

NOVEL FERROCENE-BASED UNSYMMETRICAL LIGANDS BEARING BULKY
DI(ADAMANTLY)PHOSPHINO MOTIF AND THEIR METAL CATALYSTS

Cross-Reference to Related Applications

[0001] The present application claims the benefit of priority of U.S. provisional patent application no. 63/166,094, filing date March 25, 2021, the entire content of which is incorporated herein in its entirety.

Background

[0002] Provided are a new class of ferrocenyl-based unsymmetrical ligands containing di(1-adamantyl)phosphino groups with general formula, $\text{Fc}(\text{Ad}_2\text{P})(\text{R}_2\text{P})$ and corresponding metal complexes, include metal halide complexes, N-biphenyl metal cationic complexes and R-allyl metal cationic complexes, as shown in FIG. 1, useful in catalysis.

[0003] By virtue of their flexible bite angles, tunability of steric and electronic characteristics, ferrocenyl based bidentate ligands and their corresponding metal catalysts stood out to be the most sought out bidentate systems in metal catalyzed organic transformations.¹ Since the introduction of 1,1'-bis(diphenylphosphino)ferrocene,² dppf, and its corresponding (dppf) PdCl_2 by Hayashi and Kumada in 1972,³ numerous efforts have been devoted to their commercialization and newer applications in process chemistry and discovery.⁴ Subsequent work from the Colacot group has identified for the first time that $\text{Fc}(\text{PR}_2)_2\text{PdCl}_2$ ($\text{R} = \text{'Pr, Cy, 'Bu}$) complexes are air-stable, yet highly active catalysts for challenging C-C coupling and α -arylation reactions.⁵ Today, these "privileged" bis(phosphine)ligands and catalysts are commercially available in multi-kg quantities for various organic processes.⁶

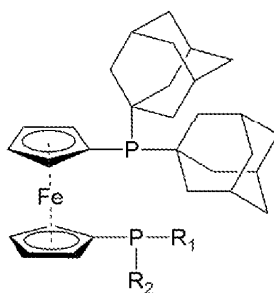
[0004] Among the new generation ligands, adamantyl based phosphine ligands are a special class of ligands, which offer very unique characteristics, such as "electron-releasing properties exceeding a boundary for organophosphines that has persisted over many decades."^{8,9} Examples include the unique cross-coupling applications of Ad_3P by Carrow's group,¹⁰ Adamantyl Brettphos by Buchwald et al.,¹¹ Dalphos class of ligands by the Stradiotto group¹² and $\text{Ad}_2(\text{n-Bu})\text{P}$ (*Catantium*) by Beller et al.¹³

(FIG. 2). However, the syntheses of these ligands are not trivial considering the isolation and purification, thereby limiting their offerings in bulk quantities for industrial applications.

[0005] Despite these advances, a need still exists for new ligands that (1) can address some of the existing challenges in cross coupling, and (2) which have syntheses that are amenable to scale up in manufacture sufficient to prepare sufficient quantities at a purity acceptable for industrial applications.

Summary

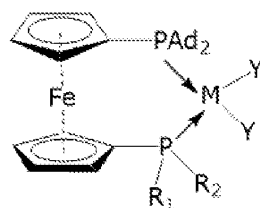
[0006] Provided are diadamantylphosphino-containing compounds useful as ligands and in precatalysts for coupling reactions. In a first embodiment, a compound of formula I is provided:



I

wherein R₁ and R₂ are independently selected from C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, C₁-C₁₂ alkoxy, -NR₄R₅, and optionally substituted phenyl. R₄ and R₅ are individually selected from H and C₁-C₁₂ alkyl, or R₄ and R₅ together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N and one or more optional substituents. Each optional substituent, when present, is individually selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkoxy.

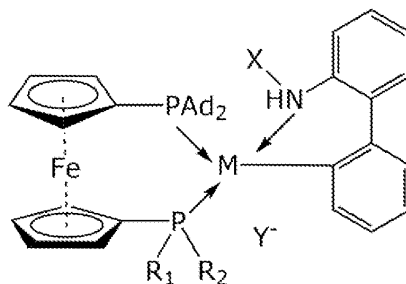
[0007] Also provided is a precatalyst is formula II:



II

wherein Ad is adamantyl; R_1 and R_2 are independently selected from C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl. R_4 and R_5 are individually selected from H and C_1 - C_{12} alkyl, or R_4 and R_5 together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N and one or more optional substituents. Each optional substituent, when present, is individually selected from C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, and C_1 - C_4 alkoxy. M is a transition metal selected from Group 9 or Group 10, and Y is halo.

[0008] Also provided is a precatalyst of formula III:

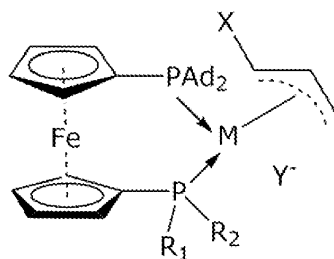


III

wherein Ad is adamantyl; R_1 and R_2 are independently selected from C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl. R_4 and R_5 are individually selected from H and C_1 - C_{12} alkyl, or R_4 and R_5 together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents. Each optional substituent, when present, is selected from C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, and C_1 - C_4 alkoxy. M represents a transition metal selected from Group 9 or Group 10. X is selected from H, C_1 - C_4 alkyl and phenyl. Y^- is an anion selected from halide, triflate (OTf), tetrafluoroborate (BF_4), hexafluorophosphate (PF_6), mesylate (OMs), tosylate (OTs), tetrakis[3,5-

bis(trifluoromethyl)phenyl]borate ($^- \text{BArF}$), hexafluoro antimonate ($^- \text{SbF}_6$) and combinations thereof.

[0009] Further provided is a precatalyst of formula IV:



IV

wherein Ad is adamantyl; R_1 and R_2 are independently selected from C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-\text{NR}_4\text{R}_5$, and optionally substituted phenyl. R_4 and R_5 are individually selected from H and C_1 - C_{12} alkyl, or R_4 and R_5 together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents. Each optional substituent, when present, is selected from C_1 - C_4 alkyl, C_1 - C_4 haloalkyl and C_1 - C_4 alkoxy. M represents a transition metal selected from Group 9 or Group 10. X is selected from H, C_1 - C_4 alkyl and phenyl. Y^- is an anion selected from halide, triflate ($^- \text{OTf}$), tetrafluoroborate ($^- \text{BF}_4$), hexafluorophosphate ($^- \text{PF}_6$), mesylate ($^- \text{OMs}$), tosylate ($^- \text{OTs}$), tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($^- \text{BArF}$), hexafluoro antimonate ($^- \text{SbF}_6$) and combinations thereof.

[0010] Further provided are methods for performing a metal-catalyzed P-C cross-coupling reaction. The methods include the steps of contacting a ligand of formula I, as described above, with a metal catalyst in the presence of an aromatic solvent and a base in a reaction vessel; adding a first substrate of formula $\text{Ar-X}'$, wherein Ar is aryl and X' is halo and a second substrate of formula $\text{R}'_2\text{PH}$, wherein R' is selected from C_1 - C_{10} alkyl and C_3 - C_{10} cycloalkyl, to the reaction vessel; heating the reaction vessel to a temperature in the range from 100 °C to 200 °C for a time sufficient to form the carbon-phosphorous bond.

[0011] Further provided are methods for performing a metal-catalyzed $\text{C}_{\text{sp}2}$ - $\text{C}_{\text{sp}3}$

cross-coupling reaction. The method includes the steps of contacting a precatalyst of formula II, as described above, with a first substrate and a second substrate in the presence of a solvent in a reaction vessel, optionally, heating the reaction vessel, and allowing first substrate and the second substrate to react in the presence of the precatalyst for a time sufficient for the C_{sp^2} - C_{sp^3} cross-coupling to occur. In various embodiments of this method, the first substrate is of formula $Ar-X'$, wherein Ar is optionally substituted aryl or optionally substituted heteroaryl and X' is chloro or bromo or iodo. The second substrate is of formula $R'[M]$, wherein R' is selected from C_1 - C_{10} alkyl and C_3 - C_{10} cycloalkyl, $[M]$ is selected from Li , MgX' , ZnX' and $B(OH)_2$ and related boron reagents, and X' is selected from chloro, bromo and iodo.

Brief Description of the Figures

[0012] FIG. 1 exemplifies the ferrocenyl-based unsymmetrical phosphines and their $PdCl_2$, G3-Palladacycles and $(R\text{-allyl})PdCl$ complexes described herein.

[0013] FIG. 2A shows Ad_3P , FIG. 2B—Dalphos, FIG. 2C—adamantyl Brettphos, and FIG. 2D— $Ad_2(n\text{-Bu})P$ (*Cataxium*), each of which are conventional phosphines bearing di-1-adamantylphosphino (Ad_2P) moiety.

[0014] FIG. 3A illustrates reaction scheme 1, the synthesis of ferrocenyl-based unsymmetrical bidentate phosphine ligands, using the Cullen method; FIG. 3B illustrates reaction scheme 1 using the Stepnicka method; compared to FIG. 3C illustrating reaction scheme 1 using the methods described herein.

