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(54) Title: SYNTHESIS OF PALLADIUM(0) PHOSPHINE COMPLEXES

(57) Abstract: Provided is an optimized process for the synthesis of palladium(O) phosphine complexes. The process described herein is characterized by a more efficient reaction control, high yield and purity, the use of readily available starting materials, and savings in reaction time and steps, thereby offering increased sustainability when compared to processes reported in the state of the art.

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SYNTHESIS OF PALLADIUM(0) PHOSPHINE COMPLEXES

Cross-Reference to Related Applications

[0001] The present application claims the benefit of priority of U.S. provisional patent application no. 63/377,558, filed on September 29, 2022, and U.S. provisional patent application no. 63/481,731, filed on January 26, 2023, wherein both of their entire content is incorporated herein in its entirety.

Field of Invention

[0002] Provided is an optimized process for the synthesis of palladium(0) phosphine complexes such as e.g. bis(tri-*tert*-butylphosphine)palladium(0).

[0003] The synthesis process starts from commercially available palladium(II) compounds, which are reduced to palladium(0) complexes in situ by addition of excess phosphine ligand. The obtained palladium(0) complex is then purified in situ by e.g. precipitating and washing, and isolated with high yield and purity. The synthesis process does not require the addition of reducing agents such as, for example, alkali metal hydroxides or alkali metal alkoxides, in particular, for example, sodium hydroxide or sodium methoxide (which may be prepared from sodium hydroxide in methanol under controlled conditions). Furthermore, the synthesis process can be carried out in a single reaction vessel as a one-pot reaction.

Background

[0004] Over the past decades, palladium-catalyzed cross-coupling reactions have emerged ed as one of the most powerful tools in organic synthesis.[1a-c] Although both Pd(II) and P(0) complexes can facilitate the cross-coupling catalysis, it is well established that $L_nPd(0)$ (n = number of ligands) is the active species in the catalytic cycle.[1c] Due to practical and safety reasons, there is an increasing interest in using preformed $(R_3P)_2Pd(0)$ catalysts for cross-coupling reactions.[1b],[2] Various methods of preparation have been reported in literature, which either lack generality or employ tedious isolation techniques.

[0005] For example, bis(tri-*tert*-butylphosphine)palladium(0) is a popular catalyst for cross-coupling reactions in both academia and industry synthetic chemistry

communities. Methods to produce this material typically involve air sensitive Pd(0) starting materials such as $Pd(dba)_2$ originally by the Hartwig group[3] and modified by others[4],[5] or from Pd(II) allyl compounds.[6],[7]

[0006] Improved methods have been developed that use an air stable Pd(II) source, but these require an additional reducing agent such as sodium hydroxide,[8]-[10] hydrogen,[11] or bis(pinacolato)diboron under controlled conditions.[12]

[0007] The synthesis process according to the present invention uses a palladium(II) compound, such as e.g. dichloro(1,5-cyclooctadiene)palladium(II), as the starting materials, which is reduced to Pd(0) in situ by addition of excess phosphine ligand and then purified by e.g. precipitating and washing to obtain the desired product in high yield and purity (e.g. > 87% yield, > 98% purity) from a single flask. Unlike previously reported methods, this process does not rely on Pd(0) starting materials[3]-[5], temperature sensitive palladium alkene dimers as starting materials[6],[7], or additional reducing agents under controlled conditions including low temperature synthesis of intermediates.[8]-[12]

[0008] Colacot et al.[8],[9] reported a synthesis in which 1 equivalent of dibromo(1,5-cyclooctadiene)palladium(II) is reacted in a two-step, synthesis with 2 equivalents of NaOH in MeOH as a solution and 2 equivalents of tri-*tert*-butylphosphine ligand in toluene at low temperature. The synthesis of MeONa from NaOH and MeOH is a very exothermic process which needs to be carried out separately under controlled conditions The reported isolated yield is ca 95%.

[0009] Colacot et al.[10] reported in a mechanistic study on the formation of bis(tri-*tert*-butylphosphine)palladium(0) from dibromo(1,5-cyclooctadiene)palladium(II) and 3 equivalents of tri-*tert*-butylphosphine a yield of 71% and 95% purity with 5% of the corresponding palladium(I) bromide dimer.

[0010] Hence, there is still a continuous need to develop improved syntheses for palladium(0) phosphine complexes, especially bis(tri-*tert*-butylphosphine)palladium(0), relatively easily using ambient conditions, which are characterized by a more efficient reaction control, comparable isolated yield and purity, the use of readily available starting materials, and savings in reaction time and steps, thereby offering increased sustainability.

Summary

[0011] The present invention provides a process for synthesizing a palladium(0) phosphine complex, wherein said process comprises the following steps:

(a) reacting a palladium(II) compound with about 3 or more equivalents of a phosphine ligand to obtain a palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II); and

(b) in situ purification of the palladium(0) phosphine complex obtained in step (a).

