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(54) **Title:** PROCESS FOR THE PRODUCTION OF BIARYL COMPOUNDS

(57) **Abstract:** A process for producing biaryl compounds by aerobic cross dehydrogenative coupling (CDC) of two arene groups comprising at least one aryl carbon-hydrogen bond, in the presence of a catalyst system, wherein the catalyst system comprises as phosphor containing acid a non-cyclopalladatable phosphinate and/or a non-cyclopalladatable phosphate monoester and/or a non-cyclopalladatable phosphate diester and/or a non-cyclopalladatable phosphonate and/or a non-cyclopalladatable phosphonate monoester as well as a palladium cation.



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PROCESS FOR THE PRODUCTION OF BIARYL COMPOUNDS.

The invention relates to a process for the production of biaryl compounds.

5 Biaryl compounds constitute an important class of compounds with a variety of applications, e.g. in market segments related to pharmaceuticals, agrochemicals, electronic chemicals and polymers.

Especially for bulk applications, for example as monomer units in polymers, it is important to produce the biaryl compounds at low costs.

10 Known processes for the production of biaryl compounds based on the coupling of two substituted arene units with prior activation of the arene units are in general not commercially viable. This is because the process requires many steps and expensive reagents, and it also generates large amounts of salt water.

An improvement was provided by a process for the production of biaryl compounds by cross dehydrogenative coupling (CDC) of two arene units, as recently reviewed in *Chem. Asian J.* **2014**, 9, 26. As is illustrated in this paper, such a process does not require prior activation of the arene units and it is economic, especially if oxygen is used as oxidant. Such a process is called aerobic CDC. Palladium (Pd) catalyzed aerobic CDC is already used commercially for coupling of dimethyl phthalate to produce tetramethyl [1,1'-biphenyl]-3,3',4,4'-tetracarboxylate, an intermediate for polyimide resins. However, such a process, as for example described in WO2008/067443, also has serious disadvantages. In the process of WO2008/067443, the CDC is carried out in a solvent in the presence of a catalyst, such as palladium acetate [Pd(OAc)₂], optionally with an oxidant such as copper acetate [Cu(OAc)₂] or phosphomolybdovanate [HMPV]. Herein the amount of catalyst was 100 mole%, or in the presence of an oxidant in the range of in the range from 10 to 25 mole% with the HMPV oxidant being present in an amount of 10 to 25 mole%. Thus apart from the solvent, very high amounts of catalyst and oxidants are needed.

As explained in *Adv. Synth. Catal.* **2010**, 352, 3223, this process could be significantly streamlined by carrying out the CDC of ortho-xylene, followed by aerobic oxidation of the benzylic methyl groups of the coupling product 3,3',4,4'-tetramethyl-1,1'-biphenyl (**3344**). This paper discloses an aerobic CDC catalyst system comprising a palladium dicarboxylate salt and 2-fluoropyridine as ligand, used in a 2/1 molar ratio relative to Pd. This catalyst system is preferably applied in acetic acid as solvent while using copper(II) triflate as cocatalyst. In high volume, low cost

applications such as those for the manufacture of bulk monomers, minimizing process costs is essential to meet the strict cost price requirements. It is therefore desirable to obtain a CDC process that operates efficiently with only a small amount of solvent or preferably no solvent at all. Such essentially or completely solvent-free conditions

5 reduce process costs because little or no solvent needs to be separated from the reaction mixture after completion of the reaction. Essentially or completely solvent-free conditions are also beneficial for increasing the productivity per unit of reactor volume (higher space time yield). This is especially important in the case of CDC of arenes to biaryl compounds, since under the low conversion conditions typically employed to

10 suppress further arene CDC to triaryl compounds, reactor productivity erodes to unacceptably low values in the presence of a substantial amount of solvent. To reduce process costs, it is also desirable to obtain a CDC process that operates efficiently with only a small amount of catalyst, i.e. with a catalyst that has a high activity. Surprisingly these aims are achieved by a process for producing biaryl compounds by aerobic CDC

15 of two arene groups comprising at least one aryl carbon-hydrogen bond, in the presence of a catalyst system comprising as phosphor containing acid a non-cyclopalladatable phosphinate and/or non-cyclopalladatable phosphate monoester and/or non-cyclopalladatable phosphate diester and/or non-cyclopalladatable phosphonate and/or non-cyclopalladatable phosphonate monoester as well as a

20 palladium cation. Preferably the catalyst system comprises as phosphor containing acid a non-cyclopalladatable phosphinate and/or a non-cyclopalladatable phosphate diester and/or a non-cyclopalladatable phosphonate and/or a non-cyclopalladatable phosphonate monoester. Phosphor containing acid is also referred to as P-acid. With non-cyclopalladatable phosphinate or non-cyclopalladatable phosphate

