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(71) Applicant: **DSM IP ASSETS B.V.** [NL/NL]; Het Overloon 1, 6411 TE HEERLEN (NL).

(72) Inventors: **BONRATH, Werner**; DSM Nutritional Products Ltd, c/o Patent Department Wurmisweg 576, 4303 Kaiseraugst (CH). **BOURGEOIS, Frederic**; Universität Basel, c/o Department of Chemistry St. Johannis-Ring 19, 4056 Basel (CH). **MEDLOCK, Jonathan, Alan**; DSM Nutritional Products Ltd, c/o Patent Department Wurmisweg 576, 4303 Kaiseraugst (CH). **SPARR, Christof**; Universität Basel, c/o Department of Chemistry St. Johannis-Ring 19, 4056 Basel (CH).

(74) Agent: **KURT, Manfred**; DSM Nutritional Products Ltd, Patent Department, Wurmisweg 576, 4303 Kaiseraugst (CH).

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(54) Title: NEW TRANSITION METAL CATALYST

(57) Abstract: The present invention relates to specific transition metal catalysts and their use in chemical reactions.



New Transition Metal Catalyst

The present invention relates to specific transition metal catalysts and their use in chemical reactions.

5

In the field of chemical reactions and chemical production processes, catalysts are used to speed up reactions and improve the reaction selectivity by accelerating specific transformations. This allows reactions to take place under milder reaction conditions, resulting in higher yields and selectivities and lower amounts of waste. Within the field of homogeneous catalysis, combinations of transition metal and organic ligands can be used for many transformations resulting in good selectivities.

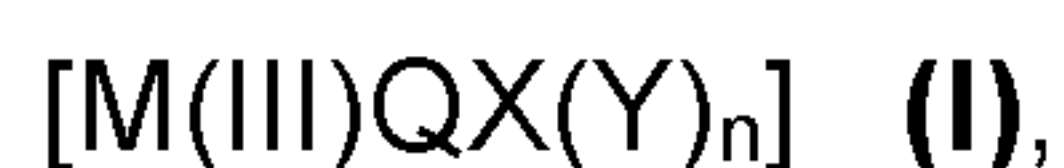
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Despite their applicability, homogeneous catalysts can be quickly deactivated, meaning that relatively high loadings of catalyst are required. Therefore there is always the need for novel catalysts that perform with higher selectivity and activity at lower loadings.

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Therefore the present invention relates to new transition metal catalysts (C), which are organo-metallic catalysts of the following formula:

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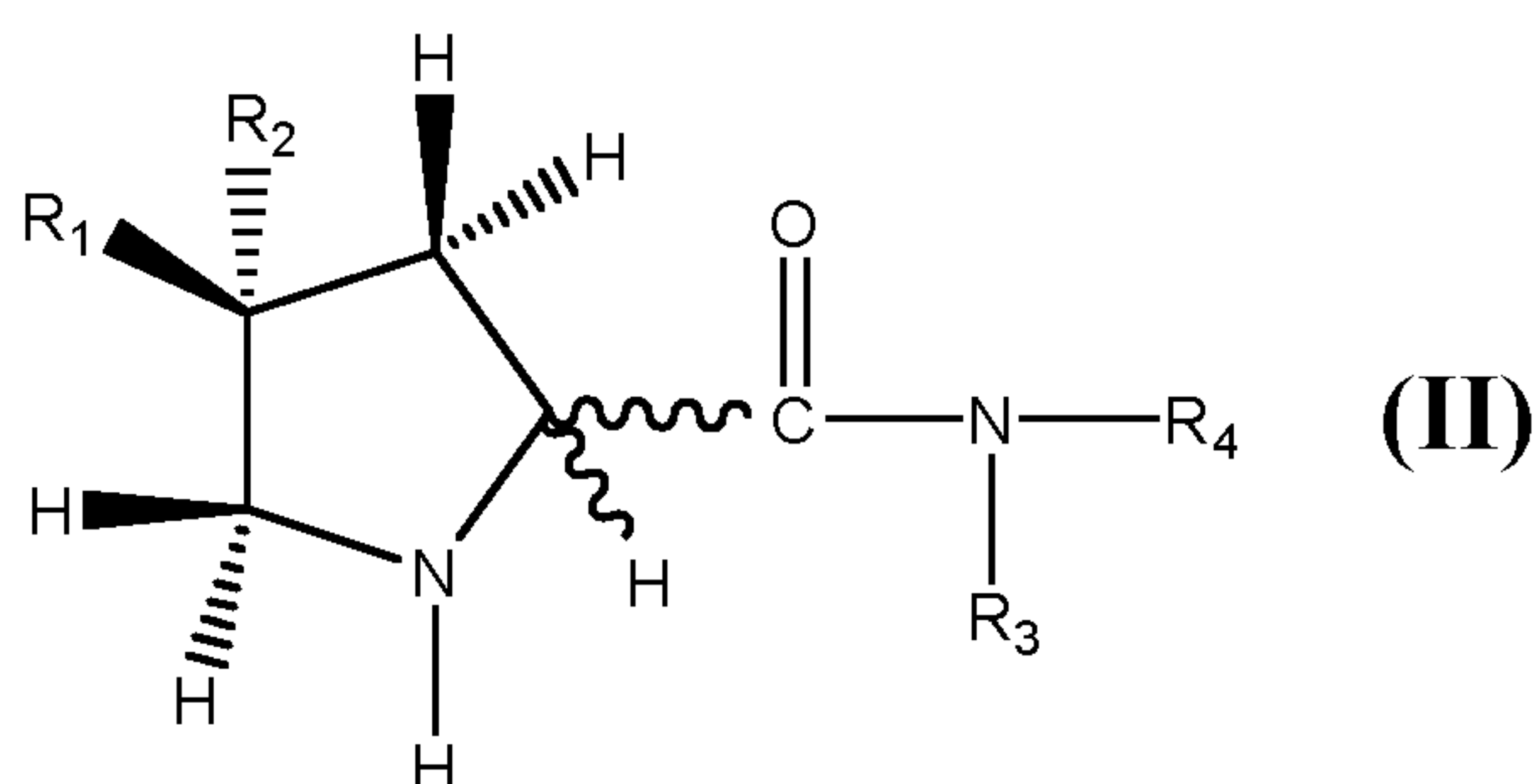
wherein

M is a transition metal chosen from the list of Ru, Rh and Ir, preferably Ir

25

Q is the ligand L or an anion of the ligand L, wherein

the ligand L has the following formula (II)



wherein

- 2 -

R_1 is H, CH_3 or OH,

R_2 is H, CH_3 or OH,

R_3 is H or CH_3

R_4 is a C_2 - C_4 alkyl group, which is substituted by at least one OH group and which is optionally further substituted,

with the provisos that

when R_1 is OH or CH_3 , then R_2 is H and

when R_2 is OH or CH_3 , then R_1 is H, and

X is cyclopentadienyl, or a substituted cyclopentadienyl group, preferably indenyl or pentamethylcyclopentadienyl, and

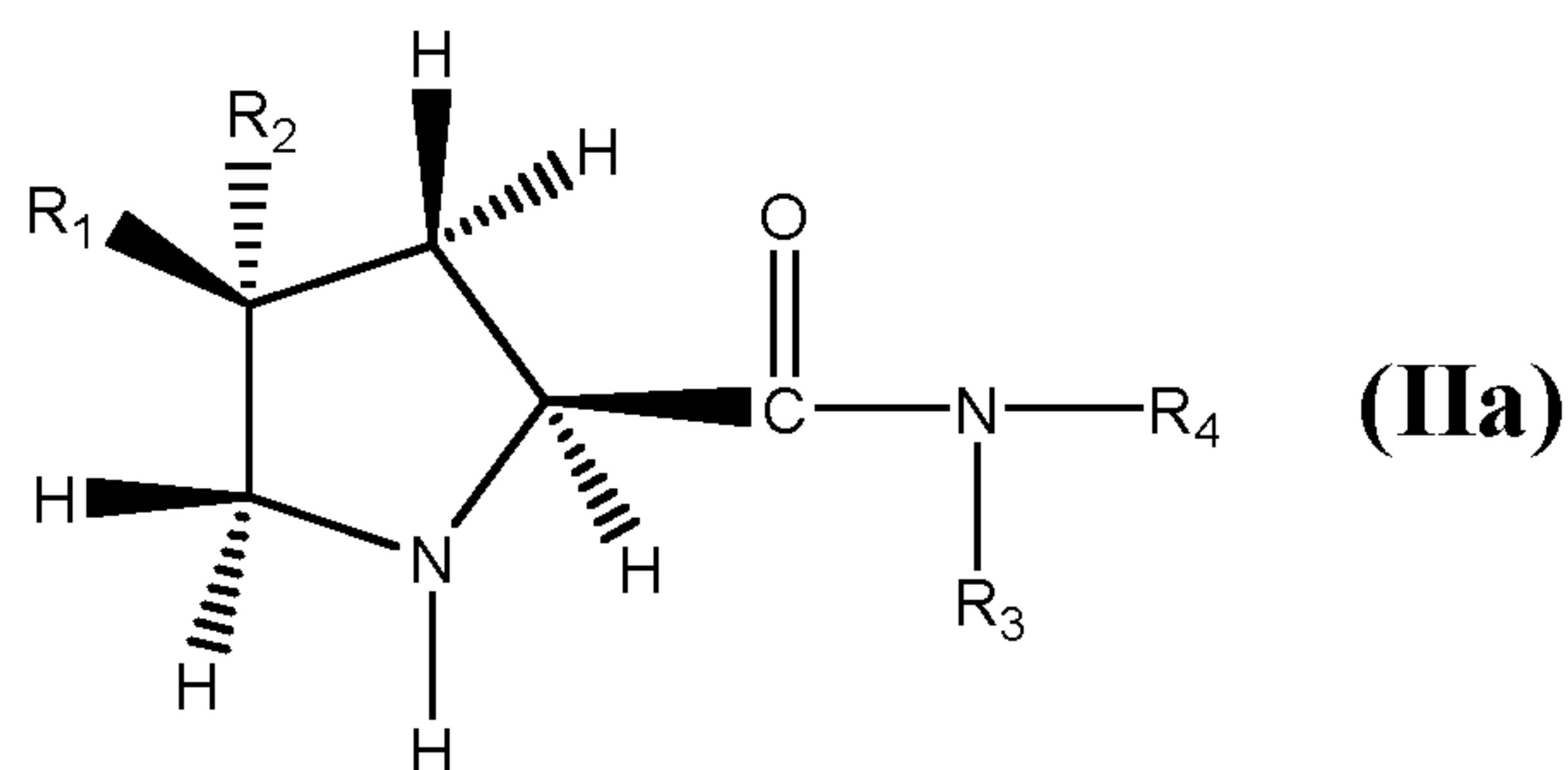
Y is an anion and n is 1 or 2, with the proviso that the value of n is chosen such that the overall metal complex is a neutral species.

The new catalyst according to the present invention can be used in a variety of chemical reactions.

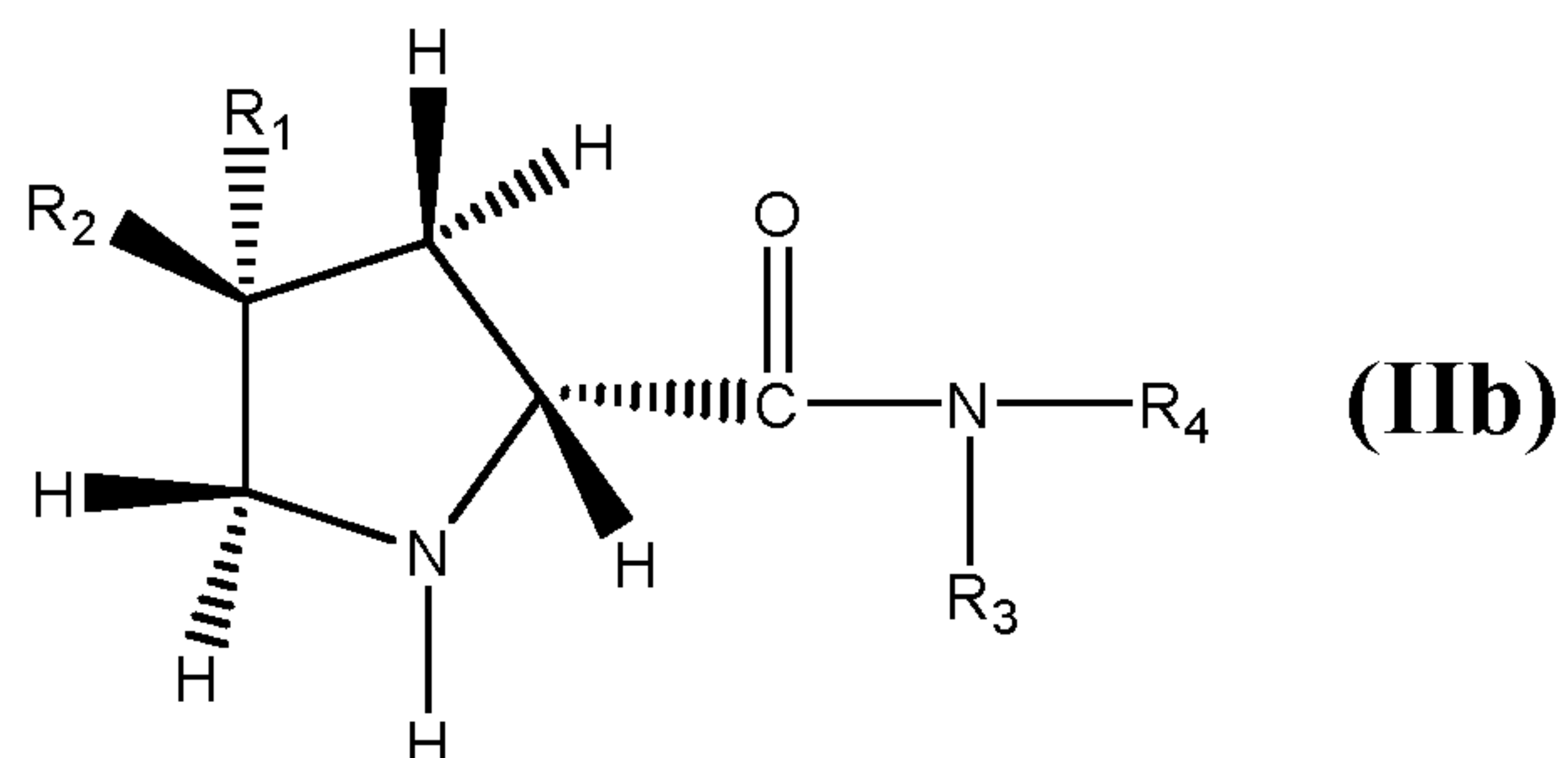
As stated above, Q is either the neutral ligand L or an anion of the ligand L. The anion of the ligand L can be prepared by deprotonation of the ligand L before complexing with the transition metal atom M to form complex C; or the anion of ligand L can be formed during the complexation to the transition metal atom M to form complex C.

