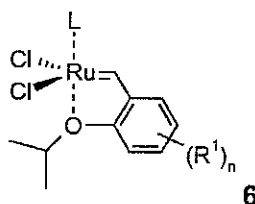


PREPARATION OF CATALYSTS

The present invention discloses a novel synthesis method for a catalyst of formula 6, wherein Mes has the meaning of mesityl.

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wherein n is an integer from 1 to 3, R¹ is a substituent and L is a neutral ligand;

10

BACKGROUND INFORMATION

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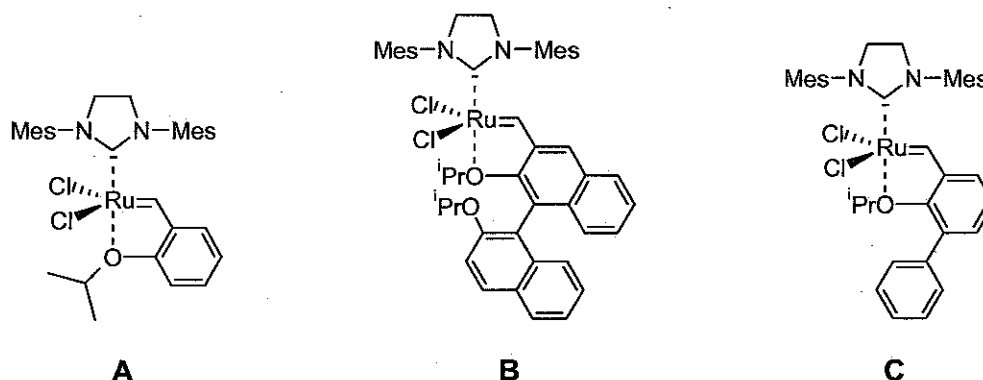
Great progress has been made in the last few years in the application of olefin metathesis in organic synthesis. Some ruthenium carbene complexes acting as (pre)catalysts have been developed, which possess a high activity in various metathesis reactions as well as a broad tolerance for a number of functional groups. This combination of characteristics is a basis for the usability of such (pre)catalysts in organic synthesis.

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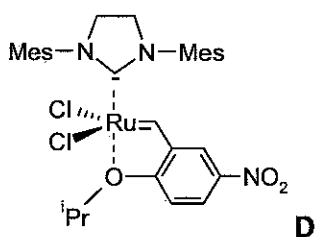
Moreover, for the practical application, especially in industrial scale, it is very desirable that these ruthenium complexes are stable for a longer period of time in the conditions of thermal load and that they can be stored, purified and applied without the atmosphere of protective gases.

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Ruthenium complexes with the above mentioned characteristics are known in literature. See J. Am. Chem. Soc. 2000, 122, 8168-8179 or Tetrahedron Lett. 2000, 41, 9973-9976. However, it has been discovered that a better stability is connected with a lower catalytic activity. Such a limitation was found for example for the (pre)catalyst of the formula **A** (see Angew. Chemie Int. Ed. 2002, 114, 832).



Next, (pre)catalysts of the formula **B** and **C** were described, which demonstrate a higher catalytic activity in comparison with the (pre)catalyst of the formula **A**. The catalysts **A**, **B** and **C** contain an *iso*-propoxy group chelating the metal atom. The reason for a higher activity of the systems **B** and **C** is a steric hindrance caused by the presence of a phenyl or a (substituted) naphthyl group in *ortho*-position to the *iso*-propoxy group (Angew. Chemie Int. Ed. 2002, 114, 832-834; Angew. Chemie Int. Ed. 2002, 114, 2509-2511). WO 2004-035596 discloses i.e. a ruthenium carbene complex of formula **D** and its practical use as catalysts for different types of metathesis reactions.



In general one can say the progress in science shows that higher activity for catalytically active systems according to compounds **A-D** is combined with lower stability of the isopropoxybenzyliden-ruthenium bond(s).

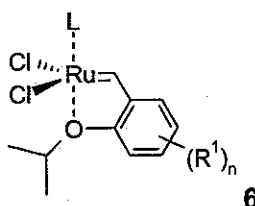
K. Grela *et al.*, Angew. Chem. Int. Ed., 2002, Vol. 41, pp. 4038-4040 discloses a process for manufacturing compounds of formula **6** via an exchange reaction between a compound of formula **3.1** and 1-isopropoxy-4-nitro-2-vinylbenzene (R=H). There is no hint to utilize the corresponding prop-1-enyl compound (R=CH₃).

The instant invention now provides a method to prepare different catalysts starting from **A** via the replacement of the one-2-isopropoxybenzylidene ligand present in **A** by differently

substituted 2-isopropoxybenzylidene ligands, possessing different affinity to the ruthenium atom. The method is especially applicable to introduce poorer chelating substituted 2-isopropoxybenzylidene ligand.

5 SUMMARY

According to a first aspect, there is provided a process for manufacturing a compound of formula 6

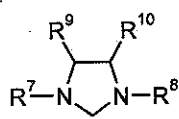


wherein

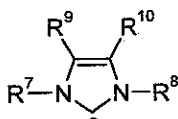
L is $P(R^{11})_3$;

R^{11} is C_{1-6} -alkyl, C_{3-8} -cycloalkyl or aryl;

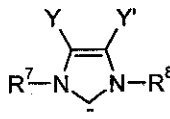
or L is a ligand of formula 7a, 7b, 7c or 7d;



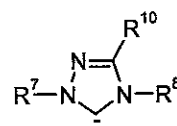
7a



7b



7c



7d

R^7 and R^8 are each independently H, C_{1-6} -alkyl, C_{2-6} -alkenyl or phenyl, wherein the phenyl is optionally substituted with up to three groups independently selected from C_{1-6} -alkyl, O- C_{1-6} -alkyl or halogen;

R^9 and R^{10} are each independently H, C_{1-6} -alkyl, C_{2-6} -alkenyl or phenyl, wherein the phenyl is optionally substituted with up to three groups independently selected from C_{1-6} -alkyl, O- C_{1-6} -alkyl or halogen; or

R^9 and R^{10} together with the carbon atoms to which they are attached are combined to form a carbocyclic 3 to 8 membered ring;