[0015] FIG. 4A shows the synthesis of ferrocenyl based unsymmetrical bidentate ligands (L1-4); FIG. 4B shows their corresponding Pd complexes ($Pd(1\text{-}4)\text{-(a-c)}$).

[0016] FIG. 5 is an X-Ray plot of the molecular structures of $(L1)PdCl_2$, Pd1-a.

[0017] FIG. 6 is an X-Ray plot of the molecular structures of $(L3)PdCl_2$, Pd3-a.

[0018] FIG. 7 is an X-Ray plot of the molecular structures of $(L4)PdCl_2$, Pd4-a.

[0019] FIG. 8 is an X-Ray plot of the molecular structures of $(L1)Pd$ G3, Pd1-b.

[0020] FIG. 9 is an X-Ray plot of the molecular structures of $(L2)Pd$ G3, Pd2-b.

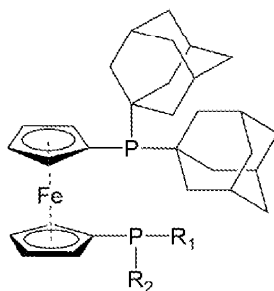
Detailed Description

[0021] The new ligands and precatalysts described herein, such as those shown in FIG 1 overcome the problems with conventional catalysts—providing powerful new routes to previously challenging cross-coupling reactions, while being scalable so that they can be provided in sufficient quantity and purity for industrial applications. These new ligands and precatalysts utilize a ferrocenyl backbone and di(adamanyl)phosphino moiety, which, as described herein, provide significant advantages over existing ligands and precatalysts.

[0022] Conventional methods to make ferrocenyl based unsymmetrical ligands, as shown in FIG. 3A and FIG. 3B are not suitable to incorporate the Ad₂P moiety to make Fc(Ad₂P)(R₂P) ligands.¹⁴

[0023] Herein is described a new class of ferrocenyl based unsymmetrical phosphines containing Ad₂P moiety FIG. 3C, as well as a convenient synthesis protocol for making the ligands, and the synthesis of their corresponding metal complexes. Also provided are methods of using the new ligands and precatalysts described herein in C_{sp2}-C_{sp3} coupling, *e.g.*, Kumada, Negishi, Suzuki and Murahashi, and C-P coupling applications with a wide variety of substrates as these class of coupling reactions are challenging and underrepresented in the literature. It is highly desirable to have such ligands and precatalysts commercially available.

[0024] First provided are diadamantylphosphino-containing compounds useful as ligands and precatalysts for coupling reactions. In a first embodiment, a compound of formula I is provided:



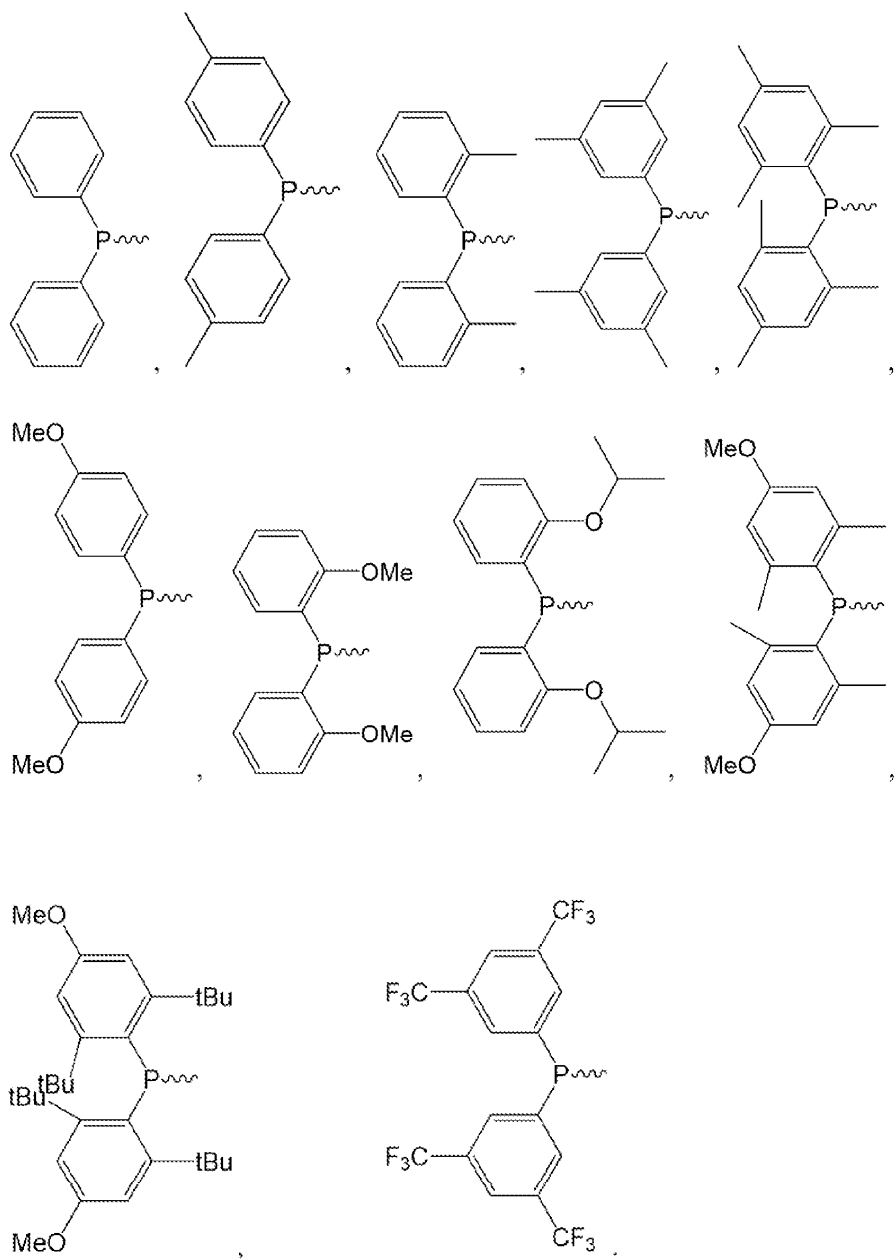
I

wherein R₁ and R₂ are independently selected from C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl,

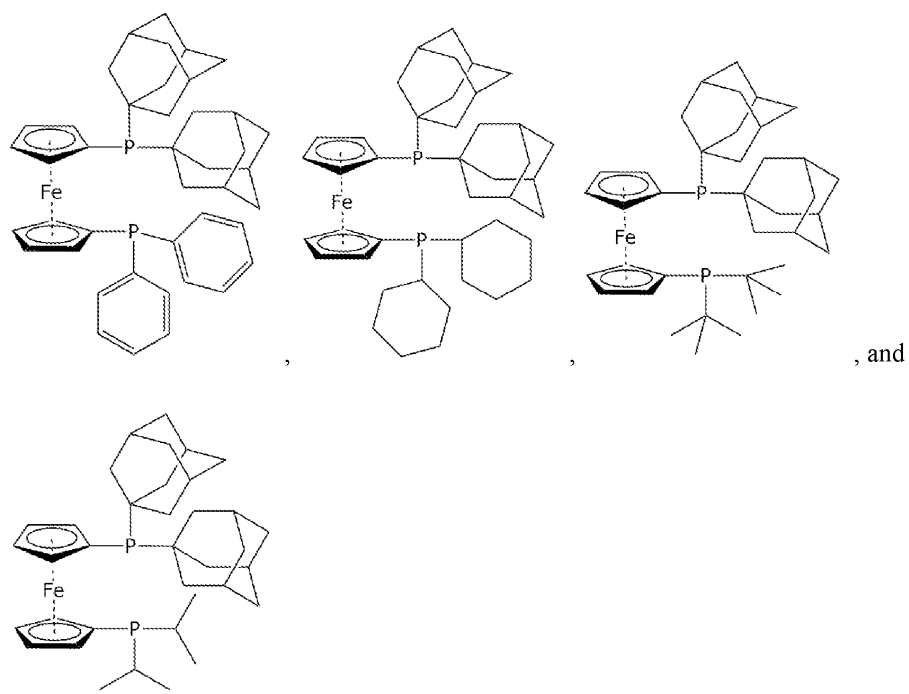
C₁-C₁₂ alkoxy, -NR₄R₅, and optionally substituted phenyl. R₄ and R₅ are individually selected from H and C₁-C₁₂ alkyl, or R₄ and R₅ together form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents. Some representative -NR₄R₅ ring structures, include but are not limited to, pyrrolo, pyrrolidino, pyrazolo, piperidino, morpholino, thiomorpholino, piperazino, N-methyl piperazino, and so forth. Each optional substituent, when present, is individually selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy. In some embodiments of compound I, R₁ and R₂ are independently selected from phenyl, optionally substituted phenyl, cyclohexyl, isopropyl, *tert*-butyl. In some embodiments, R₁ and R₂ are each substituted phenyl.