Therefore, the present invention relates to new transition metal catalysts (C1), which are catalyst (C), wherein M is Ir.

The ligand of formula (II) has the following two enantiomeric forms. These are the following ligands of formula (IIa) and (IIb):



- 3 -

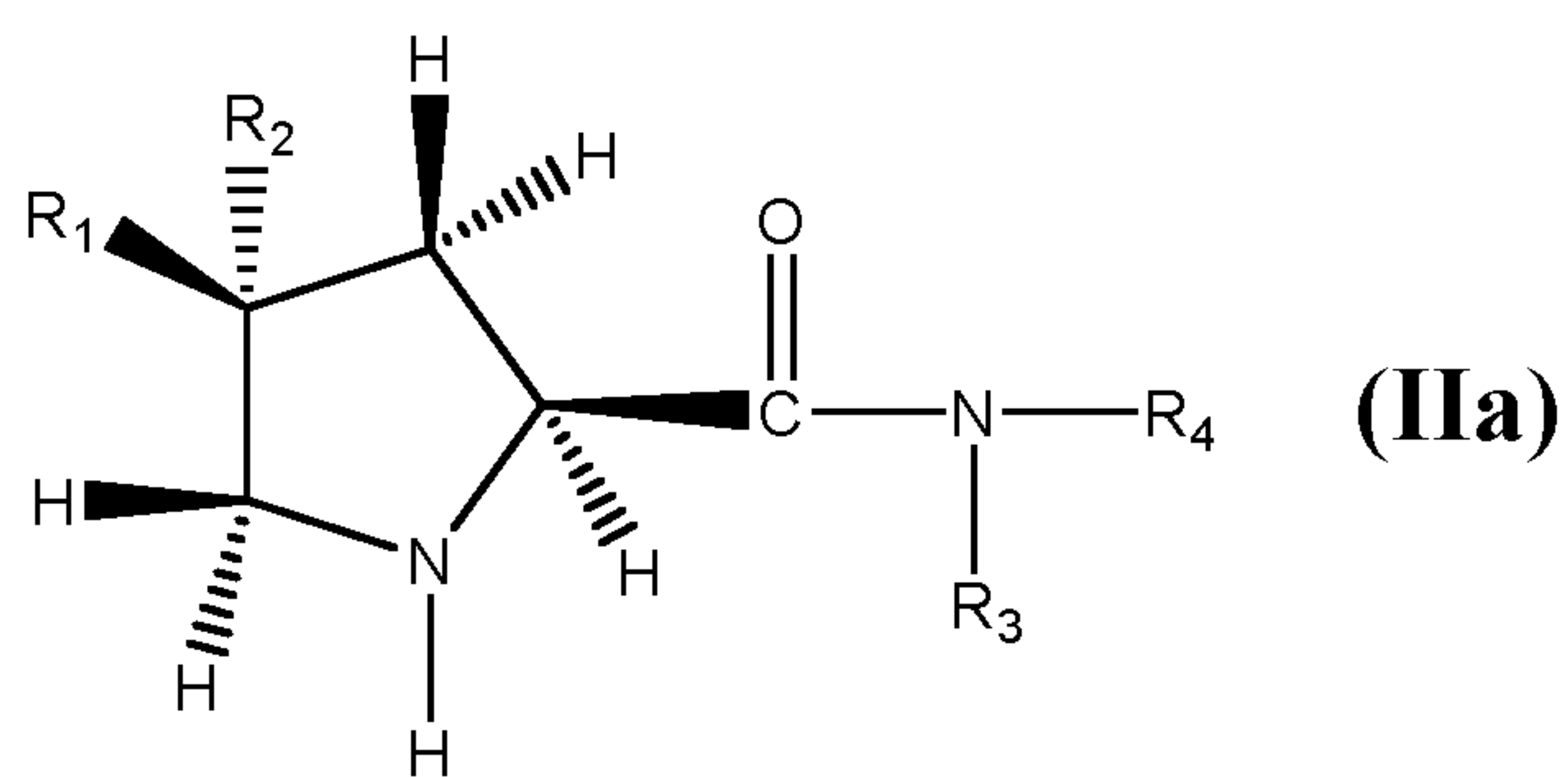


wherein

the substituents have the same meanings as for the compound of formula (I).

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Therefore, the present invention relates to new catalysts (C2), which are transition metal catalysts (C) or (C1), wherein L is a ligand of formula (IIa)

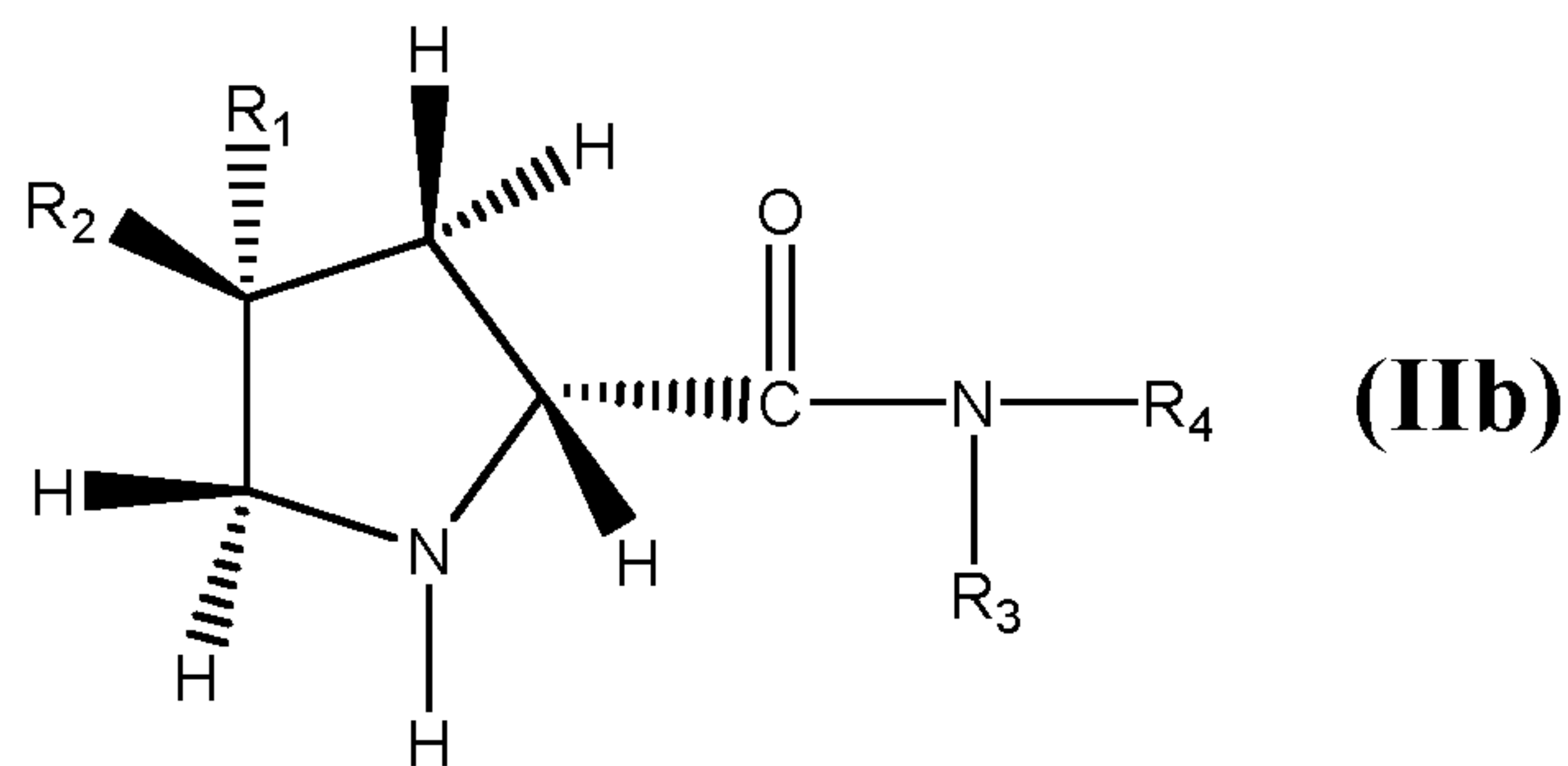


, and

wherein the substituents have the same meanings as for the compound of formula (I).

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Therefore, the present invention relates to new catalysts (C2'), which are transition metal catalysts (C) or (C1), wherein L is a ligand of formula (IIb)



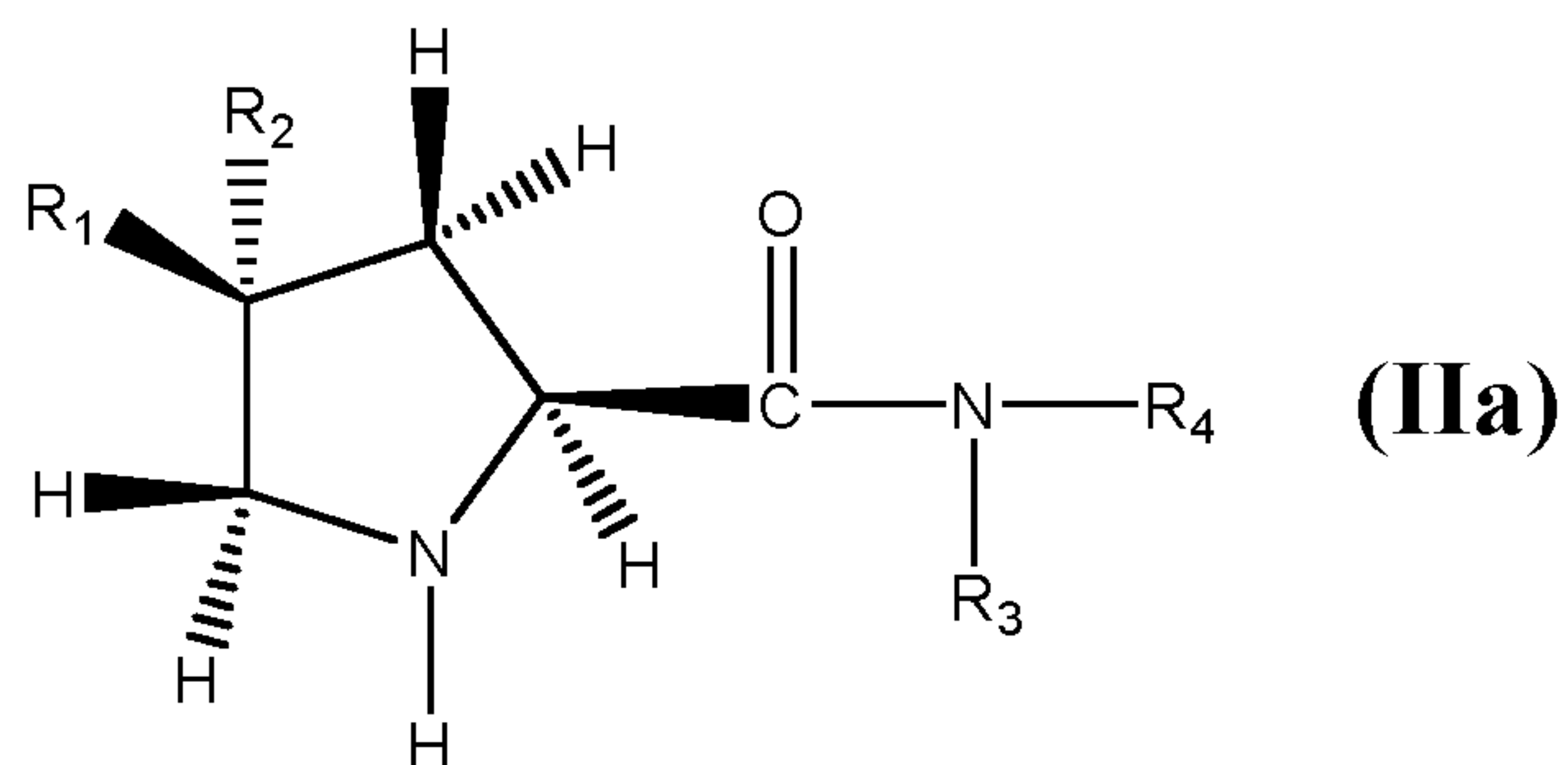
, and

wherein the substituents have the same meanings as for the compound of formula (I).

