(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 November 2017 (16.11.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/193288 A1

(51) International Patent Classification:
B01J 31/24 (2006.01) *C07C 45/68* (2006.01)
C07F 9/572 (2006.01) *C07C 49/784* (2006.01)
C07C 15/12 (2006.01) *C07C 255/50* (2006.01)
C07C 1/32 (2006.01) *C07C 253/30* (2006.01)
C07C 47/575 (2006.01)

(21) International Application Number:
PCT/CN2016/081589

(22) International Filing Date:
10 May 2016 (10.05.2016)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2017/193288 A1

(54) Title: SYNTHESIS OF PHOSPHINE LIGANDS BEARING TUNABLE LINKAGE: METHODS OF THEIR USE IN CATALYSIS

(57) Abstract: A series of novel linked indolyl phosphine ligands for transition metals, the synthesis thereof and their use in catalytic coupling reactions are provided. The ligands provide improvements of trasition-metal-catalyzed reactions, including the range of substrates scope, reaction conditions and efficieny.

SYNTHESIS OF PHOSPHINE LIGANDS BEARING TUNABLE LINKAGE: METHODS OF THEIR USE IN CATALYSIS

Technical Field

The present invention relates to a series of novel linked indolyl phosphine ligands for transition metals, the synthesis thereof and their use in catalytic reactions. The disclosed method provides improvements of transition-metal-catalyzed reactions, including the range of substrates scope, reaction conditions, and efficiency. For examples, remarkable improvements have been realized in the preparation of sterically hindered biaryl compounds by transition-metal-catalyzed cross-coupling reactions.

Background Art

Transition-metal-catalyzed cross-coupling reactions have received significant attention and became an extremely versatile protocol in organic synthesis for the connection of two different fragments *via* the formation of either carbon-carbon and/or carbon-heteroatom bonds (de Meijere, A.; Brase, S.; Oestreich, M. Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Vol. 3: Wiley-VCH, Weinheim, 2013. Colacot, T. J. Eds. *New Trends in Cross-Coupling, Theory and Applications*: Royal Society of Chemistry, Cambridge, 2015). Particularly, Suzuki-Miyaura coupling is one of the preeminent methods of the formation of carbon-carbon bonds and has been used in the construction of diversified biaryls, and they have a myriad of applications in pharmaceutical, materials, and agricultural chemistry (Miyaura, N. *Topics in Current Chemistry*, **2002**, *219*, 11). Arylamines are frequently encountered in natural and pharmaceutical products. Buchwald-Hartwig amination is a highly valuable method for the formation of carbon-nitrogen bond (Ricci, A Ed *Modern Amination Methods*: Wiley-VCH, Weinheim, 2000). Efforts have been made toward increasing the reaction efficacy and it has been recognized that ligands play essential roles during each step of the catalytic cycle including oxidative addition, transmetallation, and reductive elimination. The structural features of the ligands can greatly influence the reaction rate, regioselectivity, and stereoselectivity of the cross-coupling reaction. Thus, the strategic design of ligands with appropriate steric/electronic natures and great diversity is crucial in dealing with challenging and problematic substrates in this

area. Despite the recent advances on cross-coupling reactions, sterically hindered substrates and a further decrease of the catalyst loading remain great challenges. It was demonstrated that the sterically bulky and electron-rich phosphine ligands can have profound effects on the reactivity in catalytic reactions for carbon-carbon/ carbon-heteroatom bond coupling processes. Development of new ligands remains imperative to further increase the efficiency of cross-coupling reaction.

Noteworthy, Beller (Zapf, A.; Sundermeier, M.; Jackstell, R.; Beller, M.; Riermeier, T.; Monsees, A.; Dingerdissen, U. *WO 2004/101581 A2*), Buchwald (Buchwald, S. L.; Fors, B. P.; Surry, D. S. *WO 2009/076622 A2*; Buchwald, S. L.; Old, D. W.; Wolfe, J. P.; Palucki, M.; Kamikawa, K. *US 6307087 B1*), Tang (Haddad, N.; Qu, B.; Rodriguez, S.; Senanayake, C.; Tang, W.; Wei, X.; Yee, N. K. *WO 2011/126917 A1*), Fu, Hartwig and other groups are highly versatile in the phosphine ligand design and synthesis. The present invention is to provide novel ligands and catalysts, which are suitable for large-scale applications, are readily accessible, highly tunable, and convert haloaromatic compounds especially sterically hindered one to the respective coupling products in high yield.

Mode for Invention

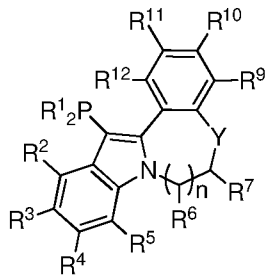
The present invention relates to a series of novel and efficient linked indolyl phosphine ligands for transition metals, to their preparation and to their use in catalytic reactions. The disclosed method provides improvements of transition-metal-catalyzed reactions, including the range of substrates scope, reaction conditions, and efficiency. With the linked indolyl phosphine ligands, several reactions can be effectively handled such as Suzuki-Miyaura, Heck, Sonogashira, Hiyama, Stille cross-coupling reactions; Buchwald-Hartwig amination; direct arylation; and cyanation with aryl halides or vinyl halides. Especially, remarkable improvements have been realized in the preparation of sterically hindered biaryl compounds by transition-metal-catalyzed Suzuki-Miyaura cross-coupling reactions. The basic indolyl phosphines bearing tunable linkage can be prepared *via* traditional Fischer Indolization protocol. A combination of phenylhydrazines and acetophenones provides a high diversification of the ligand structure. The ligands are suitable to use as scaffolds in metal-ligand complexes, which can serve as catalysts for further reactions. The ligands can be prepared in a large scale, and purified by simple

recrystallization. These ligands can exhibit exceptionally high stability in both solid and solution states.

The following description of certain exemplary embodiment(s) is merely exemplary in nature and is in no way intended to limit the invention, its application, or uses. Throughout this description, the term 'tunable' shall refer to the ability to design a chemical compound using to exhibit specific properties.

The present invention relates to indolyl phosphine ligands bearing tunable linkage, and methods of making such utilizing phenylhydrazine and acetophenones as the starting materials with various linkage reagents. The present invention further includes uses of the ligands in the synthesis of pharmaceuticals, materials, and agriculture.

In its first aspect, the present invention is achieved according to the novel phosphine ligands structure formula (I), below:



(I)

wherein: Y independently represents an oxygen atom or C-R^8 group or NR^8 group and R^1 for each of the two R^1 groups independently of the other represents C_1-C_8-alkyl; C_3-C_{10}-cycloalkyl, which includes especially both monocyclic and also bi- and tri-cyclic cycloalkyl; (5- to 11-membered)heterocycloalkyl; CF_3; ferrocenyl; C_5-C_{20}-aryl, which includes especially the phenyl, naphthyl, fluorenyl; (5- to 11-membered)heteroaryl, wherein the number of hetero atoms, selected from the group N, O, S, may be from 1 to 2; wherein the two R^1 may also be linked to one another; or wherein each such C_3-C_{10}-cycloalkyl, (5- to 11-membered)heterocycloalkyl, C_6-C_{20}-aryl or (5- to 11-membered)heteroaryl group is optionally mono- or poly-substituted. These substituents independently of one another, may be hydrogen, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_3-C_8-cycloalkyl, C_2-C_9-heteroalkyl, C_5-C_{10}-aryl, C_2-C_9-heteroaryl, wherein the number of heteroatoms, especially from the group N, O, S, may be from 1 to 4; C_1-C_{14}-alkoxy, preferably -O(C_1-C_6)alkyl, particularly preferably OMe; C_1-C_{10}-halo-alkyl, preferably CF_3, hydroxyl, secondary, tertiary amino groups; wherein two

of the mentioned substituents may also bridged with one another to form 4- to 8-membered ring which can be further substituted preferably by linear or branched C_1-C_{10}-alkyl, C_6-aryl, benzyl, C_1-C_{10}-alkoxy, hydroxyl or benzyloxy groups.

R^2, R^3, R^4, and R^5 are each independently selected from the group comprising hydrogen; halogen; C_1-C_{10}-alkyl; hydroxyl; -O(C_1-C_6)alkyl; CF_3; C_3-C_{10}-cycloalkyl; (5- to 11-membered)heterocycloalkyl; amino; silyloxy; sulfhydryl; alkylthio; thioalkyl; phosphoryl; phosphonate; phosphine; urea; thiourea; nitrile; carbonyl; carboxyl; carboxamide; C_6-C_{20}-aryl; (5- to 11-membered)heteroaryl, wherein the number of hetero atoms, selected from the group N, O, S, may be from 1 to 2; wherein any two or more adjacent instances of R^2, R^3, R^4, and R^5, taken together with the carbons to which they are bound, form a five- or six-membered substituted or unsubstituted aryl or heteroaryl ring.