Y and Y' are halogen

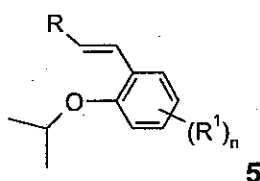
n is an integer from 1 to 3 and

R^1 has the meaning of halogen, NO_2 , C_{1-6} -alkyl, C_{1-6} -haloalkyl, $COOR^a$, SO_2-R^a , $PO(R^a)_2$, O- C_{1-6} -alkyl or aryl, while aryl may optionally be

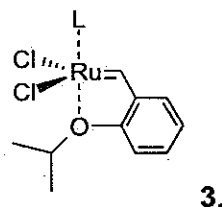
substituted by a group selected from among halogen, C₁₋₆-alkyl and O-C₁₋₆-alkyl; or in the event that n is 1, also CO-R^a;

R^a denotes C₁₋₈-alkyl, C₁₋₈-haloalkyl, C₃₋₆-cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, Br, I, C₁₋₆-alkyl, O-C₁₋₆-alkyl, NO₂, CN, CF₃, OCF₃ or O-C₁₋₆-alkylcarbonyl;

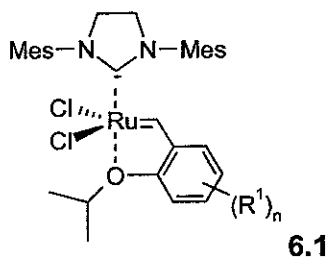
via exchange with a ligand of formula 5



wherein R is C₁₋₆-alkyl or H and R¹ and n has the above given meaning, with compound of formula 3.



According to a second aspect, there is provided a process for manufacturing a compound of formula 6.1



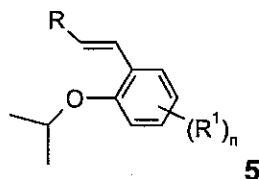
wherein Mes is a mesityl group,

n is an integer from 1 to 3 and

R¹ has the meaning of halogen, NO₂, C₁₋₆-alkyl, C₁₋₆-haloalkyl, COOR^a, SO₂-R^a, PO(R^a)₂, O-C₁₋₆-alkyl or aryl, while aryl may optionally be substituted by a group selected from among halogen, C₁₋₆-alkyl and O-C₁₋₆-alkyl; or in the event that n is 1, also CO-R^a;

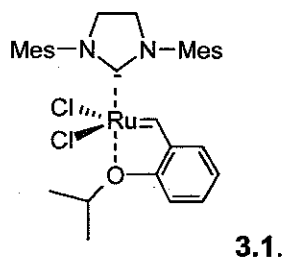
R^a denotes C_{1-8} -alkyl, C_{1-8} -haloalkyl, C_{3-6} -cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, Br, I, C_{1-6} -alkyl, O- C_{1-6} -alkyl, NO_2 , CN, CF_3 , OCF_3 or O- C_{1-6} -alkylcarbonyl;

5 via exchange with a ligand of formula 5



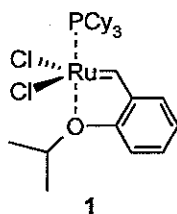
wherein R is CH_3 and R^1 and n has the above given meaning, with compound of formula 3.1.

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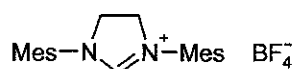


According to a third aspect, there is provided a process as defined above, wherein the compound of formula 3.1 is made from a compound of formula 1

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via exchange of the PCy_3 Ligand with

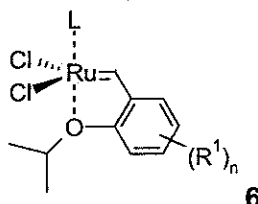


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in the presence of a base and a phosphine scavenger in a suitable solvent.

DESCRIPTION OF THE INVENTION

The instant invention relates to a process for manufacturing a compound of formula 6



5 wherein

L is a neutral ligand,

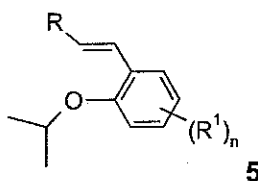
n is an integer from 1 to 3 and

10 R¹ has the meaning of halogen, NO₂, C₁₋₆-alkyl, C₁₋₆-haloalkyl, CO-R^a, COOR^a, SO₂-R^a, PO(R^a)₂, O-C₁₋₆-alkyl or aryl, while aryl may optionally be substituted by a group selected from among halogen, C₁₋₆-alkyl and O-C₁₋₆-alkyl;

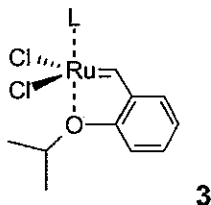
R^a denotes C₁₋₈-alkyl, C₁₋₈-haloalkyl, C₃₋₆-cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, Br, I, C₁₋₆-alkyl, O-C₁₋₆-alkyl, NO₂, CN, CF₃, OCF₃ or O-C₁₋₆-alkylcarbonyl;

15

via exchange with a ligand of formula 5



wherein R is C₁₋₆-alkyl or H and R¹ and n has the above given meaning, with compound of formula 3.



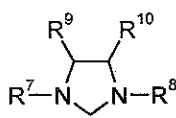
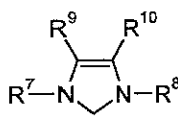
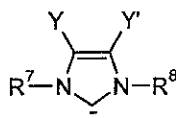
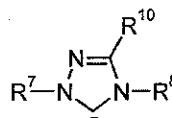
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Preferred is the above process wherein

L is P(R¹¹)₃;

R¹¹ is C₁₋₆-alkyl, C₃₋₆-cycloalkyl or aryl;

or L is a ligand of formula **7a**, **7b**, **7c** or **7d**;

**7a****7b****7c****7d**

- R⁷** and **R⁸** are each independently H, C₁₋₆-alkyl, C₂₋₆-alkenyl or phenyl, wherein the phenyl is optionally substituted with up to three groups independently selected from C₁₋₆-alkyl, O-C₁₋₆-alkyl or halogen;
- R⁹** and **R¹⁰** are each independently H, C₁₋₆-alkyl, C₂₋₆-alkenyl or phenyl, wherein the phenyl is optionally substituted with up to three groups independently selected from C₁₋₆-alkyl, O-C₁₋₆-alkyl or halogen; or
- R⁹** and **R¹⁰** together with the carbon atoms to which they are attached are combined to form a carbocyclic 3 to 8 membered ring;
- Y** and **Y'** are halogen.