[0012] The present invention further provides a palladium(0) phosphine complex obtainable by the process according to the present invention.

Brief Description of the Figures

[0013] None

Detailed Description

[0014] Herein is described a process for synthesizing a palladium(0) phosphine complex, wherein said process comprises the following steps:

(a) reacting a palladium(II) compound with about 3 or more equivalents of a phosphine ligand to obtain a palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II); and

(b) in situ purification of the palladium(0) phosphine complex obtained in step (a).

[0015] The process for synthesizing a palladium(0) phosphine complex described herein overcomes the problems with conventional processes for synthesizing palladium(0) phosphine complexes and thereby provides a powerful scalable new synthetic route towards catalysts based on palladium(0) phosphine complexes, especially geared for the production of bis(tri-*tert*-butylphosphine)palladium(0),

which is a commercial catalyst utilized for many organic transformations.

[0016] The process described herein provides the following advantages:

[0017] The process makes use of air stable Pd(II) starting materials rather than air/temperature sensitive Pd precursors. The process does not require any additional reducing agents as the additional equivalent of phosphine is used as a reducing agent. In particular, the process does not require any basic reducing agents such as, for example, alkali metal hydroxides or alkali metal alkoxides, in particular, for example, sodium hydroxide in MeOH or sodium methoxide.

[0018] The entire process can be completed in a single reaction vessel as a one-pot reaction. The process involves only a one-step reaction to obtain a palladium(0) phosphine complex from the starting materials, followed by simple in situ purification via preferably precipitation and washing. This means that the product is formed directly in a one-step reaction and no intermediates occur, making the process more robust. The one-step reaction can be carried out a room temperature (about 20 °C to about 25 °C) versus low temperature synthesis or cryogenic crystallization, e.g. at -30 °C. This is followed by simple in situ purification.

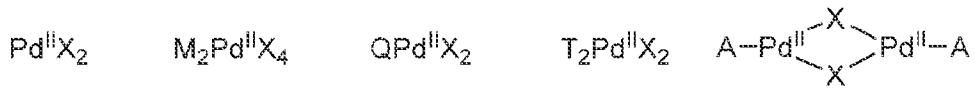
[0019] The process can utilize tetrachloropalladate(II) salts of lithium, sodium, potassium or ammonium as starting material, which are inexpensive Pd(II) sources and have less impact on the environment. Alternatively, Pd(II) compounds such as, for example, $(RCN)_2PdX_2$ (R= Me, Ph, etc.; X = Cl, Br, I), Pd(olefin)X_2 (olefin = norbornadiene, cyclooctadiene, etc.; X= Cl, Br, I), $[Pd(\pi\text{-allyl})X]_2$ (X= Cl, Br, I), etc. can be used.

[0020] The process provides high yield and purity compared to literature known processes even at larger scale.

[0021] In summary, the process described herein provides a more efficient reaction control, allows the use of more readily available and cheaper starting materials, and saves on reagents and energy, thereby offering increased sustainability when compared to literature known processes. Besides it is more robust for scale up.

[0022] In a preferred embodiment of the present invention, the palladium(II)

compound is represented by Formula (I), (II), (III), (IV) or (V):



Formula (I) Formula (II) Formula (III) Formula (IV) Formula (V)

wherein:

M is an alkali metal cation or ammonium cation, preferably selected from Li^+, Na^+, K^+, Rb^+, Cs^+ and NH_4^+, more preferably selected from Li^+, Na^+ and NH_4^+, and most preferably selected from Na^+ and NH_4^+;

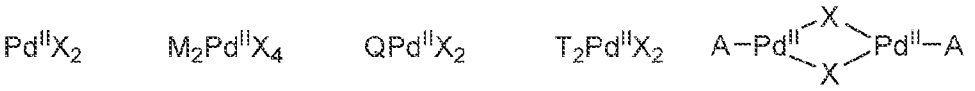
X is a halogen anion, preferably selected from Cl^-, Br^- and I^-, more preferably selected from Cl^- and Br^-, and most preferably Cl^-;

Q is a cyclic diene, preferably selected from 1,5-cyclooctadiene and bicyclo[2.2.1]hepta-2,5-diene;

T is a nitrile, preferably selected from acetonitrile and benzonitrile, or an olefin, preferably ethylene; and

A is an alkene, preferably selected from an allyl compound, crotyl compound and cinnamyl compound, more preferably selected from allyl, crotyl and cinnamyl.