R^6, R^7, and R^8 are the substituted at the linked carbon chain between the nitrogen atom and Y, wherein n = 1-9, each independently selected from the group comprising hydrogen; halogen; C_1-C_{20}-alkyl; hydroxyl; -O(C_1-C_{10})alkyl; CF_3; C_3-C_{10}-cycloalkyl; (5- to 11-membered)heterocycloalkyl; amino; silyloxy; sulfhydryl; C_6-C_{20}-aryl; (5- to 11-membered)heteroaryl, wherein the number of hetero atoms, selected from the group N, O, S, may be from 1 to 2; wherein any two or more adjacent instances of R^6, R^7, and R^8, taken together with the carbons to which they are bound, form a five- or six-membered substituted or unsubstituted aryl or heteroaryl ring.

R^9, R^{10}, R^{11}, and R^{12} are each independently selected from the group comprising hydrogen; halogen; C_1-C_{10}-alkyl; hydroxyl; –O(C_1-C_6)alkyl; CF_3; C_3-C_{10}-cycloalkyl; (5- to 11-membered)heterocycloalkyl; amino; silyloxy; sulfhydryl; alkylthio; thioalkyl; phosphoryl; phosphonate; phosphine; urea; thiourea; nitrile; carbonyl; carboxyl; carboxamide; C_6-C_{20}-aryl; (5- to 11-membered)heteroaryl, wherein the number of hetero atoms, selected from the group N, O, S, may be from 1 to 2; wherein any two or more adjacent instances of R^9, R^{10}, R^{11}, and R^{12}, taken together with the carbons to which they are bound, form five- or six-membered substituted or unsubstituted aryl or heteroaryl rings.

n is independently for each occurrence an integer in the range 1 to 8 inclusive, and the ligand is achiral or, when chiral, is a single stereoisomer or a mixture of stereoisomers.

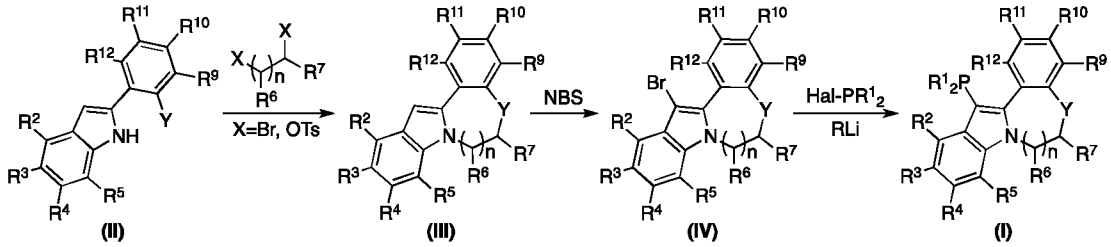
In a second aspect, the invention relates to formula (I), wherein one of the R^1 is C_1-C_8-alkyl selected from –CH_3, –CH_2CH_3, –$C(CH_2)_2CH_3$, –$CH(CH_3)_2$, –$C(CH_3)_3$, –

$C(CH_2CH_3)_3$, $-C(CH_2CH_3)(CH_3)_2$, and R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined in the first aspect.

In a third aspect, the invention relates to formula (I), wherein one of the R^1 is C_3-C_{10}-cycloalkyl, which includes especially both monocyclic and also bi- and tri-cyclic cycloalkyl, selected from cyclopentyl, cyclohexyl, 1-adamantyl, and R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined in the first aspect.

In a fourth aspect, the invention relates to formula (I), wherein one of the R^1 is C_6-C_{20}-aryl selected from phenyl, 2-methylphenyl, 4-methylphenyl, 3,5-dimethylphenyl, 3,5-di(fluoromethyl)phenyl, 3,5-di-*tert*-butylphenyl, 4-methoxyphenyl, 2-trifluoromethylphenyl, 2,4,6-trimethylphenyl, 3,5-di-*tert*-butyl-4-methoxyphenyl, and naphthyl, and R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined in the first aspect.

The present invention provides a process for the preparation of the above-described ligands of formula (I). In general, the ligands can be prepared by traditional Fischer Indolization followed the general reaction scheme 1 below.



Scheme 1

According to the invention, the novel phosphine ligands bearing tunable linkage are used as catalysts in combination with transition metal complexes. The transition metal compounds used are particularly preferably palladium compounds. The ligands according to the invention can generally be added *in situ* to corresponding transition metal precursor compounds and accordingly used for catalytic applications. However, it may occasionally be advantages for specific phosphine complexes of the mentioned transition metals to be prepared first and subsequently used as catalyst to increase the catalytic activity. The phosphine ligands bearing tunable linkage prepared in accordance with the invention have proved suitable especially as the ligand component for the biaryl synthesis from aryl halides or vinyl halides.

Catalyst compositions

The ligands described herein find application in catalyst compositions in combination with transition metal compounds. In various embodiments, catalyst compositions contain a ligand described herein and a transition metal compound. Examples of transition metal compounds include those of palladium, rhodium, ruthenium, platinum, gold, cobalt, iridium, copper, and nickel, as well as combinations. In various embodiments, the transition metal compound and the ligand are provided in the catalyst composition in stoichiometric amounts with respect to one other. In various embodiments, the optimum ligand to metal ratio depends on the metal source used as well as the specifics of the transformation being attempted. In various embodiments, the transition metal compound is provided in the catalyst composition as a salt of a central atom. A non-limiting example of such a salt is an acetate salt. When the central atom is palladium in a preferred embodiment, a preferred transition metal compound is palladium acetate, or $Pd(OAc)_2$. A catalyst composition is then formed of a mixture of palladium acetate and a ligand compound coordinated as a complex as described herein. Other embodiments of palladium sources formally in the 2+ oxidation state include but are not limited to $PdCl_2$, $Pd(TFA)_2$, $Pd(CH_3CN)_4(BF_4)_2$ and $PdCl_2(CH_3CN)_2$.

In various embodiments, the transition metal compound is in zero valence state. An example is tris(dibenzylideneacetone)dipalladium(0), commonly abbreviated as $Pd_2(dba)_3$. Other palladium sources in formally the zero or other valence states may also be suitable. Examples include but are not limited to $Pd(dba)_2$.

Catalytic reactions

The ligands described herein exhibit utility in transition metal catalyzed reactions. In embodiments, the disclosed ligands may be combined with a variety of transition metal compounds to catalyze a range of chemical transformations. In embodiments, compositions containing a transition metal compound and a disclosed ligand can be used to catalyze a variety of organic reactions. A non-limiting example of a reaction catalyzed by a disclosed ligand is given in Scheme I, illustrating the catalysis of a C-N reaction. Other reactions of interest include carbon-oxygen, carbon-carbon. In non-limiting examples, the catalysts can be used to catalyze Suzuki-Miyaura type C-C bond-forming reactions, Buchwald-Hartwig Amination C-N bond forming reactions, direct arylation C-C bond forming reactions, and Hiyama type C-C bond forming reactions.

More specifically, a combination of a ligand with a transition metal compound

catalyzes the following reactions:

i. Carbon-carbon bond forming reactions such as Suzuki-Miyaura, Hiyama, Stille, Heck, Sonogashira cross-coupling reactions and direct arylation;

ii. Carbon-nitrogen bond forming reactions such as Buchwald-Hartwig Amination reactions;

iii. Carbon-Boron bond forming reactions such as Borylation reactions;

iv. Carbon-Phosphorus bond forming reactions.

Ligands, catalyst compositions, and catalyzed reactions have been described with respect to various preferred embodiments. Further non-limiting description is given by way of the working examples in the section following.

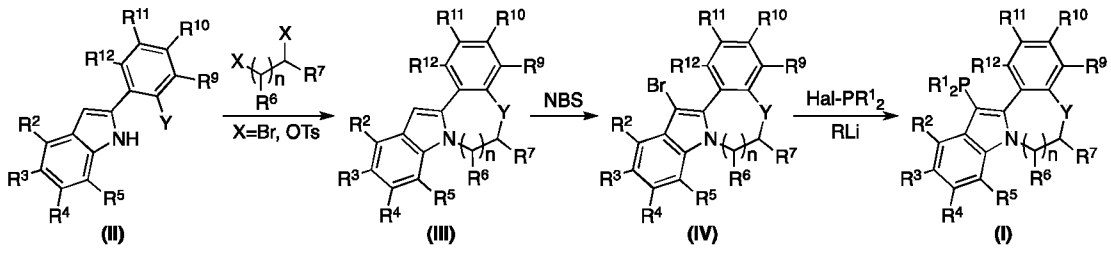
IMPLEMENTATION EXAMPLES

Reactions of compounds were carried out in standard Rotaflo®(England) resealable screw-cap tubes. The solvents 1,4-dioxane, tetrahydrofuran (THF), and toluene were degassed and freshly distilled over sodium under nitrogen. Dichloromethane and *tert*-butanol were freshly distilled over calcium hydride under nitrogen.

The following examples, which follow, serve to explain the process for making the ligands and the catalytic cross-coupling reactions without limiting it thereto.

Examples 1 to 4: General Preparation of Ligand

In general, the present invention provides a process for the preparation of the above-described ligands. These ligands may be prepared in the manner depicted in the general reaction Scheme 1.