25 monoester or non-cyclopalladatable phosphate diester or non-cyclopalladatable phosphonate or non-cyclopalladatable phosphonate monoester are meant a phosphinate or phosphate monoester or phosphate diester or phosphonate or phosphonate monoester devoid of C-H bonds prone to cleavage by palladium, typically leading to 5 or 6 membered rings with a C,O-donor set linked to the Pd center, with the

30 C-atom originating from the C-H bond that is cleaved. A phosphinate prone to cyclopalladation via C-H cleavage is known, and can be found in *Chemical Communications* **2011**, 47, 2333. A review on cyclopalladation and cyclopalladated compounds can be found in *Chem. Rev.* **2005**, 105, 2527. The phosphinate or phosphate monoester or phosphate diester or phosphonate or phosphonate monoester

35 may be non-cyclic or cyclic, with cyclic meaning that the phosphorus atom is part of a

ring system. The phosphinate may be in the form of a phosphinate salt, or preferably in the form of a phosphinic acid. The phosphate monoester may be in the form of a phosphate monoester salt, or preferably in the form of a dihydrogen phosphate. The phosphate diester may be in the form of a phosphate diester salt, or preferably in the form of a monohydrogen phosphate. The phosphonate may be in the form of a phosphonate salt, or preferably in the form of a phosphonic acid. The phosphonate monoester may be in the form of a phosphonate monoester salt, or preferably in the form of a monohydrogen phosphonate.

Preferably the P-acid is a phosphinic acid or a monohydrogen phosphate. More preferably, the P-acid is a phosphinic acid with a pK_a that is smaller than the pK_a of dimethyl hydrogen phosphate. Most preferably, the P-acid is a bis(perfluoroaryl)phosphinic acid or bis(perfluoroalkyl)phosphinic acid with a pK_a that is smaller than the pK_a of dimethyl hydrogen phosphate. The palladium cation may be in the form of a hydrogen palladate, or preferably in the form of a palladium salt. The palladium salt may be derived from a P-acid. Preferably the catalyst system comprises at least one P-acid as well as a palladium cation in the form of a palladium salt derived from an acid with a pK_a that is larger than the pK_a of the P-acids comprised in the catalyst system. Most preferably the palladium salt is a palladium dicarboxylate derived from a carboxylic acid with a pK_a that is larger than the pK_a of the P-acids comprised in the catalyst system. When the catalyst system comprises a P-acid and a palladium salt, preferably the molar ratio of P-acid/palladium is 0.8/1 – 20/1. When the P-acid is devoid of an additional functional group that may coordinate to the palladium center, most preferably the molar ratio of P-acid/palladium is 1.8/1 – 10/1. When the P-acid contains an additional functional group that may coordinate to the palladium center, it may be advantageous that the molar ratio of P-acid/palladium is 0.8/1 – 1.2/1.

Even with low concentrations of catalysts in the reaction mixture high arene conversion rates are obtained. Surprisingly also a high selectivity towards formation of the desired biaryl compound may be obtained. Especially surprising is the high selectivity towards formation of the desired biaryl compound derived from arenes that may also undergo competitive benzylic oxidation, such as methylbenzenes including ortho-xylene.

With the process of the invention improved results in terms of catalyst activity and/or selectivity are obtained, resulting in lower costs. Preferably the amount of palladium cations comprised in the catalyst system is equal or less than 1 mol% relative to the arene coupling partner or to the limiting arene coupling partner, with the

limiting arene coupling partner being the arene with the lowest molarity in the reaction mixture in case more than one arene coupling partner is used. More preferably the amount of palladium cations comprised in the catalyst system is equal or less than 0.5 mol% relative to the arene coupling partner or to the limiting arene coupling partner.

- 5 Most preferably the amount of palladium cations comprised in the catalyst system is equal or less than 0.1 mol% relative to the arene coupling partner or to the limiting arene coupling partner.

With the process according to the invention good results in terms of activity and selectivity are obtained if the process is carried out with a low amount of solvent or even without a solvent, provided the arene is in the liquid phase at the
10 reaction temperature. Preferably at most 50 wt% of solvent is used, based on the total reaction mass, more preferably at most 25 wt%, even more preferably at most 10 wt%, even more preferably at most 5 wt%, even more preferably at most 2 wt%. Most preferably no solvent at all is used.