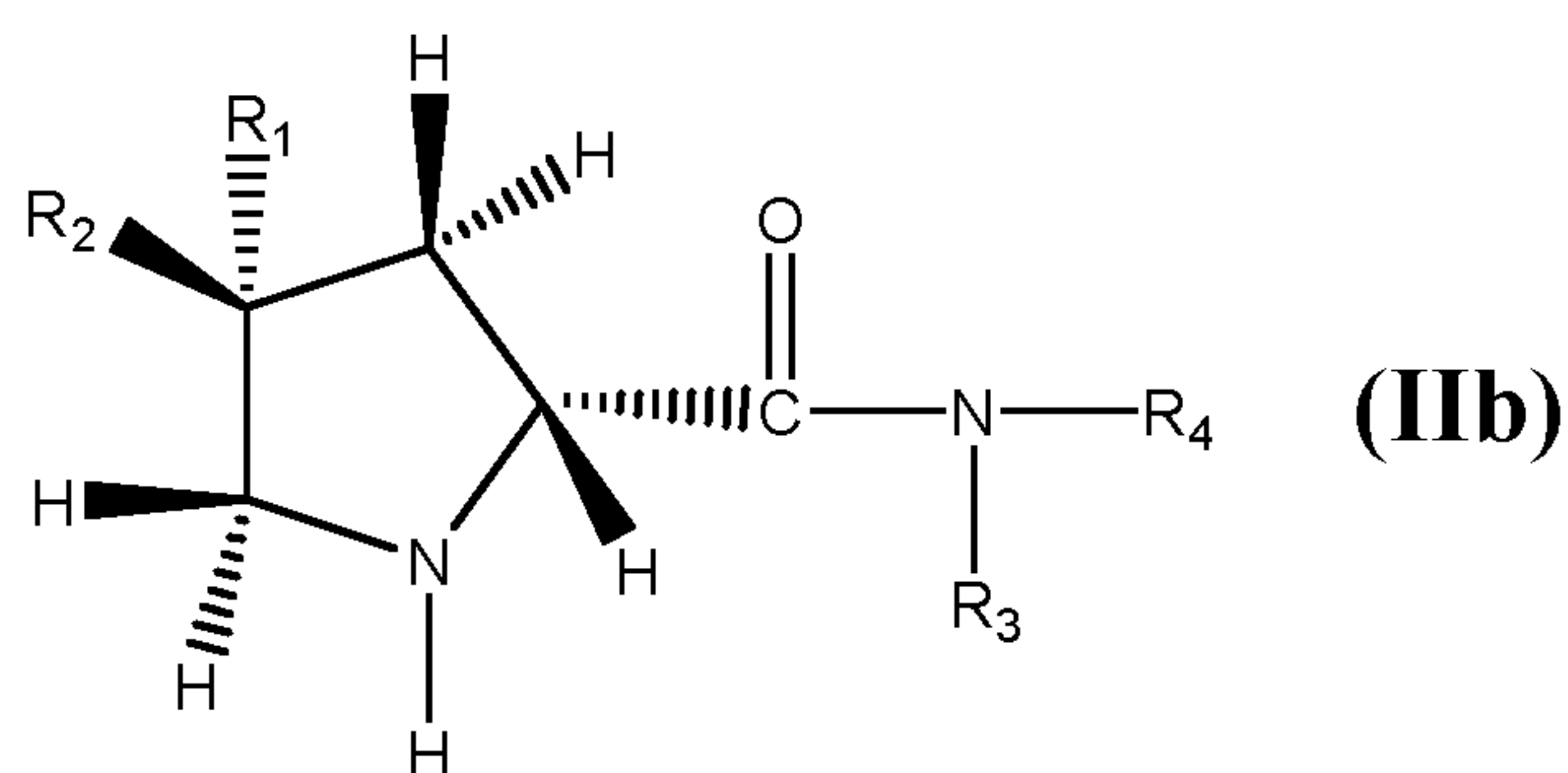
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Therefore, the present invention relates to new catalysts (C2''), which are transition metal catalysts (C) or (C1), wherein L is a mixture of ligands of formula (IIa)

- 4 -



and of formula (IIb)

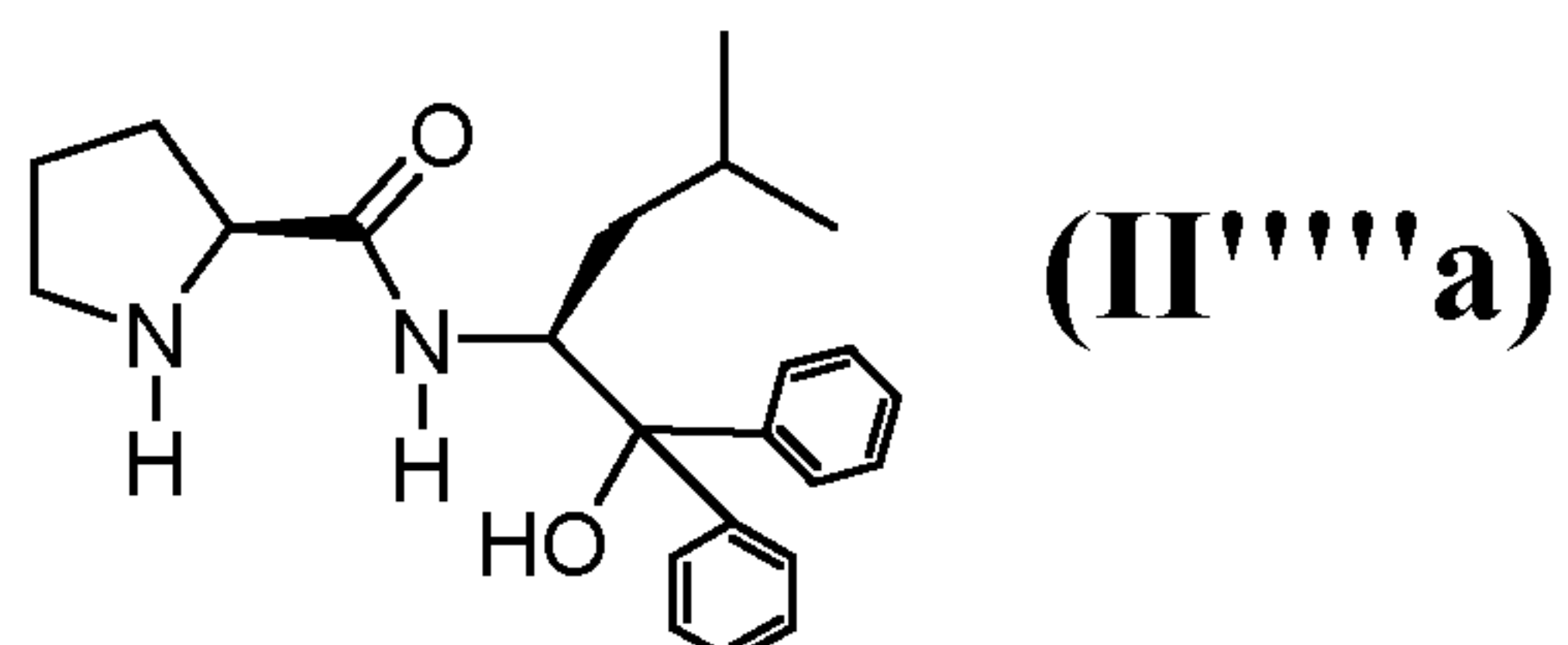
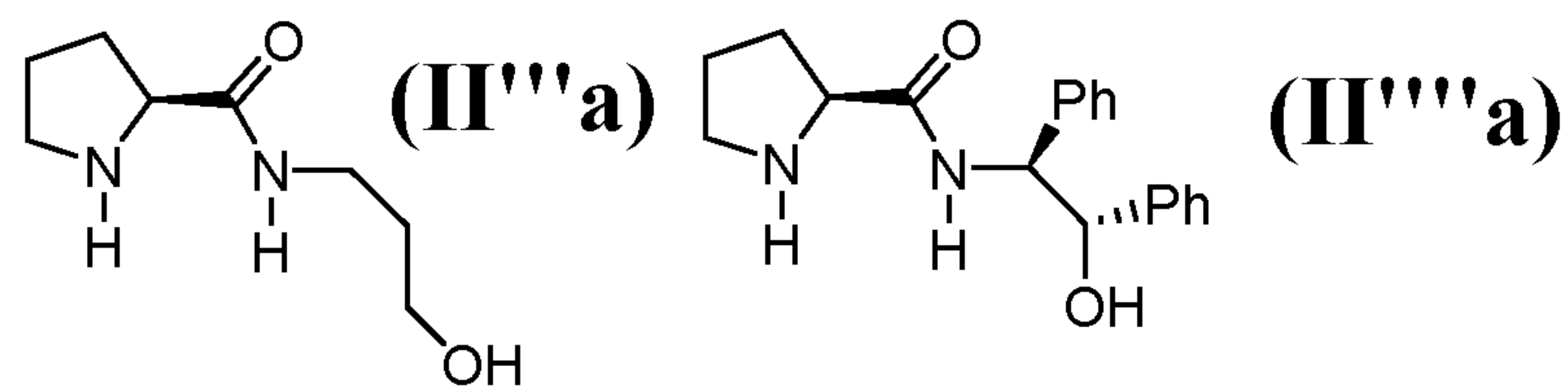
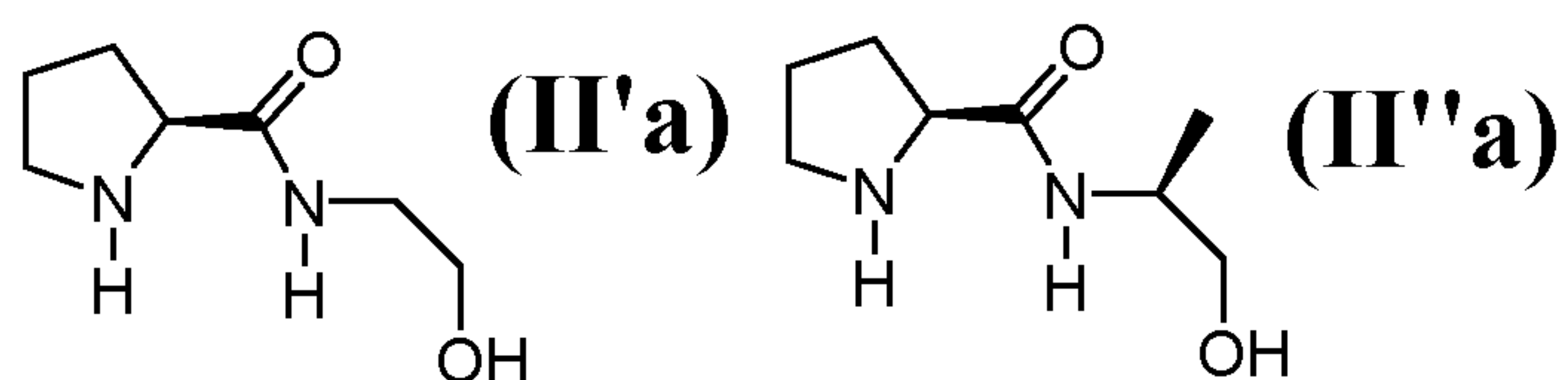


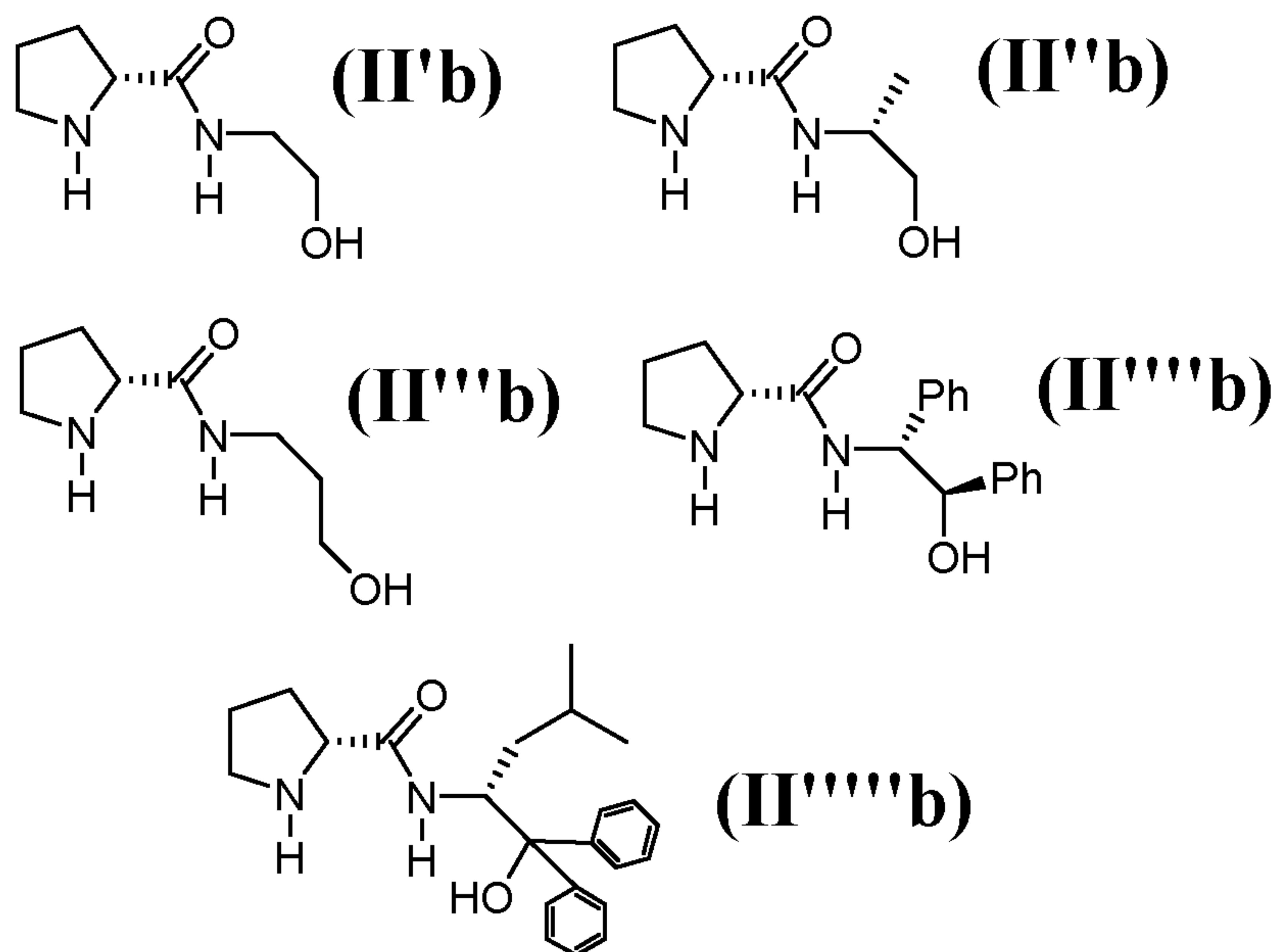
, and

wherein the substituents have the same meanings as for the compound of formula (I).