To prepare compound **II**, two general methods were used. **Method A:** Follow the general procedures of Fischer-indole synthesis, compound **II** can be obtained from corresponding substituted acetophenone (100 mmol), corresponding substituted phenylhydrazine (110 mmol) and polyphosphoric acid (PPA) as an off-white solid. Compound **II** from Method A may be made in the manner described by Kwong,

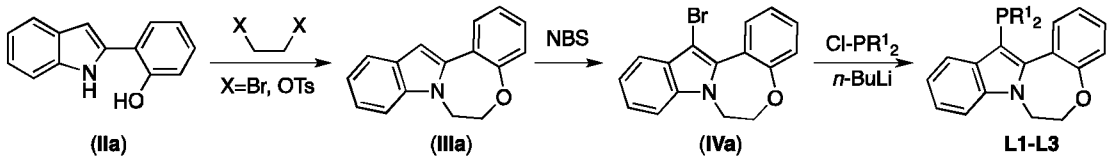
Organic Syntheses **2016**, *93*, 14-28. **Method B:** According to the literature, compound **II** can be obtained from corresponding substituted oxindole (50 mmol), 2-chloropyridine (60 mmol), trifluoromethanesulfonic anhydride (60 mmol) and corresponding substituted 2-naphthol (50 mmol) as a grey solid. Compound **II** from Method B may be made in the manner described by Ghandi, *Tetrahedron Letters* **2011**, 270-273; and Shibata, *Organic Letters* **2013**, *15*, 686-689.

To a solution of 10 mmol of **II** in 75 ml of anhydrous DMF, 30-80 mmol of potassium hydroxide was added under nitrogen, and kept stirring at room temperature until most of the KOH were dissolved. Dialkyl bromide (12-24 mmol) or dialkyl tosylate (11-22 mmol) was then added to the reaction mixture and stirred at 25–110 °C overnight. Water was added to quench the reaction and the organic layer was extracted with CH_2Cl_2, separated, dried over sodium sulfate, concentrated and purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), ligand precursor **III** can be obtained.

To a solution of **III** (8 mmol) in anhydrous DMF (40 mL), a solution of *N*-bromosuccinimide (8.8 mmol) in anhydrous DMF (25 mL) was added at room temperature and stirred overnight. The reaction mixture was poured into crushed ice and CH_2Cl_2 was added to the flask followed by water for extraction. The organic phase was washed with a large amount of water, concentrated and then purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), ligand precursor **IV** was obtained.

Compound **IV** (5 mmol) was dissolved in freshly distilled anhydrous THF at room temperature under nitrogen atmosphere. The solution was then cooled to -78 °C in dry ice/acetone bath. Titrated *n*-BuLi (5.5 mmol) was added dropwise by syringe. After stirring the reaction mixture for 30 min at -78 °C, Cl-PR^1_2 in THF (5 mL) was added. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the product was successively washed with cold MeOH/EtOH mixture. The resulting white solid was filtered off and dried *in vacuo* (purity 90-99%).

Example 1: Synthesis of ligand **L1 – L3**



Follow the general procedure of Fischer-indole synthesis (**Method A**), 2-(1*H*-indol-2-yl)phenol (**IIa**) was obtained from 1-(2-hydroxyphenyl)ethanone (100 mmol), phenylhydrazine (110 mmol) and PPA as an off-white solid.

After purification, 10 mmol of 2-(1*H*-indol-2-yl)phenol (**IIa**) was dissolved in 75 ml of anhydrous DMF under nitrogen. 40 mmol of potassium hydroxide was added to the reaction mixture and kept stirring at room temperature. After all the KOH was dissolved, 1,2-dibromoethane (12 mmol) or 1,2-ditosylethane (11 mmol) was added and stirred overnight. Water was added to quench the reaction and the organic layer is extracted with CH_2Cl_2, separated, dried over sodium sulfate, concentrated and purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), 6,7-dihydrobenzo[6,7][1,4]oxazepino[4,5-*a*]indole (**IIIa**) was obtained as a pale yellow solid.

To a solution of 6,7-dihydrobenzo[6,7][1,4]oxazepino[4,5-*a*]indole (**IIIa**) (8 mmol) in anhydrous DMF (40 mL), a solution of *N*-bromosuccinimide (8.8 mmol) in anhydrous DMF (25 mL) was added at room temperature and stirred overnight. The reaction mixture was poured into crushed ice and CH_2Cl_2 was added to the flask followed by water for extraction. The organic phase was washed with a large amount of water, concentrated and then purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), 13-bromo-6,7-dihydrobenzo[6,7][1,4]oxazepino[4,5-*a*]indole (**IVa**) was obtained as a pink solid.

13-Bromo-6,7-dihydrobenzo[6,7][1,4]oxazepino[4,5-*a*]indole (**IVa**) (5 mmol) was dissolved in freshly distilled anhydrous THF at room temperature under nitrogen atmosphere. The solution was then cooled to -78 °C in dry ice/acetone bath. Titrated *n*-BuLi (5.5 mmol) was added dropwise by syringe. After stirring the reaction mixture for 30 min at -78 °C, Cl-PR^1_2 in THF (5 mL) was added. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the product was successively washed with cold MeOH/EtOH mixture. The resulting white solid was filtered off and dried *in vacuo* (purity 90-99%).

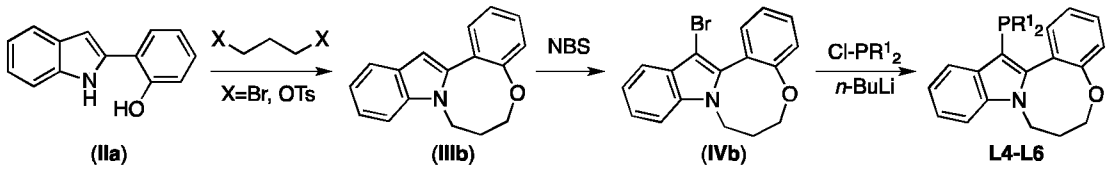
Yields:

$PR^1_2 = PCy_2$ 55% (^{31}P-NMR: -18.2 ppm) (**L1**)

$PR^1_2 = PPh_2$ 80% (^{31}P-NMR: -28.6 ppm) (**L2**)

$PR^1_2 = P\textit{i}\text{-}Pr_2$ 47% (^{31}P-NMR: -8.4 ppm) (**L3**)

Example 2: Synthesis of ligand **L4 – L6**



10 mmol of 2-(1*H*-indol-2-yl)phenol (**IIa**) was dissolved in 75 ml of anhydrous DMF under nitrogen. 40 mmol of potassium hydroxide was then added into the reaction mixture and kept stirring at room temperature. After all the KOH was dissolved, 1,3-dibromopropane (12 mmol) or 1,3-ditosylpropane (11 mmol) was added and stirred overnight. Water was added to quench the reaction and the organic layer was extracted with CH_2Cl_2, separated, dried over sodium sulfate, concentrated and purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), 7,8-dihydro-6*H*-benzo[2,3][1,5]oxazocino[5,4-*a*]indole (**IIIb**) was obtained as a pale yellow solid.

To a solution of 7,8-dihydro-6*H*-benzo[2,3][1,5]oxazocino[5,4-*a*]indole (**IIIb**) (8 mmol) in anhydrous DMF (40 mL), a solution of *N*-bromosuccinimide (8.8 mmol) in anhydrous DMF (25 mL) was added at room temperature and stirred overnight. The reaction mixture was poured into crushed ice and CH_2Cl_2 was added to the flask followed by water for extraction. The organic phase was washed with a large amount of water, and then concentrated and purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), 14-bromo-7,8-dihydro-6*H*-benzo[2,3][1,5]oxazocino[5,4-*a*]indole (**IVb**) was obtained as a pink solid.

14-Bromo-7,8-dihydro-6*H*-benzo[2,3][1,5]oxazocino[5,4-*a*]indole (**IVb**) (5 mmol) was dissolved in freshly distilled anhydrous THF at room temperature under nitrogen atmosphere. The solution was then cooled to -78 °C in dry ice/acetone bath. Titrated *n*-BuLi (5.5 mmol) was added dropwise by syringe. After stirring the reaction mixture for 30 min at -78 °C, Cl-PR^1_2 in THF (5 mL) was added. The reaction was allowed to warm to room temperature and stirred overnight. The solvent

was removed under reduced pressure, and the product was successively washed with cold MeOH/EtOH mixture. The resulting white solid was filtered off and dried *in vacuo* (purity 90-99%).

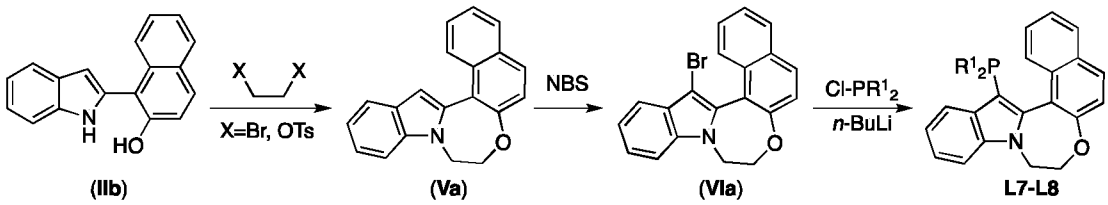
Yields:

$PR^1_2 = PCy_2$ 55% (^{31}P-NMR: -18.3 ppm) (**L4**)

$PR^1_2 = PPh_2$ 73% (^{31}P-NMR: -27.2ppm) (**L5**)

$PR^1_2 = P$*i*-Pr_2 45% (^{31}P-NMR: -6.9 ppm) (**L6**)

Example 3: Synthesis of ligand **L7 – L8**



Follow the general procedure of **Method B**, 1-(1*H*-indol-2-yl)naphthalen-2-ol (**IIb**) was obtained from oxindole (50 mmol), 2-chloropyridine (60 mmol), trifluoromethanesulfonic anhydride (60 mmol) and 2-naphthol (50 mmol) as a grey solid.