[0025] In embodiments in which R₁ and R₂ are substituted phenyl, the substituted phenyl can have from one to five substituents, and the substituents can be the same or different. In one embodiment, the substituted phenyl includes one substituent at the para position. In other embodiments, the substituted phenyl includes one substituent at the ortho position. In other embodiments, the substituted phenyl includes one substituent at the meta position. In some embodiments, the substituted phenyl includes two substituents, both at the ortho positions. In other embodiments, the substituted phenyl includes two substituents, both at the meta positions. In other embodiments, the two substituents are at the ortho and the para positions. In still other embodiments, the two substituents are at the meta and para positions. In still other embodiments, the substituted phenyl includes three substituents, which may be the same or different. In some embodiments, the three substituents are at the para position and two ortho positions. In other embodiments, the three substituents are at the para and two meta positions. In still other embodiments, the substituents are at one ortho, one meta and the para positions. In other embodiments, the substituted phenyl includes four substituents, each of which may be the same or different and which may be at the ortho and meta positions or at a combination of ortho, meta and para positions. In still other embodiments, the substituted phenyl may include five substituents, each of which may be the same or different.

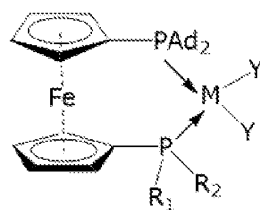
[0026] In some preferred embodiments, -PR₁R₂ is selected from



[0027] In some preferred embodiments, the compound of formula I is a ligand selected from



[0028] Also provided herein are precatalysts of formula II:



II

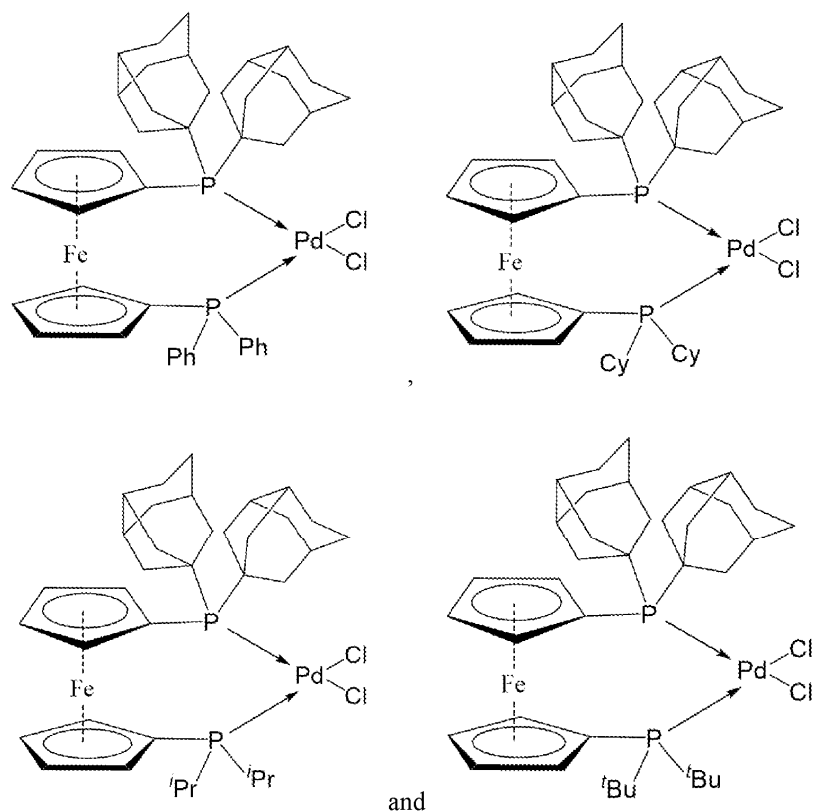
wherein Ad is adamantyl; and R_1 and R_2 are independently selected from C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl. R_4 and R_5 are individually selected from H and C_1 - C_{12} alkyl, or R_4 and R_5 together form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and optionally includes one or more substituents. Some representative $-NR_4R_5$ ring structures, include, but are not limited to, pyrrolo, pyrrolidino, pyrazolo, piperidino, morpholino, thiomorpholino, piperazino, N-methyl piperazino, and so forth. Each optional substituent, when

present, is individually selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy. In some embodiments, R₁ and R₂ are independently selected from phenyl, substituted phenyl, cyclohexyl, isopropyl, *tert*-butyl. In a preferred embodiment, R₁ and R₂ are each substituted phenyl as described above.

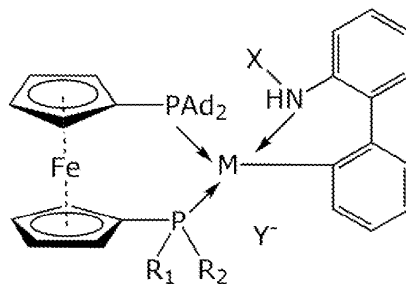
[0029] M in formula II is a transition metal selected from Group 9 or Group 10. In some embodiments, M is selected from Pd, Ni, Rh, Co, Ir and Pt. In a preferred embodiment, M is Pd.

[0030] Y in formula II is halo, i.e., in various embodiments, Y may be chloro, bromo or iodo. In a preferred embodiment, Y is chloro.

[0031] Some preferred embodiments of the precatalyst of formula II include



[0032] Also provided is a precatalyst of formula III:



III

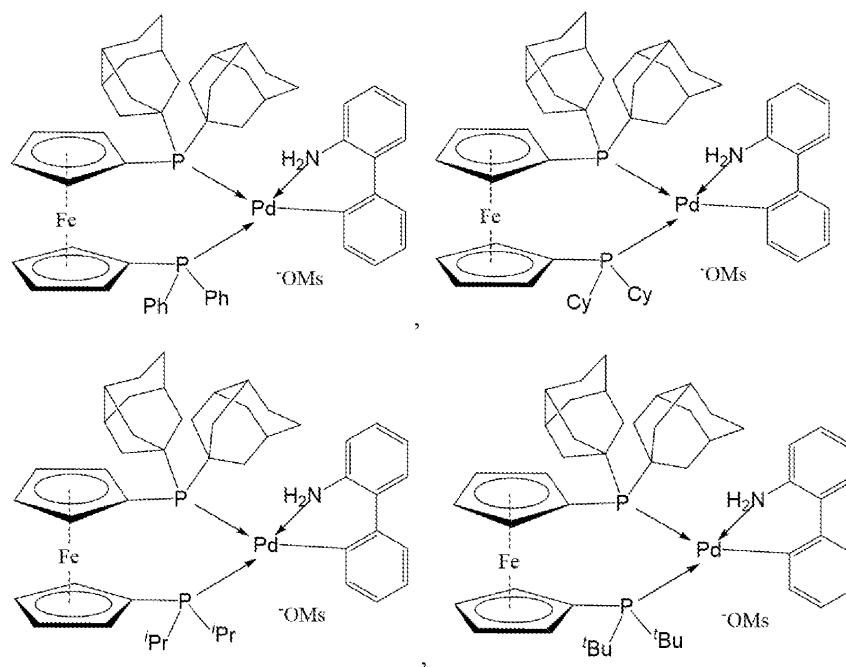
wherein Ad is adamantyl; R_1 and R_2 are independently selected from C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl. R_4 and R_5 are individually selected from H and C_1 - C_{12} alkyl, or R_4 and R_5 together form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N and may include one or more optional substituents. Some representative $-NR_4R_5$ ring structures include, but are not limited to, pyrrolo, pyrrolidino, pyrazolo, piperidino, morpholino, thiomorpholino, piperazino, N-methyl piperazino, and so forth. Each optional substituent, when present, is individually selected from C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy. In some embodiments, R_1 and R_2 are independently selected from phenyl, cyclohexyl, isopropyl, *tert*-butyl.

[0033] M in formula III represents a transition metal selected from Group 9 or Group 10. In some embodiments, M is selected from Pd, Ni, Rh, Co, Ir and Pt. In a preferred embodiment, M is Pd.

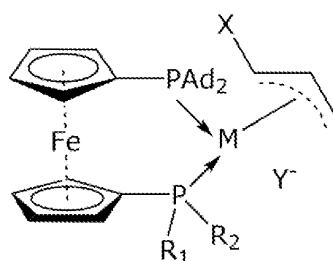
[0034] X of formula III may be selected from H, C_1 - C_4 alkyl and phenyl. In some embodiments, X is selected from H, methyl and phenyl.

[0035] In the precatalyst of formula III, Y^- is an anion selected from halide, triflate (OTf), tetrafluoroborate (BF_4^-), hexafluorophosphate (PF_6^-), mesylate (OMs), tosylate (OTs), tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($BArF^-$), hexafluoroantimonate (SbF_6^-) and combinations thereof. In various embodiments, Y^- is selected from Cl^- , Br^- , I^- , OTf , BF_4^- , OMs , OTs , PF_6^- , $BArF^-$, and SbF_6^- .