Especially preferred is the above process wherein

- R²** is H, -C₁₋₆-alkyl or aryl;
- X** and **X'** are each halogen.

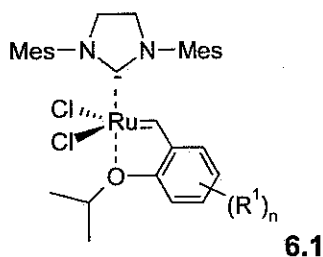
Especially preferred is the above process wherein

- L** is PCy₃ or a ligand of formula **7a**, **7b**, **7c** or **7d**;
- Cy** is cyclohexyl;
- X** and **X'** are each chlorine.

Especially preferred is the above process wherein

- L** is a ligand of formula **7a**, **7b**, **7c** or **7d**; and
- R⁷** and **R⁸** are 2-methylphenyl, 2, 6-dimethylphenyl or 2, 4, 6-trimethylphenyl.

Furthermore preferred is a process for manufacturing a compound of formula **6.1**



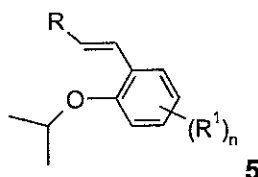
wherein Mes is a mesityl group,

n is an integer from 1 to 3 and

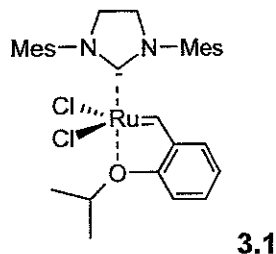
R¹ has the meaning of halogen, NO₂, C₁₋₆-alkyl, C₁₋₆-haloalkyl, CO-R^a, COOR^a, SO₂-R^a, PO(R^a)₂, O-C₁₋₆-alkyl or aryl, while aryl may optionally be substituted by a group selected from among halogen, C₁₋₆-alkyl and O-C₁₋₆-alkyl;

R^a denotes C₁₋₈-alkyl, C₁₋₈-haloalkyl, C₃₋₆-cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, Br, I, C₁₋₆-alkyl, O-C₁₋₆-alkyl, NO₂, CN, CF₃, OCF₃ or O-C₁₋₆-alkylcarbonyl;

via exchange with a ligand of formula 5



wherein R is C₁₋₆-alkyl or H and R¹ and n has the above given meaning, with compound of formula 3.1.



Preferred is the above process wherein

- the temperature during the exchange reaction is below 120°C, preferably below 100°C, most preferably below 80°C.

6/24

- the solvent for the reaction is selected from n-hexane and isomers thereof, n-pentane, petroleum ether, cyclohexane, toluene, benzene and mixtures thereof, preferably toluene.
- the ligand of formula 5 is used in over 3-fold excess compared to the catalyst 3 or 3.1, preferably over 5-fold excess, most preferably over 8-fold excess, in particular between 9 and 11-fold excess.
- the excess of ligand 5 is recycled after the reaction.
- R is CH₃.
- the product is obtained through a sequence of crystallizations from the following solvents: EtOAc, CH₂Cl₂ and methanol.

Especially preferred is the above process wherein the product is obtained through three crystallization steps:

- 1st crystallization from EtOAc,
- 2nd crystallization from CH₂Cl₂,
- 3rd crystallization from methanol.

Preferred is the above process wherein

- n is 1 and
- R¹ has the meaning of halogen, NO₂, CO-R^a, COOR^a, SO₂-R^a, PO(R^a)₂ and

R^a denotes C₁₋₈-alkyl, C₃₋₆-cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, Br, I, C₁₋₆-alkyl, O-C₁₋₆-alkyl, NO₂, CN, CF₃, OCF₃ or O-C₁₋₆-alkylcarbonyl.

In particular preferred is the above process wherein

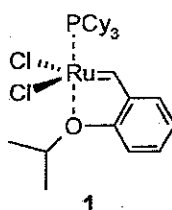
- n is 1 and
- R¹ has the meaning of NO₂.

Also preferred is the above

- n is 1 and
- R¹ has the meaning of CO-R^a, COOR^a, SO₂-R^a, PO(R^a)₂ and

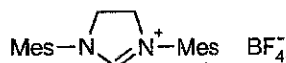
R^a denotes C_{1-8} -alkyl, C_{3-6} -cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, C_{1-6} -alkyl, O- C_{1-6} -alkyl or CF_3 .

- 5 Furthermore preferred is the above process wherein the compound of formula **3.1** is made from a compound of formula **1**



via exchange of the PCy_3 Ligand with

10



in the presence of a base and a phosphine scavenger in a suitable solvent.

- 15 Preferred is the above process wherein
- the base is potassium tert-pentanoate or a homologue thereof (e.g. potassium tert-hexanoate).
 - the phosphine scavenger is $CuCl$.
 - the solvent is selected from n-hexane and isomers thereof, n-pentane, petroleum
 - 20 ether, cyclohexane, toluene, benzene and mixtures thereof, preferably n-hexane
 - the crude reaction product is purified by crystallisation from methanol.

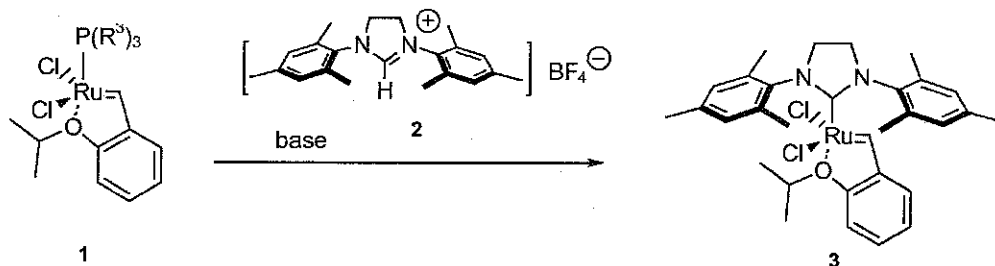
Also preferred is the use of a reaction product of formula **6** or **6.1** from a process according to claims 1-18 as a catalyst for metathesis reactions.