- 15 Optionally additives may be added. These additives may improve the activity, stability, or selectivity of the catalyst. Examples of such additives are Lewis acids, such as metal triflates, or Brønsted acids. Other examples of potentially beneficial additives are redox active compounds that inhibit catalyst deactivation by formation of metallic palladium. Such redox active compounds include copper(II) salts,
20 vanadium-containing polyoxometalates, or organic electron acceptors such as benzoquinones. In case CDC of two arene groups may lead to a mixture of biaryl regioisomers of which only one is a desired product, a particularly useful class of additives comprises non-beta-eliminatable, non-cyclopalladatable organic ligands that improve the regioselectivity of the catalyst. With a non-beta-eliminatable nitrogen donor
25 ligand is meant a nitrogen donor ligand that does not induce reduction of palladium(II) to palladium(0) via beta-hydride elimination from a Pd-N-C-H fragment, with the N-C-H fragment being part of the nitrogen donor ligand that is bound to palladium. Nitrogen donor ligands prone to beta-hydride elimination include trialkylamines containing a N-C-H fragment, such as found in for example tributylamine as described in *Chemistry*
30 **2011**, 17, 3091. With a non-cyclopalladatable nitrogen donor ligand is meant a nitrogen donor ligand devoid of C-H bonds prone to cleavage by palladium, typically leading to 5 or 6 membered rings with a C,N-donor set linked to the Pd center, with the C-atom originating from the C-H bond that is cleaved. Nitrogen donor ligands prone to cyclopalladation via C-H cleavage are well known, and examples can, among others,

be found in *Chem. Rev.* **2005**, 105, 2527 and in *Palladacycles* **2008**, 13, which also clarify rules for their formation.

Good results may be obtained when aliphatic cyclic or non-cyclic primary, secondary or tertiary amines, aromatic N-heterocycles and/or benzofused derivatives thereof are used as the one or more ligands. Preferably N-heterocycles and benzofused derivatives thereof are used that contain a sp^2 hybridized nitrogen atom with the lone electron pair on the nitrogen atom positioned in-plane with respect to the plane formed by the X-N-Y group, where X and Y denote the atoms directly bound to the sp^2 nitrogen atom. Even more preferably N-heterocyclic compounds are used that contain a sp^2 hybridized nitrogen atom with the lone electron pair on the nitrogen atom positioned in-plane with respect to the plane formed by the X-N-Y group, where X and Y denote the atoms directly bound to the sp^2 nitrogen atom and either X or Y being a carbon atom. From above defined preferred group even more preferably pyridines, pyridazines, pyrimidines, pyrazines, triazines, imidazoles, triazoles, oxazoles, 4,5-dihydrooxazoles, isoxazoles, 4,5-dihydroisoxazoles, and 5,6-dihydro-4*H*-1,3-oxazines or quinolines, isoquinolines, cinnolines, phthalazines, quinazoline, quinoxalines, 1*H*-benzo[d]imidazoles, 1*H*-benzo[d][1,2,3]triazoles, benzo[d]oxazoles, benzo[d]isoxazoles and 4*H*-benzo[e][1,3]oxazines and/or benzofused derivatives thereof are used as ligand.

Even more preferably aromatic 6 membered ring N-heterocycles or benzofused derivatives thereof are used as the one or more ligands. Preferably in this group pyridines, pyridazines, pyrimidines, pyrazines, triazines, quinolines, isoquinolines, cinnolines, phthalazine, quinazoline and quinoxalines and/or benzofused derivatives thereof are used as the one or more ligands.

The nitrogen donor ligand may be further substituted to control the activity and/or the selectivity of the catalyst. The optimum choice of the substituent depends among others on the nature of the catalyst and on the required regioselectivity of the arene CDC process, which is determined by the final application. When the final application requires the CDC of ortho-xylene to be directed towards symmetrical **3344** instead of the asymmetrical 2,3,3',4'-tetramethyl-1,1'-biphenyl (**2334**) regioisomer, it is advantageous to add a suitably substituted pyridine as ligand.

Preferably the molar ratio of ligand/palladium is 0.5/1 – 1.5/1. Most preferably the molar ratio of ligand/palladium is 0.8/1 – 1.2/1. When a ligand is present and the catalyst system comprises at least one P-acid as well as a palladium cation in the form of a palladium salt derived from an acid with a pK_a that is larger than the pK_a

of the P-acids comprised in the catalyst system, preferably the molar ratio of P-acid/palladium is 2/1 – 2.2/1.

The CDC process according to this invention is preferably carried out at temperatures above room temperature. The optimum temperature depends on the nature of the arene coupling partner(s) and the required selectivity, in particular the required regioselectivity. Preferably, the reaction temperature is between 70 and 200°C, most preferably between 90 and 180°C. The preferred oxygen pressure depends on the available infrastructure and the nature of the CDC reaction. Preferably, the CDC process according to the invention is carried out in such a way that either the explosion risk is eliminated (e.g. by operating a semi-batch reactor via continuous supply of an oxygen/nitrogen mixture with a composition below the oxygen limit concentration), or the impact of an unintended explosion is minimized to an acceptable level (e.g. by operating a continuous flow tube reactor with oxygen or a minimum-headspace semi-batch reactor via continuous supply of oxygen).