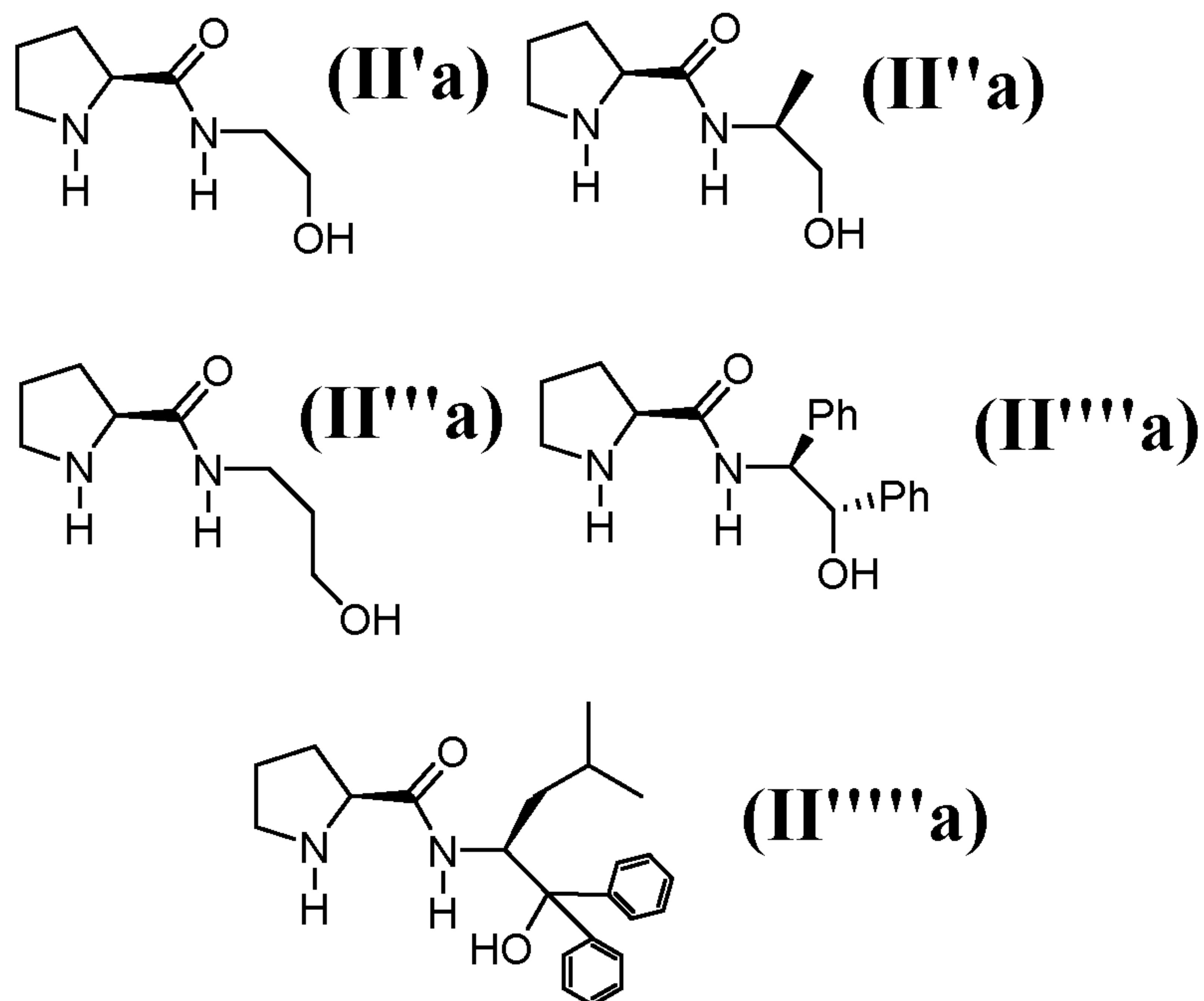
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More preferred are catalyst of formula (I), wherein the ligand L is one of the following formula (II'a) – (II''''a) or (II'b) – (II''''b):

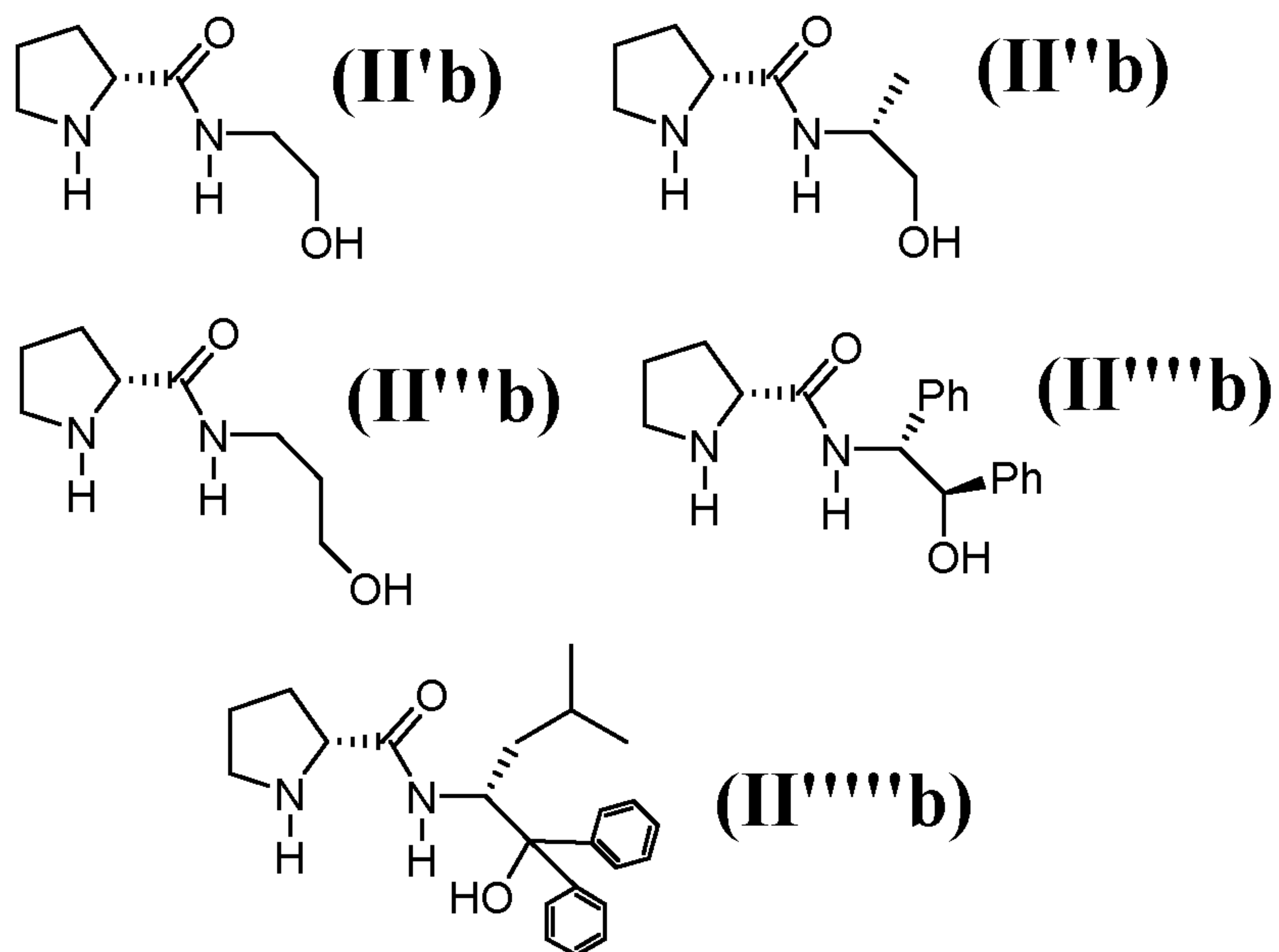




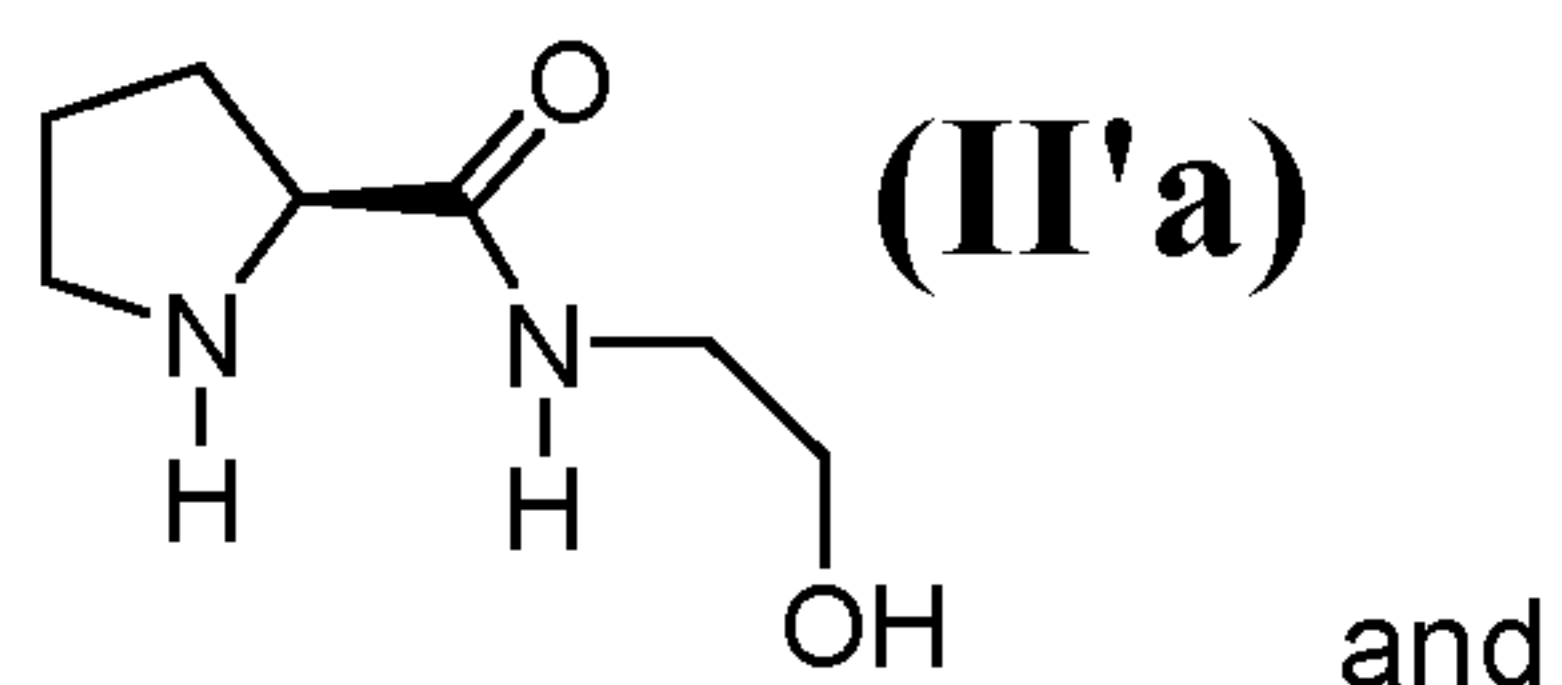
Therefore, the present invention relates to new catalysts (C2'''), which are transition metal catalysts (C) or (C1), wherein L is a ligand of formula (II'a) – (II''''a) or (II'b) – (II'''''b):