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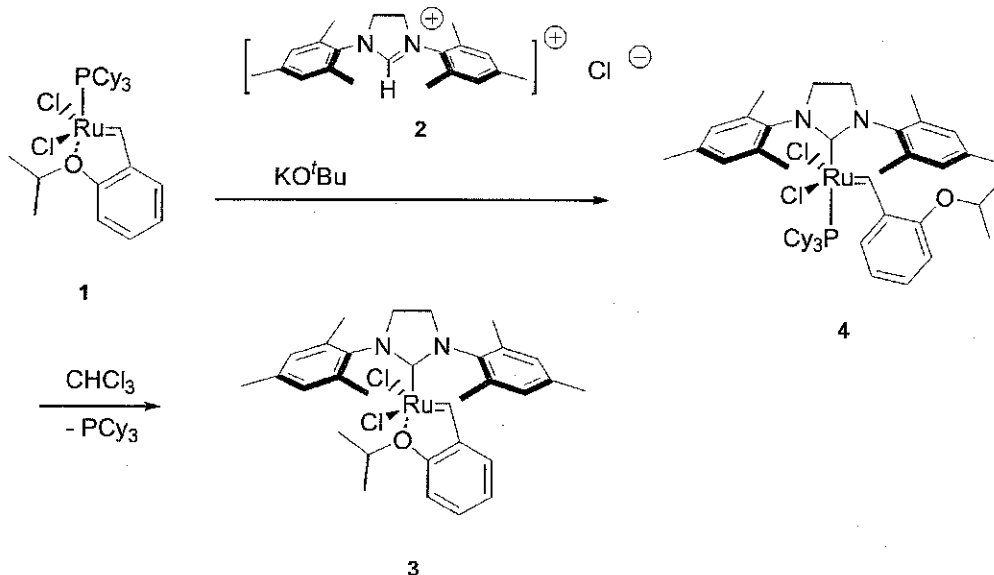
8/24

DETAILED DESCRIPTION OF THE INVENTION

One possible starting material for this preparation is a Hoveyda-Grubbs 2nd generation catalysts of formula 3 and can be synthesized i.e. in high yield (98-92%) from Hoveyda-Grubbs 1st generation catalysts of formula 1 (R = Cy, R¹ as defined below) and SIMES
 5 carbene precursor 2 under carefully optimized conditions.



A similar process using 1 (R³ = Ph, R¹ = H) as a starting material has been previously described by Hoveyda et al as being low efficient [Steven B. Garber, Jason S. Kingsbury, Brian L. Gray, and Amir H. Hoveyda J. Am. Chem. Soc. **2000**, 122, 8168-8179]. Blechert
 10 has reported a more successful two step preparation of 3 from 1 (R = Cy) in 75% yield [Simon Gessler, Stefan Randl and Siegfried Blechert Tetrahedron Letters **2000**, 41, 9973-9976]. Treatment of 1 with 1.2 equiv. of SIMES x HCl and 1.2 equiv. KO^tBu in THF / toluene at 80°C leads first to the formation of a intermediate 4 still bearing the PCy₃
 15 moiety.



9/24

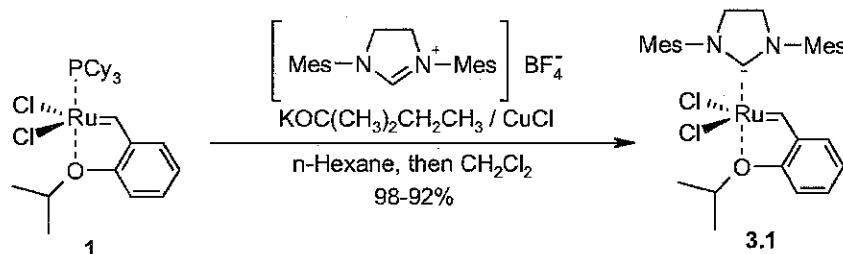
Compound **4** was isolated and was fully characterized by Blechert. Formation of the desired complex was achieved by stirring of **4** at room temperature in CHCl_3 for two hours. The final product **3** was separated from the liberated phosphine and decomposition products by flash chromatography using CH_2Cl_2 as the eluent.

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In the present invention a less polar solvent, e.g. n-hexane and isomers thereof, n-pentane, petroleum ether, cyclohexane, toluene, benzene and mixtures thereof and a more soluble base: potassium tert-pentanoate and homologues (e.g. potassium tert-hexanoate) was used. Instead of CHCl_3 solid CuCl was selected as a more effective phosphine scavenger. These modifications in which the reaction is close to heterogeneous conditions allows to develop a high-yielding one-pot process.

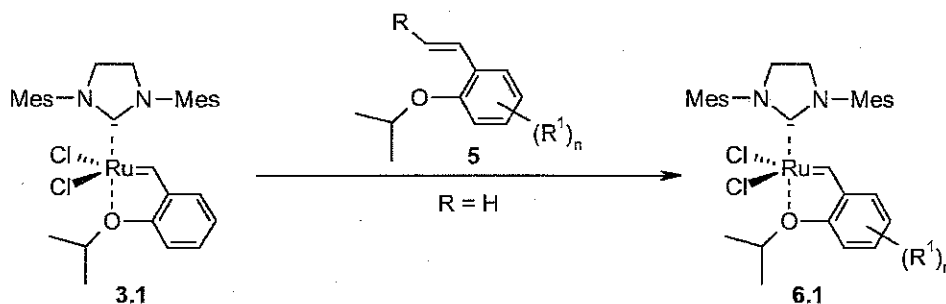
In addition, the unexpected observation that the ruthenium-containing, highly coloured reaction by-products are soluble in methanol allows to purify the crude reaction mixture by simple crystallization without need to use tedious chromatographic separation. As a result complex **3.1** can be straightforwardly obtained in a multi gram scale in a high yield (98-92%).

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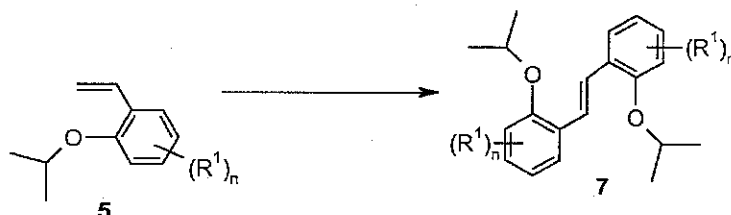
Next step requires the replacement of the good chelating 2-isopropoxybenzylidene fragment in **3.1** with the less chelating 5-nitro-2-isopropoxybenzylidene ligand **5**. The synthesis of **5** is known i. e. from WO 2004-035596.