[0023] In a more preferred embodiment of the present invention, the palladium(II) compound is represented by Formula (I), (II), (III), (IV) or (V):



Formula (I) Formula (II) Formula (III) Formula (IV) Formula (V)

wherein:

M is selected from Li^+, Na^+, K^+, Rb^+, Cs^+ and NH_4^+;

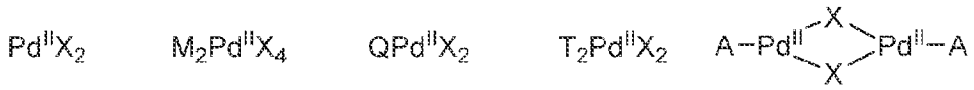
X is selected from Cl^-, Br^- and I^-;

Q is selected from 1,5-cyclooctadiene and bicyclo[2.2.1]hepta-2,5-diene;

T is selected from acetonitrile, benzonitrile and ethylene; and

A is selected from an allyl compound, crotyl compound and cinnamyl compound.

[0024] In a particularly preferred embodiment of the present invention, the palladium(II) compound is represented by Formula (I), (II), (III), (IV) or (V):



Formula (I) Formula (II) Formula (III) Formula (IV) Formula (V)

wherein:

M is selected from Li^+, Na^+ and NH_4^+;

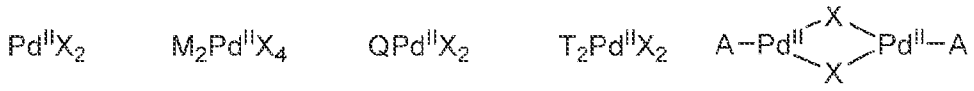
X is selected from Cl^- and Br^-;

Q is selected from 1,5-cyclooctadiene and bicyclo[2.2.1]hepta-2,5-diene;

T is selected from acetonitrile and benzonitrile; and

A is selected from an allyl compound, crotyl compound and cinnamyl compound.

[0025] In a most preferred embodiment of the present invention, the palladium(II) compound is represented by Formula (I), (II), (III), (IV) or (V):



Formula (I) Formula (II) Formula (III) Formula (IV) Formula (V)

wherein:

M is selected from Na^+ and NH_4^+;

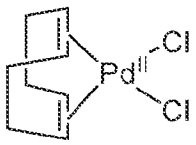
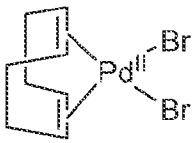
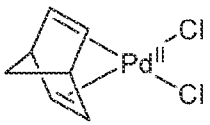
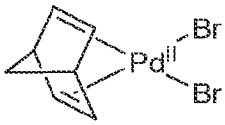
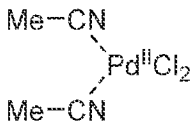
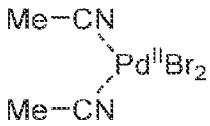
X is Cl^-;

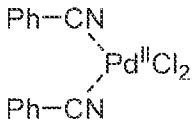
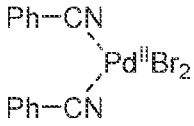
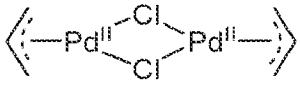
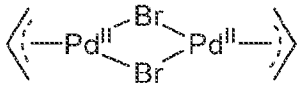
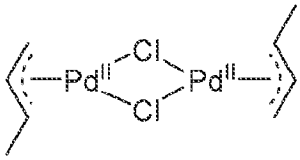
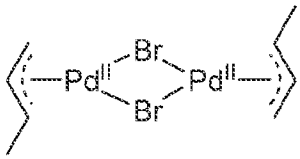
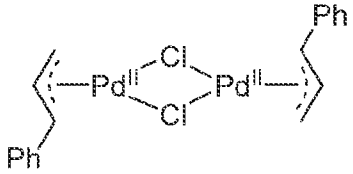
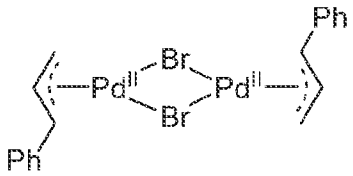
Q is selected from 1,5-cyclooctadiene and bicyclo[2.2.1]hepta-2,5-diene;

T is selected from acetonitrile and benzonitrile; and

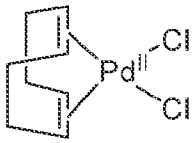
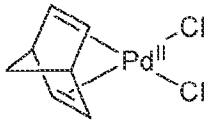
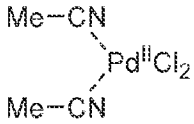
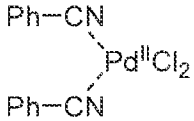
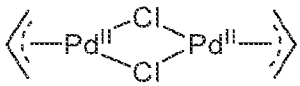
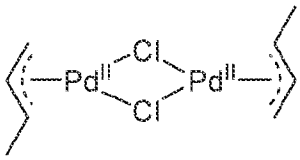
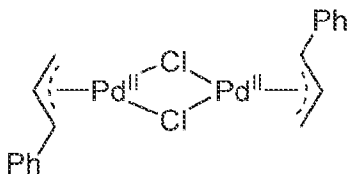
A is selected from allyl, crotyl and cinnamyl.

