2-[((*E,Z*)-2-Propenyl)-phenoxy]-propionic acid



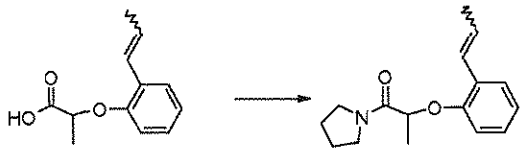
To a solution of 0.50 g (2.2 mmol) of methyl 2-[((*E,Z*)-2-propenyl)-phenoxy]-propanoate

(4:1 mixture of *E/Z*-isomers, prepared according to D. Arlt, K. Grela et al, *J. Am. Chem. Soc.* **2006**, *128*, 13652-13653) in dioxane, 11 ml (20.0 mmol) of a 2M aqueous sodium hydroxide solution was added and the reaction mixture was stirred for 16 h at room temperature. To the reaction mixture, 50 ml of water and 100 ml of tert.-butyl methyl ether were added. The organic layer was washed with 40 ml of water. After the pH of the combined aqueous layers was adjusted with 25% aqueous hydrochloric acid to a value of 1, 150 ml of dichloromethane was added. The organic layer was washed with 100 ml of brine, dried over sodium and evaporated to dryness at 40°C/10 mbar to yield 0.50 g (99% yield) of the title compound as a 3:1 mixture of *E/Z*-isomers with >99.9% purity (GC-area%) as white crystals. (GC method as described in Example 7. Retention times: Methyl 2-[((*Z*)-2-propenyl)-phenoxy]-propanoate 12.2 min, methyl 2-[((*E*)-2-propenyl)-phenoxy]-propanoate 12.9 min, 2-[((*Z*)-2-propenyl)-phenoxy]-propionic acid 13.3 min, 2-[((*E*)-2-propenyl)-phenoxy]-propionic acid 14.0 min).

Mp.: 96°C. MS: 206.0 (M^+).

Preligand Example A2

2-[((*E,Z*)-2-Propenyl)-phenoxy]-1-pyrrolidine-1-yl-propan-1-one

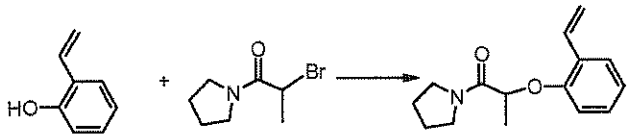


To a solution 1.92 ml (23.0 mmol) of pyrrolidine in 200 ml of *N,N*-dimethylformamide, 4.02 ml (23.0 mmol) of *N,N*-diisopropylethylamine, 1.00 g (4.6 mmol) of 2-[((*E,Z*)-2-propenyl)-phenoxy]-propionic acid (3:1 mixture of *E/Z*-isomers) and 1.92 g (5.8 mmol) of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) was added and the reaction mixture stirred for 2 h at room temperature. To the reaction mixture 200 ml of water and 400 ml ethyl acetate were added. The organic layer was separated, washed with 100 ml of water, dried over sodium sulfate and evaporated to dryness at 40°C/10 mbar. The crude title product was purified by silica gel chromatography (heptane/ethyl acetate 3:1) to yield 0.69 g (57% yield) of the title compound as a 4:1 mixture of *E/Z*-isomers with 98.1 % purity (GC-area%) as a white powder. (GC method: Column HP-5, 5% phenyl methyl siloxane, 30 m x 0.32 mm, df: 0.25 µm; injector temp.: 250°C; detector temp.: 250°C; oven temp.: 50°C to 300° (10°C/min), then 300 °C for 5 min ;Retention times: 2-[((*Z*)-2-propenyl)-phenoxy]-propanoic acid 13.9 min, 2-[((*E*)-2-propenyl)-phenoxy]-propanoic acid 14.0 min, 2-[((*Z*)-2-propenyl)-phenoxy]-1-pyrrolidine-1-yl-propan-1-one 18.0 min, 2-[((*E*)-2-propenyl)-phenoxy]-1-pyrrolidine-1-yl-propan-1-one 18.4 min).

