

(19) World Intellectual Property Organization  
International Bureau



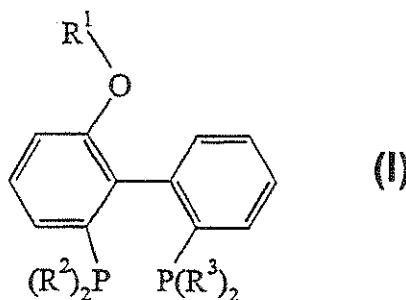
(43) International Publication Date  
12 January 2006 (12.01.2006)

PCT

(10) International Publication Number  
**WO 2006/002730 A1**

- (51) International Patent Classification<sup>7</sup>: C07F 9/50, 15/00, B01J 31/24, C07C 43/225
- (21) International Application Number: PCT/EP2005/006064
- (22) International Filing Date: 6 June 2005 (06.06.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 04014909.8 25 June 2004 (25.06.2004) EP
- (71) Applicant (for all designated States except US): LONZA AG [CH/CH]; Münchensteinerstrasse 38, CH-4052 Basel (CH).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): METTLER, Hanspeter [CH/CH]; Finkenweg 12, CH-3930 Visp (CH). LEROUX, Frédéric [DE/FR]; 13, rue Saint Yvieix, F-67760 Gumbsheim (FR). SCHLOSSER, Manfred [DE/CH]; Av. Parc Rouvraie 24, CH-1018 Lausanne (CH).
- (74) Common Representative: LONZA AG; Münchensteinerstrasse 38, CH-4052 Basel (CH).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF ASYMMETRICALLY SUBSTITUTED  
BIPHENYLDIPHOSPHINES



(57) Abstract: Provided is a process for the preparation of asymmetrically substituted biaryldiphosphine ligands of the formula (I), wherein  $R^1$  is  $C_{1-6}$ -alkyl or  $C_{3-10}$ -cycloalkyl optionally substituted with one or more halogen atoms, and  $R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,  $C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl, or  $R^2$  is  $C_{5-10}$ -cycloalkyl or  $C_{1-6}$ -alkyl, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{3-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cycloalkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms, from 2,2',6,6'-tetrabromobiphenyl by a sequence of brominemetal exchanges and subsequent reactions.

## Process for the preparation of asymmetrically substituted biphenyldiphosphines

Preparation of enantiomerically pure compounds is important to improve the effect of pharmaceutically active compounds and to restrict unwanted side effects of the "wrong" isomers. The invention relates to a process for the preparation of asymmetrically substituted biaryldiphosphine ligands and transition metal complexes thereof for the hydrogenation of unsaturated prochiral compounds using said complexes.

Asymmetric catalytic hydrogenation is one of the most efficient and convenient methods for preparing a wide range of enantiomerically pure compounds. Providing methods for the precise control of molecular chirality of pharmaceutical active compounds and compounds thereof tends to play an increasingly important role in synthetic chemistry. Several diphosphine ligand families are commonly known with their trade names, for example BINAP, CHIRAPHOS, DIOP, DUPHOS, SEGPPOS and TUNAPHOS.

- 15 Methods for the preparation of biaryldiphosphine ligands of the BINAP, SEGPPOS and TUNAPHOS families are disclosed in EP-A-025 6634, EP-A-850945 and WO-A-01/21625, respectively. Furthermore WO-A-03/029259 discloses a synthesis of a fluorine derivative of SEGPPOS and its use.
- 20 In Pai, C.-C. et al., *Tetrahedron Lett.* **2002**, 43, 2789-2792 the use of methylenedioxy and ethylenedioxy substituted biaryldiphosphine ligands for the asymmetric hydrogenation of ethyl 4-chloro-3-oxobutyrate is described. Further examples for the preparation of biaryldiphosphines and asymmetric hydrogenation reactions using catalysts derived from biaryldiphosphine ligands are disclosed in EP-A-0 926 152, EP-A-0 945 457 and EP-A-0 955 303.
- 25 Usually both symmetrically and unsymmetrically substituted biaryldiphosphines are claimed, though only examples of symmetrically substituted ligands are disclosed. With only few specific exceptions, no general applicable synthetic route to unsymmetrically substituted biaryldiphosphines and catalysts derived therefrom is disclosed.
- 30 Biaryl diphosphine ligands consist of three different moieties, a rigid biaryl core, substituents to hinder biaryl rotation and usually two phosphine groups with voluminous substituents to complex a transition metal. Known examples of ligand systems

have symmetric substitution patterns of the core and identical phosphine groups. As a rare example WO-A-02/40492 discloses asymmetric hydrogenation of ethyl 4-chloro-3-oxobutylate, using a catalyst containing the ligand (*S*)-6-methoxy-5',6'-benzo-2,2'-bis(diphenylphosphino)-biphenyl. The (*S*)-alcohol is obtained with an enantiomeric excess (ee) of 83%.

EP-A-0 647648 and WO-A-02/40492 claim diphosphines with asymmetrically substituted biaryl core, but the disclosed synthetic principles are not suitable to produce a broad variety of different asymmetrically substituted biaryldiphosphine ligands.

10

For the synthesis of the inventive asymmetric biaryldiphosphines a major obstacle had to be overcome as depicted in Scheme 1. Any 2'-diphenylphosphino-2-lithiobiphenyl generated as an intermediate failed to yield an asymmetrically substituted biaryldiphosphine by condensation with a second chlorodiorganylphosphine component, if a single fluorine, chlorine or bromine atom or a single methoxy or dimethylamino group was attached to the 6-position (Miyamoto, T.K. et al., *J. Organomet. Chem.* **1989**, 373, C8-C12; Desponds, O., Schlosser, M., *J. Organomet. Chem.* **1996**, 507, 257). The compounds undergo nucleophilic substitution at the phosphorus atom and cyclization to afford 1*H*-benzo[*b*]phosphindole (9-phosphafluorene). Known unsuccessful approaches to the inventive ligands are depicted in Scheme 1 below.

20

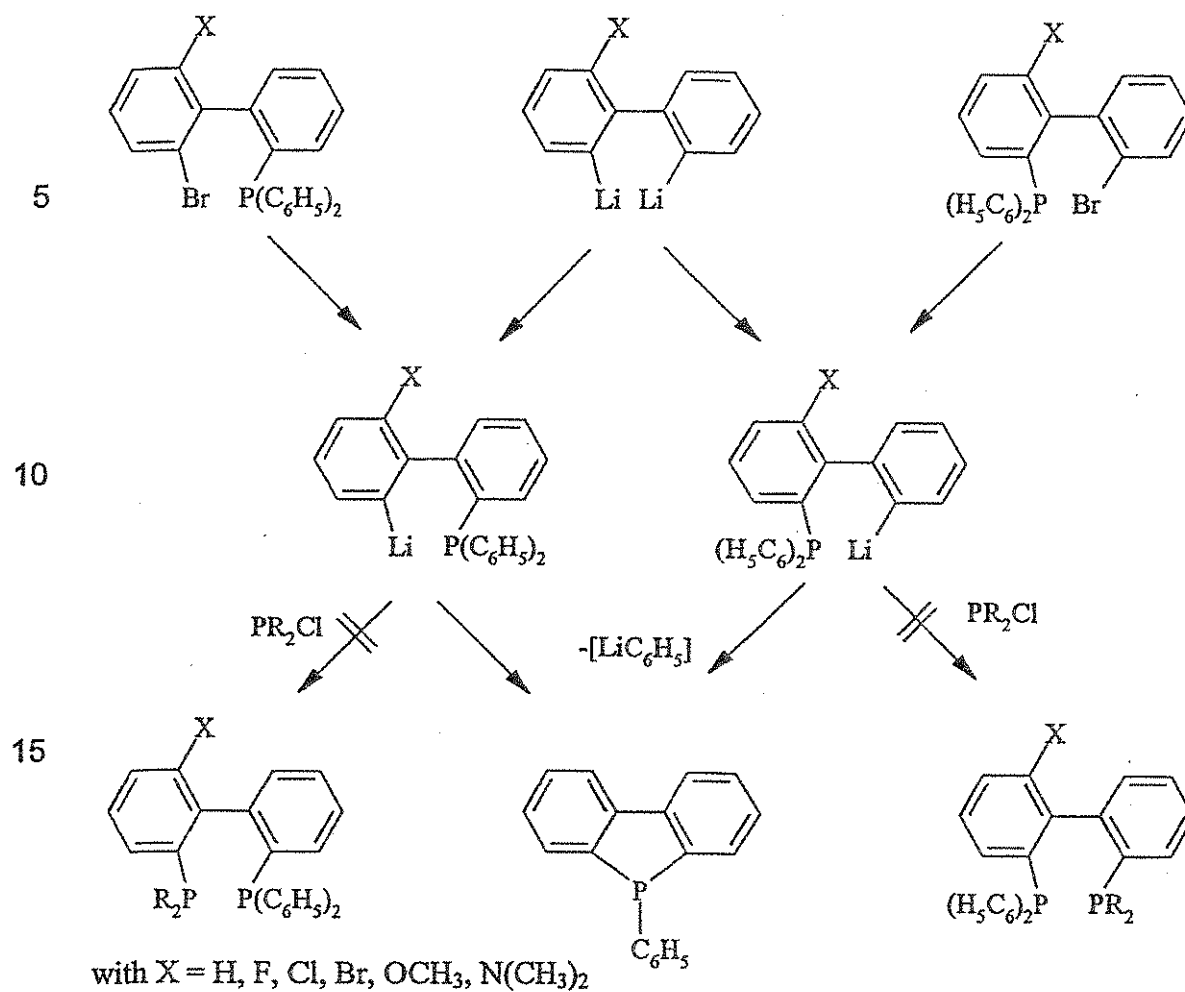
Here and hereinbelow the term "enantiomerically pure compound" comprises optically active compounds with an enantiomeric excess (ee) of at least 90 %.

25 Here and hereinbelow the term "C<sub>1-n</sub>-alkyl" represents a linear or branched alkyl group having 1 to n carbon atoms. C<sub>1-6</sub>-alkyl represents for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl and hexyl.

Here and hereinbelow the term "C<sub>1-n</sub>-alkoxy" represents a linear or branched alkoxy group having 1 to n carbon atoms. C<sub>1-6</sub>-alkoxy represents for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, pentyloxy and hexyloxy.

30

Scheme 1: Unsuccessful approaches to asymmetrically substituted diphosphine ligands.



20

Here and hereinbelow the term “C<sub>3-n</sub>-cycloalkyl” represents a cycloaliphatic group having 3 to n carbon atoms. C<sub>5-10</sub>-cycloalkyl represents mono- and polycyclic ring systems such as cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl or norbornyl.