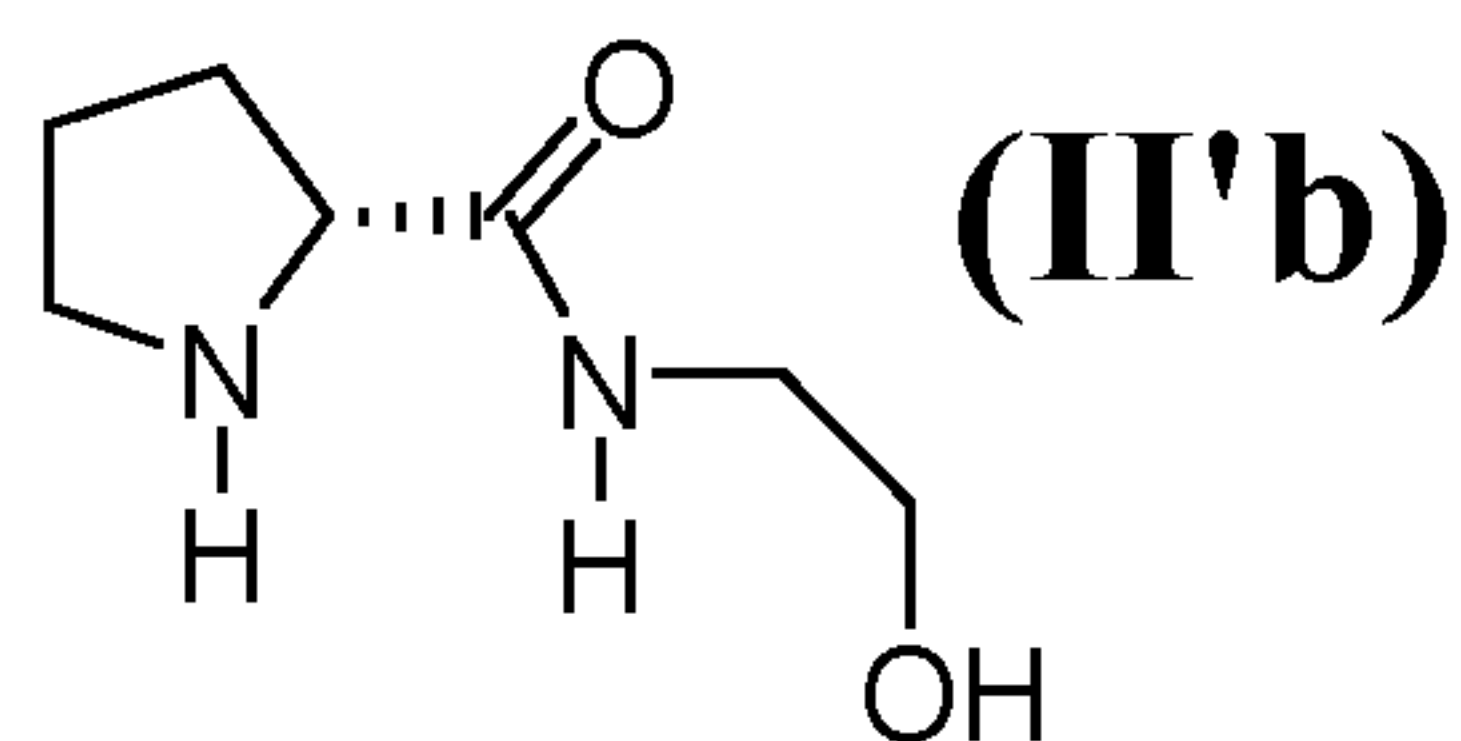
- 6 -



Most preferred are the ligands of formula (II'a) and (II'b)

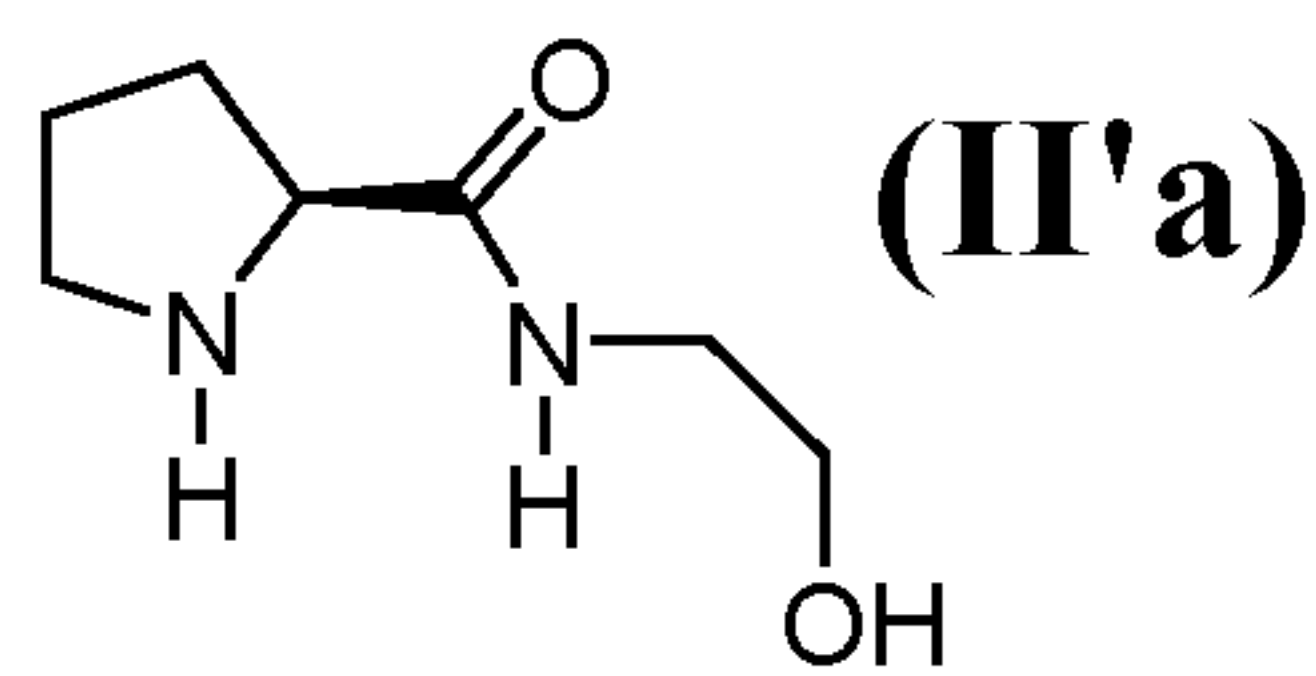


and



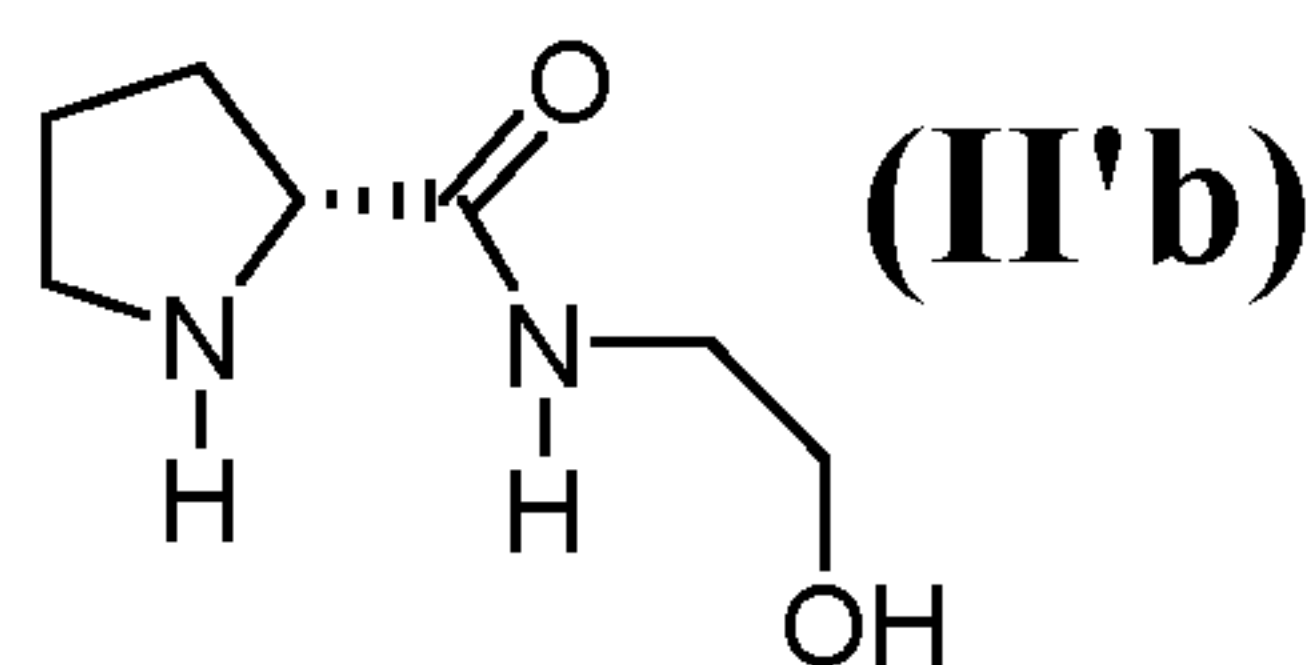
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Therefore, the present invention relates to new catalysts (C2'''), which are transition metal catalysts (C) or (C1), wherein L is a ligand of formula (II'a)



or

(II'b)



10

The counteranion Y in the compound of formula (I) may be any commonly used anion. Suitable ones include halides, carboxylates, formate (HCOO^-), hydride (H^-), borohydride (BH_4^-), borates (BR_4^-), and fluorinated anions (such as, but not restricted to: BF_4^- , PF_6^- , SbF_6^- , $\text{BAr}^{\text{F}}_4^-$ (which is tetrakis[3,5-bis(trifluoromethyl)phenyl]borate)),
5 Preferred anions Y are hydride or a halide, especially preferred is Cl^- .

Therefore, the present invention relates to new catalysts (C3), which are transition metal catalysts (C1), (C2), (C2'), (C2''), (C2''') or (C2'''), wherein Y is chosen from the
10 group consisting of a halide, carboxylate, formate, hydride, borohydride, borate, BF_4^- , PF_6^- , SbF_6^- and $\text{BAr}^{\text{F}}_4^-$.

Therefore, the present invention relates to new catalysts (C3'), which are transition metal catalysts (C1), (C2), (C2'), (C2''), (C2''') or (C2'''), wherein Y is chosen from the
15 group consisting of hydride and halide.

Therefore, the present invention relates to new catalysts (C'3'), which are transition metal catalysts (C1), (C2), (C2'), (C2''), (C2''') or (C2'''), wherein Y is Cl^- .

The catalyst according to the present invention ($[\text{M(III)QX(Y)}_n]$) can be produced by
20 combining the relevant components together such as by reacting Q with a metal precursor in a suitable solvent. Q can be the neutral ligand L or an anion of the ligand L. If Q is an anion of ligand L, the anion can be formed before the metal precursor is added, or at the time of complexation to the metal precursor. The anion is usually formed by the addition of base.

25

The catalyst solution can be used as produced, or the catalyst can be isolated and used at a later time. The catalyst according to the present invention can be used in a variety of chemical processes such as for example reduction reactions and isomerisations, in particular transfer hydrogenations and racemisations. Very preferred reactions, which are catalyzed by the catalyst according to the present invention are transfer hydrogenations.
30

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It is possible to add the catalyst as such to the reaction mixture (the order of addition of all the reactants that are added can vary). It is also possible that the catalyst is formed in situ in the reaction mixture. This means that the catalyst is not added as such but it is formed in the reaction mixture.

5

The following examples serve to illustrate the invention. If not otherwise stated, the temperature is given in °C.

Examples

The ligands used are either commercially available or can be prepared using known methods. One method to prepare a range of ligands is described below.

5

General procedure for preparation of ligands

An oven-dried flask was charged with Cbz-D-proline or Cbz-L-proline (1.00 eq.) or a proline derivative and dry dichloromethane (0.20 mol/L). The solution was cooled to 0 °C and triethylamine (1.00 eq.) and isobutyl chloroformate (1.00 eq.) were added.

10 The mixture was stirred for 0.5 h, and the relevant amine (1.00 eq.) was added. The mixture was warmed to room temperature and stirred until complete conversion (monitored by TLC). The mixture was washed with aq. sat. NH_4Cl , aq. sat. NaHCO_3 and brine. Each aqueous layer was re-extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude
15 intermediate could be purified or used in the following step without further purification. The intermediate (1.00 eq.) was dissolved in MeOH (0.40 mol/L), the flask was flushed with argon three times and Pd/C (10.0 wt.%, 5.00 mol%) was added in one portion. The mixture was evacuated and flushed with hydrogen five times. The black suspension was stirred at room temperature under a hydrogen atmosphere until com-
20 plete conversion (monitored by TLC). The reaction mixture was filtered over a plug of celite and rinsed with methanol.

Example 1 - (R)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide (Ligand II'b)

According to the procedure above: Cbz-D-proline (2.49 g, 10.0 mmol, 1.00 eq.), tri-
25 ethylamine (1.41 mL, 10.0 mmol, 1.00 eq.), isobutyl chloroformate (1.30 mL, 10.0 mmol, 1.00 eq.) and ethanolamine (1.21 mL, 10.0 mmol, 1.00 eq.) were reacted to form the intermediate (2.08 g).

The intermediate (2.03 g, 6.94 mmol, 1.00 eq.) and Pd/C (10.0 wt.%, 368 mg, 347 μmol , 5.00 mol%) yielded ligand (II'b) as a colorless liquid (1.10 g, quant.).

30

Example 2: Preparation of ethyl (R)-2-hydroxy-3,3-dimethyl-4-oxobutanoate

To a solution of (R)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide (II'b, 79.1 mg, 500 μ mol, 5.00 mol%) in t-BuOH (10.0 mL), isobutanal (910 μ L, 10.0 mmol, 1.00 eq.) and ethyl glyoxalate (50.0% in toluene, 1.98 mL, 10.0 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding ethyl (R)-2-hydroxy-3,3-dimethyl-4-oxobutanoate (VI) (1.47 g, 84%, 72% ee) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 9.57 (1H, s), 4.32 (1H, s), 4.30–4.18 (2H, m), 3.06 (1H, br), 1.27 (3H, t), 1.14 (3H, s), 1.05 (3H, s). The analytical data was in agreement with an authentic sample.