MS: 260.0 $(M+H^+)$.

Preligand Example B

1-Pyrrolidin-1-yl-2-(2-vinylphenoxy)-propan-1-one

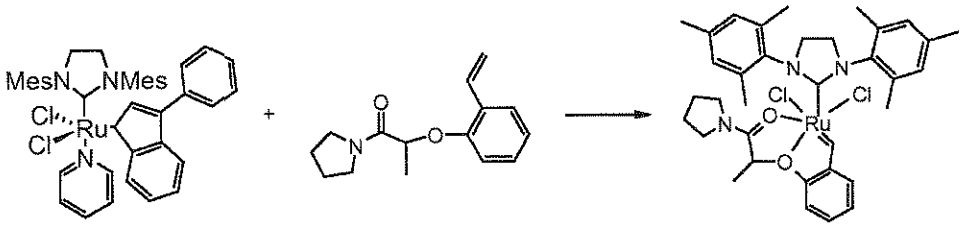


To a solution of 6.35 g (40.1 mmol) potassium 2-vinylphenolate in 110 ml of water (pH adjusted at 14 by addition of KOH) was added under argon 150 ml of toluene, 0.65 g (2.0 mmol) of tetrabutylammonium bromide and 11.54 g (50.16 mmol) of 2-bromo-1-pyrrolidin-1-yl-propan-1-one. The two-phase mixture was stirred vigorously over night at 45°C. After this time the organic phase was removed, washed with water, 4 M sodium hydroxide aqueous solution, 1 M hydrochloric acid solution and water, dried (sodium sulfate) and evaporated to dryness. Crystallization of the residue from warm heptane (200 ml) afforded the title compound as a white powder (7.0 g, 70.5% yield) with melting point of 85-86°C.

MS: 246.1496 $(M+H)^+$, 268.1317 $(M+Na)^+$.

Example 1

Catalyst No. J, [$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Pyrrolidine)Ph)(ImH_2Mes)]



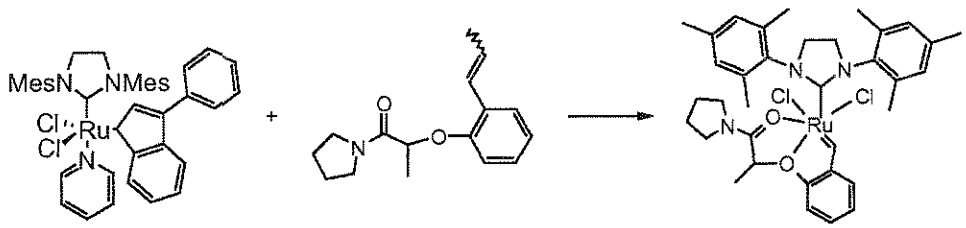
J

A mixture of 21.0 g (27.69 mmol) of [$RuCl_2$(3-phenylidenyl-1-iden)(ImH_2Mes)(pyridine)] and 7.48 g (30.46 mmol) of 1-pyrrolidin-1-yl-2-(2-vinylphenoxy)-propan-1-one in 230 ml of toluene was stirred for 2 h at 65°C under argon. The reaction mixture (a suspension) was cooled with an icebath, the precipitate was filtered off and washed with an ice-cold mixture of toluene, hexane and diethylether. The filter cake was dried at room temperature in vacuo for 20 h to afford 17.8 g of the title compound (90.6% yield) as a green powder.

Anal. calcd. for $C_{35}H_{43}Cl_2N_3O_2Ru$: C, 59.23; H, 6.11; N, 5.92, Cl 9.99. Found: C, 59.63; H, 6.52; N, 5.70. Ru content: 14.03%. 1H-NMR (CD_2Cl_2): characteristic signal at 16.5 ppm (Ru=C*H*).