25

Here and hereinbelow the term “C<sub>3-n</sub>-cycloalkoxy” represents a cycloalkoxy group having 3 to n carbon atoms. C<sub>5-10</sub>-cycloalkyl represents for example cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, cyclooctyloxy or cyclodecyloxy.

30

Here and hereinbelow the term “di-C<sub>1-6</sub>-alkylamino” represents a dialkylamino group comprising two alkyl moieties independently having 1 to 6 carbon atoms. Di-C<sub>1-6</sub>-alkyl-amino represents for example *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-propylamino, *N*-ethyl-*N*-hexylamino or *N,N*-dihexylamino.

Here and hereinbelow the term "aryl" represents an aromatic group, preferably phenyl or naphthyl optionally being further substituted with one or more halogen atoms, nitro and/or amino groups, and/or optionally substituted C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy or di-C<sub>1-6</sub>-alkylamino groups.

5

Here and hereinbelow the term "C<sub>1-3</sub>-alcohols" represents methanol, ethanol, propanol and isopropanol.

10

Here and hereinbelow the term "C<sub>1-3</sub>-alkanoic acids" represents formic acid, acetic acid and propanoic acid.

Considering the high stereocontrol and efficient action of enzymes, i.e. natural catalysts, great effort is spent to improve selectivity and efficiency of artificial catalysts, particularly for the production of pharmaceutically interesting compounds.

15

The technical problem to be solved by the present invention was to provide a method for the tailored synthesis of a series of biaryldiphosphines. A further problem to be solved was to establish said process in a robust manner to provide suitable amounts of ligands for the pharmaceutical industry. Furthermore, the general concept should start with an easily available compound and should contain few reaction steps, allowing the synthesis of a wide variety of ligands, only depending on the reaction sequence.

20

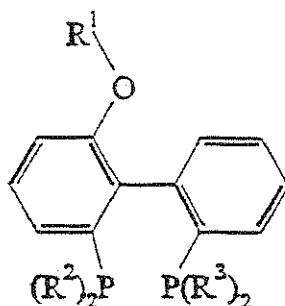
The problem could be solved according to the process of claim 1.

25

## SUMMARY

In one aspect, there is provided a process for the preparation of asymmetrically substituted biaryldiphosphine ligands of the formula

30



I,

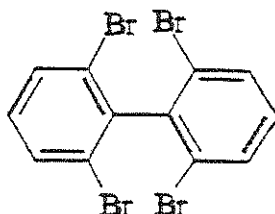
wherein  $R^1$  is  $C_{1-6}$ -alkyl or  $C_{5-10}$ -cycloalkyl optionally substituted with one or more halogen atoms, and

$R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,  $C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups,

or

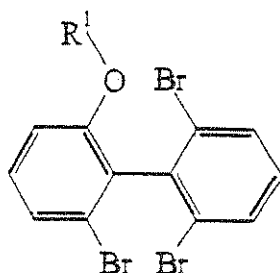
$R^2$  is  $C_{1-6}$ -alkyl or  $C_{5-10}$ -cycloalkyl, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy, di- $C_{1-6}$ -alkylamino and  $C_{5-10}$ -cycloalkyl group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms

comprising a first reaction sequence, wherein one bromine atom of 2,2',6,6'-tetrabromobiphenyl



III

is exchanged with  $OR^1$  by bromine-metal exchange and subsequent metal-hydroxy exchange, followed by an alkylation, to afford a compound of formula



IV

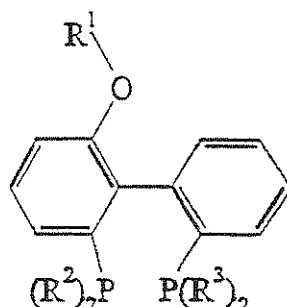
wherein  $R^1$  is as defined above,

and further reaction sequences, wherein each reaction sequence comprises at least one bromine-metal exchange and subsequent metal-substituent exchange with the respective substituent, thereby exchanging the respective bromine atoms with

substituents selected from the group consisting of hydrogen and diarylphosphino, di-C<sub>1-6</sub>-alkylphosphino and di-C<sub>5-10</sub>-cycloalkylphosphino.

In another aspect, there is provided compounds of formula

5



I,

10

wherein R<sup>1</sup> is C<sub>1-6</sub>-alkyl or C<sub>3-10</sub>-cycloalkyl optionally substituted with one or more halogen atoms, and

15

R<sup>2</sup> and R<sup>3</sup> are equal and are selected from the group consisting of aryl, C<sub>5-10</sub>-cycloalkyl and C<sub>1-6</sub>-alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups,

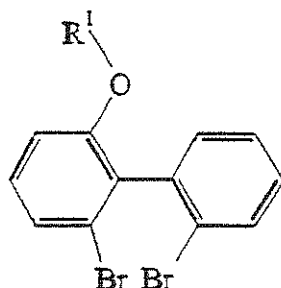
or

20

R<sup>2</sup> is C<sub>5-10</sub>-cycloalkyl or C<sub>1-6</sub>-alkyl, and R<sup>3</sup> is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups, and each C<sub>1-6</sub>-alkyl, C<sub>5-10</sub>-cycloalkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino group in R<sup>2</sup> and R<sup>3</sup> optionally being substituted with one or more halogen atoms.

In further aspect, there is provided compounds of formula

25

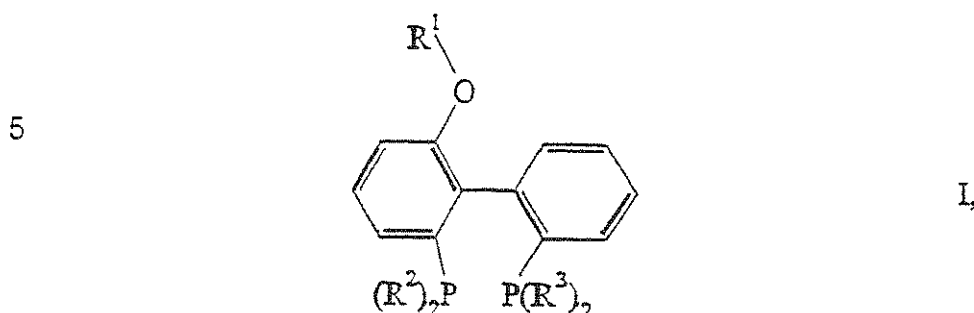


VI,

30

wherein R<sup>1</sup> is C<sub>1-6</sub>-alkyl or C<sub>3-10</sub>-cycloalkyl optionally substituted with one or more halogen atoms.

In yet another aspect, there is provided the use of compounds of formula I,



10 wherein R¹ is C<sub>1-6</sub>-alkyl or C<sub>3-10</sub>-cycloalkyl optionally substituted with one or more halogen atoms, and

R² and R³ are equal and are selected from the group consisting of aryl, C<sub>5-10</sub>-cycloalkyl and C<sub>1-6</sub>-alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups,

15 or

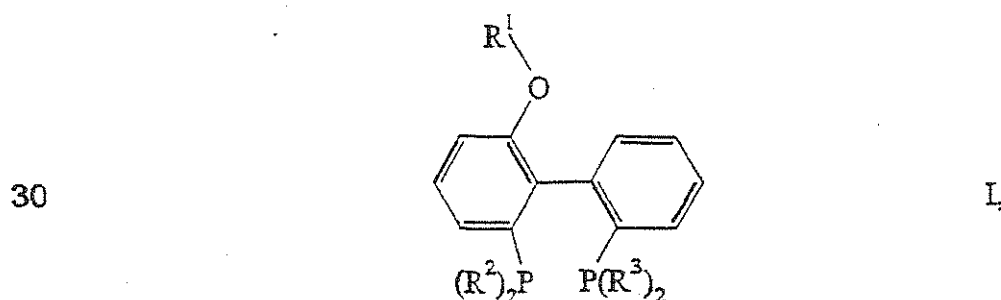
R² is C<sub>5-10</sub>-cycloalkyl or C<sub>1-6</sub>-alkyl, and R³ is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups,

20 and each C<sub>1-6</sub>-alkyl, C<sub>5-10</sub>-cycloalkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino group in R² and R³ optionally being substituted with one or more halogen atoms,

for the preparation of catalytic active complexes of transitions metal, preferably of ruthenium, rhodium or iridium.

#### DISCLOSURE OF OPTIONAL EMBODIMENTS

25 Provided is a process for the preparation of asymmetrically substituted biaryldiphosphine ligands of the formula



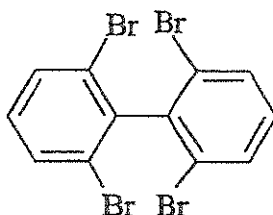
wherein  $R^1$  is  $C_{1-6}$ -alkyl or  $C_{3-10}$ -cycloalkyl optionally being substituted with one or more halogen atoms, and

$R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,  $C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups,

or

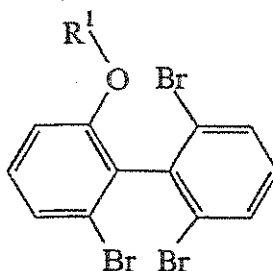
$R^2$  is  $C_{1-6}$ -alkyl or  $C_{5-10}$ -cycloalkyl, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy, di- $C_{1-6}$ -alkylamino and  $C_{5-10}$ -cycloalkyl group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms,

comprising a first reaction sequence, wherein one bromine atom of 2,2',6,6'-tetrabromobiphenyl



III

is exchanged with  $OR^1$  by bromine-metal exchange and subsequent metal-hydroxy exchange, followed by an alkylation, to afford a compound of formula



IV

wherein  $R^1$  is as defined above,

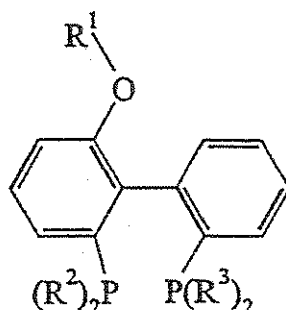
and further reaction sequences, wherein each reaction sequence comprises at least one bromine-metal exchange and subsequent metal-substituent exchange with the respective substituent, thereby exchanging the respective bromine atoms with substituents selected from the group consisting of hydrogen, diarylphosphino, di- $C_{1-6}$ -alkylphosphino and di- $C_{5-10}$ -cycloalkylphosphino.

The bromine-metal exchanges mentioned in the instant disclosure may be carried out with the required amount of the respective organometallic compound at a temperature below  $-40\text{ }^{\circ}\text{C}$  ("low temperature bromine-metal exchange") or at a temperature of at least  $0\text{ }^{\circ}\text{C}$  ("high temperature bromine-metal exchange").

