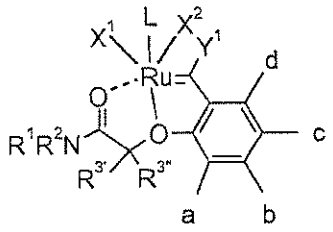
PROCESS FOR THE PREPARATION OF RUTHENIUM METATHESIS COMPLEX CATALYSTS

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



I

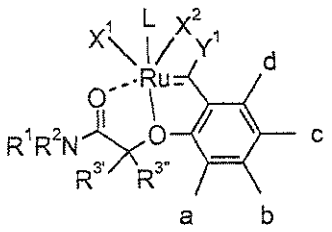
Ruthenium metathesis catalysts have been widely applied in the synthesis of macrocyclic drug compounds (see for example the PCT Publication WO 2005/037214 or PCT Publication WO 2007/015824).

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

Object of the embodiments disclosed herein~~present invention therefore~~ 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~~invention~~ as outlined below.

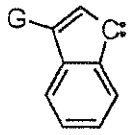
The process for the preparation of compounds of formula I



I

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

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

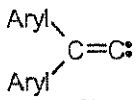


2a

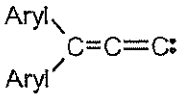
with G being hydrogen or aryl;

or

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



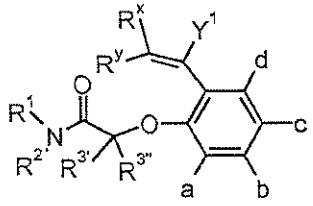
2b



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

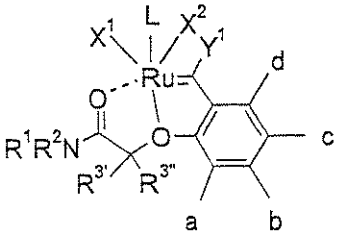


III

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;

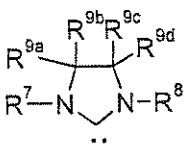
a, b, c and d independently of each other have the meaning of hydrogen, C_{1-6}-alkyl, halogen-C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, C_{2-6}-alkynyloxy, C_{1-6}-alkylcarbonyl, aryl, hydroxy, aryloxy, nitro, C_{1-6}-alkoxycarbonyl, amino, mono-C_{1-6}-alkyl-or 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

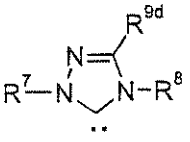
R^1 and R^2 together with the N atom form a 5 to 8 member cycle which may contain nitrogen, oxygen or sulfur as additional hetero atom;

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

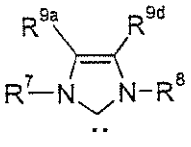
L is a neutral ligand selected from



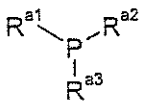
2q



2r



2s



2t

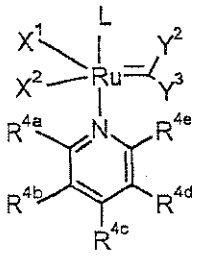
wherein R^7 and R^8 independently of each other are C_{1-6}-alkyl, aryl, C_{2-6}- alkenyl or 1-adamantyl and

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

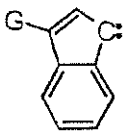


II

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

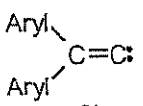


2a

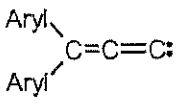
with G being hydrogen or aryl;

or

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



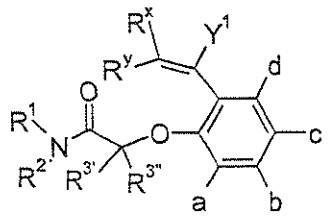
2b



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.