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10/24

A model experiment showed that the 2-isopropoxybenzylidene ligand bonds to ruthenium ca. 7 times stronger than 5-nitro-2-isopropoxybenzylidene. In order to shift this equilibrium an excess of styrene **5** has to be used. Another problem related to this step is fast homo-dimerisation of styrene **5** to the stilbene **7**.



Stilbene **7** cannot react further with catalysts of formula **3** or **3.1** to generate **6** or **6.1**, therefore its formation inhibits the reaction and decreases yield of the final product.

Separation of the crystalline stilbene by-product **7** is also difficult from the practical point of view.

After detailed optimization it was found that the corresponding 1-isopropoxy-4-nitro-2-[prop-1-en-1-yl]benzene **5** ($R = CH_3$) undergoes much slower dimerization, while it still can be used for the exchange reaction. The 10-fold excess of **5** ($R = CH_3$) gives best results allowing conversion of the 80-90% of the Hoveyda-Grubbs catalyst. The remaining unreacted **3** or **3.1** can be separated and recycled. Use of smaller excess of the ligand **5** is possible, but leads to lower conversions. For example in test exchange reactions with 5 equivalents of **5** the isolated yield of **6.1** was 45-47% instead of ca. 60% obtained typically with 10 equivalents.

Initially it was found that at a temperature about 120 - 80°C the ligand exchange reaction is easier to be controlled and gives reproducible yields of nitro-Hoveyda 2nd generation catalyst **6**, being in a range of 55-70%. The crucial parameter for a successful transformation is the time of the exchange reaction, which has to be in a range 15-25 min. Prolongated heating leads to formation of larger quantities of **7**. Under these conditions the homo-dimerization of **5** is minimized and not exceeds 35% of the starting amount of **5** used. The rest of 1-isopropoxy-4-nitro-2-[prop-1-en-1-yl]benzene **5** can be recovered after the reaction and recycled. Suitable solvents for this reaction are aliphatic and aromatic

hydrocarbons (hexane and isomers thereof, n-pentane, petroleum ether, cyclohexane benzene, toluene) and mixtures thereof, preferentially toluene.

The crude reaction mixture after the ligand exchange step, consists of the nitro-Hoveyda catalysts (**6**), small amounts of unreacted Hoveyda-Grubbs 2nd generation catalysts (**3**), large amount of unreacted ligand (**5**), stilbene (**7**) and some minor byproducts and tars. In order to avoid chromatographic techniques in isolation of product **6** from this complicated mixture the product is purified by crystallization from the crude mixture by the following sequence of crystallizations:

10

- Crystallization from EtOAc to remove the unreacted ligand **5** and catalyst **3**
- Crystallization from CH₂Cl₂ to remove stilbene **7** (repeated if necessary).
- Crystallization from methanol to remove remaining stilbene **7** and unreacted **3**.

These steps can be repeated if necessary until product of a final purity of at least 95% is obtained. Composition of samples after each crystallization step can be conveniently checked by ¹H NMR. Characteristic NMR signals are as follow:

- Stilbene **7**, 2H (CH=CH): 7.49 ppm;
- 20 • Nitro-Hoveyda **6**, 1H (CH=Ru): 16.46 ppm;
- Hoveyda-Grubbs **3**, 1H (CH=Ru): 16.56 ppm.

The filtrate after first crystallization from EtOAc contains mainly unreacted ligand **5**, smaller amounts of **3**, **6**, and some amounts of **7** and undefined products of decomposition (tars).

The undefined products of decomposition (tars) can be easily separated by filtration through a short pad of silica-gel. In a large scale preparation (10 g) i.e. a column of diameter 12 cm and gel was loaded at 9 cm high. The column was eluted gravitationally with 5% to 20% v/v of ethyl acetate in c-hexane. The first fraction contained pure ligand **5**, then a mixture of **5**, ruthenium complexes **3**, **6** and some amount of stilbene **7** was collected. From this fraction additional amounts of nitro-catalyst **6** can be easily obtained by crystallization. Regenerated ligand **5** (combined from the first fraction and filtrates after crystallization of the second fraction) can be successfully used in preparation of next

12/24

batches of the catalysts, with the same efficiency as the freshly prepared **5**. There is no need to separate the small amounts of Grubbs-Hoveyda catalyst **3** from the ligand **5**, as it is also a starting material for the exchange reaction.

5 **Summary** - The first step proceeds very smoothly, giving product **3** in high yield with practically no other by-products. The mass balance after second step is more interesting. Starting from 19.6 g of **3** and 69.6 g of the ligand **5** obtained 13.1 g of the product **6** (60% of yield) and 21.0 g (35% of yield) of stilbene **7** are obtained. In addition it is possible to regenerate in total 36.4 g (52% of starting amount) of ligand **5** and 2.6 g (13%) of starting
10 Hoveyda-Grubbs complex **3** (as a mixture with **5**). In a summary, using the above described preparation one is able to obtain in one batch 13.35 g of the Nitro-Hoveyda 2nd generation catalyst **6** (97% acc. to NMR). The total yield of the pure Nitro-Hoveyda 2nd generation catalyst is 55% after two steps.

15

USED TERMS AND DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the
20 specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to. Unless otherwise specified below, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups. The term "substituted" as used herein, means that any one or more hydrogens on the designated atom is
25 replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound.

The term "C₁₋₆-alkyl" as used herein, either alone or in combination with another substituent, means acyclic, straight or branched chain alkyl substituents containing from
30 one to six carbon atoms and includes, for example, methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl.

The term "C₂₋₆-alkenyl" as used herein, either alone or in combination with another substituent, means acyclic, straight or branched chain alkenyl substituents containing from

one to six carbon atoms and at least one double bond. For example ethenyl, propenyl, butenyl, hexenyl, 1-methylethenyl, 1-methylpropenyl, 2-methylpropenyl or 1,1-dimethylethenyl.