[0036] In some preferred embodiments, the precatalyst of formula III is



[0037] Further provided is a precatalyst of formula IV:



IV

wherein Ad is adamantyl; R_1 and R_2 are independently selected from C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl. R_4 and R_5 are individually selected from H and C_1 - C_{12} alkyl, or R_4 and R_5 together form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents. Some representative $-NR_4R_5$ ring structures include, but are not limited to, pyrrolo, pyrrolidino, pyrazolo, piperidino, morpholino, thiomorpholino, piperazino, N-methyl piperazino, and so forth. Each optional substituent, when present, is individually selected from C_1 - C_4 alkyl, C_1 - C_4 haloalkyl and C_1 - C_4 alkoxy. In some preferred embodiments, R_1 and R_2 are independently selected from phenyl,

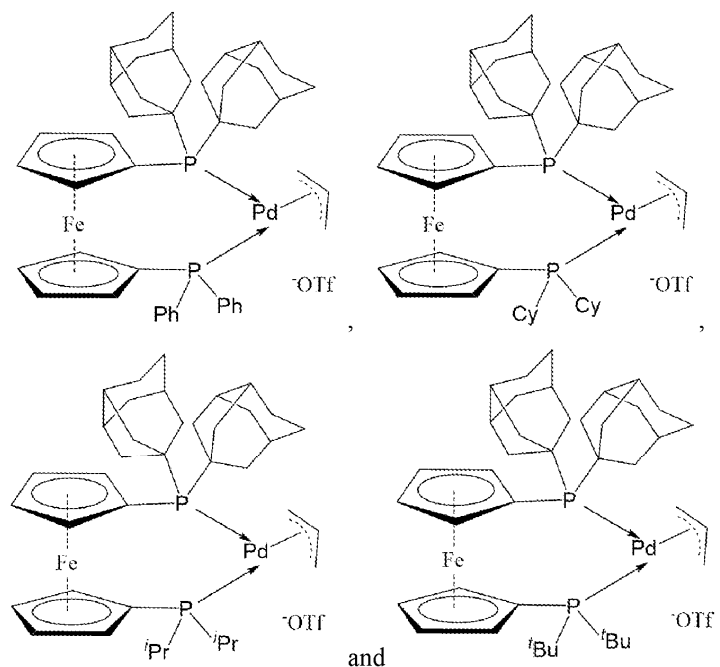
cyclohexyl, isopropyl, *tert*-butyl.

[0038] M in formula IV represents a transition metal selected from Group 9 or Group 10. In some embodiments, M is selected from Pd, Ni, Rh, Co, Ir and Pt. In a preferred embodiment of formula IV, M is Pd.

[0039] X of formula IV is selected from H, C₁-C₄ alkyl and phenyl. In some preferred embodiments, X is selected from H, methyl and phenyl.

[0040] Y⁻ is an anion selected from halide, triflate (OTf), tetrafluoroborate (BF₄⁻), hexafluorophosphate (PF₆⁻), mesylate (OMs), tosylate (OTs), tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF⁻), hexafluoro antimonate (SbF₆⁻) and combinations thereof. In some preferred embodiments, Y⁻ is selected from Cl⁻, Br⁻, I⁻, OTf, BF₄⁻, OMs, OTs, PF₆⁻, BArF, and SbF₆⁻.

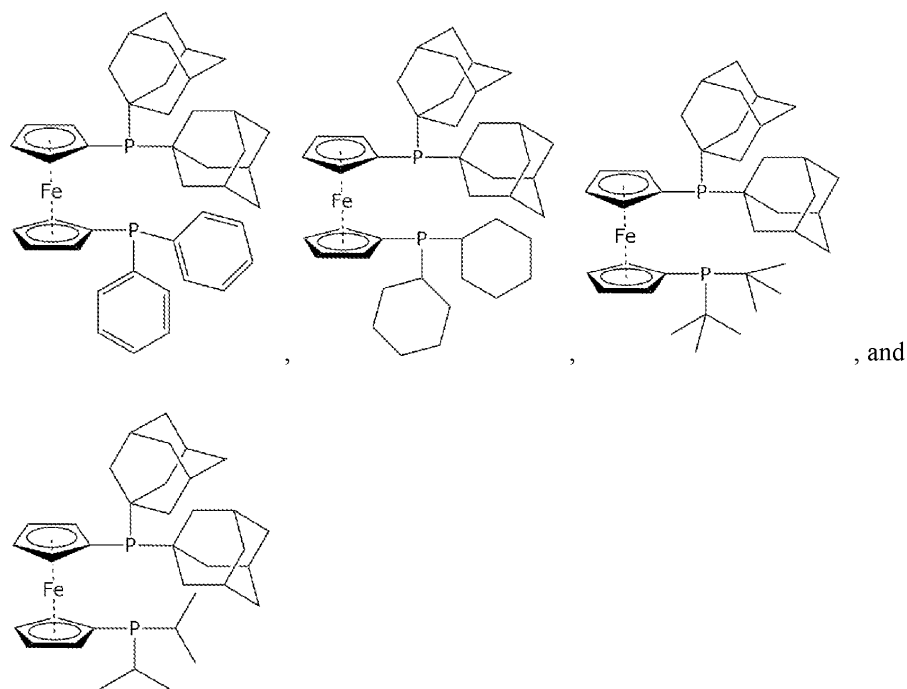
[0041] In some preferred embodiments, the precatalyst of formula IV is selected from



[0042] Further provided are methods for performing a metal-catalyzed P-C cross-

coupling reaction. The methods include the steps of contacting a ligand of formula I, as described above, with a metal catalyst in the presence of an aromatic solvent and a base in a reaction vessel; adding a first substrate of formula Ar-X', wherein Ar is aryl and X' is halo and a second substrate of formula R'₂PH, wherein R' is selected from C₁-C₁₀ alkyl and C₃-C₁₀ cycloalkyl, to the reaction vessel; heating the reaction vessel to a temperature in the range from 100 °C to 200 °C for a time sufficient to form the carbon-phosphorous bond.

[0043] In a preferred embodiment of this metal-catalyzed P-C cross-coupling reaction method, the ligand is selected from



and the catalyst is a Pd catalyst.

[0044] Further provided are methods for performing a metal-catalyzed C_{sp2}-C_{sp3} cross-coupling reaction. The method includes the steps of contacting a precatalyst of formula II, as described above, with a first substrate and a second substrate in the presence of a solvent in a reaction vessel, optionally, heating the reaction vessel, and allowing first substrate and the second substrate to react in the presence of the precatalyst for a time sufficient for the C_{sp2}-C_{sp3} cross-coupling to occur.

[0045] In various embodiments of this method, the first substrate is of formula Ar-X', wherein Ar is optionally substituted aryl or optionally substituted heteroaryl and X' is chloro or bromo or iodo. In some embodiments of this method, the first substrate is selected from optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thiophene, and optionally substituted furan.

[0046] In various embodiments, the second substrate is of formula R'[M], wherein R' is selected from C₁-C₁₀ alkyl and C₃-C₁₀ cycloalkyl, [M] is selected from Li, MgX', ZnX' and B(OH)₂, and X' is selected from chloro, bromo and iodo.

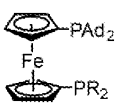
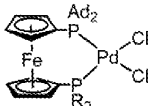
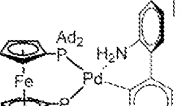
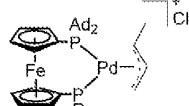
[0047] In certain embodiments according to this method, [M] is Li, the solvent is toluene, and the reaction vessel is not heated.

[0048] In certain embodiments according to this method, [M] is selected from MgX' and ZnX', the solvent is tetrahydrofuran, and the reaction vessel is heated to 50 °C.

[0049] In still other embodiments according to this method, [M] is B(OH)₂, the solvent is toluene and the reaction vessel is heated to 100 °C.

[0050] The synthesis of and use of the ligands and precatalysts described herein is provided in greater detail. Table 1 shows ferrocenyl based unsymmetrical phosphines and their PdCl₂, G3-Palladacycles and (R-allyl)PdCl complexes.

Table 1

R				
R = Ph	L1	Pd1-a	Pd1-b	Pd1-c
R = Cy	L2	Pd2-a	Pd2-b	Pd2-c
R = ⁱ Pr	L3	Pd3-a	Pd3-b	Pd3-c
R = ^t Bu	L4	Pd4-a	Pd4-b	Pd4-c

[0051] The synthesis of the ligands L1-4 were achieved in two steps from readily available 1,1'-dibromoferrocene (FIG. 3). Following the reported procedure,^{14b} the intermediate (I) was synthesized by selective lithiation of dibromoferrocene with 1 equiv. of *n*-BuLi, followed by quenching with dialkyl chlorophosphine (eg. Ph₂PCl) to give mono bromo ferrocenylphosphine (I). Stepnicka was able to perform another lithiation followed by R₂PCl quench to make a few examples of mixed ligands as shown in FIG. 3B. Applying the same protocol to incorporate the Ad₂P moiety onto the intermediate (I) did not afford the designed products (L1-4). Adding catalytic (or stoichiometric) amount copper (I) salt,¹⁵ such as CuCl, also didn't help either. Rather, Pd-catalyzed P-C coupling was used as an alternative approach (FIG. 4A).¹⁶ All ligands L1-4 were synthesized with unoptimized yields at ca. 70% in two steps, and characterized by ¹H-NMR, ¹³C-NMR, ³¹P-NMR and elemental analysis.