[0026] Preferred palladium(II) compounds are:

(I-1)	$Pd^{II}Cl_2$
(I-2)	$Pd^{II}Br_2$
(II-1)	$Na_2Pd^{II}Cl_4$
(II-2)	$Na_2Pd^{II}Br_4$
(III-1)	
(III-2)	
(III-3)	
(III-4)	
(IV-1)	
(IV-2)	

(IV-3)	
(IV-4)	
(V-1)	
(V-2)	
(V-3)	
(V-4)	
(V-5)	
(V-6)	

[0027] More preferred palladium(II) compounds are:

(I-1)	$Pd^{II}Cl_2$
(II-1)	$Na_2Pd^{II}Cl_4$
(III-1)	
(III-3)	
(IV-1)	
(IV-3)	
(V-1)	
(V-3)	
(V-5)	

[0028] In a preferred embodiment of the present invention, the phosphine ligand is represented by Formula (VI) and the palladium(0) phosphine complex is represented

by Formula (VII):

Formula (VI) Formula (VII)

wherein:

R is at each occurrence independently from each other selected from alkyl, cycloalkyl, aryl, and alkylaryl, which are optionally substituted, preferably R is at each occurrence independently from each other selected from C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, and C_7-C_{15} alkylaryl, which are optionally substituted by one or more substituents selected from F, Cl, CN, and -SO_3M, wherein M is an alkali metal cation or ammonium cation, more preferably R is at each occurrence independently from each other selected from C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, and C_7-C_{11} alkylaryl, which are optionally substituted by one or more substituents selected from F, Cl, CN, and -SO_3M, wherein M is selected from Li^+, Na^+, K^+, Rb^+, Cs^+ and NH_4^+, most preferably R is at each occurrence independently from each other selected from methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and tolyl, which are optionally substituted by one or more -SO_3M, wherein M is selected from Li^+, Na^+ and NH_4^+; and

m is 2, 3 or 4.

[0029] In a more preferred embodiment of the present invention, the phosphine ligand is represented by Formula (VI) and the palladium(0) phosphine complex is represented by Formula (VII):

Formula (VI) Formula (VII)

wherein:

R is at each occurrence independently from each other selected from C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, and C_7-C_{15} alkylaryl, which are optionally

substituted by one or more substituents selected from F, Cl, CN, and -SO_3M, wherein M is an alkali metal cation or ammonium cation; and

m is 2, 3 or 4.

[0030] In a particularly preferred embodiment of the present invention, the phosphine ligand is represented by Formula (VI) and the palladium(0) phosphine complex is represented by Formula (VII):

Formula (VI) Formula (VII)

wherein:

R is at each occurrence independently from each other selected from C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, and C_7-C_{11} alkylaryl, which are optionally substituted by one or more substituents selected from F, Cl, CN, and -SO_3M, wherein M is selected from Li^+, Na^+, K^+, Rb^+, Cs^+ and NH_4^+; and

m is 2, 3 or 4.

[0031] In a most preferred embodiment of the present invention, the phosphine ligand is represented by Formula (VI) and the palladium(0) phosphine complex is represented by Formula (VII):

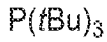
Formula (VI) Formula (VII)

wherein:

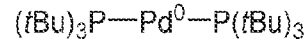
R is at each occurrence independently from each other selected from methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and tolyl, which are optionally substituted by one or more -SO_3M, wherein M is selected from Li^+, Na^+ and NH_4^+; and

m is 2, 3 or 4.

[0032] A very most preferred phosphine ligand according to Formula (V) is:



[0033] A very most preferred palladium(0) phosphine complex according to Formula (VI) is:



[0034] In a preferred embodiment of the present invention, in step (a) the palladium(II) compound is reacted with 3 or more equivalents of the phosphine ligand to obtain the palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II).

[0035] In a more preferred embodiment of the present invention, in step (a) the palladium(II) compound is reacted with about 3 to about 6 equivalents of the phosphine ligand to obtain the palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II).

[0036] In an even more preferred embodiment of the present invention, in step (a) the palladium(II) compound is reacted with 3 to 6 equivalents of the phosphine ligand to obtain the palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II).

[0037] In a most preferred embodiment of the present invention, in step (a) the palladium(II) compound is reacted with about 3 to about 4 equivalents of the phosphine ligand to obtain the palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II).

[0038] In an even most preferred embodiment of the present invention, in step (a) the palladium(II) compound is reacted with 3 to 4 equivalents of the phosphine ligand to obtain the palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II).

[0039] In a preferred embodiment of the present invention, step (a) is carried out at

room temperature.