5

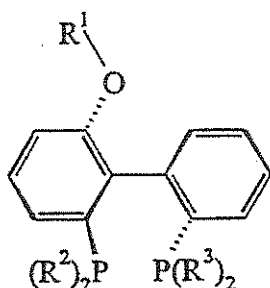
Chiral biaryldiphosphine ligands comprising a biaryl skeleton which is permanently twisted around the central carbon-carbon bond have two atropisomers. Asymmetric hydrogenation with transition metal complexes are preferably performed with one of the atropisomers and optionally further chiral auxiliaries. Therefore, it should be appreciated that any reference to ligands of formula

10

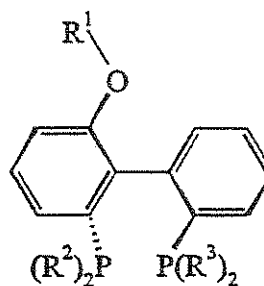


15

wherein  $R^1$ ,  $R^2$  and  $R^3$  are as defined above, implicitly includes its atropisomers



I'-S, and



I'-R

20

if not otherwise specified, e.g. by indicating their positive (+) or negative (−) optical rotation.

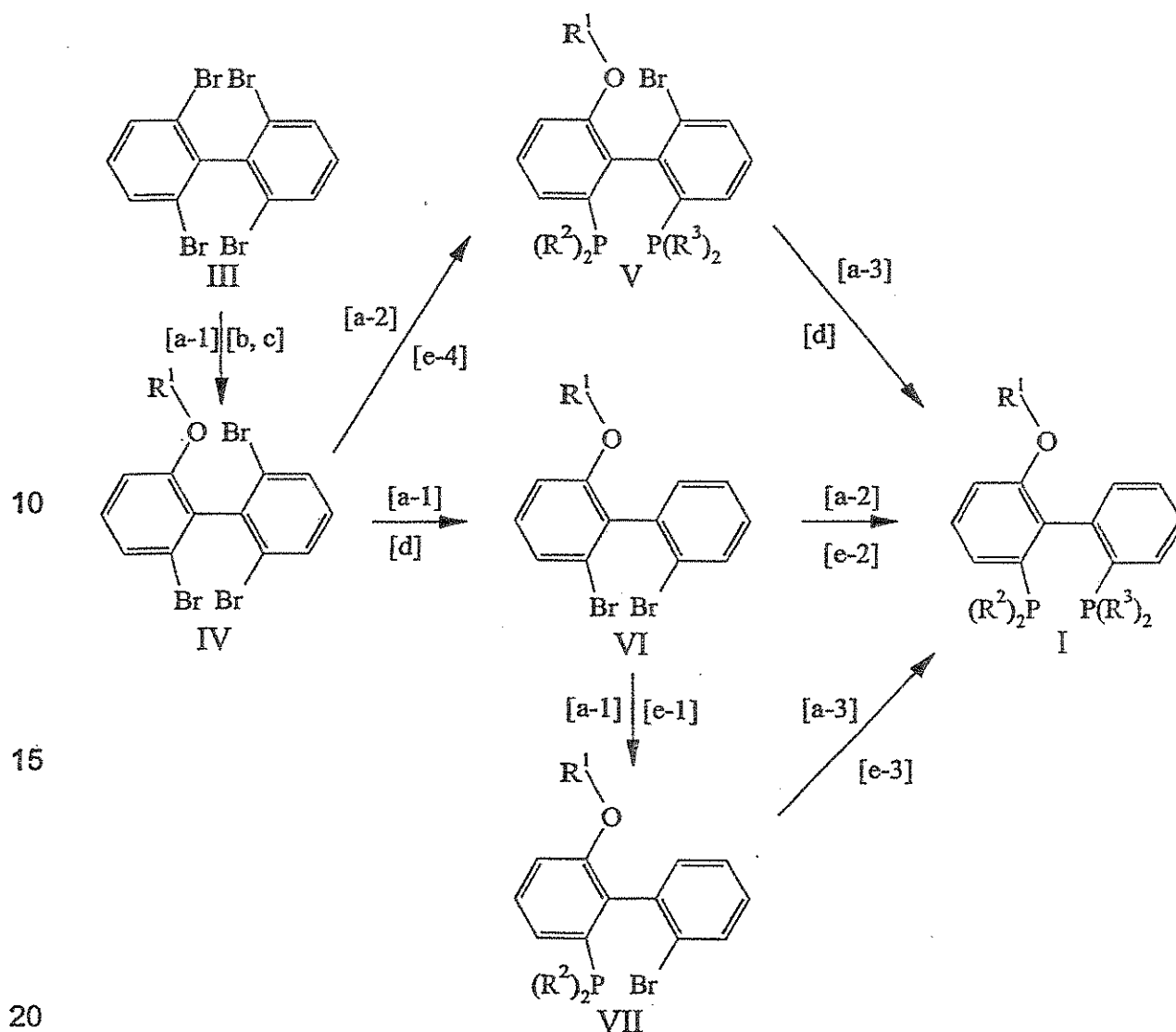
25

The undesired ring closure mentioned in Scheme 1 above can surprisingly be avoided by the inventive process. The reaction sequences of the present process for the preparation of compounds of formula I are depicted in Scheme 2. The synthetic approach of Scheme 2 starts with 2,2',6,6'-tetrabromo-1,1'-biphenyl (III), wherein one bromine atom of III is replaced by an alkoxy or cycloalkoxy group. Compound III can be obtained by condensation of 1,3-dibromo-2-iodobenzene (II) according to Rajca A. et al., *J. Am. Chem.*

30

*Soc.* 1996, 118, 7272-7279. According to Scheme 2 tailoring of ligands of formula I can be achieved by modification of the order, reaction temperature and equivalent amounts of agents of only 5 basic reactions (a to e).

- 5 Scheme 2: Preparation of ligands I from 2,2',6,6'-tetrabromobiphenyl (III) replacing one bromine atom with an organyl group



$R^1$ ,  $R^2$  and  $R^3$  as described therein,

[a-1] = 1 eq. low temperature bromine-metal exchange;

[a-2] = 2 eq. low temperature bromine-metal exchange;

[a-3] = 1 to 2 eq. high temperature bromine-metal exchange;

25 [b] = borane oxidation;

[c] = alkylation;

[d] = hydrogen quenching;

- [e-1] = 1 eq. metal-alkyl- or cycloalkylphosphine exchange;  
[e-2] = 2 eq. metal-alkyl- or cycloalkylphosphine exchange;  
[e-3] = 1 eq. metal-arylphosphine exchange;  
[e-4] = 2 eq. metal-arylphosphine exchange.

5

In a preferred embodiment, the first bromine-metal exchange of the compound of formula III is carried out with one equivalent of *n*-butyllithium at a temperature below  $-40^{\circ}\text{C}$  ("1 eq. low temperature bromine-metal exchange") in a polar solvent to afford a metallated intermediate. The following metal-hydroxy exchange is carried out by reacting the  
10 metallated intermediate with a borane or organoborate, and followed by reaction with a peroxy compound in the presence of an alkali and/or earth alkali hydroxide, and the alkylation is carried out with an alkylating agent in the presence of a base.

In a preferred embodiment, the borane or organoborate is fluorodimethoxyborane diethyl  
15 ether adduct, triisopropylborate or trimethylborate, preferably in ethereal solution.

In another preferred embodiment, the peroxy compound is selected from the group consisting of hydrogen peroxide, peracetic acid, *m*-chloroperbenzoic acid and *tert*-butyl hydroperoxide.

20

In yet another preferred embodiment, the alkali and/or earth alkali hydroxide in the reaction with the peroxy compound is selected from the group consisting of LiOH, NaOH, KOH,  $\text{Ca}(\text{OH})_2$  and  $\text{Mg}(\text{OH})_2$ .

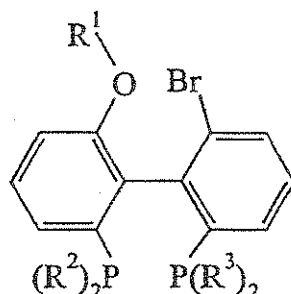
25 In a further preferred embodiment, the base of the alkylation reaction is an alkali and/or earth alkali hydroxide, selected from the group consisting of LiOH, NaOH, KOH,  $\text{Ca}(\text{OH})_2$  and  $\text{Mg}(\text{OH})_2$ .

In a preferred process the alkylating agent is a  $\text{C}_{1-6}$ -alkyl halide, a  $\text{C}_{5-10}$ -cycloalkyl halide  
30 or dimethyl sulfate. Preferably the  $\text{C}_{1-6}$ -alkyl halide is a  $\text{C}_{1-6}$ -alkyl bromide or  $\text{C}_{1-6}$ -alkyl iodide. Particularly preferred the alkylating agent is iodomethane or dimethyl sulfate.

In a preferred process, wherein a further reaction sequence is carried out starting from

compounds of formula IV above, comprising a low temperature bromine-metal exchange of two bromine atoms and subsequent metal-phosphine exchange, to afford a compound of formula

5



V,

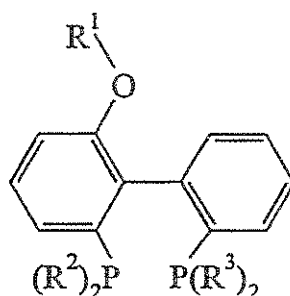
10 wherein R¹ is as defined above, and

R² and R³ are equal and are aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups, and each C<sub>1-6</sub>-alkyl, C<sub>5-10</sub>-cycloalkyl, C<sub>1-6</sub>-alkoxy and di-

15 atoms, and

the remaining bromine atom of the compound of formula V is replaced with hydrogen by high temperature bromine-metal exchange and subsequent reaction with a proton donor, to afford ligands of formula

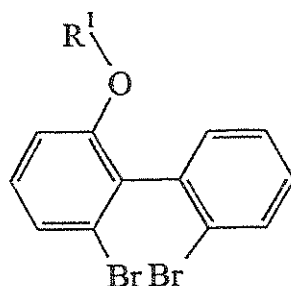
20



I,

25 wherein R¹, R² and R³ are as defined in compound V above.

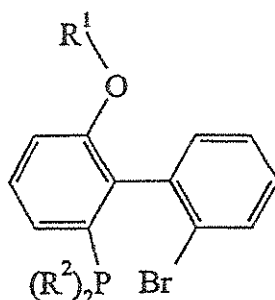
Provided is also a process, wherein a further reaction sequence is carried out starting from compounds of formula IV above, comprising a low temperature bromine-metal exchange of one bromine atom of the aryl moiety containing two bromine atoms and subsequent  
30 metal-hydrogen exchange by reaction with a proton donor, to afford a compound of formula



VI,

5 wherein  $R^1$  is as defined above, and  
 a further low temperature bromine-metal exchange of the remaining bromine atoms and  
 subsequent metal-phosphine exchange, affording ligands of formula I, wherein  $R^1$  is as  
 10 defined above, and  $R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,  
 $C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl, wherein each aryl moiety is optionally substituted with one  
 or more substituents selected from the group consisting of halogen atoms, nitro, amino,  
 $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cyclo-  
 alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^2$  and  $R^3$  optionally being substituted  
 15 with one or more halogen atoms.