- 5 The term "C₁₋₆-haloalkyl" as used herein, either alone or in combination with another substituent, means acyclic, straight or branched chain alkyl substituents containing up to six carbon atoms having one or more hydrogens substituted for a halogen selected from bromo, chloro, fluoro or iodo, preferably fluoro. Preferably the term C₁₋₆-haloalkyl represents -C₁₋₆-fluoroalkyl such as trifluoromethyl, 2,2,2-trifluoroethyl or perfluoroethyl.

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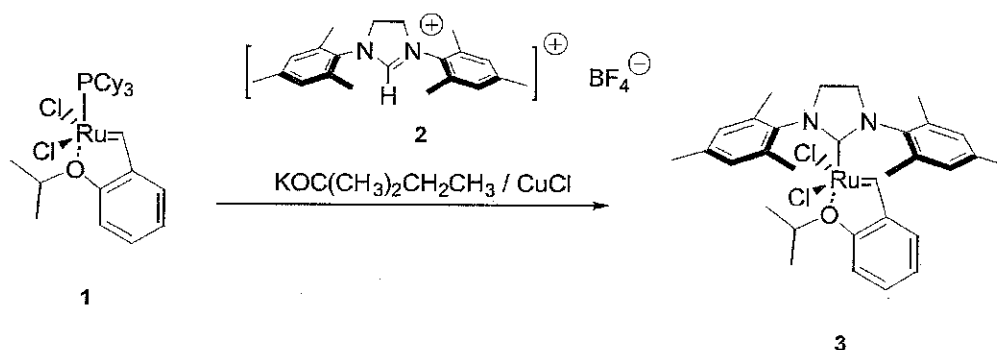
The term "C₃₋₈-cycloalkyl" as used herein, either alone or in combination with another substituent, means a cycloalkyl substituent containing from three to six carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

- 15 The term "aryl" as used herein, either alone or in combination with another substituent, means either an aromatic monocyclic system or aromatic polycyclic systems containing carbon atoms. For example, aryl includes a phenyl or a naphthyl ring system, wherein aryl means generally an aromatic system, for example phenyl.

- 20 The term "halogen" as used herein means a halogen substituent selected from fluoro, chloro, bromo or iodo.

EXAMPLE - STEP I

25



Materials:

- Hoveyda-Grubbs 1st generation **1** (Boehringer Ingelheim)
- SIMES x HBF₄ **2** (freshly prepared)
- Potassium tert-amylate (1.7 M solution in toluene, Fluka)
- 5 • Copper (I) chloride (Aldrich)
- n-Hexane (dried with CaH₂ and distilled under Ar)
- Ethyle Acetate (p.a.)
- c-Hexane (p.a.)
- Methanol(p.a.)
- 10 • Dichloromethane (p.a.)
- Celite (Fluka)

Procedure I

15

1.I. Preparation

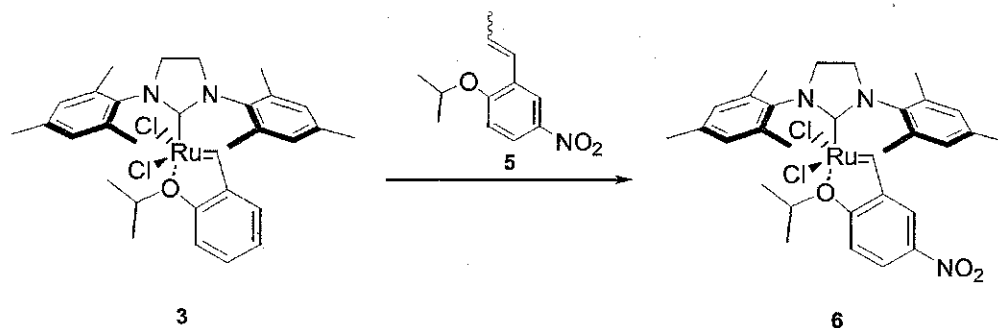
A dry, 1000-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum and an argon inlet. The flask is charged under an argon atmosphere with a solid SIMES x HBF₄ **2** (35.28 mmol, 13.9 g) and dry n-hexane (400 mL). A solution
20 of potassium tert-amylate (21.6 mL, 36.75 mmol) is added from a syringe and the resulting mixture is stirred under argon at room temperature for 1 h. To the resulted solution a solid Hoveyda-Grubbs 1st generation catalyst **1** (29.4 mmol, 17.6 g) is added in one portion. The flask is equipped with a reflux condenser with an argon inlet at the top and the reaction mixture is refluxed for 2 h. The contents of the flask are cooled to room
25 temperature and solid CuCl (51.45 mmol, 5.1 g) is added slowly in three portions and the resulting mixture is refluxed for 2 h. From this point forth, all manipulations are carried out in air.

1.II. Isolation of the product by crystallization

30 The reaction mixture is evaporated to dryness and re-dissolved in ethyl acetate (200 mL). The solution is filtrated through a Buchner funnel with glass frit filled with Celite and then concentrated in vacuo. The residue is dissolved in ambient temp. 1:10 v/v mixture of CH₂Cl₂ and methanol (220 mL). After concentration to ca. ¼ of the initial volume using a

rotary evaporator (room temperature) crystals are precipitated. These crystals are filtered-off on a Buchner funnel with glass frit. The crystals are washed twice with small portions of CH₃OH (~20 mL), and dried in vacuo to give pure Hoveyda 2nd catalysts **3** (25.3 mmol, 15.81 g). The filtrate after crystallization is evaporated to dryness and crystallized
 5 for the second time from CH₂Cl₂ and methanol using the same protocol giving an additional crop of pure Hoveyda 2nd generation catalyst (1.7 mmol, 1.08 g). The total yield of pure Hoveyda-Grubbs 2nd generation catalyst **3** is 92% (27.0 mmol, 16.9 g).