After purification, 10 mmol of 1-(1*H*-indol-2-yl)naphthalen-2-ol (**IIb**) was dissolved in 75 ml of anhydrous DMF under nitrogen. 40 mmol of potassium hydroxide was then added into the reaction mixture and kept stirring at room temperature. After all the KOH was dissolved, 1,2-dibromoethane (12 mmol) or 1,2-ditosylethane (11 mmol) was added and stirred at 110 °C overnight. Water was added to quench the reaction and the organic layer was extracted with CH_2Cl_2, separated, dried over sodium sulfate, concentrated and purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), 8,9-dihydronaphtho[1',2':6,7][1,4]oxazepino[4,5-*a*]indole (**Va**) was obtained as a pale yellow solid.

To a solution of 8,9-dihydronaphtho[1',2':6,7][1,4]oxazepino[4,5-*a*]indole (**Va**) (8 mmol) in anhydrous DMF (40 mL), a solution of *N*-bromosuccinimide (8.8 mmol) in anhydrous DMF (25 mL) was added at room temperature and stirred overnight. The reaction mixture was poured into crushed ice and CH_2Cl_2 was added to the flask followed by water for extraction. The organic phase was washed with a large amount

of water, and then concentrated and purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), 15-bromo-8,9-dihydronaphtho[1',2':6,7][1,4]oxazepino[4,5-*a*]indole (**VIa**) was obtained as a pale yellow solid.

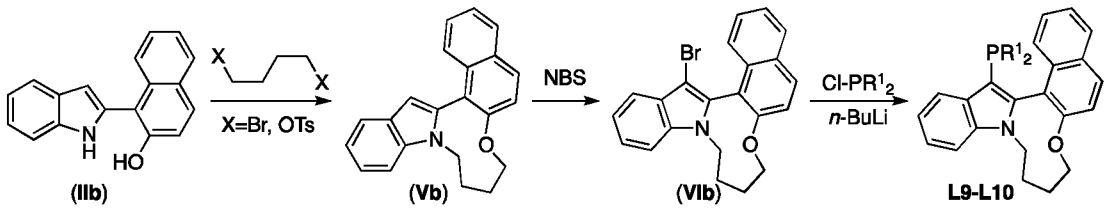
15-Bromo-8,9-dihydronaphtho[1',2':6,7][1,4]oxazepino[4,5-*a*]indole (**VIa**) (5 mmol) was dissolved in freshly distilled anhydrous THF at room temperature under nitrogen atmosphere. The solution was then cooled to -78 °C in dry ice/acetone bath. Titrated *n*-BuLi (5.5 mmol) was added dropwise by syringe. After stirring the reaction mixture for 30 min at -78 °C, Cl-PR^1_2 in THF (5 mL) was added. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the product was successively washed with cold MeOH/EtOH mixture. The resulting white solid was filtered off and dried *in vacuo* (purity 90-99%).

Yields:

$PR^1_2 = PCy_2$ 74% (^{31}P-NMR: -17.3 ppm) (**L7**)

$PR^1_2 = PPh_2$ 68% (^{31}P-NMR: -27.1 ppm) (**L8**)

Example 4: Synthesis of ligand **L9 – L10**



10 mmol of 1-(1*H*-indol-2-yl)naphthalen-2-ol (**IIb**) was dissolved in 75 ml of anhydrous DMF under nitrogen. 40 mmol of potassium hydroxide was then added into the reaction mixture and kept stirring at room temperature. After all the KOH was dissolved, 1,4-dibromobutane (12 mmol) or 1,4-ditosylbutane (11 mmol) was added and stirred at room temperature overnight. Water was added to quench the reaction and the organic layer was extracted with CH_2Cl_2, separated, dried over sodium sulfate, concentrated and purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), 8,9,10,11-tetrahydronaphtho[2',1':2,3][1,5]oxazonino[5,4-*a*]indole (**Vb**) was obtained as a pale yellow solid.

To a solution of 8,9,10,11-tetrahydronaphtho[2',1':2,3][1,5]oxazonino[5,4-*a*]indole (**Vb**) (8 mmol) in anhydrous DMF (40 mL), a solution of *N*-bromosuccinimide (8.8 mmol) in anhydrous DMF (25 mL) was added at room temperature and stirred overnight. The reaction mixture was poured into crushed ice and CH_2Cl_2 was added to the flask followed by water for extraction. The organic phase was washed with large amount of water, and then concentrated and purified by silica gel column chromatography (eluents: hexane to CH_2Cl_2), 17-bromo-8,9,10,11-tetrahydronaphtho[2',1':2,3][1,5]oxazonino[5,4-*a*]indole (**VIb**) was obtained as a pale yellow solid.

17-Bromo-8,9,10,11-tetrahydronaphtho[2',1':2,3][1,5]oxazonino[5,4-*a*]indole (**VIb**) (5 mmol) was dissolved in freshly distilled anhydrous THF at room temperature under nitrogen atmosphere. The solution was then cooled to -78 °C in dry ice/acetone bath. Titrated *n*-BuLi (5.5 mmol) was added dropwise by syringe. After stirring the reaction mixture for 30 min at -78 °C, Cl-PR^1_2 in THF (5 mL) was added. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the product was successively washed with cold MeOH/EtOH mixture. The resulting white solid was filtered off and dried *in vacuo* (purity 90-99%).

Yields:

$PR^1_2 = PCy_2$ 64% (^{31}P-NMR: -16.9 ppm) (**L9**)

$PR^1_2 = PPh_2$ 57% (^{31}P-NMR: -27.3 ppm) (**L10**)

Example 5-6: Catalysis Examples – Suzuki-Miyaura Couplings

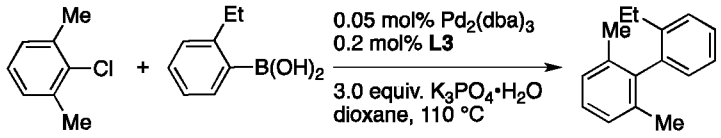
General procedure for reaction screening in Suzuki-Miyaura coupling of aryl chlorides (Pd(II) catalysts loading ranging from 1-2 mol %): Pd(II) source and ligand were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen for three cycles. Precomplexation was applied by adding freshly distilled dichloromethane and Et_3N into the tube. The palladium complex stock solution was stirred and warmed using hair drier for about 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under high vacuum. Aryl chloride (0.5 mmol), boron source (1.0 mmol), and base (1.5 mmol) were then added to Schlenk tubes. 1.0 mL of solvent was added (to rinse the

tube wall) with stirring at room temperature for several minutes. The tube was then placed in a preheated oil bath and stirred for 12-24 hours. After the completion of reaction as judged by GC or TLC analysis, the reaction was cooled down to room temperature and quenched with water and diluted with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

General procedure for reaction screening in Suzuki-Miyaura coupling of aryl chlorides (Pd(II) catalysts loading lower than 0.5 mol %): A stock solution of Pd(II) source with ligand in freshly distilled dichloromethane was initially prepared with continuous stirring at room temperature. The Schlenk tube was equipped with a Teflon-coated magnetic stir bar and evacuated and flushed with nitrogen for three cycles. Different volume of stock solution of palladium complex was added to the Schlenk tube by syringe according to the Pd loading indicated. Precomplexation was then applied by adding distilled Et_3N into the tube. The palladium complex solution was stirred and warmed using hair drier for about 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under high vacuum (If Pd(0) was used, this step was unnecessary). Aryl chloride (0.5 mmol), boron source (1.0 mmol), and base (1.5 mmol) were then added to Schlenk tubes. 1.0 mL of solvent was added (to rinse the tube wall) with stirring at room temperature for several minutes. The tube was then placed into a preheated oil bath and stirred for the duration as indicated (12-24 hours). After the completion of reaction as judged by GC or TLC analysis, the reaction was cooled down to room temperature and quenched with water and diluted with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

Example 5: Catalytic Suzuki-Miyaura Couplings of aryl chlorides and arylboronic acids

Experiment 1: Preparation of 2'-ethyl-2,6-dimethyl-1,1'-biphenyl [Table 1, entry 12] – A typical example of Suzuki-Miyaura coupling (using arylboronic acid as coupling partner) catalyzed by a metal complex of a ligand according to the present invention as described herein above *(0.1 mol % Pd catalysts loading)*:



A stock solution of $Pd_2(dba)_3$ (1.0 mol%, 0.0023 g) with **L3** (4.0 mol%, 0.0099 g) in freshly distilled dioxane (5.0 ml) was initially prepared by continuously stirring at room temperature for 10 min. 1 ml of the stock solution was transferred to another nitrogen-filled tube for further dilution. Freshly distilled dioxane was then added to the tube to give the needed concentration of palladium complex in total 4 ml final solution volume. 2-Chloro-1,3-dimethylbenzene (0.5 mmol, 0.07 g), (2-ethylphenyl)boronic acid (1.0 mmol, 0.15 g, 2.0 equiv.), potassium phosphate tribasic monohydrate (1.5 mmol, 0.345 g, 3.0 equiv.) and magnetic stirrer bar were charged to another Schlenk tube. The tube was carefully evacuated and backfilled with nitrogen (3 cycles). 1 ml of the diluted stock solution was then transferred to Schlenk tube via syringe. The tube was then placed into a preheated oil bath (110 °C) and stirred for 24 hours. The reaction was cooled down to room temperature and quenched with water and diluted with ethyl acetate. The organic phase was separated, washed, concentrated, and purified by column chromatography to provide pure desired product 2'-ethyl-2,6-dimethyl-1,1'-biphenyl as an off-white solid (0.1 g, 0.475 mmol, 95%).