[0040] In a preferred embodiment of the present invention, step (a) is carried out at a temperature between about 20 °C to about 25 °C.

[0041] In a preferred embodiment of the present invention, step (a) is carried out in an aromatic hydrocarbon solvent.

[0042] In a more preferred embodiment of the present invention, step (a) is carried out in toluene.

[0043] In a preferred embodiment of the present invention, in step (b) the palladium(0) phosphine complex obtained in step (a) is purified by precipitating from a first solvent and washing with a second solvent, wherein the first solvent is a hydrocarbon and the second solvent is an alcohol. Preferably, the first solvent is a C_6-C_{14} aromatic hydrocarbon. More preferably, the first solvent is benzene or toluene. Most preferably, the first solvent is toluene. Preferably, the second solvent is a C_1-C_{10} alcohol. More preferably, the second solvent is selected from methanol, ethanol, propanol and butanol. Most preferably, the second solvent is methanol.

[0044] In a preferred embodiment of the present invention, precipitating from the first solvent is performed by adding the first solvent.

[0045] In a preferred embodiment of the present invention, precipitating from the first solvent is performed by adding the second solvent.

[0046] In a preferred embodiment of the present invention, washing with the second solvent is carried out at a temperature between about -20 °C to about 20 °C.

[0047] In a more preferred embodiment of the present invention, washing with the second solvent is carried out at a temperature between about -20 °C to about -10 °C.

[0048] In a most preferred embodiment of the present invention, washing with the second solvent is carried out at a temperature of about -10 °C.

[0049] In a preferred embodiment of the present invention, washing with the second

solvent is repeated until a clear and colorless filtrate is obtained.

[0050] In a preferred embodiment of the present invention, step (b) is carried out twice or more times in succession. In a more preferred embodiment of the present invention, step (b) is carried out twice or three times in succession.

[0051] In a preferred embodiment of the present invention, the process for synthesizing a palladium(0) phosphine complex is carried out in a single reaction vessel.

[0052] In a preferred embodiment of the present invention, the process for synthesizing a palladium(0) phosphine complex does not involve the addition of basic reducing agents such as, for example, alkali metal hydroxides or alkali metal alkoxides, in particular, for example, sodium hydroxide or sodium methoxide.

[0053] The present invention further relates to a palladium(0) phosphine complex obtainable by the process for synthesizing described herein above.

Definitions

[0054] As used herein, the term "about" or "approximately", when used in connection with a measurable numerical variable, refers to the indicated value of the variable and to all values of the variable that tare within the experimental error of the indicated value (e.g., within 95% confidence limit for the mean) or within ± 10%, preferably ± 5%, of the indicated value, whichever is greater.

[0055] As used herein, the term "*t*Bu" refers to a *tert*-butyl group, i.e. a branched alkyl group of formula (-C_4H_9), which may also be written as (-$C(CH_3)_3$).

[0056] As used herein, the term "alkyl" refers to a saturated hydrocarbon chain, such as, but not limited to, methyl, ethyl, propyl and butyl. The alkyl group may be straight-chain or branched-chain. For example, as used herein, propyl encompasses both *n*-propyl and *iso*-propyl; butyl encompasses *n*-butyl, *sec*-butyl, *iso*-butyl and *tert*-butyl, and so forth.

[0057] As used herein, the term "cycloalkyl" refers to a saturated hydrocarbon cyclic group, such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl and

cyclohexyl. Also included are bridged saturated hydrocarbon (poly)cyclic groups such as, but not limited to, adamantyl.

[0058] As used herein, the term "aryl" refers to an aromatic hydrocarbon group. Aryl includes, e.g., phenyl, biphenyl, naphthyl, anthracenyl, and so forth, as well as the substituted forms of each.

[0059] As used herein, the term "allyl" refers to a substituent with the structural formula R-CH_2-CH=CH_2, where R is the rest of the molecule or H. It consists of a methylene bridge (-CH_2-) attached to a vinyl group (-CH=CH_2).

[0060] As used herein, the term "crotyl" refers to a substituent with the structural formula R-CH_2-CH=CH-CH_3, where R is the rest of the molecule or H. Systematically, it is called a but-2-en-1-yl group and exhibits geometric isomerism, being either *cis* (*Z*) or *trans* (*E*).

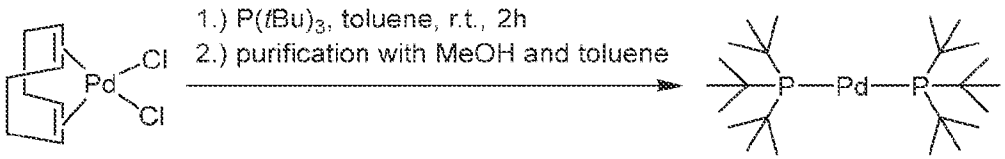
[0061] As used herein, the term "cinnamyl" refers to a substituent with the structural formula R-CH_2-CH=CH-Ph, where R is the rest of the molecule or H. Systematically, it is called a 3-phenylprop-2-enyl group and exhibits geometric isomerism, being either *cis* (*Z*) or *trans* (*E*).