The CDC process according to this invention may involve a homocoupling (i.e. with a single arene that is coupled to form a biaryl product) or a heterocoupling (i.e. with two different arene coupling partners). CDC processes of these types according to this invention may be either intermolecular or intramolecular.

Examples of suitable arenes in homo- or heterocoupling processes according to this invention are arenes (such as benzene, naphthalene, anthracene, phenanthrene), alkylarenes (such as toluene, 1-methylnaphthalene, 2-methylnaphthalene, ortho-xylene, meta-xylene, para-xylene, ethylbenzene, cumene, tert.-butylbenzene, diphenylmethane, propane-2,2-diyl dibenzene), aryl carboxylic acid esters (such as methyl benzoate, methyl 1-naphthoate, methyl 2-naphthoate, dimethyl phthalate, methyl ortho-toluate, methyl meta-toluate, methyl para-toluate, dimethyl isophthalate, dimethyl terephthalate), halogenated arenes (such as fluorobenzene, 1-fluoronaphthalene, 2-fluoronaphthalene, (trifluoromethyl)benzene, chlorobenzene, 1-chloronaphthalene, 2-chloronaphthalene, 1-(trifluoromethyl)naphthalene, 2-(trifluoromethyl)naphthalene), aryl ethers (such as anisole, 1-methoxynaphthalene, 2-methoxynaphthalene, diphenylether), and diaryl amines (such as N,N-diphenylacetamide). The arene in a homocoupling process according to this invention may also be a heteroarene, as long as the heteroarene does not have a heteroatom that interferes negatively in the CDC process, e.g. by competing with a nitrogen donor ligand in its coordination to the palladium salt. Examples of suitable heteroarenes can

be found in *Chem. Asian J.* **2014**, 9, 26 (such as furans, thiophenes, pyrroles, pyridine-*N*-oxides, and benzofused derivatives thereof).

Examples

5

In the examples below dealing with the CDC of ortho-xylene, yields refer to the percentages of ortho-xylene that are converted into biaryl products, benzylic oxidation products, or triaryl isomers. Benzylic oxidation products refer to 2-methylbenzaldehyde, 2-methylbenzyl alcohol, and 2-methylbenzoic acid. Triaryl isomers refer to products with a molecular weight that equals that of a compound with the formula C₂₄H₂₆. The turnover number is defined as the combined **2334+3344** yield (in %) per palladium cation amount unit (in mol%). The space time yield of **3344+2334** biaryls is defined as the combined **2334+3344** yield (in milligrams) per added ortho-xylene and solvent volume unit (in milliliters) per reaction time unit (in hours). P refers to the molar amount of P-acid comprised in the catalyst system, Pd refers to the molar amount of Pd cations comprised in the catalyst system.

Gas Chromatography (GC) measurements were carried out on an Agilent 6890 instrument equipped with an Agilent HP-5 column (length, 30 m; diameter, 0.32 mm; film, 0.25 µm). Settings: initial temperature, 80°C (1 min); ramp rate, 20°C/min; final temperature, 300°C (3 min). Retention times (min): Bald, 4.04; hexadecane internal standard, 7.45; **2334**, 8.45; **3344**, 9.04. In the examples below dealing with the CDC of substrates other than ortho-xylene, GC area percentages of biaryl isomers refer to the sum of peak areas ascribed to biaryl isomers, as percentage of the total peak area excluding the peak of the solvent used for sample dilution.

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Example 1: CDC of ortho-xylene without solvent at 85°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; 0.1 mol% Pd; P/Pd = 4.

A mixture of ortho-xylene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to ortho-xylene), and bis(perfluorophenyl)phosphinic acid (0.4 mol% relative to ortho-xylene) was stirred for ~17 hrs at 85°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

Yield of **3344+2334** biaryls: 8.9%

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Turnover number:	89
Space time yield of 3344+2334 biaryls:	4.6 mg·mL ⁻¹ ·h ⁻¹
Yield of benzylic oxidation products:	0.0%
Yield of triaryl isomers:	0.6%
5 Molar 3344/2334 biaryl ratio:	3.3

Comparative experiment A: CDC of ortho-xylene carried out with the catalyst system as described in *Adv. Synth. Catal.* **2010**, 352, 3223.