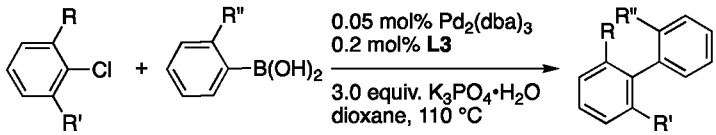
Table 1: Summary of the optimaization of the results of Catalysis Experiment 1[a]

entry	Pd source/ mol%	ligand	Pd:L	Base	Solvent	% yield[b]
1	$Pd_2(dba)_3$ (0.5)	**L1**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	99
2	$Pd_2(dba)_3$ (0.5)	**L2**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	60
3	$Pd_2(dba)_3$ (0.5)	**L3**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	99
4	$Pd_2(dba)_3$ (0.5)	**L4**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	88
5	$Pd_2(dba)_3$ (0.5)	**L5**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	79
6	$Pd_2(dba)_3$ (0.5)	**L6**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	99
7	$Pd_2(dba)_3$ (0.5)	**L7**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	45
8	$Pd_2(dba)_3$ (0.5)	**L8**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	83
9	$Pd_2(dba)_3$ (0.5)	**L9**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	57
10	$Pd_2(dba)_3$ (0.5)	**L10**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	99
11	$Pd_2(dba)_3$ (0.05)	**L1**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	83
12	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	95

13	$Pd_2(dba)_3$ (0.05)	**L10**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	57
14	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	KOH	dioxane	86
15	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	K_2CO_3	dioxane	32
16	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	NaH_2PO_4	dioxane	68
17	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	Cs_2CO_3	dioxane	46
18	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	KOAc	dioxane	53
19	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	KO(*t*-Bu)	dioxane	0
20	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	$K_3PO_4{\cdot}H_2O$	toluene	58
21	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	$K_3PO_4{\cdot}H_2O$	THF	90
22	$Pd_2(dba)_3$ (0.05)	**L3**	1:4	$K_3PO_4{\cdot}H_2O$	*t*-butanol	46
23	$Pd(OAc)_2$ (0.05)	**L3**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	0
24	$PdCl_2$ (0.05)	**L3**	1:4	$K_3PO_4{\cdot}H_2O$	dioxane	0

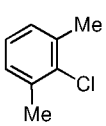
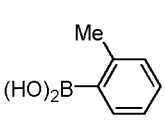
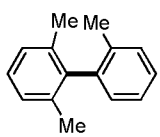
[a]Reaction conditions: 2-Chloro-1,3-dimethylbenzene (0.5 mmol, 70 mg), (2-ethylphenyl)boronic acid (1.0 mmol, 136 mg, 2.0 equiv.), Pd source: Ligand (indicated in table), base (1.5 mmol, 3.0 equiv.) and solvent (1 mL) were stirred for 24 h at 110 °C under nitrogen. [b]Calibrated GC yields were reported using dodecane as the internal standard.

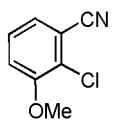
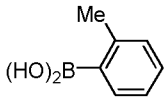
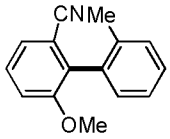
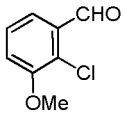
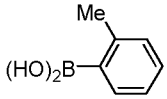
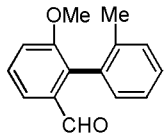
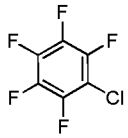
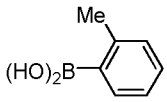
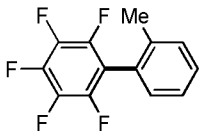
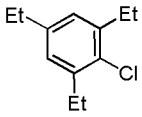
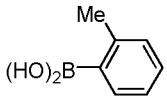
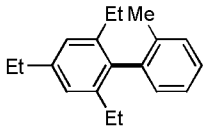
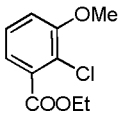
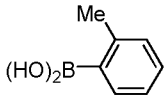
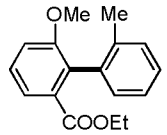
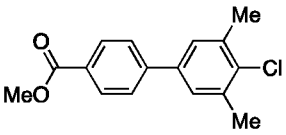
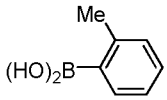
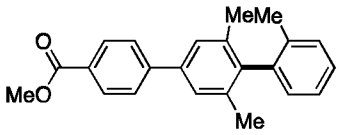
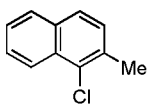
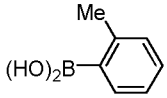
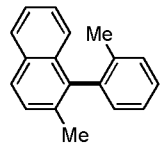
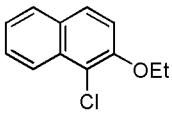
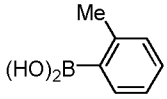
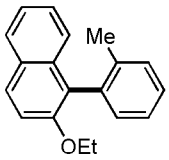
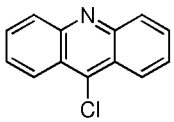
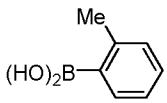
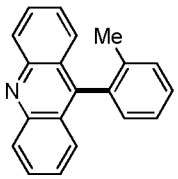
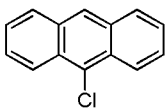
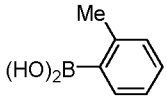
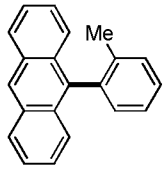
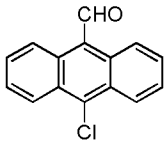
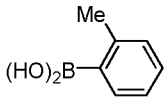
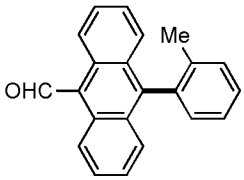
Experiment 2: Catalysis Examples – Suzuki-Miyaura Couplings of aryl chlorides with arylboronic acids using ligand **L3**

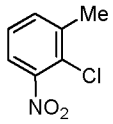
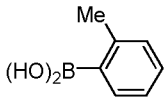
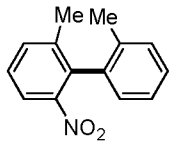


Aryl chlorides (0.5 mmol), arylboronic acids (1.0 mmol, 2.0 equiv.), $Pd_2(dba)_3$ (0.05 mol%), Pd/**L3** = 1:4, K_3PO_4 (1.5 mmol, 3.0 equiv.) and dioxane (1 mL) were stirred at 110 °C under nitrogen for 24 h. The reactions were then cooled down to room temperature, quenched with water and diluted with ethyl acetate. The organic phase was purified by column chromatography to provide pure desired product. The results of the catalysis are summarized in Table 2 and Table 3.

Table 2: Summary of the results of Catalysis Experiment 2 using *o*-tolylboronic acids

entry	ArCl	Ar'B(OH)$_2$	product	% yield[b]
1				98

2				88
3				93
4				87
5				90
6				89
7				82
8				95
9				98
10				85
11				86
12				90

13[c]				96

[a]Reaction conditions: ArCl (0.5 mmol), *o*-tolylboronic acid (1.0 mmol, 2.0 equiv.), Pd loading (0.05 mol%), $Pd_2(dba)_3$: **L3** = 1:4, K_3PO_4 (1.5 mmol, 3.0 equiv.) and dioxane (1 mL) were stirred for 24 h at 110 °C under nitrogen. [b]Isolated yield was reported. [c]0.2 mol% of $Pd_2(dba)_3$ was used.