Example 2

Catalyst No. J, [$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Pyrrolidine)Ph)(ImH_2Mes)]



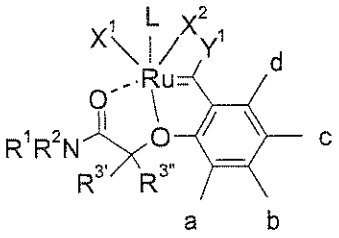
J

A mixture of 3.00 g (3.96 mmol) of [$RuCl_2$(3-phenylidenyl-1-iden)(ImH_2Mes)(pyridine)] and 1.16 g (4.35 mmol) of 2-[((*E,Z*)-2-propenyl)-phenoxy]-1-pyrrolidine-1-yl-propan-1-one in 50 ml of toluene was stirred for 4 h at 60°C under argon. The reaction mixture (a suspension) was cooled with an icebath, the precipitate was filtered off and washed with an ice-cold mixture of toluene, pentane and diethylether. The filter cake was dried at room temperature in vacuo for 20 h to afford 2.38 g of the title compound (84.8% yield) as a green powder.

Anal. calcd. for $C_{35}H_{43}Cl_2N_3O_2Ru$: C, 59.23; H, 6.11; N, 5.92, Cl 9.99. Found: C, 60.12; H, 6.06; N, 5.52. Ru content: 14.50%. 1H-NMR (CD_2Cl_2): characteristic signal at 16.5 ppm (Ru=C*H*).

Claims

1. Process for the preparation of compounds of formula I



I

wherein the dotted line either signifies the existence of a bond or no bond;

X^1 and X^2 independently of each other are anionic ligands;

Y^1 is hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, C_{2-6}-alkynyloxy, aryloxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylthio, aryl, arylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulfinyl;

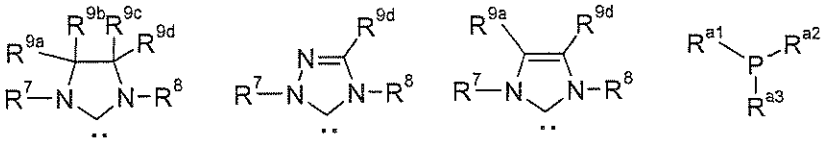
a, b, c and d independently of each other have the meaning of hydrogen, C_{1-6}-alkyl, halogen-C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, C_{2-6}-alkynyloxy, C_{1-6}-alkylcarbonyl, aryl, hydroxy, aryloxy, nitro, C_{1-6}-alkoxycarbonyl, amino, mono-C_{1-6}-alkyl-or di-C_{1-6}-alkylamino, halogen, thio, C_{1-6}-alkylthio, arylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulfinyl, arylsulfonyl, SO_3H, C_{1-6}-alkylcarbonyl amino, aryl carbonyl amino, C_{1-6}-alkyl sulfonyl amino, aryl sulfonyl amino, halogen-C_{1-6}-alkyl sulfonyl amino, SO_3-C_{1-6}-alkyl or $OSi(C_{1-6}\text{-alkyl})_3$ and SO_2-NR'R'' wherein R' and R'' independently of each other have the meaning of hydrogen, aryl or C_{1-6}-alkyl or R' and R'' together with the N atom form a cycle;

R^1 and R^2 independently of each other are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl or

R^1 and R^2 together with the N atom form a 5 to 8 member cycle which may contain nitrogen, oxygen or sulfur as additional hetero atom;

$R^{3'}$ and $R^{3''}$ independently of each other are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl;

L is a neutral ligand selected from



2q 2r 2s 2t

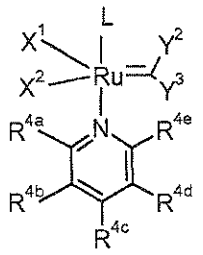
wherein R^7 and R^8 independently of each other are C_{1-6}-alkyl, aryl, C_{2-6}- alkenyl or 1-adamantyl and