A mixture of ortho-xylene (0.4 g; 0.46 mL), acetic acid (solvent; 0.4 g; 0.38 mL; solvent), palladium(II) acetate (0.1 mol% relative to ortho-xylene), copper(II) triflate (0.1 mol% relative to ortho-xylene), trifluoroacetic acid (0.13 mol% relative to ortho-xylene), and 2-fluoropyridine (0.2 mol% relative to ortho-xylene) was stirred for 17 hrs at 85°C (external temperature) in a glass vial under 1 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard. In various separate experiments, the color of the reaction mixture ranged from bright green to dark brown, and the yield of **3344+2334** biaryls ranged from 0.7-5.2% (corresponds to space time yields ranging from 0.2-1.4 mg·mL⁻¹·h⁻¹, respectively). Comparison of example 1 with comparative experiment A shows that both the **3344+2334** biaryl yield and the space time yield are significantly higher in example 1 than in comparative experiment A.

Example 2: CDC of ortho-xylene without solvent at 135°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; 0.03 mol% Pd; P/Pd = 2.

A mixture of ortho-xylene (1.0 mL), palladium(II) pivalate (0.03 mol% relative to ortho-xylene), and bis(perfluorophenyl)phosphinic acid (0.06 mol% relative to ortho-xylene) was stirred for ~8 hrs at 135°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

Yield of 3344+2334 biaryls:	8.7%
Turnover number:	290
Space time yield of 3344+2334 biaryls:	9.5 mg·mL ⁻¹ ·h ⁻¹
Yield of benzylic oxidation products:	0.0%
35 Yield of triaryl isomers:	0.9%

Molar **3344/2334** biaryl ratio: 1.1

Example 3: CDC of ortho-xylene without solvent at 85°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; 0.1 mol% Pd; P/Pd =2.

A mixture of ortho-xylene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to ortho-xylene), and bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to ortho-xylene) was stirred for ~17 hrs at 85°C (external temperature) in an autoclave under 11 bar O₂.

The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

Yield of **3344+2334** biaryls: 6.4%

Turnover number: 64

Space time yield of **3344+2334** biaryls: 3.3 mg·mL⁻¹·h⁻¹

Yield of benzylic oxidation products: 0.0%

Yield of triaryl isomers: 0.4%

Molar **3344/2334** biaryl ratio: 3.0

Example 4: CDC of ortho-xylene without solvent at 110°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; 0.1 mol% Pd; P/Pd =2.

A mixture of ortho-xylene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to ortho-xylene), and bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to ortho-xylene) was stirred for ~17 hrs at 110°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

Yield of **3344+2334** biaryls: 15.1%

Turnover number: 151

Space time yield of **3344+2334** biaryls: 7.7 mg·mL⁻¹·h⁻¹

Yield of benzylic oxidation products: 0.0%

Yield of triaryl isomers: 2.1%

Molar **3344/2334** biaryl ratio: 2.2

Example 5: CDC of ortho-xylene without solvent at 110°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid, a palladium cation in the form of a palladium salt, as well as a ligand; 0.1 mol% Pd; P/Pd =2.

- 5 A mixture of ortho-xylene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to ortho-xylene), bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to ortho-xylene), and 2-(difluoromethyl)pyridine (ligand; 0.1 mol% relative to ortho-xylene) was stirred for ~17 hrs at 110°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using
- 10 hexadecane as internal standard.

Yield of **3344+2334** biaryls: 9.9%

Turnover number: 99

Space time yield of **3344+2334** biaryls: 5.1 mg·mL⁻¹·h⁻¹

Yield of benzylic oxidation products: 0.4%

- 15 Yield of triaryl isomers: 0.3%

Molar **3344/2334** biaryl ratio: 4.3

From the molar **3344/2334** biaryl ratios of 4.3 in example 6 and 2.2 in example 5, it follows that the addition of a ligand in the form of 2-(difluoromethyl)pyridine improves the regioselectivity of the catalyst towards formation of **3344**.

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Example 6: CDC of ortho-xylene without solvent at 135°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; 0.1 mol% Pd; P/Pd = 2.