Table 3: Summary of the results of Catalysis Experiment 2 using arylboronic acids

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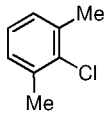
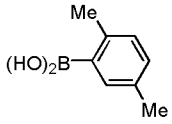
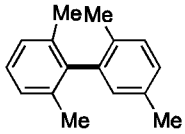
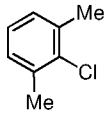
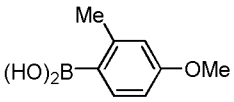
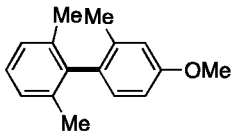
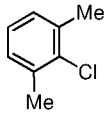
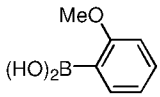
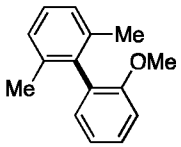
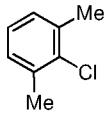
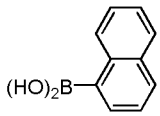
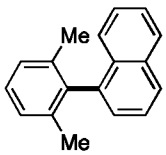
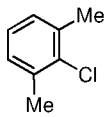
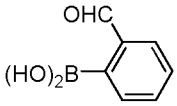
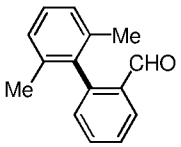
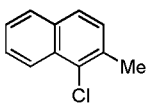
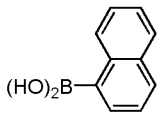
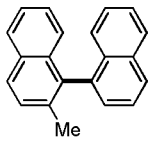
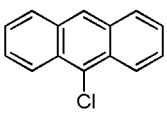
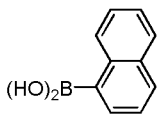
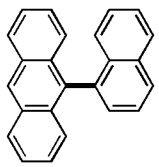
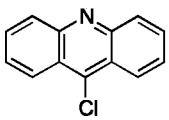
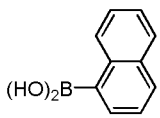
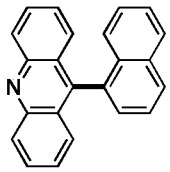
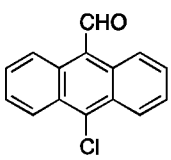
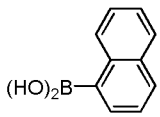
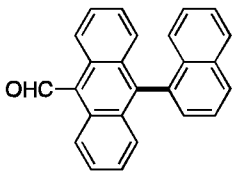
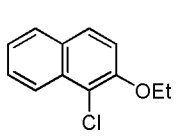
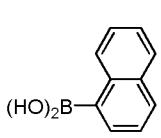
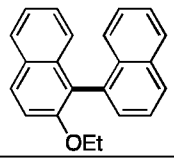
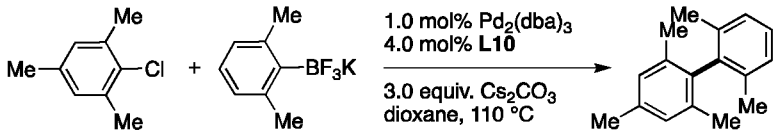
1				92
2				87
3				80
4				90
5[c]				51
6				83
7				89
8				92
9				94

10			 98

[a]Reaction conditions: ArCl (0.5 mmol), arylboronic acid (1.0 mmol, 2.0 equiv.), Pd loading (0.1 mol%), $Pd_2(dba)_3$: **L3** = 1:4, K_3PO_4 (1.5 mmol, 3.0 equiv.) and dioxane (1 mL) were stirred for 24 h at 110 °C under nitrogen. [b]Isolated yield was reported. [c]0.5 mol% of $Pd_2(dba)_3$ was used.

Example 6: Catalytic Suzuki-Miyaura Couplings of aryl chlorides and potassium aryltrifluoroborates

Experiment 3: Preparation of 2,2',4,6,6'-pentamethyl-1,1'-biphenyl – A typical example of Suzuki-Miyaura coupling (using potassium aryltrifluoroborates as coupling partner) catalyzed by a metal complex of a ligand according to the present invention as described herein above *(Pd catalysts loading ranging from 1-2 mol %)*:



$Pd_2(dba)_3$ (1.0 mol%, 0.0023 g) and **L3** (4.0 mol%, 0.0099 g) were loaded into a Schlenk tube equipped with a magnetic stir bar. The tube was carefully evacuated and backfilled with nitrogen (3 cycles). Precomplexation was applied by adding freshly distilled dioxane (0.5 ml) into the tube. The palladium complex stock solution was continuously stirred at room temperature for 10 min. 2-Chloro-1,3,5-trimethylbenzene (0.5 mmol, 0.077 g), potassium 2,6-dimethylphenyltrifluoroborate (1.0 mmol, 0.21 g, 2.0 equiv.) and cesium carbonate (1.5 mmol, 0.49 g, 3.0 equiv.) were charged to Schlenk tube. Further 0.5 ml of dioxane was added (to rinse the tube wall) with stirring at room temperature for 1-2 minutes. The tube was then placed into a preheated oil bath (110 °C) and stirred for 24 hours. The reaction was cooled down to room temperature, quenched with water and diluted with diethyl ether. The organic phase was separated, washed, concentrated, and purified by column chromatography to provide pure desired product 2,2',4,6,6'-pentamethyl-1,1'-biphenyl as an off-white solid (0.097 g, 0.435 mmol, 87%).

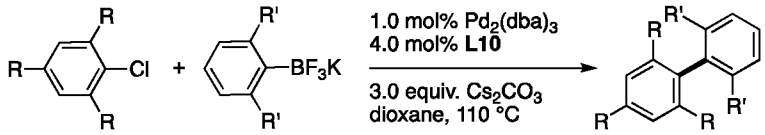
Table 4: Summary of the optimaization of the results of Catalysis Experiment 3[a]

entry	Pd source/ mol%	ligand	Pd:L	Base	Solvent	% yield[b]
1	$Pd_2(dba)_3$ (1.0)	**L1**	1:4	Cs_2CO_3	dioxane	trace
2	$Pd_2(dba)_3$ (1.0)	**L2**	1:4	Cs_2CO_3	dioxane	trace

3	$Pd_2(dba)_3$ (1.0)	**L3**	1:4	Cs_2CO_3	dioxane	trace
4	$Pd_2(dba)_3$ (1.0)	**L4**	1:4	Cs_2CO_3	dioxane	trace
5	$Pd_2(dba)_3$ (1.0)	**L5**	1:4	Cs_2CO_3	dioxane	trace
6	$Pd_2(dba)_3$ (1.0)	**L6**	1:4	Cs_2CO_3	dioxane	trace
7	$Pd_2(dba)_3$ (1.0)	**L7**	1:4	Cs_2CO_3	dioxane	trace
8	$Pd_2(dba)_3$ (1.0)	**L8**	1:4	Cs_2CO_3	dioxane	66
9	$Pd_2(dba)_3$ (1.0)	**L9**	1:4	Cs_2CO_3	dioxane	trace
10	$Pd_2(dba)_3$ (1.0)	**L10**	1:4	Cs_2CO_3	dioxane	89
11	$Pd(OAc)_2$ (1.0)	**L10**	1:4	Cs_2CO_3	dioxane	12
12	$Pd(TFA)_2$ (1.0)	**L10**	1:4	Cs_2CO_3	dioxane	55
13	$Pd_2(dba)_3$ (2.0)	**L10**	1:4	Cs_2CO_3	dioxane	87
14	$Pd_2(dba)_3$ (3.0)	**L10**	1:4	Cs_2CO_3	dioxane	85
15	$Pd_2(dba)_3$ (1.0)	**L10**	1:4	K_2CO_3	dioxane	30
16	$Pd_2(dba)_3$ (1.0)	**L10**	1:4	K_3PO_4	dioxane	76
17	$Pd_2(dba)_3$ (1.0)	**L10**	1:4	$K_3PO_4 \cdot H_2O$	dioxane	20
18	$Pd_2(dba)_3$ (1.0)	**L10**	1:1	Cs_2CO_3	dioxane	23
19	$Pd_2(dba)_3$ (1.0)	**L10**	1:2	Cs_2CO_3	dioxane	22
20	$Pd_2(dba)_3$ (1.0)	**L10**	1:3	Cs_2CO_3	dioxane	40
21	$Pd_2(dba)_3$ (1.0)	**L10**	1:4	Cs_2CO_3	toluene	7
22	$Pd_2(dba)_3$ (1.0)	**L10**	1:4	Cs_2CO_3	THF	28
23	$Pd_2(dba)_3$ (1.0)	**L10**	1:4	Cs_2CO_3	*t*-butanol	20

[a]Reaction conditions: 2-Chloro-1,3,5-trimethylbenzene (0.5 mmol), potassium 2,6-dimethylphenyltrifluoroborate (1.0 mmol, 136 mg, 2.0 equiv.), Pd source: Ligand (indicated in table), base (1.5 mmol, 3.0 equiv.) and solvent (1 mL) were stirred for 24 h at 110 °C under nitrogen. [b]Calibrated GC yields were reported using dodecane as the internal standard.