[0052] The corresponding three classes of palladium pre-catalysts were synthesized in high yields and were characterized by NMR and elemental analysis (FIG. 4). Several of them, ((L1)PdCl₂, Pd1-a; (L3)PdCl₂, Pd3-a; (L4)PdCl₂, Pd4-a; (L1)Pd G3, Pd1-b; (L2)Pd G3, Pd2-b), were unambiguously characterized with single crystal X-Ray studies (see FIGS. 5-9). X-Ray crystal structures of five palladium complexes are also reported here-in, where single crystals were obtained by slow diffusion of pentane into dichloromethane solution.

[0053] FIG. 5 shows the X-Ray plot of the molecular structures of (L1)PdCl₂, Pd1-a; selected bond lengths (Å) and bond angles (deg): Pd-P1 2.3370(5), Pd-P2 2.2964(5), Pd-Cl1 2.3484(4), Pd-Cl2 2.3541(4); P1-Pd-P2 100.973(16), Cl1-Pd-Cl2 84.988(15), P1-Pd-Cl1 91.834(16), P1-Pd-Cl2 174.508(16), P2-Pd-Cl1 166.954(17), P2-Pd-Cl2 82.048(16).

[0054] FIG. 6 shows the X-Ray plot of the molecular structures of (L3)PdCl₂, Pd3-a; selected bond lengths (Å) and bond angles (deg): Pd-P1 2.3365(4), Pd-P2 2.3127(4), Pd-Cl1 2.3519(4), Pd-Cl2 2.3673(4); P1-Pd-P2 103.587(15), Cl1-Pd-Cl2 84.089(14), P1-Pd-Cl1 90.173(14), P1-Pd-Cl2 174.226(15), P2-Pd-Cl1 166.239(15), P2-Pd-Cl2 82.153(15).

[0055] FIG. 7 shows the X-Ray plot of the molecular structures of (L4)PdCl₂, Pd4-

a; selected bond lengths (Å) and bond angles (deg): Pd-P1 2.3679(5), Pd-P2 2.3736(6), Pd-Cl1 2.3370(6), Pd-Cl2 2.3290(6); P1-Pd-P2 106.72(2), Cl1-Pd-Cl2 82.56(2), P1-Pd-Cl1 87.18(2), P1-Pd-Cl2 166.82(2), P2-Pd-Cl1 164.89(2), P2-Pd-Cl2 84.45(2).

[0056] FIG. 8 shows the X-Ray plot of the molecular structures of (L1)Pd G3, Pd1-b; selected bond lengths (Å) and bond angles (deg): Pd-P1 2.2791(8), Pd-P2 2.4635(7), Pd-N1 2.147(2), Pd-C43 2.033(3); P1-Pd-P2 102.68(3), N1-Pd-C43 80.64(11), P1-Pd-N1 152.16(7), P1-Pd-C43 86.39(8), P2-Pd-N1 97.22(7), P2-Pd-C43 161.22(9).

[0057] FIG. 9 shows the X-Ray plot of the molecular structures of (L2)Pd G3, Pd2-b. Selected bond lengths (Å) and bond angles (deg): Pd-P1 2.3094(4), Pd-P2 2.4626(4), Pd-N1 2.1657(14), Pd-C43 2.0454(17); P1-Pd-P2 103.304(17), N1-Pd-C43 80.40(6), P1-Pd-N1 153.33(4), P1-Pd-C43 87.65(5), P2-Pd-N1 95.50(4), P2-Pd-C43 160.31(5).

[0058] Selected P-Pd-P bite angles (in deg) are presented in Table 2, as well as other analogues taken from literature data for comparison purpose. All Pd centers have a distorted square planar geometry with the two phosphorus atoms in a cis configuration. Notably, (L4)PdCl₂, Pd4-a, has a very large P-Pd-P bite angle (106.72°, entry 3). To best of our knowledge, it is the largest P-Pd-P bite angle reported in literature among the PdCl₂ complexes with ferrocenyl based bidentate ligands. While comparing to the bite angle of the “state of the art catalyst,” (dtbpf)PdCl₂ (104.22°, entry 6), the P-Pd-P bite angle of (L4)PdCl₂ is significantly high.

Table 2

Entry	Pd Complexes	P-Pd-P (deg)
1	(L1)PdCl ₂ , Pd1-a	100.97
2	(L3)PdCl ₂ , Pd3-a	103.60
3	(L4)PdCl ₂ , Pd4-a	106.72
4	(dppf)PdCl ₂ ^(14a)	97.98
5	(d ⁱ ppf)PdCl ₂ ^(14c)	103.59
6	(d ^b ppf)PdCl ₂ ^(5b)	104.22
7	[Fc(PPh ₂)(PCy ₂))PdCl ₂ ^(14b)	101.28
8	[Fc(PPh ₂)(P ⁱ Pr ₂))PdCl ₂ ^(14b)	102.49
9	[Fc(PPh ₂)(P ⁱ Bu ₂))PdCl ₂ ^(14b)	101.97
10	(L1)Pd G3, Pd1-b	102.68
11	(L2)Pd G3, Pd2-b	103.30

[0059] Owing to the bidentate nature and steric bulkiness of the ferrocenyl ligands, all (L)Pd G3 complexes are in cationic form, as illustrated in the structures of (L1)Pd G3 (Pd1-b) and (L2)Pd G3 (Pd2-b). The MsO group in each structure is displaced by second phosphine on the ferrocenyl ligand to form a mesylate anion, while the NH₂ group stay coordinated with Pd center. Similar phenomena were reported by Buchwald as well.¹⁷ (BINAP)Pd G3, tBuXPhos Pd G3 and BrettPhos Pd G3 are in cationic forms with mesylate (MsO) out of the coordination sphere, while in XPhos Pd G3 is in a covalent form even with MsO. Both structures from Pd1-b and Pd2-b have significant tetrahedral distortion on Pd center (28.6° in Pd1-b and 28.2° in Pd2-b).

[0060] Applications of the ligands and precatalysts described herein in catalysis, particularly for two challenging and underrepresented class of reactions namely C_{sp2}-C_{sp3} coupling and P-C coupling was also done, as detailed in the examples below.

[0061] As used herein the term “Ad” refers to an adamantyl functional group, i.e., a tricyclo bridged hydrocarbon of formula (-C₁₀H₁₅), which may also be written as (-C(CH)₃(CH₂)₆).

[0062] The term "alkyl" refers to a saturated hydrocarbon chain of 1 to 10 carbon

atoms in length, 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.

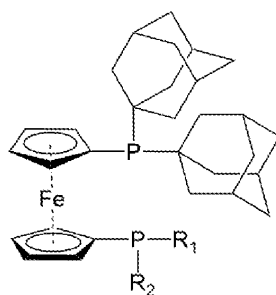
[0063] The term “aryl” refers to an aromatic hydrocarbon group. Aryl includes, e.g., phenyl, biphenyl, naphthyl, anthracenyl, and so forth, as well as the substituted forms of each. Heteroaryl refers to aromatic hydrocarbons in which one or more of the aromatic carbon atoms has been replaced with another atom such as nitrogen, oxygen or sulfur. Some examples of heteroaryl groups include, but are not limited to, pyridyl (pyridinyl) ((C₅H₄N)-), furyl (furanlyl) (OC₄H₃-), thienyl ((C₄H₃S)-), and the substituted forms thereof.

[0064] “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 limited to, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy. When a functional group is described as “optionally substituted” that functional group may have one or more substituents or no substituents.

[0065] The precatalyst complexes described herein have at least one metallic center comprising a transition metal ("M"). Examples of transition metals include, but are not limited to, transition metals of Groups 9 and 10 of the periodic table. Group 9 metals include Co, Rh and Ir. Group 10 elements include Ni, Pd and Pt.