R^{9a-d} are independently of each other hydrogen, C_{1-6}-alkyl, C_{2-6}- alkenyl or aryl, or R^{9b} and R^{9c} or R^{9a} and R^{9d} taken together form a-$(CH_2)_4$-bridge;

or R^{9a} and R^{9d} in formula 2s both have the meaning of halogen;

R^{a1}, R^{a2} and R^{a3} independently of each other are C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl, heteroaryl or R^{a1} and R^{a2} or R^{a2} and R^{a3} or R^{a1} and R^{a3} taken together form a 1,5-bridged cyclooctyl group,

comprising the conversion of a Ru precursor compound of the formula II

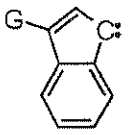


II

wherein X^1, X^2 and L are as defined above and

Y^2 and Y^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkylthio, aryl, arylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulfinyl,

or Y^2 and Y^3 taken together form a cycle of the type

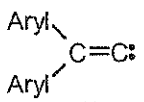


2a

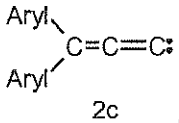
with G being hydrogen or aryl;

or

Y^2 and Y^3 together form a cumulenyl group of the type



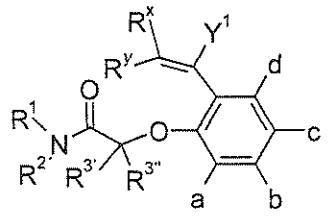
2b



2c ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e} independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkyloxy, aryl, aryloxy, halogen, C_{1-6}-alkylcarbonyl amino or arylcarbonyl amino;

with a preligand of the formula III

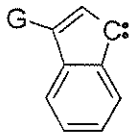


III

wherein R^1, R^2, $R^{3'}$, $R^{3''}$, Y^1 and a,b,c,d are as defined above;

R^x and R^y independently of each other denote hydrogen, C_{1-6}-alkyl optionally substituted by one or more halogen atoms or aryl optionally substituted by one or more halogen atoms or by C_{1-6}-alkyl.

2. Process of claim 1, characterized in that Y^2 and Y^3 in the Ru precursor compound of the formula II are preferably taken together to form a cycle of the type



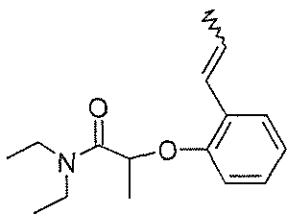
2a

with G being hydrogen or aryl.

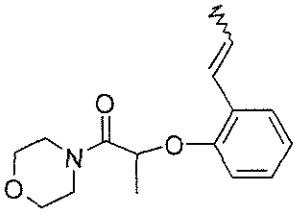
3. Process of claim 1, characterized in that X^1 and X^2 in the Ru precursor compound of the formula II stand for a halogenide or a pseudo halogenide.

4. Process of claim 1, characterized in that R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e} stand for hydrogen, methyl or for a halogen atom.

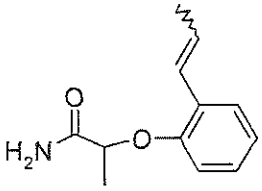
5. Process of claim 1, characterized in that the preligands of formula III are selected from



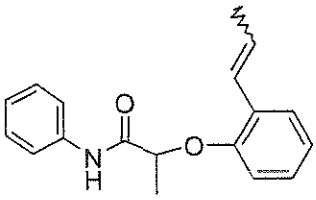
IIIa ;



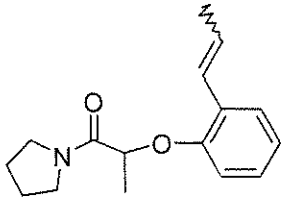
IIIb ;



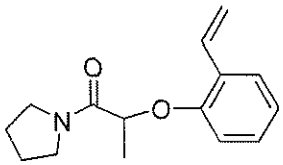
IIIc ;



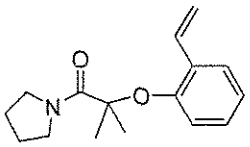
IIId ;