[0062] "Substituted" as used herein means that one or more hydrogen atoms of the described compound or functional group is replaced with another functional group, or substituent. For example, substituted phenyl may include one or more substituents in place of any hydrogen atom on the phenyl ring. In some embodiment, there may be one substituent at the *ortho*, *meta* or *para* position. In other embodiments, there may be substituents at both *ortho* positions or both *meta* positions. In still other embodiments, the optionally substituted phenyl may include substituents at, e.g., both the *ortho* and *para* positions, or both *meta* and *para* positions. In some embodiments with multiple substituents, the substituents are all the same, in other embodiments with multiple substituents, the substituents are different from each other. Typical substituents include, but are not limit to, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy. When a functional group is described as "optionally substituted" that

functional group may have one or more substituents or no substituents.

Examples

[0063] Example 1. Synthesis of Bis(tri-*tert*-butylphosphine)palladium(0) from Dichloro(1,5-cyclooctadiene)palladium(II)



[0064] Dichloro(1,5-cyclooctadiene)palladium(II), 99% (10.00 g; 35.03 mmol; 1.00 eq.) was added to a flask with a stir bar and a thermometer or thermocouple probe. It was purged with nitrogen for 30 minutes. A 1 molar solution of tri-*tert*-butylphosphine, 98% (22.68 g; 112.08 mmol; 3.20 eq.) in toluene was added to the flask via nitrogen pressure cannula transfer or syringe. The reaction mixture was stirred for 2 hours at room temperature (20-25 °C).

[0065] Degassed methyl alcohol (anhydrous, 99.8% (120.00 ml)) was added to the flask and the reaction mixture was allowed to stir for 20 – 30 minutes. Then, the reaction mixture was cooled to -10 to -20 °C and the solids were allowed to settle. The liquid was filtered away with a canula and it was washed with more methanol until the filtrate is clear and colorless. Then, toluene (anhydrous, 99.8% (75 ml) was added to the flask and it was stirred at 55-60 °C for 30 min. The reaction mixture was allowed to cool to at least 30 °C and degassed methyl alcohol (anhydrous, 99.8% (120.00 ml)) was added to the flask. The reaction mixture was allowed to stir for 20 – 30 minutes. Then, the reaction mixture was cooled to -10 to -20 °C and the solids were allowed to settle. The liquid was filtered away with a canula and it was washed with more methanol until the filtrate is clear and colorless. The slurry was transferred onto a Schlenk filter under vacuum for filtration. The white solid product was dried under inert conditions.

[0066] Yield: 87%, purity: > 98%. 1H NMR (C_6D_6, 500 MHz): δ = 1.51 (t, 54H) ppm. 31P{1H} NMR (C_6D_6, 202 MHz): δ = 84.8 ppm.

[0067] Example 2. Synthesis of Bis(tri-*tert*-butylphosphine)palladium(0) from Dichloro(norbornadiene)palladium(II)

[0068] The procedure of Example 1 was repeated using dichloro(norbornadiene)palladium(II), 99% (2.00 g; 7.42 mmol; 1.00 eq.) instead of dichloro(1,5-cyclooctadiene)palladium(II). The quantitative ratios and volumes of the used reagents and solvents were adjusted accordingly. The desired product was obtained in 80% yield.

[0069] Example 3. Synthesis of Bis(tri-*tert*-butylphosphine)palladium(0) from Bis(acetonitrile)dichloropalladium(II)

[0070] The procedure of Example 1 was repeated using bis(acetonitrile)dichloropalladium(II), 99% (2.00 g; 7.71 mmol; 1.00 eq.) instead of dichloro(1,5-cyclooctadiene)palladium(II). The quantitative ratios and volumes of the used reagents and solvents were adjusted accordingly. The desired product was obtained in 70% yield.

[0071] Example 4. Synthesis of Bis(tri-*tert*-butylphosphine)palladium(0) from Bis(benzonitrile)dichloropalladium(II)

[0072] The procedure of Example 1 was repeated using bis(benzonitrile)dichloropalladium(II), 99% (2.00 g; 5.21 mmol; 1.00 eq.) instead of dichloro(1,5-cyclooctadiene)palladium(II). The quantitative ratios and volumes of the used reagents and solvents were adjusted accordingly. The desired product was obtained in 78% yield.

[0073] The examples provided herein are not meant to limit the scope of the invention as set forth in the claims.