[0066] The present disclosure further provides the following embodiments set forth in the clauses below:

[0067] {1} A compound of formula I



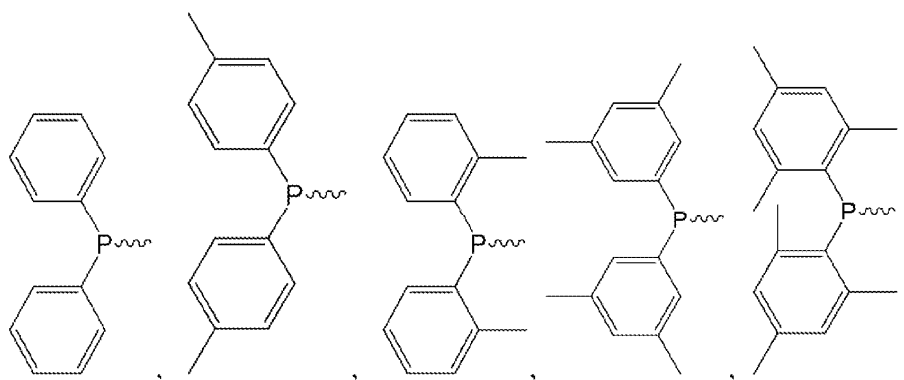
I

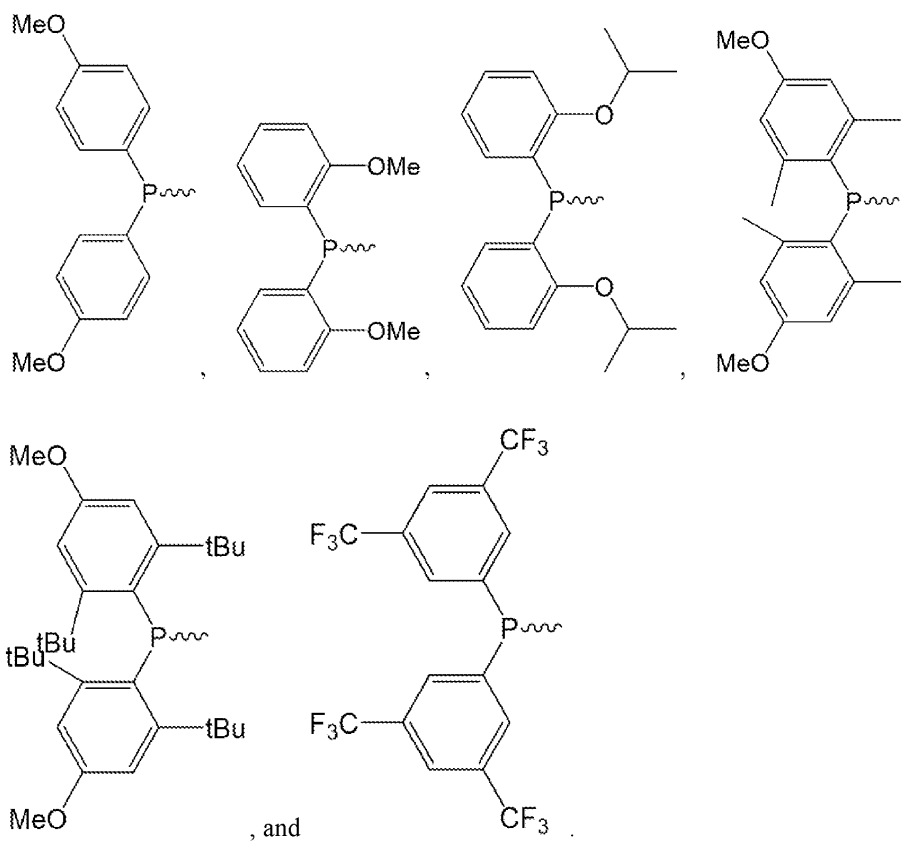
wherein R_1 and R_2 are independently selected from the group consisting of C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl; R_4 and R_5 are individually selected from the group consisting of H and C_1 - C_{12} alkyl, or R_4 and R_5 together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents; and each optional substituent, when present, is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 haloalkyl and C_1 - C_4 alkoxy.

[0068] {2} The compound according to clause {1} wherein R_1 and R_2 are independently selected from the group consisting of phenyl, optionally substituted phenyl, cyclohexyl, isopropyl and *tert*-butyl. In some embodiments, R_1 and R_2 are the same. In other embodiments, R_1 and R_2 are different. In some embodiments, R_1 and R_2 are both aryl groups. In some embodiments, R_1 and R_2 are both alkyl groups. In some embodiments, R_1 is an aryl moiety and R_2 is an alkyl moiety. In some embodiments, R_1 and R_2 are both phenyl. In some embodiments, R_1 and R_2 are both substituted phenyl. In some embodiments, R_1 and R_2 are both cyclohexyl. In some embodiments, R_1 and R_2 are both isopropyl. In some embodiments, R_1 and R_2 are both *tert*-butyl. In some embodiments, R_1 is phenyl and R_2 is substituted phenyl. In some embodiments, R_1 is phenyl and R_2 is cyclohexyl. In some embodiments, R_1 is phenyl and R_2 is isopropyl. In some embodiments, R_1 is phenyl and R_2 is *tert*-butyl. In some embodiments, R_1 is substituted phenyl and R_2 is cyclohexyl. In some embodiments, R_1 is substituted phenyl and R_2 is isopropyl. In some embodiments, R_1 is substituted phenyl and R_2 is *tert*-butyl. In some embodiments, R_1 is cyclohexyl and R_2 is isopropyl. In some embodiments, R_1 is cyclohexyl and R_2 is *tert*-butyl. In some embodiments, R_1 is *tert*-butyl and R_2 is isopropyl.

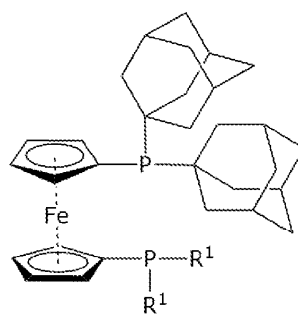
[0069] {3} The compound according to either of clauses {1} or {2} wherein R_1 and R_2 are each substituted phenyl. In some embodiments, the substituent is alkyl. In certain embodiments, the substituent is methyl. In some embodiments, the substituent is alkoxy. In certain embodiments, the substituent is methoxy. In certain embodiments, the substituent is isopropoxy. In some embodiments, the substituent is haloalkyl. In certain embodiments, the substituent is trifluoromethyl. In certain embodiments, there are multiple substituents. In some embodiments, each substituted phenyl has two alkyl substituents. In such embodiments, the alkyl substituents are C_1 - C_4 alkyl or haloalkyl. In some embodiments, the alkyl substituents are methyl, isopropyl, *tert*-butyl or trifluoromethyl groups. In other embodiments, each substituted phenyl has three substituents. In such embodiments, the alkyl substituents are C_1 - C_4 alkyl or haloalkyl. In some embodiments, the alkyl substituents are methyl, isopropyl, *tert*-butyl or trifluoromethyl groups. In still other embodiments, each substituted phenyl has one or more alkyl substituents and one or more alkoxy substituents. In some embodiments, each substituted phenyl has one or more C_1 - C_4 alkyl or haloalkyl substituents and one or more C_1 - C_4 alkoxy substituents. In some embodiments, each substituted phenyl has two C_1 - C_4 alkyl substituents and one C_1 - C_4 alkoxy substituents.

[0070] {4} The compound according to any of clauses {1}, {2} or {3} wherein PR_1R_2 is selected from





[0071] {5} A ligand of formula I:



I

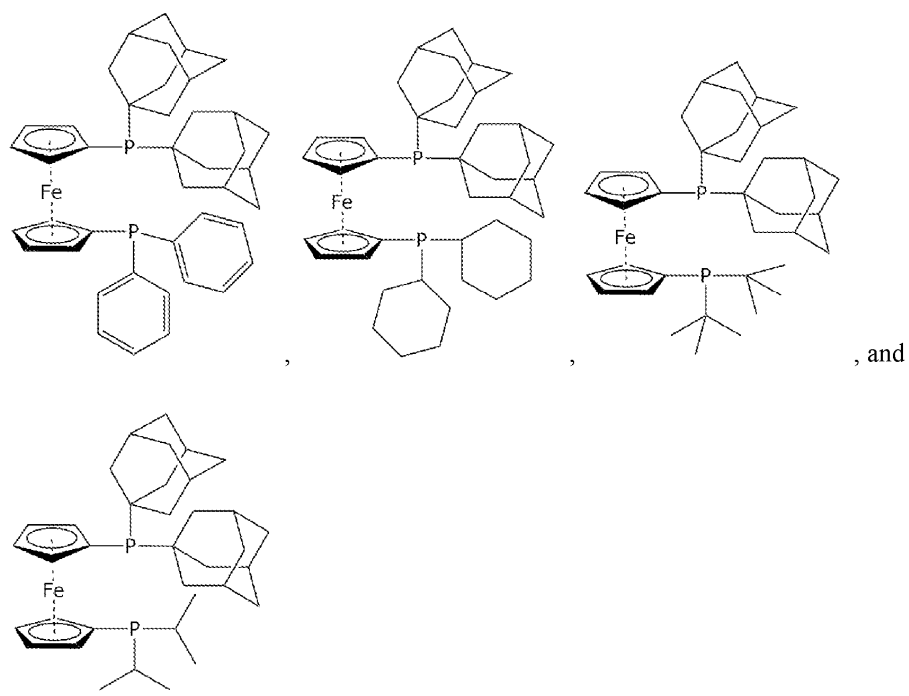
wherein R_1 and R_2 are independently selected from the group consisting of C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl; R_4 and R_5 are individually selected from the group consisting of H and C_1 - C_{12} alkyl, or R_4 and R_5 together can form a saturated or unsaturated 5- or 6-membered ring, the

ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents; and each optional substituent, when present, is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy.