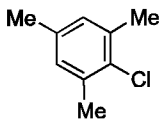
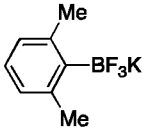
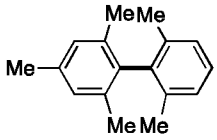
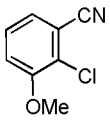
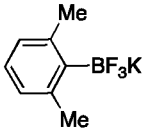
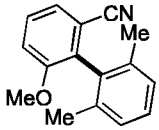
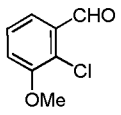
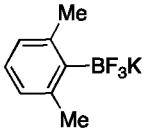
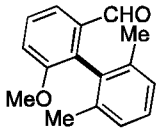
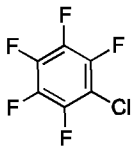
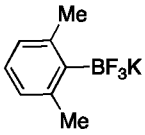
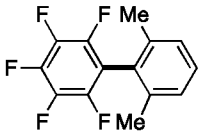
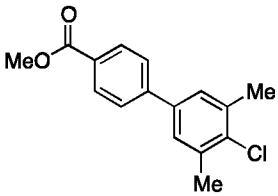
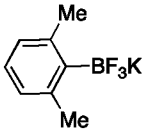
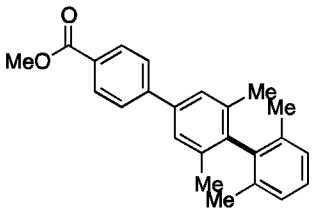
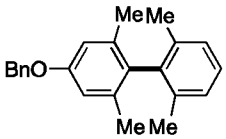
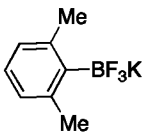
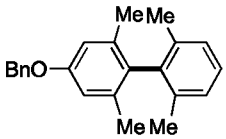
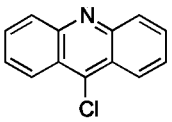
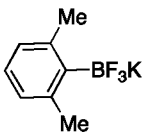
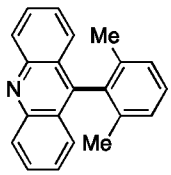
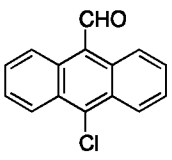
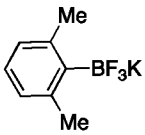
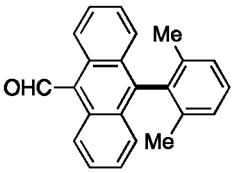
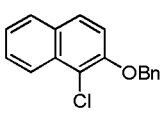
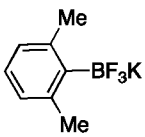
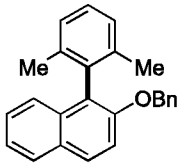
Experiment 4: Catalysis Examples – Suzuki Couplings of aryl chlorides with potassium aryltrifluoroborates using ligand **L10**

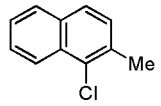
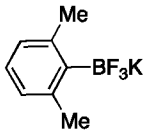
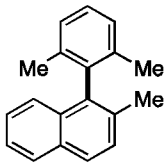


Aryl chlorides (0.5 mmol), potassium aryltrifluoroborates (1.0 mmol, 2.0 equiv.), $Pd_2(dba)_3$ (0.05 mol%), Pd/**L10** = 1:4, Cs_2CO_3 (1.5 mmol, 3.0 equiv.) and dioxane (1 mL) were stirred for 24 h at 110 °C under nitrogen. The reactions were cooled down to room temperature, quenched with water and diluted with ethyl acetate. The organic phase was purified by column chromatography to provide pure desired product. The

results of the catalysis are summarized in Table 5 and Table 6.

Table 5: Summary of the results of Catalysis Experiment 4 using potassium 2,6-dimethylphenyltrifluoroborates

entry	ArCl	Ar'B(OH)$_2$	product	% yield[b]
1				87
2				95
3				84
4				74
5				87
6				71
7				91
8				95
9				55

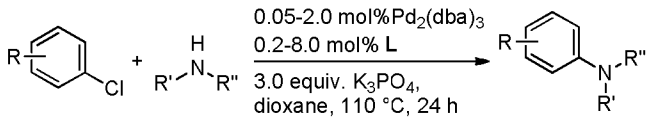
10				52

[a]Reaction conditions: Aryl chloride (0.5 mmol), potassium aryltrifluoroborate (1.0 mmol, 2.0 equiv.), $Pd_2(dba)_3$: **L10** = 1:4, Cs_2CO_3 (1.5 mmol, 3.0 equiv.) and dioxane (1 mL) were stirred for 24 h at 110 °C under nitrogen. [b]Isolated yield was reported.

Example 7-10: Catalysis Examples –General Cross-Couplings

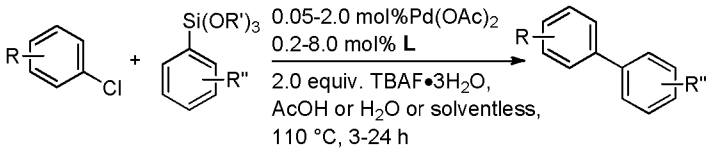
General procedure for cross-coupling of aryl chlorides with Pd catalysts: Pd source and ligand were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen for three cycles. Precomplexation was applied by adding freshly distilled dichloromethane and Et_3N into the tube. The palladium complex stock solution was stirred and warmed using hair drier for about 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under high vacuum. Aryl chloride (0.5 mmol), coupling partner (0.75-2.0 mmol), and base (1.25-3.0 mmol) were then added to Schlenk tubes. 1.0 mL of solvent was added (to rinse the tube wall) with stirring at room temperature for several minutes. The tube was then placed in a preheated oil bath and stirred for 12-24 hours. After the completion of reaction as judged by GC or TLC analysis, the reaction was cooled down to room temperature and quenched with water and diluted with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

Example 7: Catalytic Buchwald-Hartwig Amination of aryl chlorides and amines



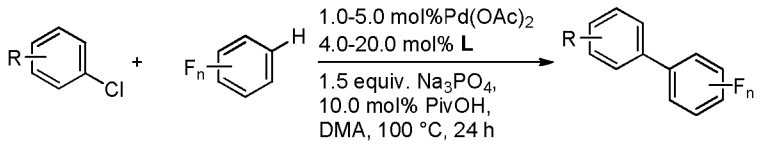
Following the general procedures, $Pd_2(dba)_3$ (0.05-2.0 mol%), Pd/**L** = 1:4, aryl chlorides (0.5 mmol), amines (0.75 mmol, 1.5 equiv.), $PhB(OH)_2$ (0.02 mmol, 0.04 equiv.), K_3PO_4 (1.5 mmol, 3.0 equiv.) and dioxane (1 mL) were stirred at 110 °C under nitrogen for 24 h. The reactions were then cooled down to room temperature, quenched with water and diluted with ethyl acetate. The organic phase was purified by column chromatography to provide pure desired product.

Example 8: Catalytic Hiyama Cross-coupling Reaction of aryl chlorides and aryl trialkoxysilanes



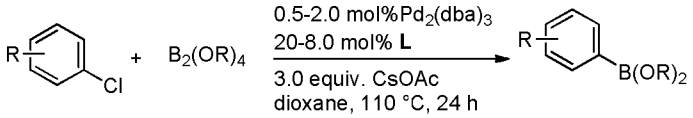
Following the general procedures, $Pd(OAc)_2$ (0.05-2.0 mol%), Pd/**L** = 1:4, aryl chlorides (0.5 mmol), aryl trialkoxysilanes (1.0 mmol, 2.0 equiv.), $TBAF{\cdot}3H_2O$ (1.0 mmol, 2.0 equiv.), acetic acid or water and/or toluene (0.5-1.0 mL) were stirred at 110 °C under nitrogen for 3-24 h. The reactions were then cooled down to room temperature, quenched with water and diluted with ethyl acetate. The organic phase was purified by column chromatography to provide pure desired product.

Example 9: Catalytic direct arylation of aryl chlorides and polyfluoroarene



Following the general procedures, $Pd(OAc)_2$ (1.0-5.0 mol%), Pd/**L** = 1:4, aryl chlorides (0.5 mmol), polyfluoroarenes (1.0 mmol, 2.0 equiv.), Na_3PO_4 (0.75 mmol, 1.5 equiv.), pivalic acid (0.05 mmol, 0.1 equiv.) and DMA (1 mL) were stirred at 100 °C under nitrogen for 24 h. The reactions were then cooled down to room temperature, quenched with water and diluted with ethyl acetate. The organic phase was purified by column chromatography to provide pure desired product.

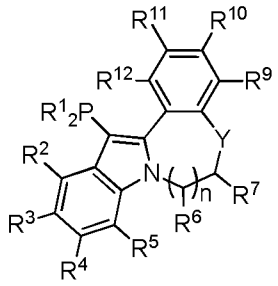
Example 10: Catalytic Borylation of aryl chlorides and boron reagents



Following the general procedures, $Pd_2(dba)_3$ (0.05-2.0 mol%), Pd/**L** = 1:4, aryl chlorides (0.5 mmol), boron reagents such as B_2neop_2 or B_2pin_2 or B_2Cat_2 or HBpin or HBCat (0.6 mmol, 1.2 equiv.), CsOAc (1.5 mmol, 3.0 equiv.) and dioxane (1 mL) were stirred at 110 °C under nitrogen for 24 h. The reactions were then cooled down to room temperature, quenched with water and diluted with ethyl acetate. The organic phase was purified by column chromatography to provide pure desired product.