- 25 A mixture of ortho-xylene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to ortho-xylene), and bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to ortho-xylene) was stirred for ~8 hrs at 135°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

- 30 Yield of **3344+2334** biaryls: 16.2%

Turnover number: 162

Space time yield of **3344+2334** biaryls: 17.6 mg·mL⁻¹·h⁻¹

Yield of benzylic oxidation products: 0.0%

Yield of triaryl isomers: 3.3%

- 35 Molar **3344/2334** biaryl ratio: 1.4

Example 7: CDC of ortho-xylene without solvent at 135°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; pivalic acid used as

5 Brønsted acid additive; 0.1 mol% Pd; P/Pd = 2.

A mixture of ortho-xylene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to ortho-xylene), bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to ortho-xylene), and pivalic acid (Brønsted acid additive; 0.6 mol% relative to ortho-xylene) was stirred for ~8 hrs at 135°C (external temperature) in an autoclave under 11 bar O₂. The reaction
10 mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

Yield of 3344+2334 biaryls:	21.0%
Turnover number:	210
Space time yield of 3344+2334 biaryls:	22.9 mg·mL ⁻¹ ·h ⁻¹
15 Yield of benzylic oxidation products:	0.0%
Yield of triaryl isomers:	4.0%
Molar 3344/2334 biaryl ratio:	1.8

From both the combined **3344+2334** yield of 16.2% in example 6 and 21.0% in example 7 and the molar **3344/2334** biaryl ratios of 1.4 in example 6 and 1.8 in
20 example 7, it follows that the addition of a Brønsted acid in the form of pivalic acid improves both the activity of the catalyst towards biaryl formation and the regioselectivity of the catalyst towards formation of **3344**.

Example 8: CDC of ortho-xylene without solvent at 85°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphate in the form of a non-cyclic monohydrogen phosphate as well as a palladium cation in the form of a palladium salt;
25 0.5 mol% Pd; P/Pd = 2.

A mixture of ortho-xylene (1.0 mL), palladium(II) acetate (0.5 mol% relative to ortho-xylene), and dimethyl hydrogen phosphate (1 mol% relative to ortho-xylene) was stirred
30 for ~17 hrs at 85°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

Yield of 3344+2334 biaryls:	10.4%
Turnover number:	20.8
35 Space time yield of 3344+2334 biaryls:	5.3 mg·mL ⁻¹ ·h ⁻¹

Yield of benzylic oxidation products:	0.4%
Yield of triaryl isomers:	0.4%
Molar 3344/2334 biaryl ratio:	4.1

- 5 Example 9: CDC of ortho-xylene without solvent at 135°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphate in the form of a cyclic monohydrogen phosphate as well as a palladium cation in the form of a palladium salt; 0.5 mol% Pd; P/Pd = 2.

10 A mixture of ortho-xylene (1.0 mL), palladium(II) acetate (0.5 mol% relative to ortho-xylene), and 2-hydroxy-1,3,2-dioxaphosphhepane 2-oxide (1 mol% relative to ortho-xylene) was stirred for ~17 hrs at 135°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

Yield of 3344+2334 biaryls:	13.9%
15 Turnover number:	27.8
Space time yield of 3344+2334 biaryls:	7.1 mg·mL ⁻¹ ·h ⁻¹
Yield of benzylic oxidation products:	0.2%
Yield of triaryl isomers:	1.1%
Molar 3344/2334 biaryl ratio:	3.6

20

Example 10: CDC of ortho-xylene without solvent at 85°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphate in the form of a monohydrogen phosphonate as well as a palladium cation in the form of a palladium salt; 0.5 mol% Pd; P/Pd = 2.

25 A mixture of ortho-xylene (1.0 mL), palladium(II) acetate (0.5 mol% relative to ortho-xylene), and ethyl hydrogen methylphosphonate (1 mol% relative to ortho-xylene) was stirred for ~17 hrs at 85°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

30 Yield of 3344+2334 biaryls:	7.7%
Turnover number:	15.4
Space time yield of 3344+2334 biaryls:	3.9 mg·mL ⁻¹ ·h ⁻¹
Yield of benzylic oxidation products:	0.3%
Yield of triaryl isomers:	0.2%
35 Molar 3344/2334 biaryl ratio:	4.7

Example 11: CDC of ortho-xylene without solvent at 110°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphonate in the form of a phosphonic acid with an additional functional group that may coordinate to the palladium center, a palladium cation in the form of a palladium salt, as well as a ligand; 0.1 mol% Pd; P/Pd = 1.

A mixture of ortho-xylene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to ortho-xylene), (pyridin-2-ylmethyl)phosphonic acid (0.1 mol% relative to ortho-xylene), and 2-(difluoromethyl)pyridine (ligand; 0.1 mol% relative to ortho-xylene) was stirred for ~17 hrs at 110°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

Yield of 3344+2334 biaryls:	7.9%
Turnover number:	79
Space time yield of 3344+2334 biaryls:	4.0 mg·mL ⁻¹ ·h ⁻¹
Yield of benzylic oxidation products:	2.4%
Yield of triaryl isomers:	0.2%
Molar 3344/2334 biaryl ratio:	8.4

Example 12: CDC of ortho-xylene without solvent at 85°C/11 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate as well as a palladium cation in the form of a palladium phosphinate salt; 0.5 mol% Pd.