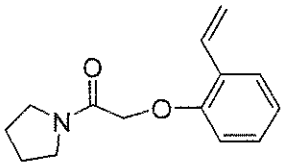
IIIe ;



IIIf ;



IIIg ;

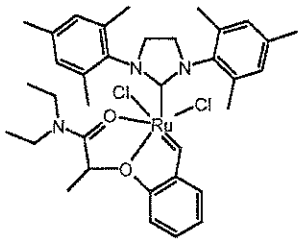
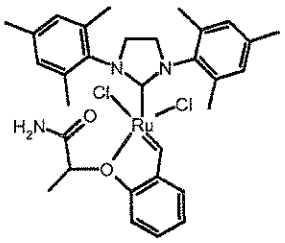
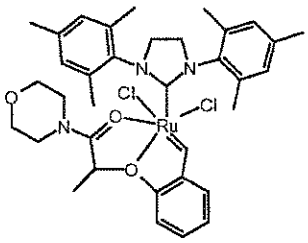
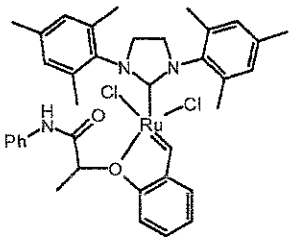
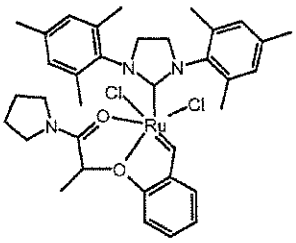
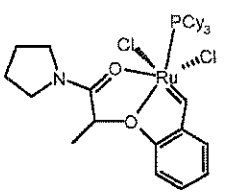


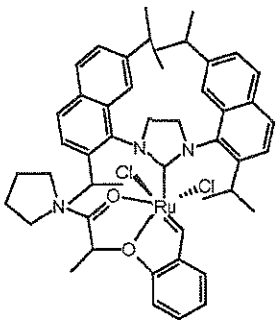
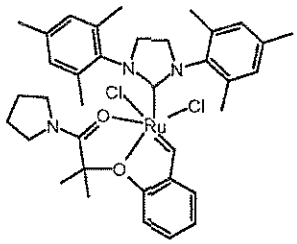
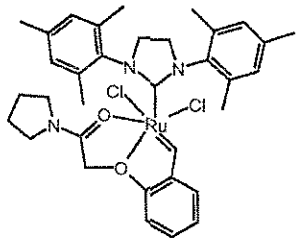
IIIh

6. Process of claims 1 to 5, characterized in that the conversion is performed in an inert organic solvent at a temperature of 0°C to 100°C.

7. Process of claim 6, characterized in that the inert organic solvent is an aromatic solvent, a halogenated aromatic solvent, a halogenated hydrocarbon and mixtures thereof or a mixture of said solvents with an aliphatic hydrocarbon.

8. Process of claim 1, characterized in that the compounds of formula I are selected from

	[$RuCl_2$(=CH(o-OCH(Me)$CONEt_2$)Ph)(ImH_2Mes)]
	[$RuCl_2$(=CH(o-OCH(Me)$CONH_2$)Ph)(ImH_2Mes)]
	[$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Morpholine)Ph)(ImH_2Mes)]
	[$RuCl_2$(=CH(o-OCH(Me)CONHPh)Ph)(ImH_2Mes)]
	[$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Pyrrolidine)Ph)(ImH_2Mes)]
	[$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Pyrrolidine)Ph)(PCy_3)]

	[$RuCl_2$(=CH(o-OCH(Me)CO-*N*-Pyrrolidine)Ph)(SIPrNap)]
	[$RuCl_2$(=CH(o-$OCMe_2$CO-*N*-Pyrrolidine)Ph)(ImH_2Mes)]
	[$RuCl_2$(=CH(o-OCH_2CO-*N*-Pyrrolidine)Ph)(ImH_2Mes)]