10 EXAMPLE - STEP II



Materials:

- 15 "Ligand" 1-isopropoxy-4-nitro-2-[prop1-en-1-yl]benzene **5** (E:Z mixture 1:1)
 Hoveyda-Grubbs 2nd catalyst **3** (prepared previously)
 Toluene (distilled over Na, stored under Ar)
 Ethyl acetate (p.a.)
 Methanol (p.a.)
 20 Dichloromethane (p.a.)
 c-Hexane (p.a.)
 Silicagel 60 (230-400 mesh; Merck)

Procedure II

25

2.1. The ligand exchange

A dry one-necked round-bottomed 1L flask is equipped with a magnetic stirring bar, rubber septum and argon inlet. The flask is charged under argon with the ligand **5** (1-

isopropoxy-4-nitro-2-[prop-1-en-1-yl]benzene) (0.314 mol, 69.57 g) and dry toluene (450 mL). To the solution catalyst **3** (31.28 mmol, 19.60 g) is added in one portion at 80 °C and stirred at 80 °C for 20 min. After this time TLC analysis [Silica gel GF₂₅₄ TLC plates (Merck), eluent: 20% v/v of ethyl acetate in c-hexane] indicates the formation of a new green spot of the product. The ratio of the area of green spots of Hoveyda-Grubbs 2nd **3** and Nitro-catalyst **6** should be ~1:3 according to TLC and at this point reaction is stopped. The content of the flask is cooled in ice-bath to room temperature. From this point forth, all manipulations are carried out in air.

10 2.II. Isolation of the product by crystallization

The reaction mixture is evaporated without heating to dryness. The resulting viscous oil is dissolved in cold EtOAc (200 mL). The solution is then cooled in a freezer (-30 °C) for 45 min. After this time the cold solution is filtrated through a Buchner funnel with glass frit. The filtrate (FILTRATE I) is kept for regeneration of ligand **5** (see 2.III). The solid collected on a filter, being a mixture of stilbene and Nitro 2nd generation catalyst, is then dissolved in refluxing CH₂Cl₂ (~200 mL) until a homogeneous solution is formed. Then the obtained solution is cooled in a freezer (-30 °C) for 30 min. After this time a mixture of crystals precipitates. These crystals are filtered-off on a Buchner funnel with glass frit and washed with cold ethyl acetate until only yellow solid (30.69 mmol, 11.86 g, stilbene) left on Buchner funnel. The filtrate is evaporated to dryness and then it is re-dissolved as before in a minimal amount of CH₂Cl₂ until homogeneous solution is obtained. To this solution methanol is added in a volume three times greater than the volume of CH₂Cl₂ used. The solution is concentrated using a rotary evaporator until crystals precipitated (approximately half of the initial volume of solvent must be evaporated). The solution is decanted to the round bottom flask and the crystals are collected on a Buchner funnel with glass frit. The crystals are washed once with small portion of methanol (~30 mL), and next with the minimal small amount of ethyl acetate (~20 mL) and dried in vacuum to give the first crop of pure catalyst **6** (11.98 mmol, 8.05 g). The filtrate and the methanol solution from decantation are combined and evaporated to dryness. The residue is dissolved in refluxed CH₂Cl₂ until homogeneous solution is obtained and the above described crystallizations sequence (2.II.A to 2.II.C) is repeated to give the second crop of pure catalyst **6** (4.04 mmol, 2.72 g). The third crop of Hoveyda catalyst is obtained from the filtrate (FILTRATE I) after crystallization of the crude reaction mixture from ethyl acetate (see bellow).

2.III. Regeneration of the ligand for further recycling

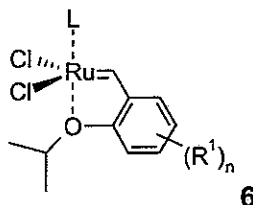
The filtrate (FILTRATE I) after crystallization of the crude reaction mixture from ethyl acetate is evaporated to dryness and passed through a short pad of silica gel. Two
5 fractions are obtained: the first fraction (FRACTION I) giving after evaporation a yellow oil (22.15 g) and the second one (FRACTION II) giving a green oil (28.6 g). The second fraction is collected until the colour of eluent changed from green to brown. The second fraction is concentrated to dryness in vacuo and dissolved in CH_2Cl_2 . Then methanol (in a volume three times greater than the volume of CH_2Cl_2 used) is added to the resulted
10 homogeneous solution. The solution is concentrated using a rotary evaporator until green crystals precipitated (approximately half of the initial volume of solvent is evaporated). These crystals are collected on a Buchner funnel with glass frit and then washed once with a small portion of methanol (~20 mL). Obtained crystals are re-dissolved in refluxed CH_2Cl_2 until homogeneous solution is obtained and the procedure of crystallization (2.II.C
15 to 2.II.D) is repeated to give the third crop of the Nitro-catalyst (3.85 mmol, 2.58 g). Finally three crops of the Nitro-Hoveyda 2nd generation catalyst are combined (19.87 mmol, 13.35 g) and subjected to final precipitation from CH_2Cl_2 / MeOH. The obtained green crystals are dried under vacuum. The total yield of the pure (97% acc. to NMR) Nitro-Hoveyda 2nd generation catalyst is 60% (19.45 mmol, 13.06 g).

20

The first fraction (FRACTION I) after silica gel filtration and filtrates after crystallization of the second fraction (FRACTION II) can be combined and recycled in next preparations of the catalyst.

WHAT WE CLAIM

1. A process for manufacturing a compound of formula 6

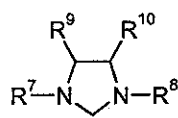


wherein

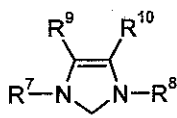
L is $P(R^{11})_3$;

R^{11} is C_{1-6} -alkyl, C_{3-8} -cycloalkyl or aryl;

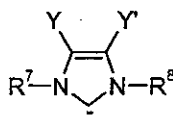
or L is a ligand of formula **7a**, **7b**, **7c** or **7d**;



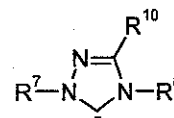
7a



7b



7c



7d

R^7 and R^8 are each independently H, C_{1-6} -alkyl, C_{2-6} -alkenyl or phenyl, wherein the phenyl is optionally substituted with up to three groups independently selected from C_{1-6} -alkyl, O- C_{1-6} -alkyl or halogen;

R^9 and R^{10} are each independently H, C_{1-6} -alkyl, C_{2-6} -alkenyl or phenyl, wherein the phenyl is optionally substituted with up to three groups independently selected from C_{1-6} -alkyl, O- C_{1-6} -alkyl or halogen; or