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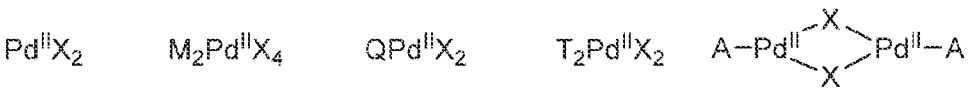
We claim:

1. A process for synthesizing a palladium(0) phosphine complex, wherein said process comprises the following steps:

(a) reacting a palladium(II) compound with about 3 or more equivalents of a phosphine ligand to obtain a palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II); and

(b) in situ purification of the palladium(0) phosphine complex obtained in step (a).

2. The process according to claim 1, wherein the palladium(II) compound is represented by Formula (I), (II), (III), (IV) or (V):



Formula (I) Formula (II) Formula (III) Formula (IV) Formula (V)

wherein:

M is an alkali metal cation or ammonium cation;

X is a halogen anion;

Q is a cyclic diene;

T is a nitrile or an olefin; and

A is an alkene.

3. The process according to claim 2, wherein:

M is selected from Li^+, Na^+, K^+, Rb^+, Cs^+ and NH_4^+;

X is selected from Cl^-, Br^- and I^-;

Q is selected from 1,5-cyclooctadiene and bicyclo[2.2.1]hepta-2,5-diene;

T is selected from acetonitrile, benzonitrile and ethylene; and

A is selected from an allyl compound, crotyl compound and cinnamyl compound.

4. The process according to claim 2, wherein:

M is selected from Li^+, Na^+ and NH_4^+;

X is selected from Cl^- and Br^-;

Q is selected from 1,5-cyclooctadiene and bicyclo[2.2.1]hepta-2,5-diene;

T is selected from acetonitrile and benzonitrile; and

A is selected from an allyl compound, crotyl compound and cinnamyl compound.

5. The process according to claim 2, wherein:

M is selected from Na^+ and NH_4^+;

X is Cl^-;

Q is selected from 1,5-cyclooctadiene and bicyclo[2.2.1]hepta-2,5-diene;

T is selected from acetonitrile and benzonitrile; and

A is selected from allyl, crotyl and cinnamyl.

6. The process according to one or more of claims 1 to 5, wherein the phosphine ligand is represented by Formula (V) and the palladium(0) phosphine complex is represented by Formula (VI):

Formula (V) Formula (VI)

wherein:

R is at each occurrence independently from each other selected from alkyl, cycloalkyl, aryl, and alkylaryl, which are optionally substituted; and

m is 2, 3 or 4.

7. The process according to claim 6, wherein:

R is at each occurrence independently from each other selected from C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, and C_7-C_{15} alkylaryl, which are optionally substituted by one or more substituents selected from F, Cl, CN, and -SO_3M, wherein M is an alkali metal cation or ammonium cation; and

m is 2, 3 or 4.

8. The process according to claim 6, wherein:

R is at each occurrence independently from each other selected from C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, and C_7-C_{11} alkylaryl, which are optionally substituted by one or more substituents selected from F, Cl, CN, and -SO_3M, wherein M is selected from Li^+, Na^+, K^+, Rb^+, Cs^+ and NH_4^+; and

m is 2, 3 or 4.

9. The process according to claim 6, wherein:

R is at each occurrence independently from each other selected from methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and tolyl, which are optionally substituted by one or more -SO_3M, wherein M is selected from Li^+, Na^+ and NH_4^+; and

m is 2, 3 or 4.

10. The process according to one or more of claims 1 to 9, wherein in step (a) the palladium(II) compound is reacted with about 3 to about 6 equivalents of the phosphine ligand to obtain the palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II).

11. The process according to one or more of claims 1 to 9, wherein in step (a) the palladium(II) compound is reacted with about 3 to about 4 equivalents of the phosphine ligand to obtain the palladium(0) phosphine complex, wherein the equivalents are based on the amount of palladium(II).

12. The process according to one or more of claims 1 to 11, wherein step (a) is carried out at room temperature.

13. The process according to one or more of claims 1 to 12, wherein step (a) is carried out at a temperature between about 20 °C to about 25 °C.

14. The process according to one or more of claims 1 to 13, wherein step (a) is carried out in an aromatic hydrocarbon solvent.

15. The process according to one or more of claims 1 to 14, wherein step (a) is carried out in toluene.

16. The process according to one or more of claims 1 to 15, wherein in step (b) the palladium(0) phosphine complex obtained in step (a) is purified by precipitating and washing.

17. The process according to one or more of claims 1 to 16, wherein in step (b) the palladium(0) phosphine complex obtained in step (a) is purified by precipitating from a first solvent and washing with a second solvent, wherein the first solvent is a hydrocarbon and the second solvent is an alcohol.