Further provided is also a process, wherein a further reaction sequence is carried out  
 starting from compounds of formula IV above, comprising a low temperature bromine-  
 metal exchange of one bromine atom of the aryl moiety containing two bromine atoms and  
 20 subsequent metal-hydrogen exchange by reaction with a proton donor, to afford a  
 compound of formula VI, wherein  $R^1$  is as defined above, and a low temperature bromine-  
 metal exchange of one bromine atom and subsequent metal-phosphine exchange, to afford  
 a compound of formula



VII

25 wherein  $R^1$  is defined above, and  $R^2$  is  $C_{5-10}$ -cycloalkyl or  $C_{1-6}$ -alkyl, the  $C_{1-6}$ -alkyl or  
 $C_{5-10}$ -cycloalkyl group optionally being substituted with one or more halogen atoms, and  
 a high temperature bromine-metal exchange of the remaining bromine atom and  
 subsequent metal-phosphine exchange, affording ligands of formula I, wherein  $R^1$  and  $R^2$   
 30

are as defined above, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cycloalkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^3$  optionally being substituted with one or more halogen atoms.

5

In a preferred embodiment, each low temperature bromine-metal exchange is carried out with an organometallic compound such as *n*-butyllithium, isopropylmagnesium chloride or lithium tributylmagnesate at a temperature below  $-40\text{ }^{\circ}\text{C}$ , preferably in the range of  $-60$  to  $-90\text{ }^{\circ}\text{C}$ .

10 In a preferred embodiment each low temperature bromine-metal exchange is carried out in a polar solvent, preferably containing tetrahydrofuran.

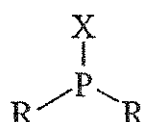
The removal of the last remaining bromine atom from compounds of formulae V and VII, as depicted in Scheme 2, requires different reaction conditions for the halogen-metal  
15 exchange. In this reaction sequence, in a preferred embodiment, the halogen-metal exchange is carried out with an organometallic compound such as *n*-butyllithium, *tert*-butyllithium, isopropylmagnesium chloride or lithium tributylmagnesate, at a temperature of at least  $0\text{ }^{\circ}\text{C}$ , preferably in the range of  $0$  to  $+40\text{ }^{\circ}\text{C}$ . The amount of the organometallic compound (1 to 2 equivalents) depends on the substituents attached to the biaryl moiety. In  
20 most cases one equivalent of the organometallic compound is sufficient to replace the halogen atom with the metal.

In a preferred embodiment the high temperature bromine-metal exchange is carried out in a solution containing toluene and/or tetrahydrofuran.

25 In a preferred embodiment the hydrogen donor is selected from the group consisting of  $C_{1-3}$ -alcohols, water, non-oxidizing inorganic proton acids, and  $C_{1-3}$ -alkanoic acids. Preferably the non-oxidizing inorganic proton acid is HCl.

Preferably, the reaction with the hydrogen donor (hydrogen quenching) is carried out at a  
30 temperature in the range of  $-60$  to  $-90\text{ }^{\circ}\text{C}$ .

In a preferred embodiment the metal-phosphine exchange is carried out using a halo-phosphine of the formula



VIII,

wherein X is chlorine, bromine or iodine and both substituents R are equal and are R<sup>2</sup> or R<sup>3</sup>, wherein R<sup>2</sup> and R<sup>3</sup> are as defined above.

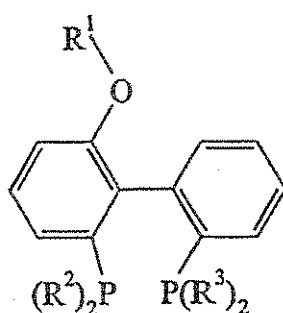
Depending on the intended substituents, the halophosphine of the formula VIII is selected from the group consisting of halodiarylphosphines, halodi-(C<sub>5-10</sub>-cycloalkyl)phosphines and halodi-(C<sub>1-6</sub>-alkyl)phosphines.

10

Each aryl substituent of the halodiarylphosphine moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups. Optionally each C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, di-C<sub>1-6</sub>-alkylamino and C<sub>5-10</sub>-cycloalkyl group of the halophosphine of the formula VIII is substituted with one or more halogen atoms. In a preferred embodiment the halophosphine of the formula VIII is selected from the group consisting of halodiarylphosphines and halodi-(C<sub>5-10</sub>-cycloalkyl)phosphines, more preferably is chlorodicyclohexylphosphine, bromodicyclohexylphosphine, chlorodiphenylphosphine or bromodiphenylphosphine.

20

Provided are compounds of formula



I,

25

wherein R<sup>1</sup> is C<sub>1-6</sub>-alkyl or C<sub>3-10</sub>-cycloalkyl optionally substituted with one or more halogen atoms, and

R<sup>2</sup> and R<sup>3</sup> are equal and are selected from the group consisting of aryl, C<sub>5-10</sub>-cycloalkyl and C<sub>1-6</sub>-alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups,

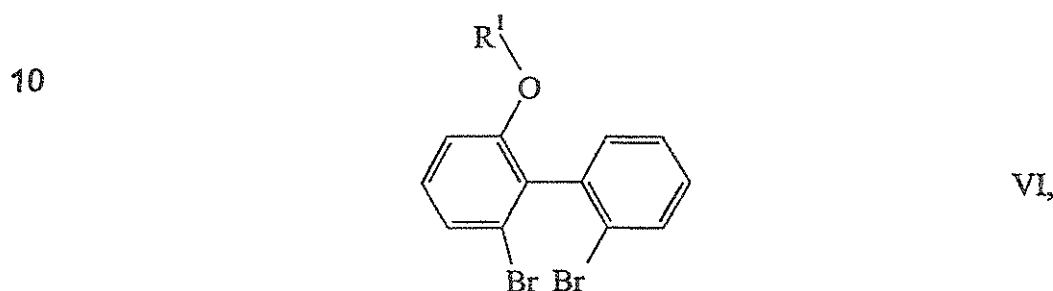
30

or

$R^2$  is  $C_{5-10}$ -cycloalkyl or  $C_{1-6}$ -alkyl, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups,

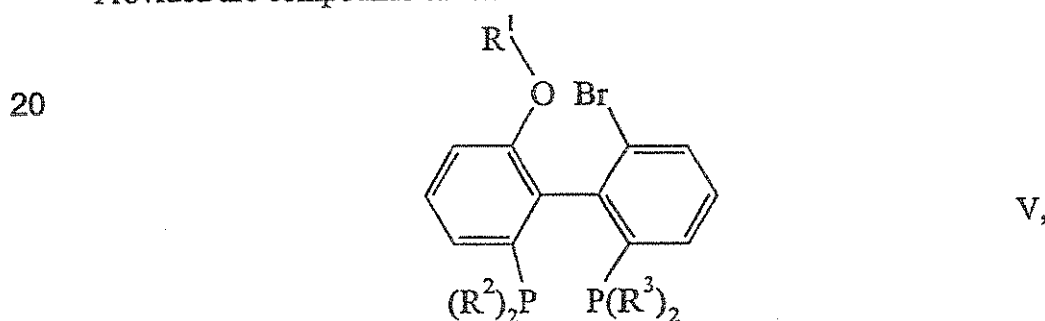
- 5 and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cycloalkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms.

Furthermore provided are compounds of formula



- 15 wherein  $R^1$  is  $C_{1-6}$ -alkyl or  $C_{3-10}$ -cycloalkyl optionally substituted with one or more halogen atoms.

Provided are compounds of formula



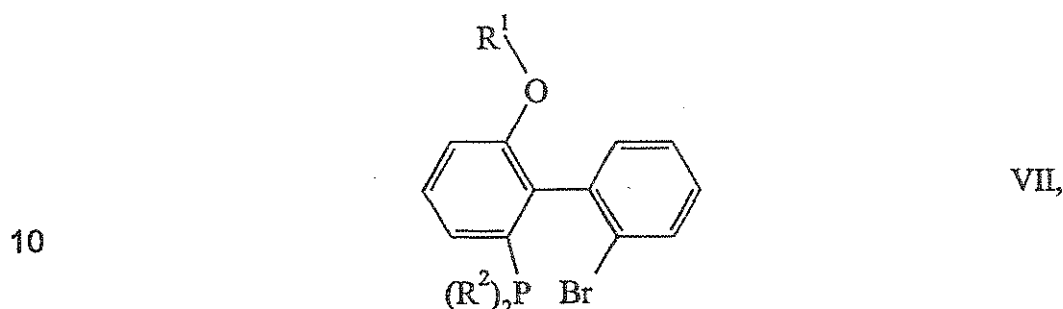
- 25 wherein  $R^1$  is  $C_{1-6}$ -alkyl or  $C_{3-10}$ -cycloalkyl optionally substituted with one or more halogen atoms, and  
 $R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,  $C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups,
- 30

or

$R^2$  is  $C_{5-10}$ -cycloalkyl or  $C_{1-6}$ -alkyl, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,

C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups,  
and each C<sub>1-6</sub>-alkyl, C<sub>5-10</sub>-cycloalkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino group in R<sup>2</sup> and R<sup>3</sup> optionally being substituted with one or more halogen atoms.

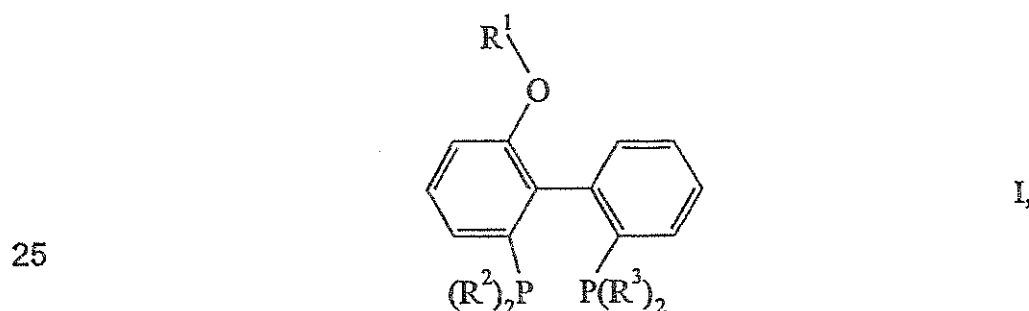
5 The invention provides compounds of formula



wherein R<sup>1</sup> is C<sub>1-6</sub>-alkyl or C<sub>3-10</sub>-cycloalkyl optionally substituted with one or more halogen atoms, and

15 R<sup>2</sup> is selected from the group consisting of aryl, C<sub>5-10</sub>-cycloalkyl and C<sub>1-6</sub>-alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkyl-amino groups, and each C<sub>1-6</sub>-alkyl, C<sub>5-10</sub>-cycloalkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino group in R<sup>2</sup> optionally being substituted with one or more halogen atoms.