The palladium(II) salt of bis(perfluorophenyl)phosphinic acid was prepared by evaporation of solvent and acetic acid from a dichloromethane solution of bis(perfluorophenyl)phosphinic acid and palladium(II) acetate in a 2/1 molar ratio. A mixture of ortho-xylene (1.0 mL) and the palladium(II) salt of bis(perfluorophenyl)phosphinic acid (0.5 mol% relative to ortho-xylene) was stirred for ~17 hrs at 85°C (external temperature) in an autoclave under 11 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC, using hexadecane as internal standard.

Yield of 3344+2334 biaryls:	9.8%
Turnover number:	19.6
Space time yield of 3344+2334 biaryls:	5.0 mg·mL ⁻¹ ·h ⁻¹
Yield of benzylic oxidation products:	0.0%
Yield of triaryl isomers:	0.7%

Molar **3344/2334** biaryl ratio: 3.4

Example 13: CDC of toluene without solvent at 110°C/13 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; 0.1 mol% Pd; P/Pd = 2.

A mixture of toluene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to toluene), and bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to toluene) was stirred for ~17 hrs at 110°C (external temperature) in an autoclave under 13 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC.

GC area percentage of biaryl isomers: 15.8%

Example 14: CDC of (trifluoromethyl)benzene without solvent at 110°C/13 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; 0.1 mol% Pd; P/Pd = 2.

A mixture of (trifluoromethyl)benzene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to (trifluoromethyl)benzene), and bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to (trifluoromethyl)benzene) was stirred for ~17 hrs at 110°C (external temperature) in an autoclave under 13 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC.

GC area percentage of biaryl isomers: 3.9%

Example 15: CDC of meta-xylene without solvent at 110°C/13 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; 0.1 mol% Pd; P/Pd = 2.

A mixture of meta-xylene (1.0 mL), palladium(II) pivalate (0.1 mol% relative to meta-xylene), and bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to meta-xylene) was stirred for ~17 hrs at 110°C (external temperature) in an autoclave under 13 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC.

GC area percentage of biaryl isomers: 11.0%

Example 16: CDC of naphthalene without solvent at 110°C/13 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic

acid as well as a palladium cation in the form of a palladium salt; 0.1 mol% Pd; P/Pd = 2.

A mixture of naphthalene (1.0 g), palladium(II) pivalate (0.1 mol% relative to naphthalene), and bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to naphthalene) was stirred for ~17 hrs at 110°C (external temperature) in an autoclave under 13 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC.

GC area percentage of biaryl isomers: 18.6%

10 Example 17: CDC of ortho-xylene and meta-xylene; illustration of heterocoupling of two different arenes without solvent at 110°C/13 bar O₂ with a catalyst system comprising a non-cyclopalladatable phosphinate in the form of a phosphinic acid as well as a palladium cation in the form of a palladium salt; 0.1 mol% Pd; P/Pd = 2.

A mixture of ortho-xylene (0.5 g), meta-xylene (0.5 g), palladium(II) pivalate (0.1 mol% relative to the combined xylenes), and bis(perfluorophenyl)phosphinic acid (0.2 mol% relative to ortho-xylene) was stirred for ~17 hrs at 110°C (external temperature) in an autoclave under 13 bar O₂. The reaction mixture was diluted and a sample was subsequently analyzed by GC.

GC/MS analysis showed the presence of 3,3',4,5'-tetramethyl-1,1'-biphenyl (heterocoupling product) besides 3,3',4,4'-tetramethyl-1,1'-biphenyl and 3,3',5,5'-tetramethyl-1,1'-biphenyl (homocoupling products).