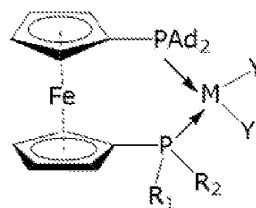
[0072] {6} The ligand according to clause {5} wherein R₁ and R₂ are independently selected from the group consisting of phenyl, optionally substituted phenyl, cyclohexyl, isopropyl and *tert*-butyl.

[0073] {7} The ligand according to either of clauses {5} or {6} wherein R₁ and R₂ are each substituted phenyl. In some embodiments, the substituent is alkyl. In certain embodiments, the substituent is methyl. In some embodiments, the substituent is alkoxy. In certain embodiments, the substituent is methoxy. In certain embodiments, the substituent is isopropoxy. In some embodiments, the substituent is haloalkyl. In certain embodiments, the substituent is trifluoromethyl. In certain embodiments, there are multiple substituents. In some embodiments, each substituted phenyl has two alkyl substituents. In such embodiments, the alkyl substituents are C₁-C₄ alkyl or haloalkyl. In some embodiments, the alkyl substituents are methyl, isopropyl, *tert*-butyl or trifluoromethyl groups. In other embodiments, each substituted phenyl has three substituents. In such embodiments, the alkyl substituents are C₁-C₄ alkyl or haloalkyl. In some embodiments, the alkyl substituents are methyl, isopropyl, *tert*-butyl or trifluoromethyl groups. In still other embodiments, each substituted phenyl has one or more alkyl substituents and one or more alkoxy substituents. In some embodiments, each substituted phenyl has one or more C₁-C₄ alkyl or haloalkyl substituents and one or more C₁-C₄ alkoxy substituents. In some embodiments, each substituted phenyl has two C₁-C₄ alkyl substituents and one C₁-C₄ alkoxy substituents.

[0074] {8} A ligand according to either of clauses {5} or {6}, wherein the ligand is selected from



[0075] {9} A precatalyst of formula II:



II

wherein Ad is adamantyl; R_1 and R_2 are independently selected from the group consisting of C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl; R_4 and R_5 are individually selected from the group consisting of H and C_1 - C_{12} alkyl, or R_4 and R_5 together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents; each optional substituent, when present, is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 haloalkyl and C_1 - C_4 alkoxy; M is a transition metal selected from Group 9 or Group 10; and Y is halo.

[0076] {10} The precatalyst according to clause {9} wherein R₁ and R₂ are independently selected from the group consisting of phenyl, optionally substituted phenyl, cyclohexyl, isopropyl and *tert*-butyl.

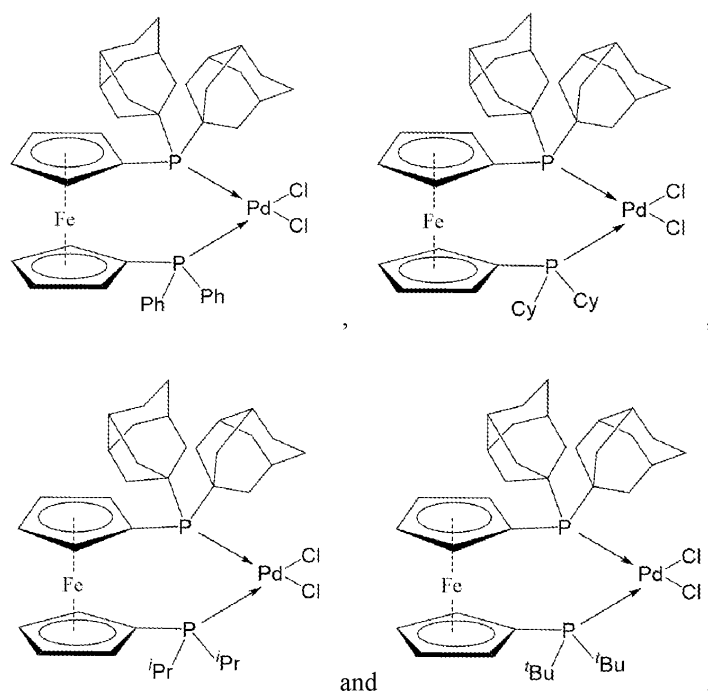
[0077] {11} The precatalyst according to either of clauses {9} or {10} wherein R₁ and R₂ are each substituted phenyl. In some embodiments, the substituent is alkyl. In certain embodiments, the substituent is methyl. In some embodiments, the substituent is alkoxy. In certain embodiments, the substituent is methoxy. In certain embodiments, the substituent is isopropoxy. In some embodiments, the substituent is haloalkyl. In certain embodiments, the substituent is trifluoromethyl. In certain embodiments, there are multiple substituents. In some embodiments, each substituted phenyl has two alkyl substituents. In such embodiments, the alkyl substituents are C₁-C₄ alkyl or haloalkyl. In some embodiments, the alkyl substituents are methyl, isopropyl, *tert*-butyl or trifluoromethyl groups. In other embodiments, each substituted phenyl has three substituents. In such embodiments, the alkyl substituents are C₁-C₄ alkyl or haloalkyl. In some embodiments, the alkyl substituents are methyl, isopropyl, *tert*-butyl or trifluoromethyl groups. In still other embodiments, each substituted phenyl has one or more alkyl substituents and one or more alkoxy substituents. In some embodiments, each substituted phenyl has one or more C₁-C₄ alkyl or haloalkyl substituents and one or more C₁-C₄ alkoxy substituents. In some embodiments, each substituted phenyl has two C₁-C₄ alkyl substituents and one C₁-C₄ alkoxy substituents.

[0078] {12} The precatalyst according to any of clauses {9} through {11} wherein M is selected from the group consisting of Pd, Ni, Rh, Co, Ir and Pt.

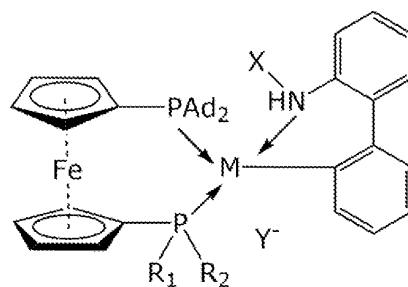
[0079] {13} The precatalyst according to any of clauses {9} through {12} wherein M is Pd.

[0080] {14} The precatalyst according to any of clauses {9} through {13} wherein Y is selected from chloro, bromo and iodo.

[0081] {15} The precatalyst according to any of clauses {9}, {10} or {12}-{14} selected from



[0082] {16} A precatalyst of Formula III:



III

wherein Ad is adamantyl; R_1 and R_2 are independently selected from the group consisting of C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl; R_4 and R_5 are individually selected from the group consisting of H and C_1 - C_{12} alkyl, or R_4 and R_5 together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents; each optional substituent, when present, is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 haloalkyl and C_1 - C_4 alkoxy; M is a transition metal selected from Group 9 or Group 10; X is selected from the group consisting of H, C_1 - C_4 alkyl and phenyl; and Y^- is an

anion selected from the group consisting of halide, triflate (OTf), tetrafluoroborate (BF_4^-), hexafluorophosphate (PF_6^-), mesylate (OMs), tosylate (OTs), tetrakis{3,5-bis(trifluoromethyl)phenyl}borate (BArF), hexafluoro antimonate (SbF_6^-) and combinations thereof.

[0083] {17} The precatalyst according to clause {16} wherein R_1 and R_2 are independently selected from the group consisting of phenyl, cyclohexyl, isopropyl and *tert*-butyl.

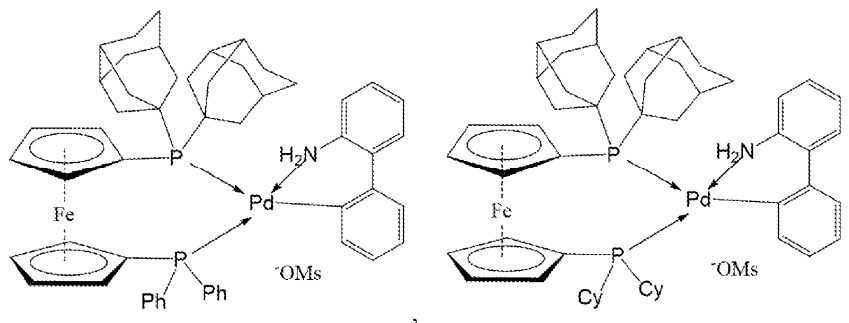
[0084] {18} The precatalyst according to either of clauses {16} or {17} wherein M is selected from the group consisting of Pd, Ni, Rh, Co, Ir and Pt.