CLAIMS

1. A compound of phosphine ligands having the following molecular formula (I):



(I)

wherein:

Y independently represents an oxygen atom or C-R^8 group or NR^8 group and $R^1$for each of the two R^1 groups independently of the other represents C_1-C_8-alkyl; C_3-C_{10}-cycloalkyl, which includes especially both monocyclic and also bi- and tricyclic cycloalkyl; (5- to 11-membered)heterocycloalkyl; CF_3; ferrocenyl; C_5-C_{20}-aryl, which includes especially the phenyl, naphthyl, fluorenyl; (5- to 11-membered)heteroaryl, wherein the number of hetero atoms, selected from the group N, O, S, may be from 1 to 2; wherein the two R^1 may also be linked to one another; or wherein each such C_3-C_{10}-cycloalkyl, (5- to 11-membered)heterocycloalkyl, C_6-C_{20}-aryl or (5- to 11-membered)heteroaryl group is optionally mono- or poly-substituted. These substituents independently of one another, may be hydrogen, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_3-C_8-cycloalkyl, C_2-C_9-heteroalkyl, C_5-C_{10}-aryl, C_2-C_9-heteroaryl, wherein the number of heteroatoms, especially from the group N, O, S, may be from 1 to 4; C_1-C_{14}-alkoxy, preferably -O(C_1-C_6)alkyl ,particularly preferably OMe; C_1-C_{10}-halo-alkyl, preferably CF_3, hydroxyl, secondary, tertiary amino groups; wherein two of the mentioned substituents may also bridged with one another to form 4- to 8-membered ring which can be further substituted preferably by linear or branched C_1-C_{10}-alkyl, C_6-aryl, benzyl, C_1-C_{10}-alkoxy, hydroxyl or benzyloxy groups;

R^2, R^3, R^4, and R^5 are each independently selected from the group comprising hydrogen; halogen; C_1-C_{10}-alkyl; hydroxyl; -O(C_1-C_6)alkyl; CF_3; C_3-C_{10}-cycloalkyl; (5- to 11-membered)heterocycloalkyl; amino; silyloxy; sulfhydryl; alkylthio; thioalkyl; phosphoryl; phosphonate; phosphine; urea; thiourea; nitrile; carbonyl;

carboxyl; carboxamide; C_6-C_{20}-aryl; (5- to 11-membered)heteroaryl, wherein the number of hetero atoms, selected from the group N, O, S, may be from 1 to 2; wherein any two or more adjacent instances of R^2, R^3, R^4, and R^5, taken together with the carbons to which they are bound, form a five- or six-membered substituted or unsubstituted aryl or heteroaryl ring;

R^6, R^7, and R^8 are the substituted at the linked carbon chain between the nitrogen atom and Y, wherein n = 1-9, each independently selected fr om the group comprising hydrogen; halogen; C_1-C_{20}-alkyl; hydroxyl; -O(C_1-C_{10})alkyl; CF_3; C_3-C_{10}-cycloalkyl; (5- to 11-membered)heterocycloalkyl; amino; silyloxy; sulfhydryl; C_6-C_{20}-aryl; (5- to 11-membered)heteroaryl, wherein the number of hetero atoms, selected from the group N, O, S, may be from 1 to 2; wherein any two or more adjacent instances of R^6, R^7, and R^8, taken together with the carbons to which they are bound, form a five- or six-membered substituted or unsubstituted aryl or heteroaryl ring;

R^9, R^{10}, R^{11}, and R^{12} are each independently selected from the group comprising hydrogen; halogen; C_1-C_{10}-alkyl; hydroxyl; –O(C_1-C_6)alkyl; CF_3; C_3-C_{10}-cycloalkyl; (5- to 11-membered)heterocycloalkyl; amino; silyloxy; sulfhydryl; alkylthio; thioalkyl; phosphoryl; phosphonate; phosphine; urea; thiourea; nitrile; carbonyl; carboxyl; carboxamide; C_6-C_{20}-aryl; (5- to 11-membered)heteroaryl, wherein the number of hetero atoms, selected from the group N, O, S, may be from 1 to 2; wherein any two or more adjacent instances of R^9, R^{10}, R^{11}, and R^{12}, taken together with the carbons to which they are bound, form five- or six-membered substituted or unsubstituted aryl or heteroaryl rings;

n is independently for each occurrence an integer in the range 1 to 8 inclusive, and the ligand is achiral or, when chiral, is a single stereoisomer or a mixture of stereoisomers.

2. The compound of phosphine ligands according to claim 1, wherein one of the R^1 is C_1-C_8-alkyl selected from –CH_3, –CH_2CH_3, –$C(CH_2)_2CH_3$, –$CH(CH_3)_2$, –$C(CH_3)_3$, –$C(CH_2CH_3)_3$– and $C(CH_2CH_3)(CH_3)_2$.

3. The compound of phosphine ligands according to claim 1, wherein one of the R^1 is C_3-C_{10}-cycloalkyl, which includes especially both monocyclic and also bi- and tri-cyclic cycloalkyl, selected from cyclopentyl, cyclohexyl and 1-adamantyl.

4. The compound of phosphine ligands according to claim 1, wherein one of the R^1 is C_6-C_{20}-aryl selected from phenyl, 2-methylphenyl, 4-methylphenyl, 3,5-dimethylphenyl, 3,5-di(fluoromethyl)phenyl, 3,5-di-*tert*-butylphenyl, 4-

methoxyphenyl, 2-trifluoromethylphenyl, 2,4,6-trimethylphenyl, 3,5-di-*tert*-butyl-4-methoxyphenyl, and naphthyl.

5. A catalyst composition comprising a transition metal catalyst precursor and a compound of phosphine ligands according to any one of claim 1-4.

6. The catalyst composition according to claim 5, wherein the transition metal catalyst precursor is selected from a group consisting of nickel, palladium, platinum, rhodium, iridium, ruthenium and cobalt.

7. The catalyst composition according to claim 5, wherein the transition metal catalyst precursor contains palladium.

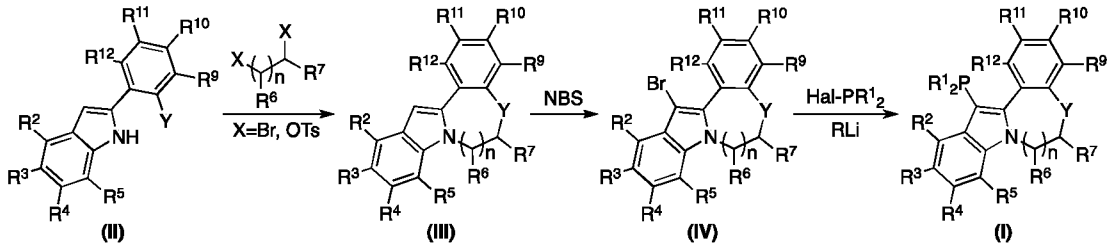
8. The catalyst composition according to claim 6, wherein the transition metal catalyst precursor is a mono-, di-, tri- or tetra-phosphine complex of the transition metal.

9. A heterogeneous catalyst composition comprising a compound of phosphine ligands according to any one of claim 1-4 covalently bonded to a solid catalyst support.

10. A method for preparing ligands according to any one of claims 1-4, wherein the method comprises:

performing a general procedure of Fischer-indole synthesis; and

performing a general reaction as the following Scheme 1,



Scheme 1

11. A method of performing a cross-coupling reaction comprising catalyzing said reaction with a compound of phosphine ligands of any one of claim 1-4.

12. A method of performing a Suzuki-Miyaura coupling reaction comprising catalyzing said reaction with a compound of phosphine ligands of any one of claim 1-4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/081589

A. CLASSIFICATION OF SUBJECT MATTER

B01J 31/24(2006.01)i; C07F 9/572(2006.01)i; C07C 15/12(2006.01)i; C07C 1/32(2006.01)i; C07C 47/575(2006.01)i; C07C 45/68(2006.01)i; C07C 49/784(2006.01)i; C07C 255/50(2006.01)i; C07C 253/30(2006.01)i

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)

C07F9/-; B01J31/-; C07C15/-; C07C1/-; C07C47/-; C07C45/-; C07C49/-; C07C255/-; C07C253/-

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)

CNABS, CNKI, EPODOC, WPI, ISI Web of Knowledge:THE HONG KONG POLYTECHNIC UNIVERSITY SHENZHEN RESEARCH INSTITUTE, KWONG FUK YEE, phosph+ ligand?, transition, metal?, Pd,nitrogen, amine, alkyl, cycolalkyl, cyclic,heterocycloalkyl,pheneyl, naphthyl, fluorenyl

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 104945434 A (SHENZHEN RES INST THE HONG KONG POLYTECHNIC UNIVERSITY) 30 September 2015 (2015-09-30) the whole document	1-12
A	CN 105152827 A (SHENZHEN RES INST THE HONG KONG POLYTECHNIC UNIVERSITY) 16 December 2015 (2015-12-16) the whole document	1-12
A	Chau Ming So, et al. "Suzuki-Miyaura coupling of Aryl Tosylates Catalyzed by an Array of Indolyl Phosphine-Palladium Catlysts" *J.Org.Chem*, Vol. 73, 09 November 2008 (2008-11-09), abstract	1-12
A	US 5886182 A (UNIV HONG KONG POLYTECHNIC) 23 March 1999 (1999-03-23) description, volume2, lines 40-57	1-12

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 February 2017	**17 February 2017**

Name and mailing address of the ISA/CN	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2016/081589

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	104945434	A	30 September 2015	None			
CN	105152827	A	16 December 2015	None			
US	5886182	A	23 March 1999	GB	2332201	A8	24 November 1999
				GB	9827259	D0	03 February 1999
				HK	1021188	A1	11 July 2003
				GB	2332201	A	16 June 1999
				GB	2332201	B	23 October 2002