20 Provided is the use of compounds of formula



wherein R<sup>1</sup> is C<sub>1-6</sub>-alkyl or C<sub>3-10</sub>-cycloalkyl optionally substituted with one or more halogen atoms, and

30 R<sup>2</sup> and R<sup>3</sup> are equal and are selected from the group consisting of aryl, C<sub>5-10</sub>-cycloalkyl and C<sub>1-6</sub>-alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups,

or

$R^2$  is  $C_{5-10}$ -cycloalkyl or  $C_{1-6}$ -alkyl, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cycloalkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms,

for the preparation of catalytic active complexes of transition metals, preferably of ruthenium, rhodium or iridium. Said catalytic active complexes of transition metals can be used for hydrogenating, preferably asymmetrically hydrogenating, of a compound containing at least one unsaturated prochiral system. Preferably the products obtained by said asymmetrically hydrogenating are enantiomerically pure compounds.

Several examples for general applicable methods for the preparations of catalysts and catalyst solutions are disclosed in Ashworth, T. V. et al. *S. Afr. J. Chem.* 1987, 40, 183-188, WO 00/29370 and Mashima, K. *J. Org. Chem.* 1994, 59, 3064-3076.

In a preferred embodiment the hydrogen pressure during hydrogenating is in the range of 1 to 60 bar, particularly preferred in the range of 2 to 35 bar.

In a further preferred embodiment hydrogenating is carried out at a temperature in the range of 0 to 150 °C.

In a preferred embodiment, the compounds containing at least one unsaturated prochiral system are selected from the group consisting of compounds containing a prochiral carbonyl group, a prochiral alkene group or a prochiral imine group.

In a particular preferred embodiment, the compound containing at least one unsaturated prochiral carbonyl, alkene or imine group is selected from the group consisting of  $\alpha$ - and  $\beta$ -ketoesters,  $\alpha$ - and  $\beta$ -ketoamines,  $\alpha$ - and  $\beta$ -ketoalcohols, acrylic acid derivatives, acylated enamines or N-substituted imines of aromatic ketones and aldehydes.

Preferably the hydrogenation reactions are carried out with a catalyst solution in a polar solvent like  $C_{1-4}$ -alcohols, water, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetonitrile (MeCN), ethers or mixtures thereof. Preferably the polar solvent contains methanol, ethanol or isopropyl alcohol or a mixture thereof. Particularly preferred, the solution may contain further additives.

The present invention is illustrated by the following non-limiting examples.

**Examples:**

**Example 1: 1,3-Dibromo-2-iodobenzene (II)**

- 5 Diisopropylamine (0.14 L, 0.10 kg, 1.0 mol) and 1,3-dibromobenzene (0.12 L, 0.24 kg, 1.0 mol) were consecutively added to a solution of *n*-butyllithium (1.0 mol) in tetrahydrofuran (2.0 L) and hexanes (0.64 L) at  $-75^{\circ}\text{C}$ . After 2 h at  $-75^{\circ}\text{C}$ , a solution of iodine (0.26 kg, 1.0 mol) in tetrahydrofuran (0.5 L) was added. The solvents were evaporated and the residue dissolved in diethyl ether (1.0 L). After washing with a 10% aqueous solution
- 10 of sodium thiosulfate ( $2 \times 0.1$  L), the organic layer was dried over sodium sulfate before being evaporated to dryness. Upon crystallization from ethanol (1.0 L) 0.33 kg (91%) colorless platelets were obtained;
- m.p.  $99$  to  $100^{\circ}\text{C}$ ;
- $^1\text{H}$ -NMR ( $\text{CHCl}_3$ , 400 MHz):  $\delta = 7.55$  (d,  $J = 8.1$  Hz, 2 H),  $7.07$  (t,  $J = 8.1$  Hz, 2 H).
- 15  $\text{C}_6\text{H}_3\text{Br}_2\text{I}$  (361.80): calculated (%) C 19.92, H 0.84; found C 19.97, H 0.80.

**Example 2: 2,2',6,6'-Tetrabromo-1,1'-biphenyl (III)**

- At  $-75^{\circ}\text{C}$  butyllithium (14 mmol) in hexanes (5.6 mL) was added to a solution of 1,3-dibromo-2-iodobenzene (4.3 g, 12 mmol) in diethyl ether (0.18 L). After the solution was
- 20 stirred for 2 h at  $-75^{\circ}\text{C}$ , copper(II)chloride (9.7 g, 72 mmol) was added, and the reaction mixture was allowed to attain  $25^{\circ}\text{C}$  over a 12 h period. Cold water was added to the reaction mixture and the organic layer was separated. The aqueous phase was extracted with ethyl acetate ( $2 \times 0.10$  L). The combined organic layers were dried over sodium sulfate before being evaporated. 2,2',6,6'-tetrabromo-1,1'-biphenyl precipitates upon treatment of
- 25 the residue with hexanes cooled to  $-20^{\circ}\text{C}$ . The product (9.0 g, 33%) is pure enough for further reaction;
- m.p.  $214$  to  $215^{\circ}\text{C}$ ;
- $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 7.67$  (d,  $J = 8.3$  Hz, 4 H),  $7.17$  (t,  $J = 8.0$  Hz, 2 H).

30 **Example 3: 2,6,6'-Tribromo-2'-methoxy-1,1'-biphenyl (IVa;  $\text{R}^1 = \text{Me}$ )**

To a solution of 2,2',6,6'-tetrabromo-1,1'-biphenyl (47 g, 0.10 mol) in tetrahydrofuran (0.50 L) *n*-Butyllithium (0.10 mol) in hexanes (63 mL) was added at  $-75^{\circ}\text{C}$ . The mixture was consecutively treated with fluorodimethoxyborane diethyl ether adduct (19 mL, 16 g,

0.10 mol), a 3.0 M aqueous solution of sodium hydroxide (36 mL) and 30% aqueous hydrogen peroxide (10 mL, 3.6 g, 0.10 mol). The reaction mixture was neutralized at 25 °C with 2.0 M hydrochloric acid (0.10 L) and extracted with diethyl ether (3×0.10 L). The combined organic layers were washed with a 10% aqueous solution of sodium sulfite (0.10 L), dried over sodium sulfate and evaporated. The oily residue was dissolved in dimethyl sulfoxide (0.20 L) before iodomethane (7.5 mL, 17 g, 0.12 mol) and potassium hydroxide powder (6.7 g, 0.12 mol) were consecutively added. After 1 h, water (0.50 L) was added and the product was extracted with diethyl ether (3×0.10 L). The organic layers were dried over sodium sulfate and evaporated. Crystallization from ethanol (0.10 L) afforded 35 g (82%) product as colorless cubes;  
m.p. 184 to 185 °C;  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.64 (d, *J* = 8.3 Hz, 2 H), 7.3 (m, 2 H), 7.11 (t, *J* = 8.1 Hz, 1 H), 6.96 (dd, *J* = 7.2, 2.2 Hz, 1 H), 3.77 (s, 3 H);  
C<sub>13</sub>H<sub>9</sub>Br<sub>3</sub>O (420.92): calculated (%) C 37.09, H 2.16; found C 37.10, H 2.03.

15

**Example 4: 6-Bromo-2,6'-bis(diphenylphosphinyl)-2'-methoxy-1,1'-biphenyl (Va; R<sup>1</sup> = Me and R<sup>2</sup> = R<sup>3</sup> = phenyl)**

At -75 °C, *n*-butyllithium (0.10 mol) in hexanes (57 mL) was added to a solution of compound IVa (21 g, 50 mmol) in tetrahydrofuran (0.25 L). The reaction mixture was treated with a 2.0 M solution of chlorodiphenylphosphine (18 mL, 22 g, 0.10 mol) in tetrahydrofuran (50 mL). The mixture was allowed to reach 25 °C and treated with a saturated aqueous solution of ammonium chloride (0.20 L). The reaction mixture was extracted with ethyl acetate (3×0.10 L), and the combined organic layers were dried over sodium sulfate. Evaporation of the solvents and crystallization from ethyl acetate (0.10 L) afforded 23 g (71%) colorless needles;  
m.p. 224 to 226 °C (decomposition);  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.56 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.38 (dt, *J* = 7.0, 1.6 Hz, 2 H), 7.3 (m, 12 H), 7.1 (m, 6 H), 6.99 (ddd, *J* = 7.7, 2.9, 1.3 Hz, 1 H), 6.8 (m, 3 H), 6.63 (d, *J* = 8.6 Hz, 1 H), 3.01 (s, 3 H);  
<sup>31</sup>P-NMR (CDCl<sub>3</sub>, 162 MHz): δ = -10.1 (d, *J* = 24.6 Hz), -13.9 (d, *J* = 24.9 Hz);  
C<sub>37</sub>H<sub>29</sub>BrOP<sub>2</sub> (631.49): calculated (%) C 70.37, H 4.63; found C 69.13, H 4.60.

**Example 5: 2',6-Bis(diphenylphosphinyl)-2-methoxy-1,1'-biphenyl (Ia;  $R^1 = \text{Me}$  and  $R^2 = R^3 = \text{phenyl}$ )**

At 0 °C, *n*-butyllithium (50 mmol) in hexanes (30 mL) was added to a solution of compound Va (16 g, 25 mmol) in toluene (0.1 L). After 45 min at 25 °C, methanol (2 mL) was added followed by water (25 mL) and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2×25 mL) and the combined organic layers were dried over sodium sulfate before being evaporated. Crystallization from dichloromethane (50 mL) afforded 7.9 g (57%) colorless prisms;

m.p. 227 to 228 °C (decomposition);

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 7.3 (m, 18 H), 7.15 (dt,  $J$  = 6.8, 2.6 Hz, 4 H), 7.06 (dt,  $J$  = 7.3, 1.7 Hz, 2 H), 6.82 (dd,  $J$  = 7.6, 4.2 Hz, 1 H), 6.77 (d,  $J$  = 8.2 Hz, 1 H), 6.66 (dd,  $J$  = 7.9 Hz, 3.1, 1 H), 3.22 (s, 3 H);

<sup>31</sup>P-NMR (CDCl<sub>3</sub>, 162 MHz):  $\delta$  = -13.1 (d,  $J$  = 17.8 Hz), -13.6 (d,  $J$  = 17.8 Hz);

C<sub>37</sub>H<sub>30</sub>OP<sub>2</sub> (552.59): calculated (%) C 80.42, H 5.47; found C 80.53, H 5.52.