Example 3: Preparation of catalyst [IrCl(Cp*)(anion of Ligand II'b)]

To a solution of (IrCl₂(Cp*))₂ (19.9 mg, 25.0 μ mol, 1.00 eq.) in dry toluene was added (R)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide (II'b, 7.91 mg, 50.0 μ mol, 2.00 eq.) and triethylamine (11.0 μ L, 75.0 μ mol, 3.00 eq.). The solution was stirred at room temperature for 4h. The solvent was decanted with a syringe to obtain a yellow precipitate. The catalyst could be recrystallised from hexane/chloroform. ¹H NMR (500 MHz, CDCl₃) δ = 5.63 (1H, br), 4.33 (1H, br), 3.98 (1H, m), 3.79 (2H, m), 3.64 (1H, m), 3.58 (1H, br), 3.44 (1H, m), 3.13 (1H, m), 2.14 (1H, m), 2.02 (1H, m), 1.85 (1H, m), 1.78 (1H, m), 1.67 (15H, s); ¹³C NMR (126 MHz, CDCl₃) δ = 181.5, 85.5, 65.1, 64.0, 54.3, 52.4, 29.8, 26.7, 9.5.

General procedure for transfer hydrogenation ethyl (R)-2-hydroxy-3,3-dimethyl-4-oxobutanoate to yield (R)-2-hydroxy-3,3-dimethyl- γ -butyrolactone

The preformed transition metal catalyst or the transition metal salt and the ligand were added to a solution of ethyl (R)-2-hydroxy-3,3-dimethyl-4-oxobutanoate (from example 2) in water:tert-butanol (2:1). The mixture was degassed, sodium formate (5 eq.) was added and the mixture was stirred at the desired temperature for the stated time. The reaction mixture extracted with MTBE or dichloromethane and the combined organic phases were dried, filtered and concentrated in vacuo.

Example	Ligand	Metal precursor and loading	T [°C]	T [h]	Conv. [%]
3a	II'b	(RuCl ₂ (p-cymene)) ₂ 0.50 mol%	rt	26	98
3b	II'b	(IrCl ₂ Cp*) ₂ 0.50 mol%	40	1	99
3c	II'b	(IrCl ₂ Cp*) ₂ 0.50 mol%	rt	4	99
3d	II'b	(IrCl ₂ Cp*) ₂ 0.25 mol%	40	2	93
3e	II'b	(IrCl ₂ Cp*) ₂ 0.10 mol%	40	5	99
3f	II'b	(RhCl ₂ Cp*) ₂ 0.50 mol%	40	2.5	97

Examples 3b to 3f are the examples claimed by the present patent claims, whereas 3a is a comparison example.

Claims

1. A transition metal catalyst of the formula (I)

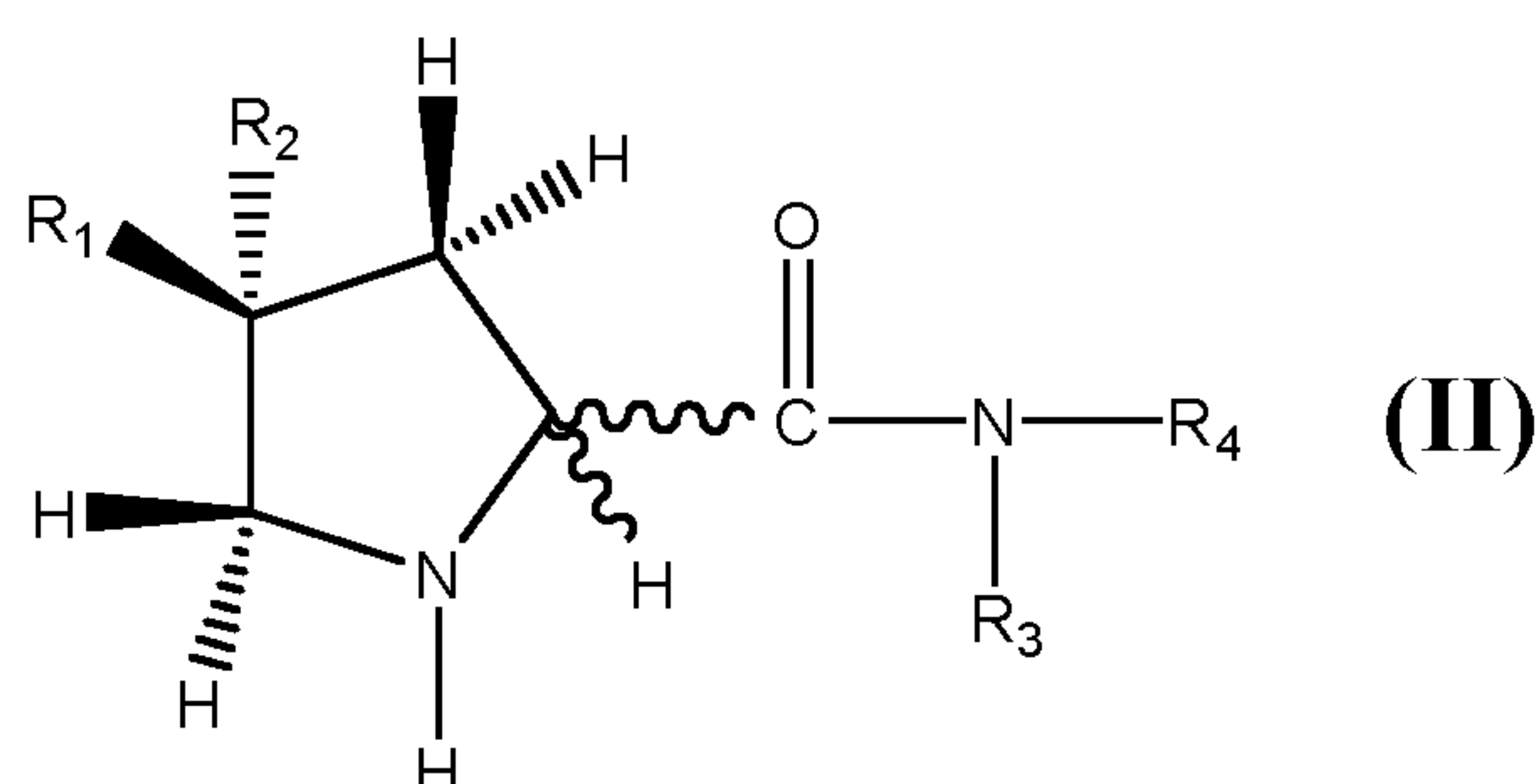


wherein

M is a transition metal chosen from the list of Ru, Rh and Ir, preferably Ir, and

Q is the ligand L or an anion of the ligand L, wherein

10 the ligand L has the following formula (II)



wherein

R₁ is H, CH₃ or OH,

R₂ is H, CH₃ or OH,

15 R₃ is H or CH₃

R₄ is a C₂-C₄ alkyl group, which is substituted by at least one OH group and which is optionally further substituted,

with the provisos that

when R₁ is OH or CH₃, then R₂ is H and

20 when R₂ is OH or CH₃, then R₁ is H, and

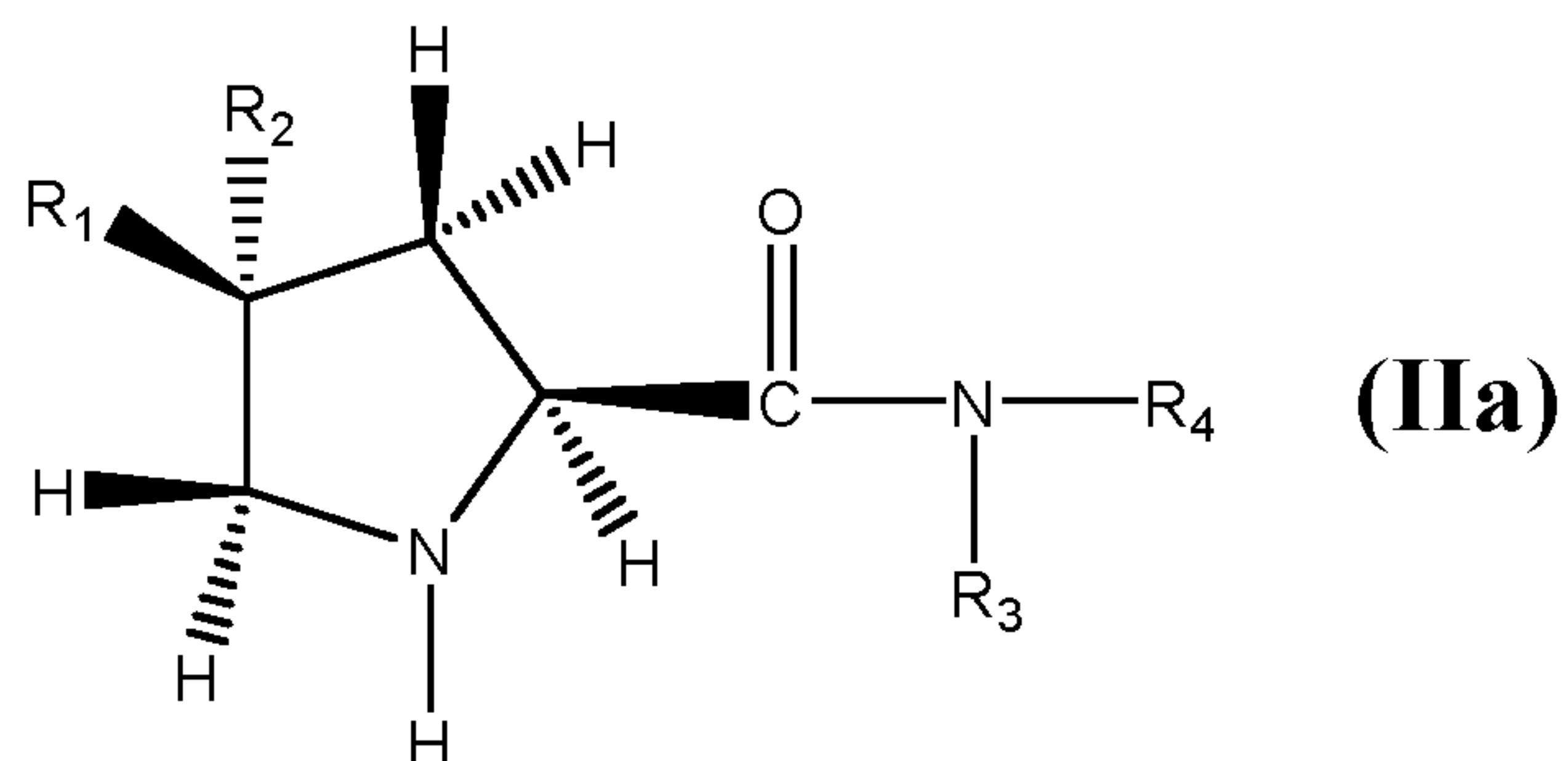
X is cyclopentadienyl, or a substituted cyclopentadienyl group, preferably indenyl or pentamethylcyclopentadienyl, and

Y is an anion and n is 1 or 2, with the proviso that the value of n is chosen such that the overall metal complex is a neutral species.

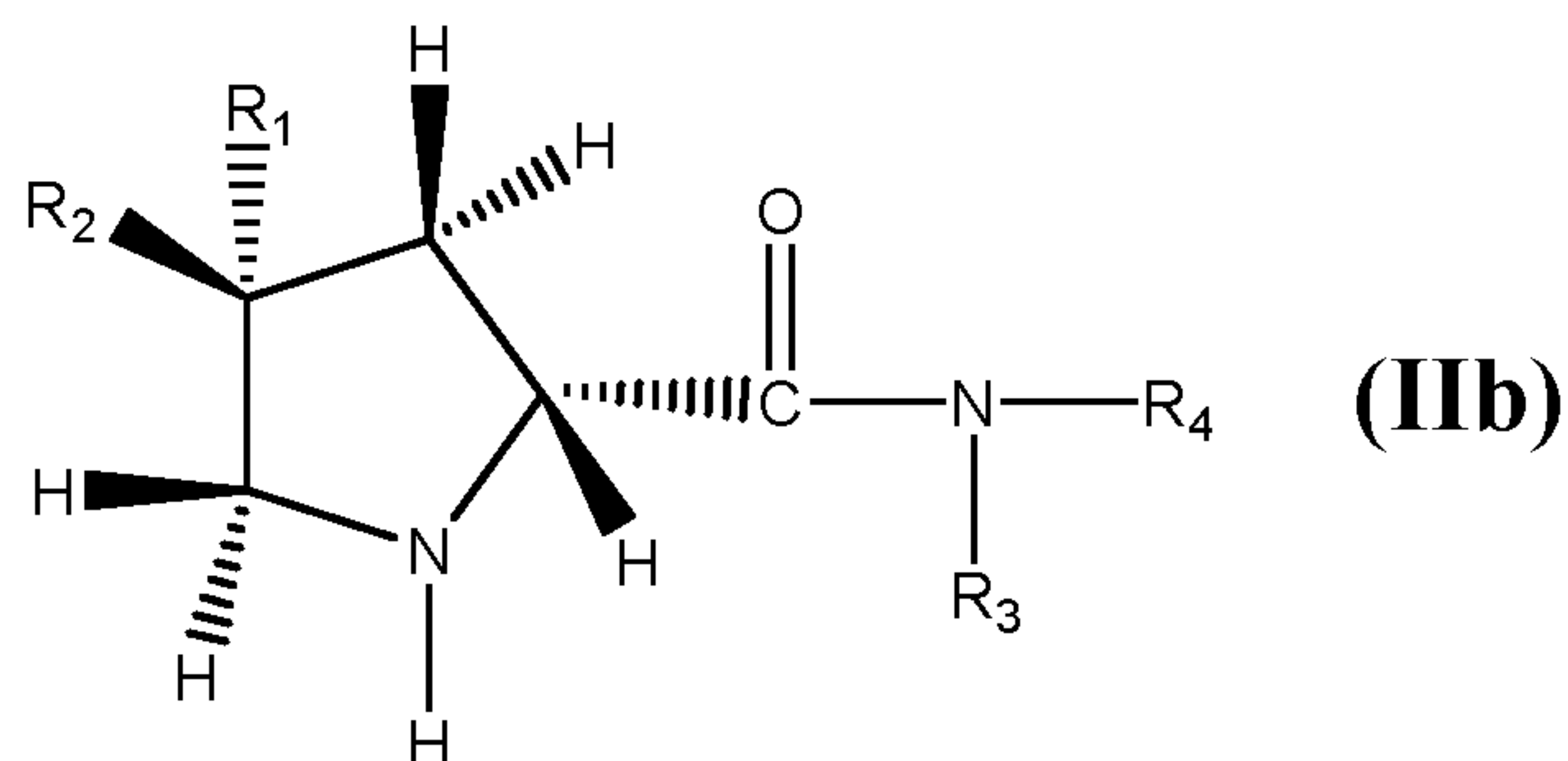
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2. Transition metal catalyst according to claim 1, wherein M is Ir.