CLAIMS

1. A process for producing biaryl compounds by aerobic cross dehydrogenative coupling (CDC) of two arene groups comprising at least one aryl carbon-hydrogen bond, in the presence of a catalyst system, characterized in that the catalyst system comprises as phosphor containing acid a non-cyclopalladatable phosphinate and/or a non-cyclopalladatable phosphate monoester and/or a non-cyclopalladatable phosphate diester and/or a non-cyclopalladatable phosphonate and/or a non-cyclopalladatable phosphonate monoester as well as a palladium cation.
2. A process according to claim 1, wherein the catalyst system comprises as phosphor containing acid a non-cyclopalladatable phosphinate and/or a non-cyclopalladatable phosphate diester and/or a non-cyclopalladatable phosphonate and/or a non-cyclopalladatable phosphonate monoester.
3. A process according to claim 1 or 2, wherein the phosphinate is in the form of a phosphinic acid.
4. A process according to any one of claims 1-3, wherein the phosphate monoester is in the form of a dihydrogen phosphate.
5. A process according to any one of claims 1-4, wherein the phosphate diester is in the form of a monohydrogen phosphate.
6. A process according to any one of claims 1-5, wherein the phosphonate is in the form of a phosphonic acid.
7. A process according to any one of claims 1-5, wherein the phosphonate monoester is in the form of a monohydrogen phosphonate.
8. A process according to claim 3, wherein the phosphinic acid has a pK_a that is smaller than the pK_a of dimethyl hydrogen phosphate.
9. A process according to claim 8, wherein the phosphinic acid is a bis(perfluoroaryl)phosphinic acid or bis(perfluoroalkyl)phosphinic acid.
10. A process according to any one of the preceding claims, wherein the catalyst system comprises a palladium cation in the form of a palladium salt.
11. A process according to claim 10, wherein the palladium salt is derived from an acid with a pK_a that is larger than the pK_a of the P-acid or P-acids.
12. A process according to claim 10, wherein the palladium salt is a palladium dicarboxylate.

13. A process according to any one of claims 10-12, wherein the molar ratio of phosphor containing acid/palladium is 1.8/1 – 10/1 and the P-acid is devoid of an additional functional group that may coordinate to the palladium center.
14. A process according to any one of claims 10-12, wherein the molar ratio of phosphor containing acid /palladium is 0.8 /1 – 1.2/1 and the phosphor containing acid contains an additional functional group that may coordinate to the palladium center.
15. A process according to any one of the preceding claims, wherein at most 50 wt% of solvent is used relative to the total reaction mass.
16. A process according to claim 15, wherein at most 25 wt% of solvent is used relative to the total reaction mass.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/081190

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C2/84 C07C15/14
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)
C07C

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/067443 A1 (RHODE ISLAND EDUCATION [US]; DEBOEF BRENTON [US]) 5 June 2008 (2008-06-05) abstract pages 7-8 page 9; table 1 pages 11-17 claims 1-7 ----- -/--	1-16



Further documents are listed in the continuation of Box C.



See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/081190

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PEREIRA KYLE C ET AL: "Insight into the palladium-catalyzed oxidative arylation of benzofuran: heteropoly acid oxidants evoke a Pd(II)/Pd(IV) mechanism", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 69, no. 22, 26 February 2013 (2013-02-26), pages 4429-4435, XP028584934, ISSN: 0040-4020, DOI: 10.1016/J.TET.2013.02.061 abstract page 4430; tables 1-3 page 4432; table 4 page 4433, paragraphs 3., 4. - page 4435	1-16
A	YUSUKE IZAWA ET AL: "Aerobic Oxidative Coupling of o-Xylene: Discovery of 2-Fluoropyridine as a Ligand to Support Selective Pd-Catalyzed C-H Functionalization", ADVANCED SYNTHESIS & CATALYSIS, vol. 352, no. 18, December 2010 (2010-12), pages 3223-3229, XP055160718, ISSN: 1615-4150, DOI: 10.1002/adsc.201000771 cited in the application abstract page 3225 - page 3226; figures 1-3 page 3227; table 1 page 3228, left-hand column, paragraph 1-2	1-16
A	I V Kozhevnikov ET AL: "PHYSICAL CHEMISTRY MECHANISM OF OXIDATION OF XYLENES WITH Pd(II) COMPLEXES", October 1985 (1985-10), pages 2001-2006, XP055161363, Retrieved from the Internet: URL:http://rd.springer.com/content/pdf/10.1007/BF00963221.pdf [retrieved on 2015-01-12] * reaction schemes 1-3 *; page 2001 page 2002; table 1 page 2003; table 2	1-16

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/081190

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YINUO WU ET AL: "Palladium-Catalyzed Cross-Dehydrogenative Functionalization of C(sp ²)-H Bonds", CHEMISTRY - AN ASIAN JOURNAL, vol. 9, no. 1, 2 October 2013 (2013-10-02) , pages 26-47, XP055160713, ISSN: 1861-4728, DOI: 10.1002/asia.201300990 cited in the application abstract page 36, paragraph 3.1.-3.3. - page 41 -----	1-16
A	CHAO LIU ET AL: "Bond Formations between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions", CHEMICAL REVIEWS, vol. 111, no. 3, 9 March 2011 (2011-03-09) , pages 1780-1824, XP055142723, ISSN: 0009-2665, DOI: 10.1021/cr100379j page 1799, paragraph 2.3.4.1 - page 1802 * Schemes 81-99 *; page 1799 - page 1802 -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/081190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008067443 A1	05-06-2008	US 2009253921 A1 WO 2008067443 A1	08-10-2009 05-06-2008