**Example 6: 2',6-Dibromo-2-methoxy-1,1'-biphenyl (VIa;  $R^1 = \text{Me}$ )**

At -75 °C, *n*-butyllithium (25 mmol) in hexanes (13 mL) was added to a solution of compound IVa (11 g, 25 mmol) in tetrahydrofuran (0.20 L). Immediately after the addition was completed, methanol (2.0 mL) was added. After addition of water (0.10 L) the organic phase was separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over sodium sulfate before being evaporated. After crystallization from ethanol (25 mL) 7.9 g (92%) 2',6-dibromo-2-methoxy-1,1'-biphenyl was obtained as colorless cubes;

m.p. 93 to 95 °C;

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 7.67 (d,  $J$  = 8.0 Hz, 1 H), 7.38 (t,  $J$  = 7.5 Hz, 1 H), 7.3 (m, 4 H), 6.92 (d,  $J$  = 8.1 Hz, 1 H), 3.73 (s, 3 H);

C<sub>13</sub>H<sub>10</sub>Br<sub>2</sub>O (342.03): calculated (%) C 45.32, H 2.95; found C 45.32, H 2.85.

**Example 7: 2',6-Bis(dicyclohexylphosphinyl)-2-methoxy-1,1'-biphenyl (Ib;  $R^1 = \text{Me}$ ,  $R^2 = R^3 = \text{cyclohexyl}$ )**

At -75 °C, *n*-butyllithium (0.10 mol) in hexanes (63 mL) was added to a solution of compound VIIa (17 g, 50 mmol) in tetrahydrofuran (0.25 L). After the addition was completed, the mixture was treated with a 2.0 M solution of chlorodicyclohexylphosphine

(22 mL, 24 g, 0.10 mol) in tetrahydrofuran (50 mL). The mixture was allowed to reach 25 °C and treated with a saturated aqueous solution of ammonium chloride (0.10 L). The mixture was extracted with ethyl acetate (3×50 mL), and the combined organic layers were dried over sodium sulfate. The diphosphine 43 g (74%) was obtained after evaporation of the solvents and crystallization from methanol (0.10 L) as colorless cubes;

m.p. 220 to 221 °C (decomposition);

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.56 (m sym., 1 H), 7.4 (m, 3 H), 7.16 (d, *J* = 7.5 Hz, 1 H), 7.08 (m sym., 1 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 3.66 (s, 3 H), 1.7 (m, 24 H), 1.2 (m, 20 H);

<sup>31</sup>P-NMR (CDCl<sub>3</sub>, 162 MHz): δ = -9.9 (d, *J* = 12.1 Hz), -11.5 (d, *J* = 12.2 Hz);  
C<sub>37</sub>H<sub>54</sub>OP<sub>2</sub> (576.79): calculated (%) C 77.05, H 9.44; found C 77.17, H 9.14.

**Example 8: (2'-Bromo-6-methoxy-1,1'-biphenyl-2-yl)dicyclohexylphosphine (VIIa; R<sup>1</sup> = Me and R<sup>2</sup> = cyclohexyl)**

At -75 °C, *n*-butyllithium (0.10 mol) in hexanes (63 mL) was added to a solution of compound VIa (34 g, 0.10 mol) in tetrahydrofuran (0.50 L). After the addition was completed, the mixture was treated with a 2.0 M solution of chlorodicyclohexylphosphine (22 mL, 24 g, 0.10 mol) in tetrahydrofuran (0.10 L). The mixture was allowed to reach 25 °C and treated with a saturated aqueous solution of ammonium chloride (0.20 L). The mixture was extracted with ethyl acetate (3×0.10 L), and the combined organic layers were dried over sodium sulfate. Evaporation of the solvents and crystallization from a 9 : 1 mixture (v/v) hexanes / ethyl acetate (50 mL) afforded 36 g (79%) colorless needles;

m.p. 100 to 102 °C;

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.61 (d, *J* = 7.8 Hz, 1 H), 7.38 (t, *J* = 7.9 Hz, 1 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 7.21 (dt, *J* = 7.9, 1.5 Hz, 2 H), 7.14 (dd, *J* = 7.6, 1.8 Hz, 1 H), 6.96 (d, *J* = 8.2 Hz, 1 H), 3.72 (s, 3 H), 1.7 (m, 12 H), 1.2 (m, 10 H);

<sup>31</sup>P-NMR (CDCl<sub>3</sub>, 162 MHz): δ = -13.8 (s);

C<sub>25</sub>H<sub>32</sub>BrOP (459.41): calcd. (%) C 65.36, H 7.02; found C 65.52, H 7.07.

**Example 9: 6-Dicyclohexylphosphanyl-2'-diphenylphosphanyl-2-methoxy-1,1'-biphenyl (Ic; R<sup>1</sup> = Me, R<sup>2</sup> = cyclohexyl and R<sup>3</sup> = phenyl)**

At 0 °C, *n*-butyllithium (25 mmol) in hexanes (30 mL) was added to a solution of compound VIIa (11 g, 25 mmol) in toluene (0.1 L). After 45 min the mixture was cooled to

- 75 °C and a 1.0 M solution of chlorodiphenylphosphine (4.4 mL, 5.5 g, 25 mmol) in toluene (25 mL) was added. The mixture was allowed to reach 25 °C. A saturated aqueous solution of ammonium chloride (50 mL) was added and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (3×25 mL) and the combined organic layers were dried over sodium sulfate before being evaporated. Crystallization from methanol (50 mL) gave 7.9 g (56%) of diphosphine as colorless cubes; m.p. 170 to 171 °C;
- <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.3 (m, 16 H), 6.78 (d, *J* = 7.9 Hz, 1 H), 3.23 (s, 3 H);
- <sup>31</sup>P-NMR (CDCl<sub>3</sub>, 162 MHz): δ = -11.3 (d, *J* = 10.7 Hz), -14.0 (d, *J* = 10.8 Hz);
- 10 C<sub>37</sub>H<sub>42</sub>OP<sub>2</sub> (564.69): calculated (%) C 78.70, H 7.50; found C 78.59, H 7.43.

**Example 10: (-)- and (+)-6-dicyclohexylphosphanyl-2'-diphenylphosphinyl-2-methoxy-1,1'-biphenyl (Ic; R<sup>1</sup> = Me, R<sup>2</sup> = cyclohexyl and R<sup>3</sup> = phenyl)**

- The racemic diphosphine Ic was separated into its enantiomers by preparative chromatography using a chiral stationary phase. The column used was CHIRALCEL<sup>®</sup> OD 20 μm, the mobile phase was n-Heptane / EtOH 2000:1. From 360 mg racemic material 142 mg of (+)-6-dicyclohexylphosphanyl-2'-diphenylphosphanyl-2-methoxy-1,1'-biphenyl and 123 mg of (-)-6-dicyclohexylphosphanyl-2'-diphenylphosphanyl-2-methoxy-1,1'-biphenyl were isolated. The enantiomeric purity of both compound was 100% (measured by HPLC on an analytic CHIRALCEL<sup>®</sup> OD 10 μm column), the optical rotation of the (-)-isomer is α<sub>D</sub><sup>24</sup> (*c* = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>) = -1.4.
- 15
- 20

**Example 11: (-)- and (+)-2',6-bisdicyclohexylphosphinyl-2-methoxy-1,1'-biphenyl (Ib; R<sup>1</sup> = Me, R<sup>2</sup> = R<sup>3</sup> = cyclohexyl)**

- The separation was performed as described in example 10. The enantiomeric purity was 99.2% for the (-)-isomer and 96.9% for the (+)-isomer (measured by HPLC on an analytic CHIRALCEL<sup>®</sup> OD 10 μm column), the optical rotation of the (+)-isomer is α<sub>D</sub><sup>24</sup> (*c* = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>) = 16.4.
- 25

- Example 12: (-)- and (+)-2',6-bisdiphenylphosphinyl-2-methoxy-1,1'-biphenyl (Ia; R<sup>1</sup> = Me, R<sup>2</sup> = R<sup>3</sup> = phenyl)**
- 30

The separation was performed as described in example 10. The optical rotation of the (+)-isomer is α<sub>D</sub><sup>20</sup> (*c* = 0.5 in CHCl<sub>3</sub>) = 6.0.

**Example 13: (S)-Ethyl 3-hydroxybutyrate**

In a 150 mL autoclave under argon atmosphere RuCl<sub>3</sub> (5.3 mg, 0.026 mmol), (+)-ligand Ia (14.3 mg, 0.026 mmol) and ethyl acetoacetate (0.65 g, 5.0 mmol) is dissolved in degassed ethanol (30 mL). After flushing the autoclave with argon hydrogenation is carried out during 6 h at 50°C and at 4 bar hydrogen pressure. After cooling to room temperature the reaction solution is directly analyzed by GC for conversion (column: HP-101 25 m / 0.2 mm) and, after derivatization with trifluoroacetic acid anhydride, enantiomeric excess (column: Lipodex-E 25 m / 0.25 mm). Conversion is 99.7% at an ee of 99.0%.

**Example 14: (R)-Ethyl 3-hydroxybutyrate**

In a 15 mL autoclave under argon atmosphere RuCl<sub>3</sub> (1.5 mg, 0.007 mmol), (–)-ligand Ib (4.3 mg, 0.007 mmol) and ethyl acetoacetate (0.15 g, 1.1 mmol) is dissolved in degassed ethanol (7 mL). After flushing the autoclave with argon hydrogenation is carried out during 15 h at 50°C and at 4 bar hydrogen pressure. After cooling to room temperature the reaction solution is directly analyzed by GC for conversion (column: HP-101 25 m / 0.2 mm) and, after derivatization with trifluoroacetic acid anhydride, enantiomeric excess (column: Lipodex-E 25 m / 0.25 mm). Conversion is 98.3% at an ee of 86.7%.

**Example 15: (R)-Ethyl 4-chloro-3-hydroxybutyrate**

In a 150 mL autoclave in an argon atmosphere bis(1-isopropyl-4-methylbenzene)dichlororuthenium (7.6 mg, 0.012 mmol), (+)-ligand Ia (14.0 mg, 0.025 mmol) and ethyl 4-chloro-3-oxobutyrate 98.4% (0.83 g, 5.0 mmol) is dissolved in degassed ethanol (30 mL). After flushing the autoclave with argon hydrogenation is carried out during 4 h at 80 °C and at 4 bar hydrogen pressure. After cooling to room temperature the reaction solution is directly analyzed by GC for conversion (column: HP-101 25 m / 0.2 mm) and ee (column: Lipodex-E 25 m / 0.25 mm). Conversion is 99.9% at an ee of 88%.