18. The process according to claim 17, wherein the first solvent is a C_6-C_{14} aromatic hydrocarbon.

19. The process according to claim 17, wherein the first solvent is benzene or toluene.

20. The process according to claim 17, wherein the first solvent is toluene.

21. The process according to claim 17, wherein the second solvent is a C_1-C_{10} alcohol.

22. The process according to claim 17, wherein the second solvent is selected from methanol, ethanol, propanol and butanol.

23. The process according to claim 17, wherein the second solvent is methanol.

24. The process according to one or more of claims 17 to 23, wherein precipitating from the first solvent is performed by adding the second solvent.

25. The process according to one or more of claims 17 to 24, wherein washing with the second solvent is carried out at a temperature between about -20 °C to about 20 °C.

26. The process according to one or more of claims 17 to 24, wherein washing with the second solvent is carried out at a temperature between about -20 °C to about -10 °C.

27. The process according to one or more of claims 17 to 24, wherein washing with the second solvent is carried out at a temperature of about -10 °C.

28. The process according to one or more of claims 17 to 27, wherein washing with the second solvent is repeated until a clear and colorless filtrate is obtained.

29. The process according to one or more of claims 1 to 28, wherein the process is carried out in a single reaction vessel.

30. Palladium(0) phosphine complex obtainable by the process according to one or more of claims 1 to 29.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/073550

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

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/073559 A1 (JOHNSON MATTHEY PLC [GB]) 26 April 2018 (2018-04-26) example 12 claims 31-37 table 1 page 11, line 4 - page 12, line 19	1-30
X	KURAN ET AL: "Synthesis and Characterization of Tertiary Phosphine Pd(O) Complexes", LNORGANLCTZ CHIMIC:A ACTA,, vol. 12, 1 January 1975 (1975-01-01), pages 187-193, XP055472100, paragraph [Experimental]	1-30

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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"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

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"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2023	30/11/2023

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Eberhard, Michael

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIN WENBIN ET AL: "Synthesis and X-ray Crystal Structure of the New Palladium(I) Dimer [Pd2(PMe3)6][hfac]2 and Its Conversion to [PdMe(PMe3)3][hfac] via Activation of Phosphorus-Carbon Bonds", INORGANIC CHEMISTRY, vol. 33, no. 10, 1 May 1994 (1994-05-01), pages 2265-2272, XP093103150, Easton , US ISSN: 0020-1669, DOI: 10.1021/ic00088a032 page 2271, column 1, last paragraph - column 2, paragraph 2 -----	1-30
X	KAKIZOE DAICHI ET AL: "Photophysical Properties of Simple Palladium(0) Complexes Bearing Triphenylphosphine Derivatives", INORGANIC CHEMISTRY, vol. 60, no. 13, 9 June 2021 (2021-06-09), pages 9516-9528, XP093103152, Easton , US ISSN: 0020-1669, DOI: 10.1021/acs.inorgchem.1c00631 paragraph [Synthesis] -----	1-30
X	DERVISI ET AL: "Synthesis and chemistry of diphenyl-2-pyridylphosphine complexes of palladium(o). X-Ray characterisation of Pd(Ph2Ppy)2- (112-DMAD) and trans-Pd(Ph1Ppy)2(PhC-CHJ(CF3COJ", THE ROYAL SOCIETY OF CHEMISTRY, 1 January 2000 (2000-01-01), pages 523-528, XP055472084, page 527, column 1, paragraph 2 -----	1-30
X	PAUL F ET AL: "structural charachterization and simple synthesis of {Pd[P(o-Tol)3]2},dimeric Palladium(II) complexes obtained by oxidative addition of aryl bromides, and corresponding monometallic amine complexes", ORGANOMETALLICS, AMERICAN CHEMICAL SOCIETY, vol. 14, 1 January 1995 (1995-01-01), pages 3030-3039, XP002358606, ISSN: 0276-7333, DOI: 10.1021/OM00006A053 cited in the application page 3032, column 1 - page 3033, column 1 * equation (1) * ----- -/--	1-30

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/073550

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	MACQUEEN PRESTON M. ET AL: "Convenient One-Pot Synthesis of L 2 Pd(0) Complexes for Cross-Coupling Catalysis", ORGANOMETALLICS, vol. 42, no. 18, 17 April 2023 (2023-04-17), pages 2644-2650, XP093103151, ISSN: 0276-7333, DOI: 10.1021/acs.organomet.3c00059 Retrieved from the Internet: URL:https://pubs.acs.org/doi/pdf/10.1021/acs.organomet.3c00059> the whole document -----	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/073550

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018073559 A1	26-04-2018	CN 110312728 A	08-10-2019
		EP 3529253 A1	28-08-2019
		JP 6983233 B2	17-12-2021
		JP 2019531322 A	31-10-2019
		RU 2019115341 A	23-11-2020
		US 2019248819 A1	15-08-2019
		WO 2018073559 A1	26-04-2018