R^9 and R^{10} together with the carbon atoms to which they are attached are combined to form a carbocyclic 3 to 8 membered ring;

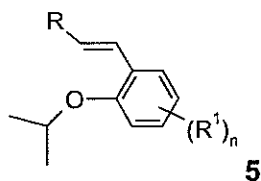
Y and Y' are halogen

n is an integer from 1 to 3 and

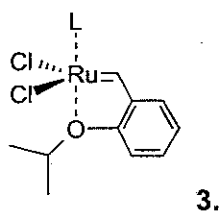
R^1 has the meaning of halogen, NO_2 , C_{1-6} -alkyl, C_{1-6} -haloalkyl, $COOR^a$, SO_2-R^a , $PO(R^a)_2$, O- C_{1-6} -alkyl or aryl, while aryl may optionally be substituted by a group selected from among halogen, C_{1-6} -alkyl and O- C_{1-6} -alkyl; or in the event that n is 1, also CO- R^a ;

R^a denotes C_{1-6} -alkyl, C_{1-6} -haloalkyl, C_{3-6} -cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, Br, I, C_{1-6} -alkyl, O- C_{1-6} -alkyl, NO_2 , CN, CF_3 , OCF_3 or O- C_{1-6} -alkylcarbonyl;

via exchange with a ligand of formula 5



wherein R is CH_3 and R^1 and n has the above given meaning, with compound of formula 3.



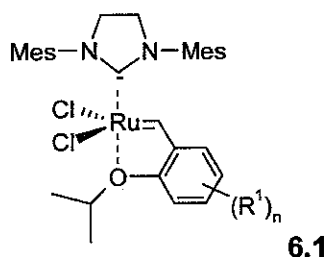
2. A process according to claim 1 wherein
R² is H, -C₁₋₆-alkyl or aryl;
X and X' are each halogen.

3. A process according to claims 1-2 wherein
L is PCy₃ or a ligand of formula **7a**, **7b**, **7c** or **7d**;
Cy is cyclohexyl;
X and X' are each chlorine.

4. A process according to claims 1-3 wherein
L is a ligand of formula **7a**, **7b**, **7c** or **7d**; and

R^7 and R^8 are 2-methylphenyl, 2, 6-dimethylphenyl or 2, 4, 6-trimethylphenyl.

5. A process for manufacturing a compound of formula 6.1



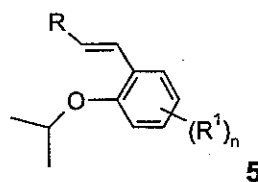
wherein Mes is a mesityl group,

n is an integer from 1 to 3 and

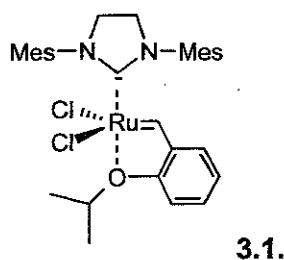
R^1 has the meaning of halogen, NO_2 , C_{1-6} -alkyl, C_{1-6} -haloalkyl, COOR^a , SO_2R^a , $\text{PO}(\text{R}^a)_2$, O-C_{1-6} -alkyl or aryl, while aryl may optionally be substituted by a group selected from among halogen, C_{1-6} -alkyl and O-C_{1-6} -alkyl; or in the event that n is 1, also CO-R^a ;

R^a denotes C_{1-8} -alkyl, C_{1-8} -haloalkyl, C_{3-6} -cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, Br, I, C_{1-6} -alkyl, O-C_{1-6} -alkyl, NO_2 , CN, CF_3 , OCF_3 or O-C_{1-6} -alkylcarbonyl;

via exchange with a ligand of formula 5



wherein R is CH_3 and R^1 and n has the above given meaning, with compound of formula 3.1.



6. A process according to claims 1 to 5, wherein the temperature during the exchange reaction is below 120°C.
7. A process according to claims 1 to 6, wherein the ligand of formula 5 is used in over 3-fold excess compared to the catalyst 3 or 3.1.
8. A process according to claims 1 to 7, wherein the product is obtained through a sequence of crystallizations from the following solvents: EtOAc, CH₂Cl₂ and methanol.
9. A process according to claims 1 to 8 wherein the excess of ligand 5 is recycled after the reaction.
10. A process according to claims 1 to 9 wherein

n is 1 and

R¹ has the meaning of halogen, NO₂, CO-R^a, COOR^a, SO₂-R^a, PO(R^a)₂ and

R^a denotes C₁₋₈-alkyl, C₃₋₆-cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, Br, I, C₁₋₆-alkyl, O-C₁₋₆-alkyl, NO₂, CN, CF₃, OCF₃ or O-C₁₋₆-alkylcarbonyl.
11. A process according to claims 1 to 10 wherein

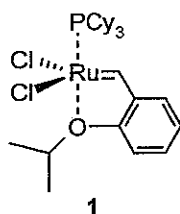
n is 1 and

R¹ has the meaning of NO₂.

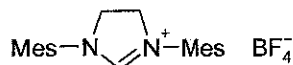
12. A process according to claims 1 to 10 wherein
 n is 1 and
 R^1 has the meaning of CO-R^a , COOR^a , $\text{SO}_2\text{-R}^a$, $\text{PO(R}^a)_2$ and

R^a denotes C_{1-8} -alkyl, C_{3-6} -cycloalkyl or aryl, optionally substituted by a group selected from among F, Cl, C_{1-6} -alkyl, O-C_{1-6} -alkyl or CF_3 .

13. A process according to one of the claims 5 to 12, wherein the compound of formula 3.1 is made from a compound of formula 1



via exchange of the PCy_3 Ligand with



in the presence of a base and a phosphine scavenger in a suitable solvent.

14. A process according to claim 13 wherein the base is potassium tert-pentanoate or potassium tert-hexanoate.
15. A process according to claims 13 or 14 wherein the phosphine scavenger is CuCl .

16. A process according to claims 13 to 15 wherein the solvent is selected from n-hexane and isomers thereof, n-pentane, petroleum ether, cyclohexane, toluene, benzene and mixtures thereof, preferably n-hexane
17. A process according to claims 13 to 16 wherein the crude reaction product is purified by crystallisation from methanol.