**Example 16: (S)-Ethyl 4-chloro-3-hydroxybutyrate**

In a 150 mL autoclave under argon atmosphere bis(1-isopropyl-4-methylbenzene)dichlororuthenium (7.5 mg, 0.012 mmol), (+)-ligand Ic (14.4 mg, 0.025 mmol) and ethyl 4-chloro-3-oxobutyrate (0.83 g, 5.0 mmol) is dissolved in degassed ethanol (30 mL). After flushing the autoclave with argon hydrogenation is carried out during 3 h at 80 °C and at 4 bar hydrogen pressure. After cooling to room temperature the reaction solution is directly

analyzed by GC for conversion (column: HP-101 25 m / 0.2 mm) and ee (column: Lipodex-E 25 m / 0.25 mm). Conversion is 100% at an ee of 80%.

**Example 17: *N*-Acetyl-D-phenylalanine**

- 5 In a 15 mL autoclave in an argon atmosphere bis(benzene)dichlor-ruthenium (2.6 mg, 0.005 mmol), (+)-ligand Ia (6.0 mg, 0.011 mmol) and *N*-acetylaminocinnamic acid (0.53 g, 2.5 mmol) is dissolved in degassed methanol (5 mL). After flushing the autoclave with argon hydrogenation is carried out during 16 h at 40 °C and at 50 bar hydrogen pressure. After cooling to room temperature the reaction solution is evaporated and the residue
- 10 analysed by HPLC for conversion (column: Bischoff Kromasil 100 C8) and enantiomeric excess (column: Nucleodex Beta-PM). Conversion is 100% at an ee of 43%.

**Example 18: *N*-Acetyl-L-phenylalanine**

- In a 15 mL autoclave in an argon atmosphere bis(benzene)dichlor-ruthenium (2.6 mg,
- 15 0.005 mmol), (–)-ligand Ib (3.2 mg, 0.006 mmol) and 2-(*N*-acetyl-amino)-cinnamic acid (0.53 g, 2.5 mmol) is dissolved in degassed methanol (5 mL). After flushing the autoclave with argon hydrogenation is carried out during 15 h at 40 °C and at 50 bar hydrogen pressure. After cooling to room temperature the reaction solution is evaporated and the residue analysed by HPLC for conversion (column: Bischoff Kromasil 100 C8) and
- 20 enantiomeric excess (column: Nucleodex Beta-PM). Conversion is 34% at an ee of 66%.

**Example 19: (*S*)-2-Acetyl-amino-3-phenyl-propionic acid methyl ester**

- In a 15 mL autoclave in an argon atmosphere bis(1,5-cyclooctadiene)-rhodium(I) tetra-
- 25 fluoroborate (1.9 mg, 0.005 mmol), (+)-ligand Ic (2.8 mg, 0.005 mmol) and methyl 2-(*N*-acetyl-amino)-cinnamate (0.10 g, 0.5 mmol) is dissolved in degassed methanol (6 mL). After flushing the autoclave with argon hydrogenation is carried out during 15 h at 25 °C and at 2 bar hydrogen pressure. After cooling to room temperature the reaction solution is evaporated and the residue analysed by HPLC for conversion (column: Bischoff Kromasil 100 C8) and by GC for enantiomeric excess (column: Lipodex-E 25 m / 0.25 mm).
- 30 Conversion is 100% at an ee of 93.8%.

**Example 20: (*R*)-*N*-Benzyl-1-phenylethylamine**

In a 15 mL autoclave in an argon atmosphere bis(1,5-cyclooctadiene)-di(iridium(I))di

chloride) 98% (6.7 mg, 0.010 mmol), (+)-ligand Ia (11.0 mg, 0.020 mmol), benzylamine (5.6 mg, 0.052 mmol) and *N*-benzyl-*N*-(1-phenylethylidene)amine (0.21 g, 1.0 mmol) is dissolved in degassed methanol (5 mL) and stirred for 1h at room temperature. After flushing the autoclave with argon hydrogenation is carried out during 17 h at 30 °C and at 50 bar hydrogen pressure. The reaction solution is directly analysed by GC for conversion (column: HP-101 25 m / 0.2 mm) and enantiomeric excess (column: Macherey-Nagel, Nucleodex Beta-PM CC200/4). Conversion is 100% at an ee of 29%.

**Example 21: (*S*)-*N*-Benzyl-1-phenylethylamine**

In a 15 mL autoclave in an argon atmosphere bis(1,5-cyclooctadiene)-di(iridium(I))dichloride 98% (6.7 mg, 0.010 mmol), (+)-ligand Ic (5.7 mg, 0.010 mmol), benzylamine (5.6 mg, 0.052 mmol) and *N*-benzyl-*N*-(1-phenylethylidene)amine (0.21 g, 1.0 mmol) is dissolved in degassed methanol (5 mL) and stirred for 1h at room temperature. After flushing the autoclave with argon hydrogenation is carried out during 15 h at 30 °C and at 50 bar hydrogen pressure. The reaction solution is directly analysed by GC for conversion (column: HP-101 25 m / 0.2 mm) and enantiomeric excess (column: Macherey-Nagel, Nucleodex Beta-PM CC200/4). Conversion is 100% at an ee of 10%.

**Example 22: (*R*)-Dimethyl methylsuccinate**

Bis(1,5-cyclooctadiene)-rhodium(I) tetrafluoroborate (2.1 mg, 0.005 mmol) and ligand (+)-Ic (3.1 mg, 0.005 mmol) are dissolved in 5 mL degassed methanol in a 15 mL autoclave under argon atmosphere. Dimethyl itaconate (97%, 0.15 g, 0.9 mmol) is added via syringe. After flushing the autoclave with argon, hydrogenation is carried out during 15 h at 23 °C and at 2 bar hydrogen pressure. The reaction solution is directly analysed by GC for conversion (column: HP-101 25 m / 0.2 mm) and enantiomeric excess (column: Macherey-Nagel, Nucleodex Beta-PM CC200/4). Conversion is 100% at an ee of 30%.

**Example 23: (*R*)-Dimethyl methylsuccinate**

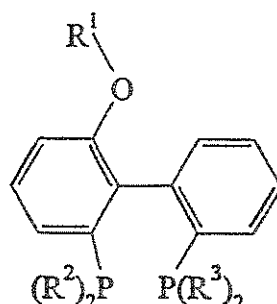
Bis(1,5-cyclooctadiene)-rhodium(I) tetrafluoroborate (2.1 mg, 0.005 mmol) and (–)-ligand Ib (3.2 mg, 0.006 mmol) are dissolved in 5 mL degassed methanol in a 15 mL autoclave under argon atmosphere. Dimethyl itaconate (97%, 0.15 g, 0.9 mmol) is added via syringe. After flushing the autoclave with argon, hydrogenation is carried out during 15 h at 23 °C and at 2 bar hydrogen pressure. The reaction solution is directly analysed by GC for

conversion (column: HP-101 25 m / 0.2 mm) and enantiomeric excess (column: Macherey-Nagel, Nucleodex Beta-PM CC200/4). Conversion is 60% at an ee of 24%.

## Claims

1. A process for the preparation of asymmetrically substituted biaryldiphosphine ligands of the formula

5



I,

10

wherein  $R^1$  is  $C_{1-6}$ -alkyl or  $C_{3-10}$ -cycloalkyl optionally substituted with one or more halogen atoms, and

$R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,

$C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups,

15

or

$R^2$  is  $C_{1-6}$ -alkyl or  $C_{5-10}$ -cycloalkyl, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and

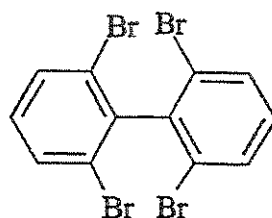
20

each  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy, di- $C_{1-6}$ -alkylamino and  $C_{5-10}$ -cycloalkyl group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms

comprising a first reaction sequence, wherein one bromine atom of

25

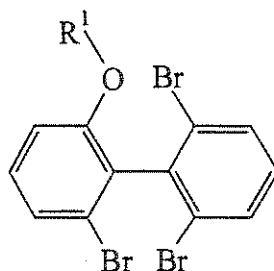
2,2',6,6'-tetrabromobiphenyl



III

30

is exchanged with  $OR^1$  by bromine-metal exchange and subsequent metal-hydroxy exchange, followed by an alkylation, to afford a compound of formula



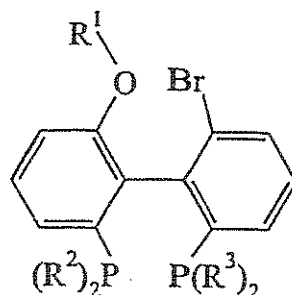
IV

wherein R<sup>1</sup> is as defined above,

and further reaction sequences, wherein each reaction sequence comprises at least one bromine-metal exchange and subsequent metal-substituent exchange with the respective substituent, thereby exchanging the respective bromine atoms with substituents selected from the group consisting of hydrogen and diarylphosphino, di-C<sub>1-6</sub>-alkylphosphino and di-C<sub>5-10</sub>-cycloalkylphosphino.

2. The process of claim 1, wherein the first bromine-metal exchange is carried out with one equivalent of *n*-butyllithium at a temperature below -40 °C, the metal-hydroxy exchange is carried out with a borane or organoborate, and followed by reaction with a peroxy compound in the presence of an alkali and/or earth alkali hydroxide, and the alkylation is carried out with an alkylating agent in the presence of a base.
3. The process of claim 2, wherein the borane or organoborate is fluoromethoxyborane ethyl ether adduct or trimethylborate.
4. The process of claim 2 or 3, wherein the peroxy compound is selected from the group consisting of hydrogen peroxide, peracetic acid, *m*-chloroperbenzoic acid and *tert*-butyl peroxide.
5. The process of any of claims 2 to 4, wherein the alkylating agent is a C<sub>1-6</sub>-alkyl halide, a C<sub>5-10</sub>-cycloalkyl halide or dimethyl sulfate.
6. The process of any of claims 1 to 5, wherein a further reaction sequence is carried out starting from compounds of formula IV, comprising a low temperature bromine-metal exchange of two bromine atoms and subsequent metal-phosphine exchange, to afford a compound of formula

5

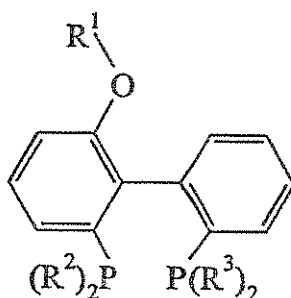


V,

10

wherein  $R^1$  is as defined above, and  $R^2$  and  $R^3$  are equal and are aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cycloalkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms, and the remaining bromine atom of the compound of formula V is replaced with hydrogen by high temperature bromine-metal exchange and subsequent reaction with a proton donor, to afford ligands of formula

15



I,

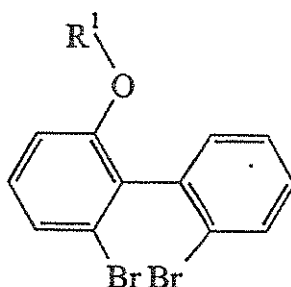
20

wherein  $R^1$ ,  $R^2$  and  $R^3$  are as defined in compound V above.