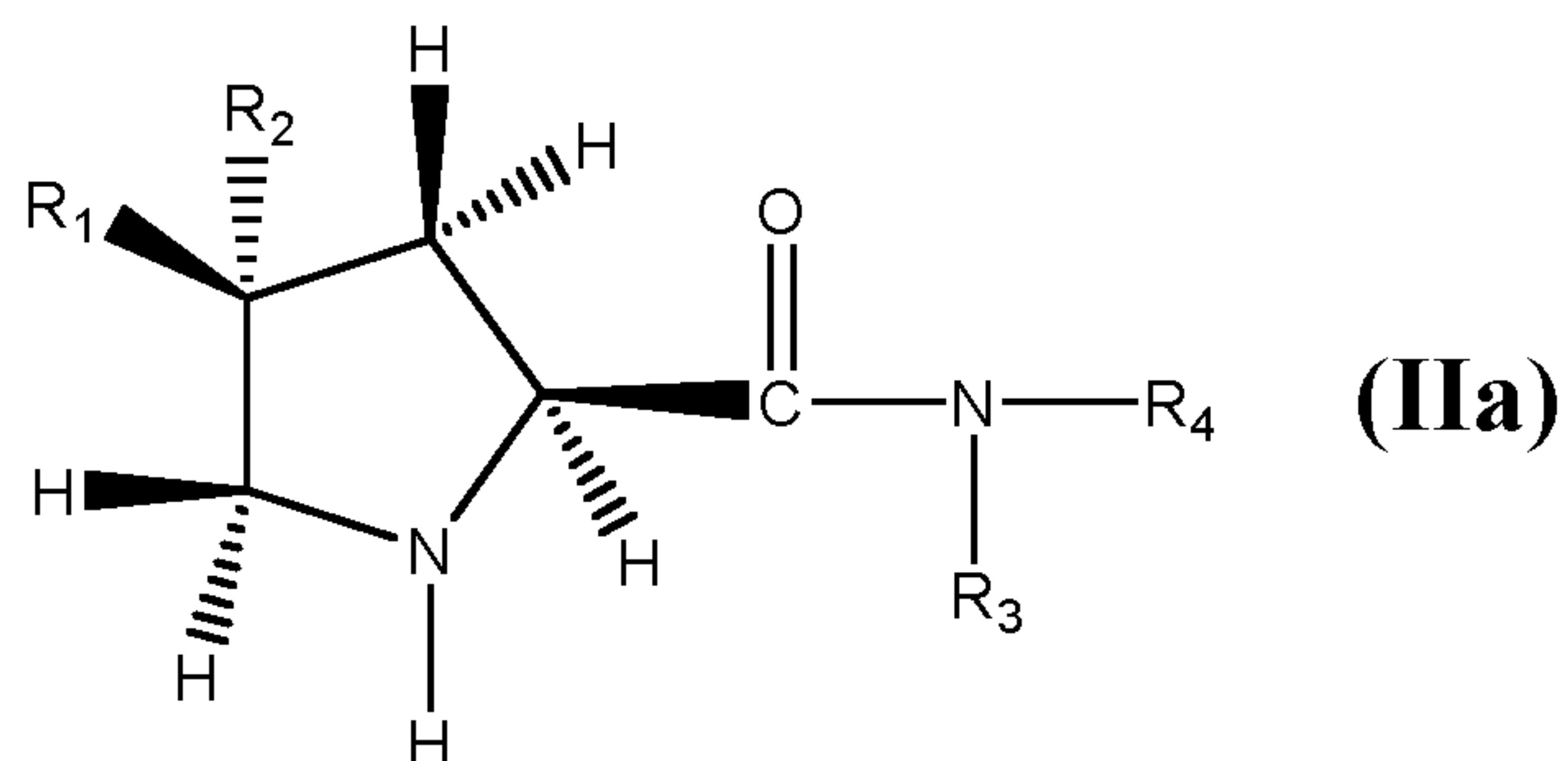
3. Transition metal catalyst according to claim 1 or claim 2, wherein L is a ligand of formula (IIa)



5 **4.** Transition metal catalyst according to claim 1 or claim 2, wherein L is a ligand of formula (IIb)

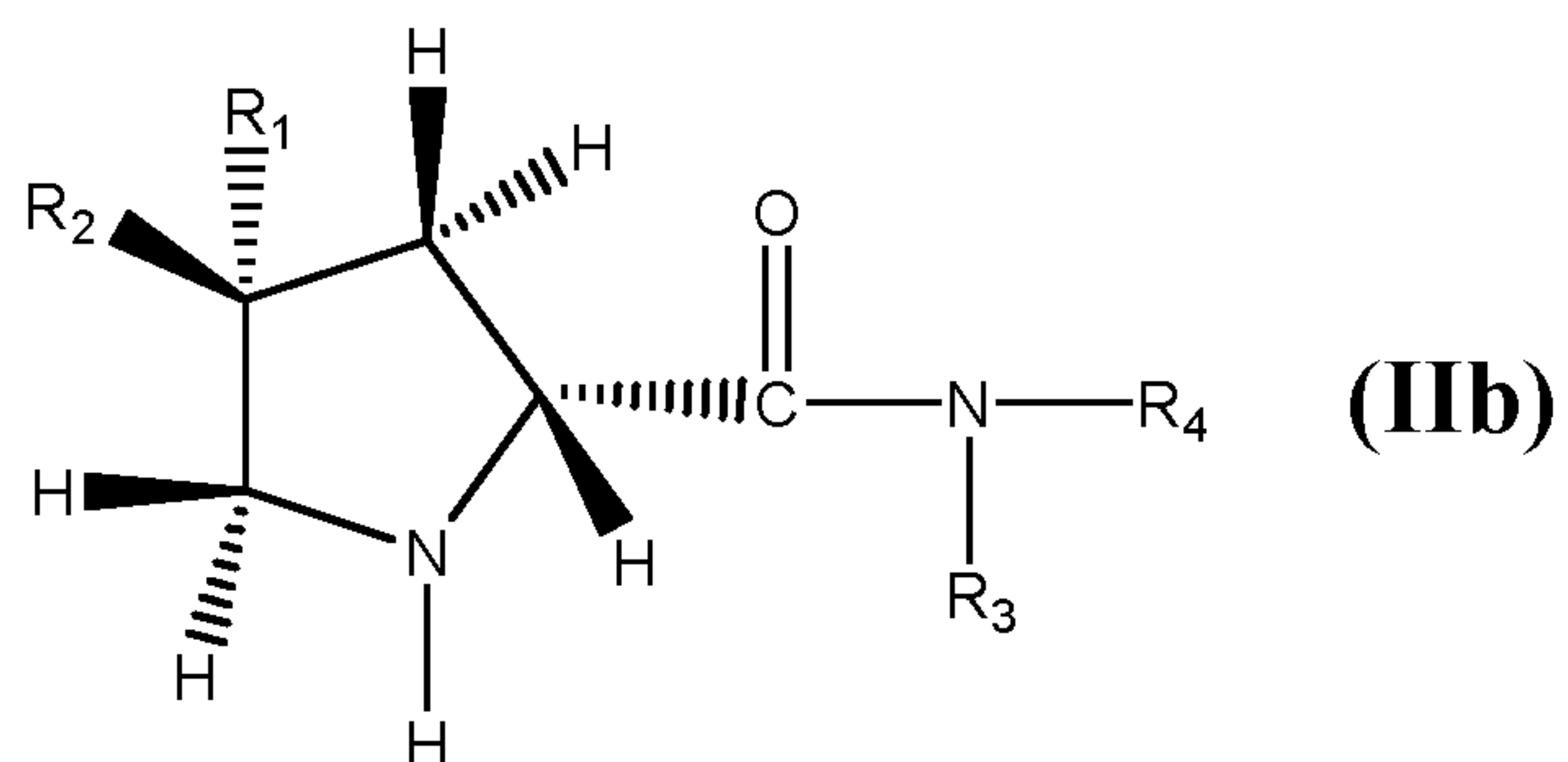


5. Transition metal catalyst according to claim 1 or claim 2, wherein L is a mixture
10 of ligands of formula (IIa)

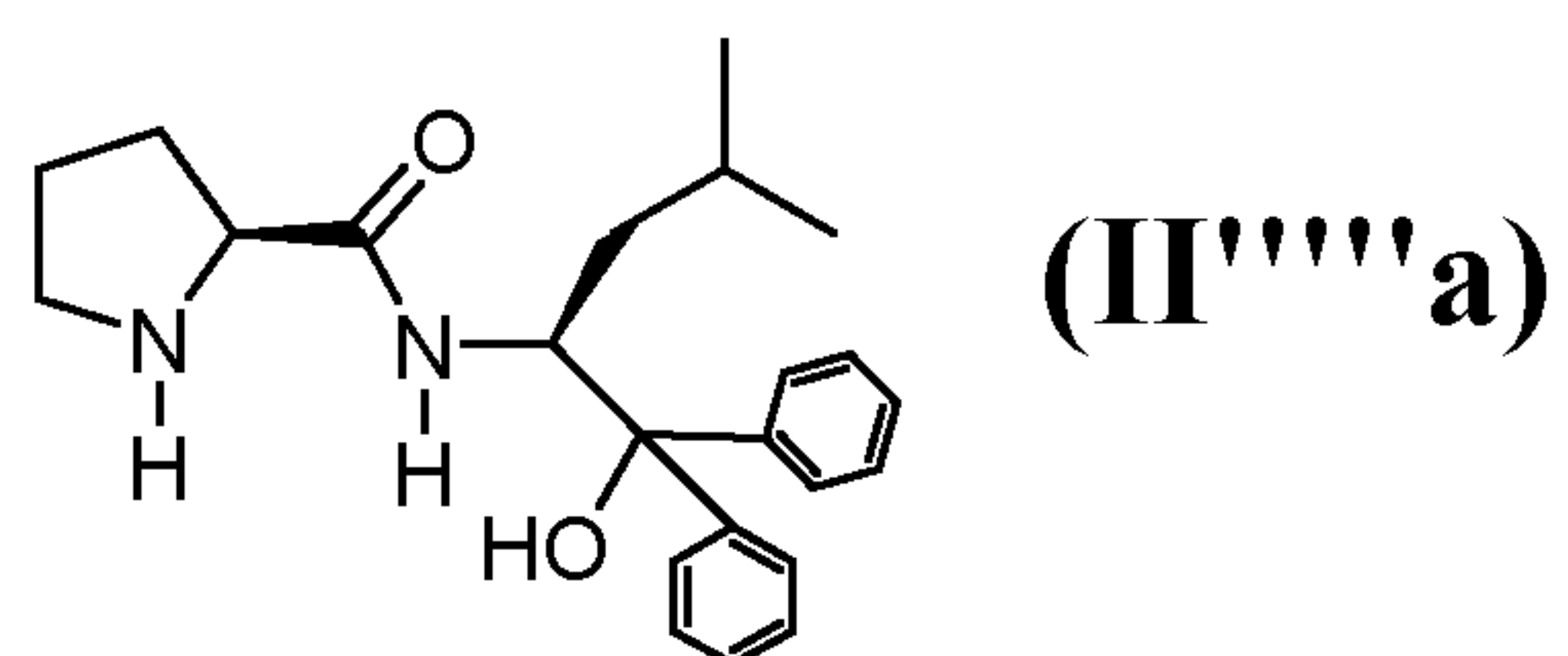
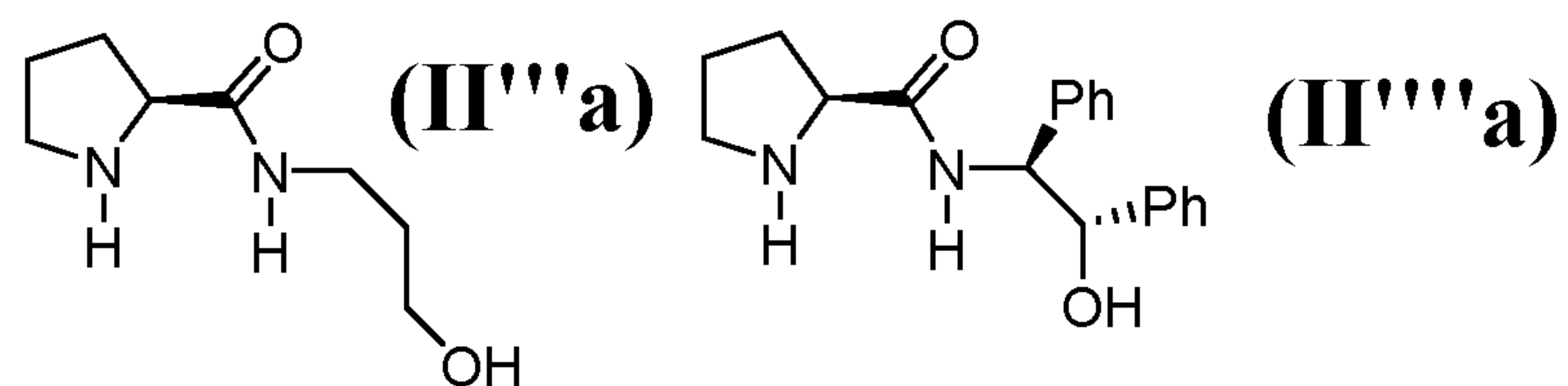
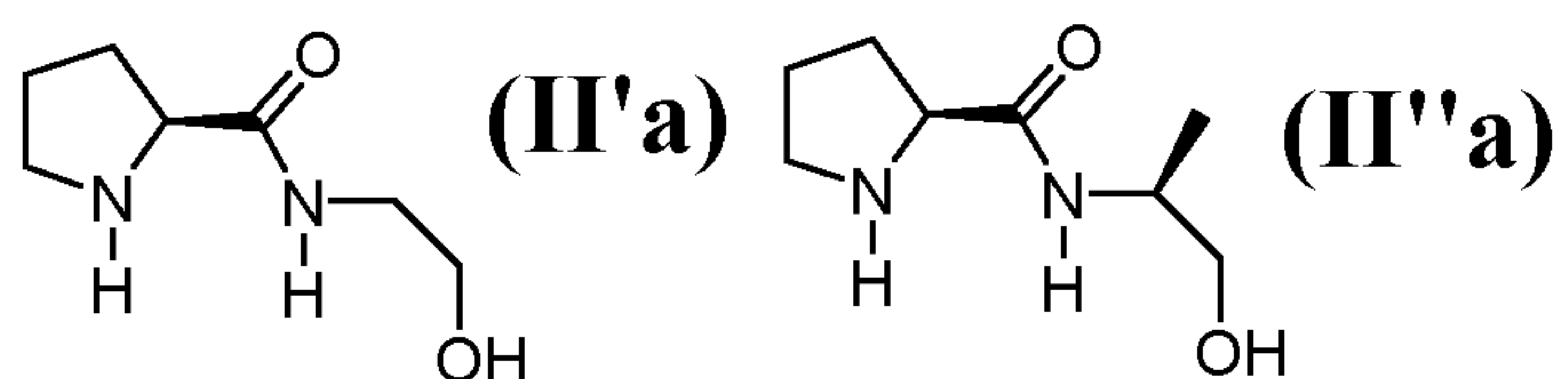


and of formula (IIb)

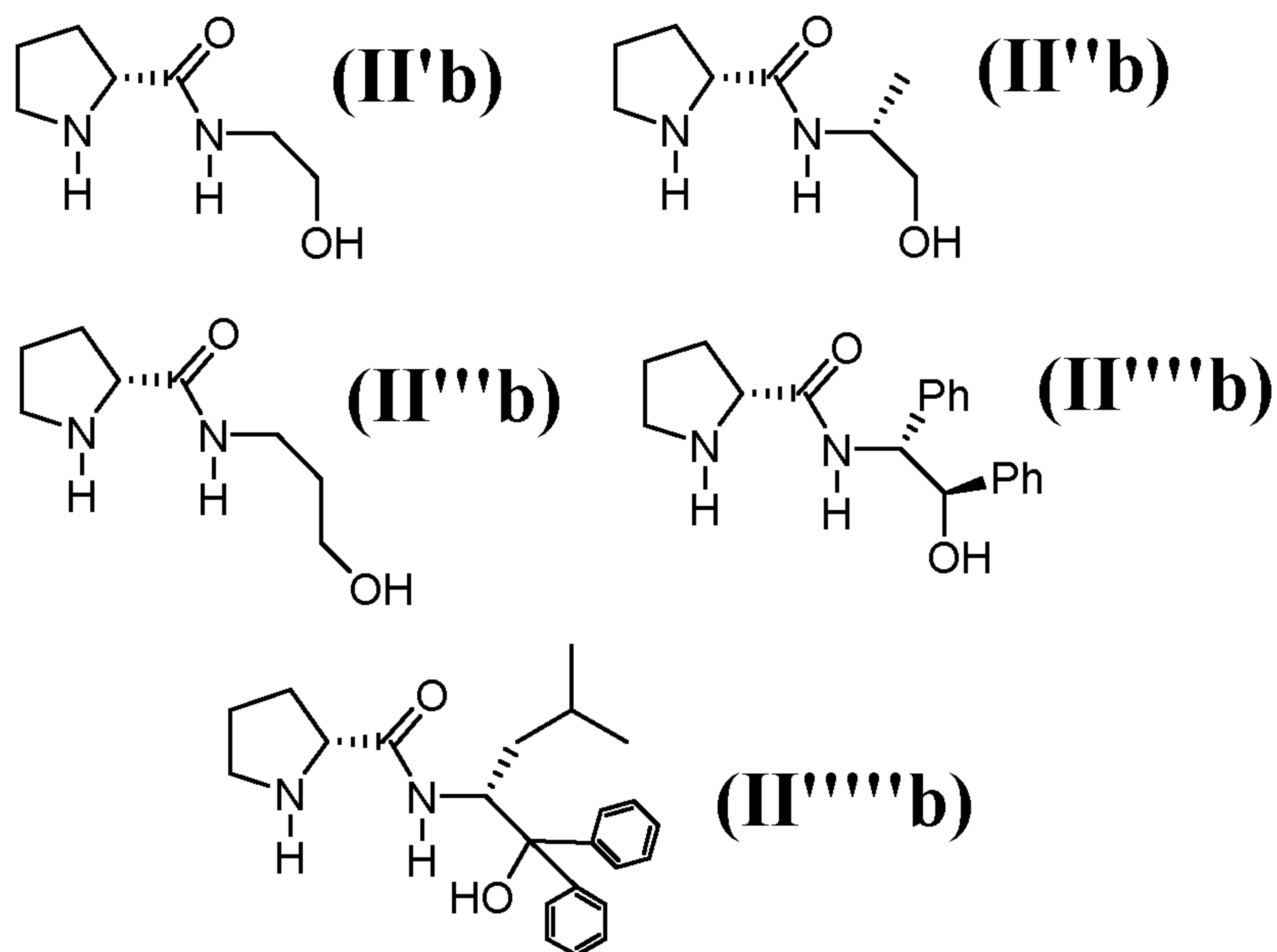
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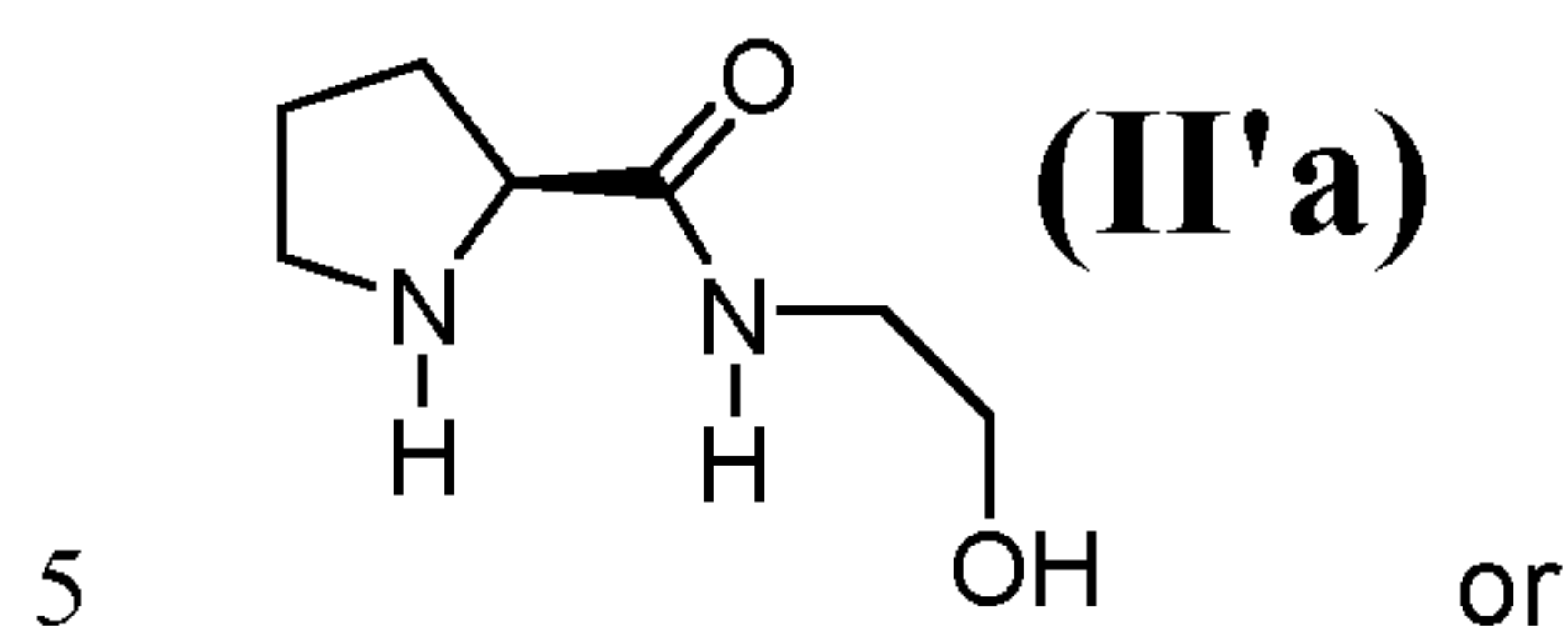
6. Transition metal catalyst according to claim 1 or claim 2, wherein L is a ligand of formula (II'a) – (II''''a) or (II'b) – (II''''b):



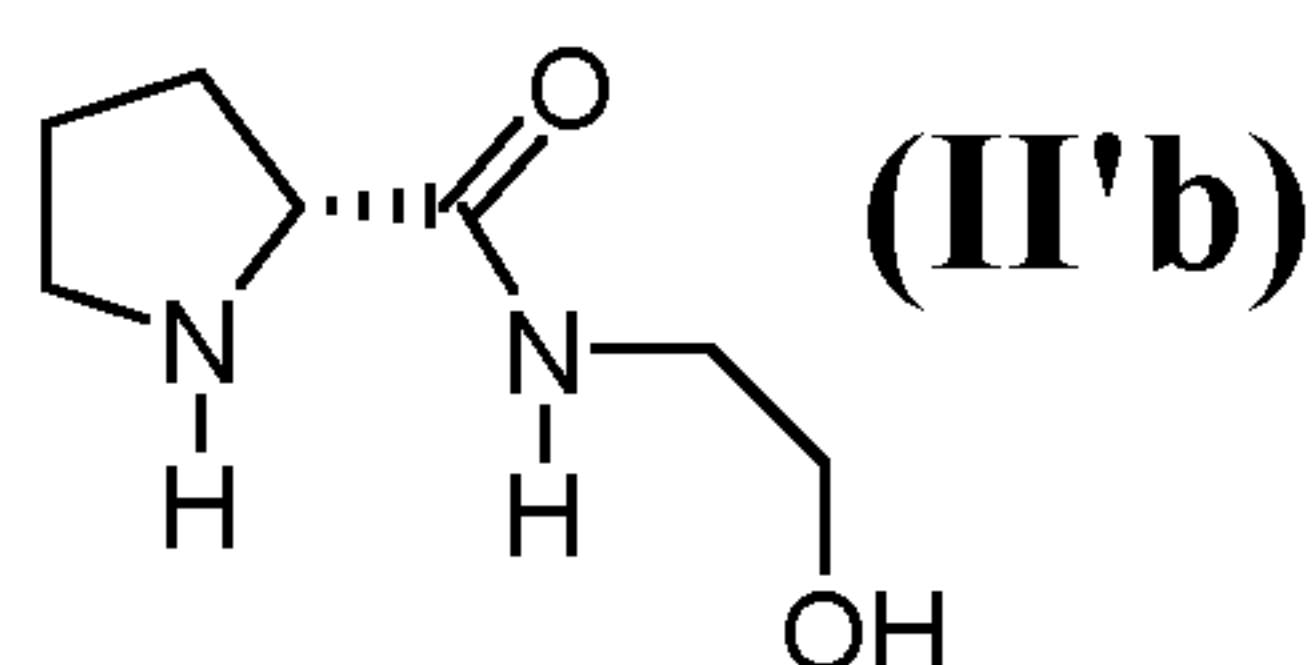
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7. Transition metal catalyst according to claim 1 or claim 2, wherein L is a ligand of formula (II'a)



(II'b)



8. Transition metal catalyst according to any of the preceding claims, wherein Y is chosen from the group consisting of a halide, carboxylate, formate, hydride, borohydride, borate, BF₄⁻, PF₆⁻, SbF₆⁻ and BAr₄⁻.

9. Transition metal catalyst according to any of the preceding claims 1 - 7, wherein Y is chosen from the group consisting of hydride and halide.

10. Transition metal catalyst according to any of the preceding claims 1 - 7, wherein Y is Cl⁻.

- 11.** Use of at least one transition metal catalyst according to any of the preceding claims 1 – 10 in a chemical process.
- 5 **12.** Use according to claim 11, which is reduction reaction.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2020/080685

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07F15/00 B01J31/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07F B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FUJIEDA, HIROKI ET AL: "New synthetic route to the important (S)-5-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-methylthiophene-3- carboxylic acid intermediate for the synthesis of a novel glucokinase activator", SYNTHETIC COMMUNICATIONS, vol. 49, no. 6, 18 March 2019 (2019-03-18) , pages 814-822, XP002798566, ISSN: 0039-7911, DOI: 10.1080/00397911.2019.1570267 10.1080/00397911.2019.1570267 page 818, figure 3, Cp*IrCl[(S)-PA), Cp*IrCl[(R)-PA)] -----	1-12



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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Bourghida, E