25

7. The process of any of claims 1 to 5, wherein a further reaction sequence is carried out starting from compounds of formula IV, comprising a low temperature bromine-metal exchange of one bromine atom and subsequent metal-hydrogen exchange by reaction with a proton donor, to afford a compound of formula

30

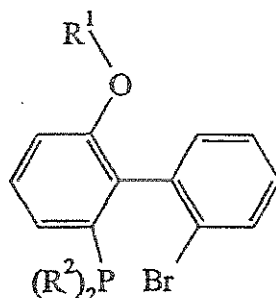


VI,

wherein  $R^1$  is as defined above, and a further low temperature bromine-metal

exchange of the remaining bromine atoms and subsequent metal-phosphine exchange, affording ligands of formula I, wherein  $R^1$  is as defined above, and  $R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,  $C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cycloalkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms.

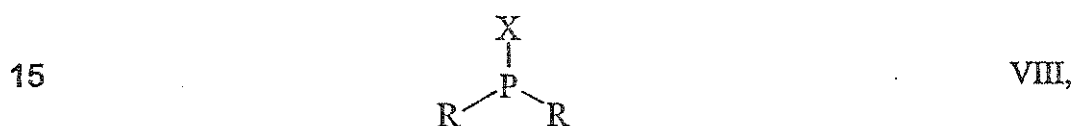
8. The process of any of claims 1 to 5, wherein a further reaction sequence is carried out starting from compounds of formula IV, comprising a low temperature bromine-metal exchange of one bromine atom and subsequent metal-hydrogen exchange by reaction with a proton donor, to afford a compound of formula VI, wherein  $R^1$  is as defined above, and a low temperature bromine-metal exchange of one bromine atom and subsequent metal-phosphine exchange, to afford a compound of formula



VII

- wherein  $R^1$  is defined above, and  $R^2$  is  $C_{5-10}$ -cycloalkyl or  $C_{1-6}$ -alkyl, the  $C_{1-6}$ -alkyl or  $C_{5-10}$ -cycloalkyl group optionally being substituted with one or more halogen atoms, and a high temperature bromine-metal exchange of the remaining bromine atom and subsequent metal-phosphine exchange, affording ligands of formula I, wherein  $R^1$  and  $R^2$  are as defined above, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cycloalkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^3$  optionally being substituted with one or more halogen atoms.

9. The process of any of claims 6 to 8, wherein each low temperature bromine-metal exchange is carried out with *n*-butyllithium at a temperature below  $-40^{\circ}\text{C}$ , preferably in the range of  $-40$  to  $-90^{\circ}\text{C}$ .
- 5 10. The process of any of claims 6 or 8, wherein the high temperature bromine-metal exchange is carried out with *n*-butyllithium or *tert*-butyllithium at a temperature of at least  $+0^{\circ}\text{C}$ , preferably in the range of  $+0$  to  $+40^{\circ}\text{C}$ .
11. The process of any of claims 6 to 8, wherein the hydrogen donor is selected from the  
10 group consisting of  $\text{C}_{1-3}$ -alcohols, water,  $\text{HCl}$  and  $\text{C}_{1-3}$ -alkanoic acids.
12. The process of any of claims 6 to 8, wherein the metal-phosphine exchange is carried out using a halophosphine of the formula

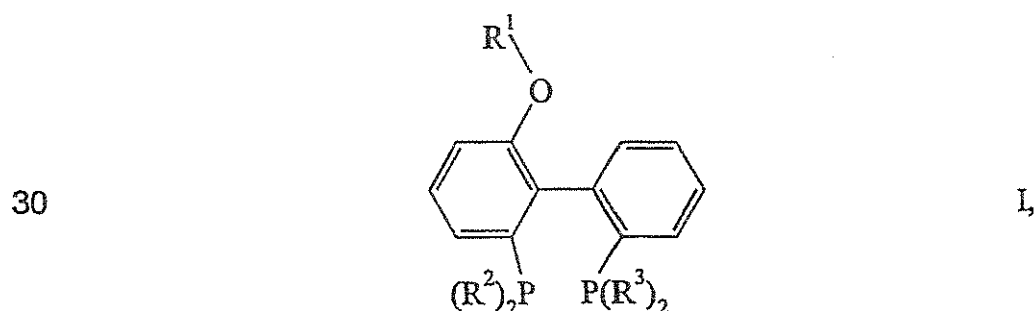


wherein X is chlorine, bromine or iodine and R are equal and are  $\text{R}^2$  or  $\text{R}^3$ , wherein  $\text{R}^2$  and  $\text{R}^3$  are as defined above.

- 20 13. The process of claim 12, wherein the halophosphine of the formula VIII selected from the group consisting of halodi- $(\text{C}_{5-10}$ -cycloalkyl)phosphines and halodiarylphosphines, preferably is selected from the group consisting of chlorodicyclohexylphosphine, bromodicyclohexylphosphine, chlorodiphenylphosphine or bromodiphenylphosphine.

25

14. Compounds of formula



wherein  $\text{R}^1$  is  $\text{C}_{1-6}$ -alkyl or  $\text{C}_{3-10}$ -cycloalkyl optionally substituted with one or more

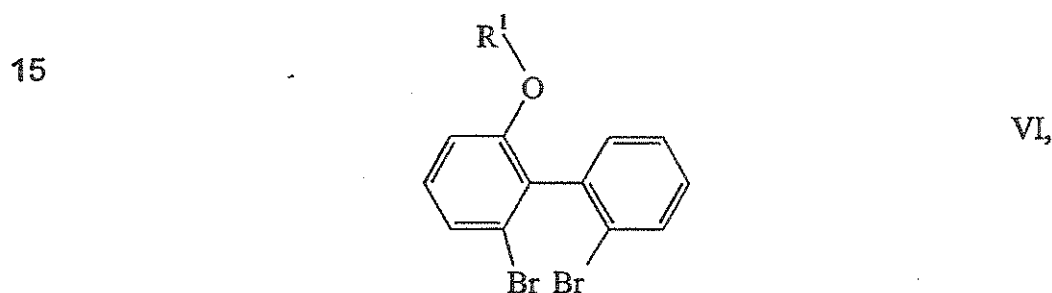
halogen atoms, and

$R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,  $C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl, wherein each aryl moiety is optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups,

or

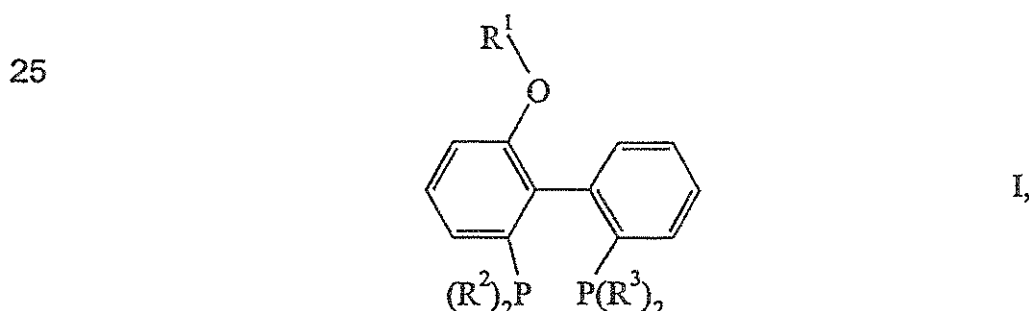
$R^2$  is  $C_{5-10}$ -cycloalkyl or  $C_{1-6}$ -alkyl, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cycloalkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms.

15. Compounds of formula



20 wherein  $R^1$  is  $C_{1-6}$ -alkyl or  $C_{3-10}$ -cycloalkyl optionally substituted with one or more halogen atoms.

16. Use of compounds of formula I,



30 wherein  $R^1$  is  $C_{1-6}$ -alkyl or  $C_{3-10}$ -cycloalkyl optionally substituted with one or more halogen atoms, and

$R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,  $C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl, wherein each aryl moiety is optionally substituted

with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups,

or

5 R<sup>2</sup> is C<sub>5-10</sub>-cycloalkyl or C<sub>1-6</sub>-alkyl, and R<sup>3</sup> is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino groups,

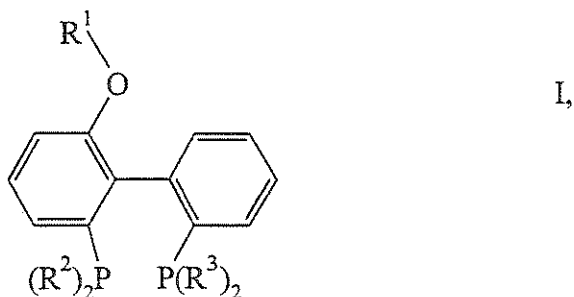
and each C<sub>1-6</sub>-alkyl, C<sub>5-10</sub>-cycloalkyl, C<sub>1-6</sub>-alkoxy and di-C<sub>1-6</sub>-alkylamino group in R<sup>2</sup> and R<sup>3</sup> optionally being substituted with one or more halogen atoms,

10 for the preparation of catalytic active complexes of transitions metal, preferably of ruthenium, rhodium or iridium.

## Abstract

Process for the preparation of asymmetrically substituted biphenyldiphosphines

5



10

wherein  $R^1$  is  $C_{1-6}$ -alkyl or  $C_{3-10}$ -cycloalkyl optionally substituted with one or more halogen atoms, and

$R^2$  and  $R^3$  are equal and are selected from the group consisting of aryl,  $C_{5-10}$ -cycloalkyl and  $C_{1-6}$ -alkyl,

or

15

$R^2$  is  $C_{5-10}$ -cycloalkyl or  $C_{1-6}$ -alkyl, and  $R^3$  is aryl optionally substituted with one or more substituents selected from the group consisting of halogen atoms, nitro, amino,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino groups, and each  $C_{1-6}$ -alkyl,  $C_{5-10}$ -cycloalkyl,  $C_{1-6}$ -alkoxy and di- $C_{1-6}$ -alkylamino group in  $R^2$  and  $R^3$  optionally being substituted with one or more halogen atoms, from 2,2',6,6'-tetrabromobiphenyl by a sequence of bromine-metal exchanges and subsequent reactions.

20

25

30