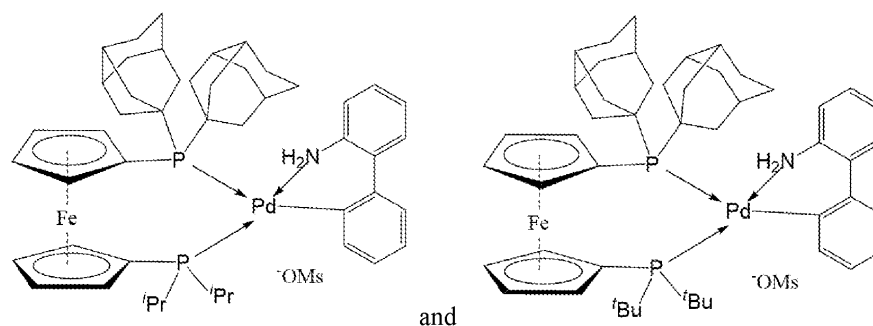
[0085] {19} The precatalyst according to any of clauses {16} through {18} wherein M is Pd.

[0086] {20} The precatalyst according to any of clauses {16} through {19} wherein X is selected from the group consisting of H, methyl and phenyl.

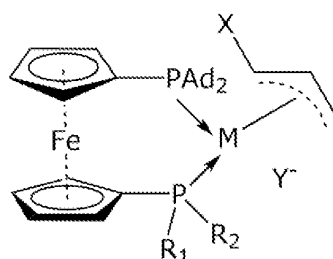
[0087] {21} The precatalyst according to any of clauses {16} through {20} wherein Y^- is selected from the group consisting of Cl^- , Br^- , I^- , OTf , BF_4^- , OMs , OTs , PF_6^- , BArF , and SbF_6^- .

[0088] {22} The precatalyst according to any of clauses {16} through {21} selected from the group consisting of





[0089] {23} A precatalyst of formula IV:



IV

wherein Ad is adamantyl; R_1 and R_2 are independently selected from the group consisting of C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl; R_4 and R_5 are individually selected from the group consisting of H and C_1 - C_{12} alkyl, or R_4 and R_5 together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents; wherein each optional substituent, when present, is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 haloalkyl and C_1 - C_4 alkoxy; M is a transition metal selected from Group 9 or Group 10; X is selected from the group consisting of H, C_1 - C_4 alkyl and phenyl; and Y^- is an anion selected from the group consisting of halide, triflate (^-OTf), tetrafluoroborate ($^-BF_4$), hexafluorophosphate ($^-PF_6$), mesylate (^-OMs), tosylate (^-OTs), tetrakis{3,5-bis(trifluoromethyl)phenyl}borate (^-BArF), hexafluoroantimonate ($^-SbF_6$) and combinations thereof.

[0090] {24} The precatalyst according to clause {23} wherein R_1 and R_2 are independently selected from the group consisting of phenyl, cyclohexyl, isopropyl and *tert*-butyl.

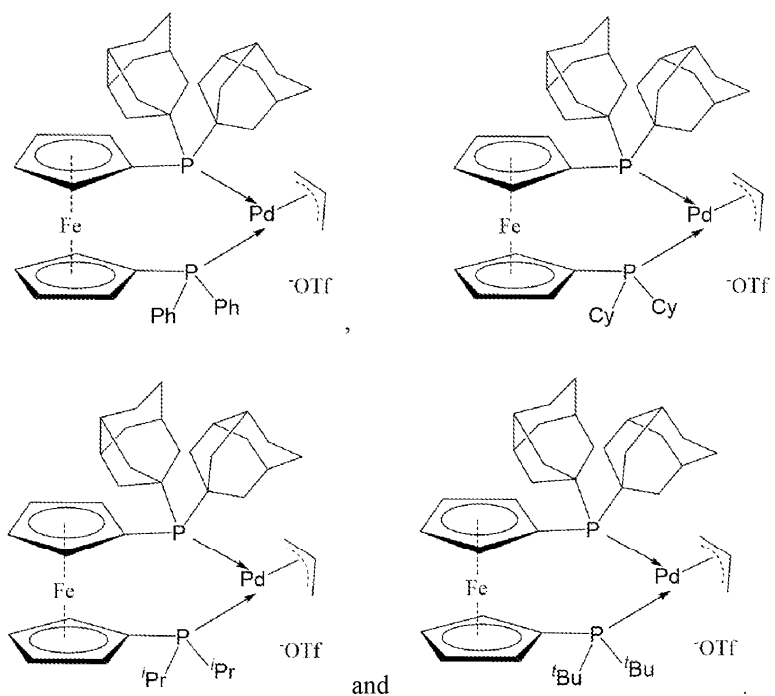
[0091] {25} The precatalyst according to either of clauses {23} or {24} wherein M is selected from the group consisting of Pd, Ni, Rh, Co, Ir and Pt.

[0092] {26} The precatalyst according to any of clauses {23} through {25} wherein M is Pd.

[0093] {27} The precatalyst according to any of clauses {23} through {26} wherein X is selected from the group consisting of H, methyl and phenyl.

[0094] {28} The precatalyst according to any of clauses {23} through {27} wherein Y⁻ is selected from the group consisting of Cl⁻, Br⁻, I⁻, ⁻OTf, ⁻BF₄, ⁻OMs, ⁻OTs, ⁻PF₆, ⁻BARF, and ⁻SbF₆.

[0095] {29} The precatalyst according to any of clauses {23} through {28} selected from the group consisting of



[0096] {30} A method for performing a metal-catalyzed P-C cross-coupling reaction comprising the steps of: contacting a ligand according to any of clauses {5} through {8} with a metal catalyst in the presence of an aromatic solvent and a base in a reaction vessel; adding a first substrate of formula Ar-X', wherein Ar is aryl and X'

is halo and a second substrate of formula R'_2PH , wherein R' is selected from the group consisting of C_1 - C_{10} alkyl and C_3 - C_{10} cycloalkyl, to the reaction vessel; heating the reaction vessel to a temperature in the range from 100 °C to 200 °C for a time sufficient to form the carbon-phosphorous bond.

[0097] {31} The method of clause {30} wherein the ligand is a ligand according to clause {8}, the catalyst is a Pd catalyst.

[0098] {32} A method for performing a metal-catalyzed C_{sp2} - C_{sp3} cross-coupling reaction comprising the steps of: contacting a precatalyst of Formula II according to any of clauses {9} through {15} with a first substrate and a second substrate in the presence of a solvent in a reaction vessel; wherein the first substrate is of formula $Ar-X'$, wherein Ar is optionally substituted aryl or optionally substituted heteroaryl and X' is chloro or bromo or iodo; wherein the second substrate is of formula $R'\{M\}$, wherein R' is selected from the group consisting of C_1 - C_{10} alkyl, C_1 - C_{10} fluoroalkyl and C_3 - C_{10} cycloalkyl, $\{M\}$ is selected from the group consisting of Li , MgX' , ZnX' and $B(OH)_2$ and related boron reagents, wherein X' is selected from the group consisting of chloro, bromo and iodo; optionally, heating the reaction vessel and allowing first substrate and the second substrate to react in the presence of the precatalyst for a time sufficient for the C_{sp2} - C_{sp3} cross-coupling to occur.

[0099] {33} The method according to clause {32} wherein the first substrate is selected from the group consisting of optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thienyl, and optionally substituted furyl.

[0100] {34} The method according to either of clauses {32} or {33} wherein $\{M\}$ is Li , the solvent is toluene, and the reaction vessel is not heated.

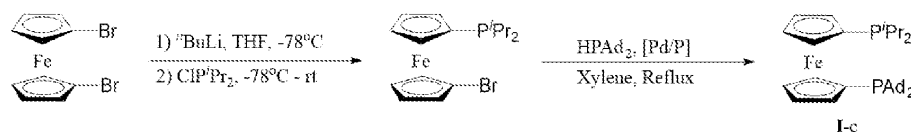
[0101] {35} The method according to either of clauses {32} or {33} wherein $\{M\}$ is selected from MgX' and ZnX' , the solvent is tetrahydrofuran, and the reaction vessel is heated to 50°C.

[0102] {36} The method according to either of clauses {32} or {33} wherein $\{M\}$ is $B(OH)_2$, the solvent is toluene and the reaction vessel is heated to 100°C.

[0103] Examples

[0104] Synthesis of ligands of formula I.

[0105] Example 1. Synthesis of (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene (I-c).



[0106] Under nitrogen, 1,1'-dibromoferrocene (5g, 0.015 mol) was placed in a 250 mL Schlenk flask and dissolved in 50 mL anhydrous THF. This solution was then cooled to -78 °C using dry ice / acetone bath. *n*BuLi (2.5M in hexanes, 6 mL, 0.015 mol) was slowly added dropwise into the reaction solution at -78 °C. The result orange reaction solution was stirred at -78°C for about 1 hour. Chlorodiisopropylphosphine (ClP*i*Pr₂, 2.5 mL, 0.016 mol) was slowly added dropwise using a syringe at -78 °C. The reaction mixture was slowly warmed up to room temperature and stirred at room temperature for about 3 hours. Methanol (2 mL) was added into the reaction mixture to quench the reaction. Solvent was removed on a rotary evaporator, and the residue was dissolved in 20 mL hexanes and filtered through a plug of silica. The plug was washed with hexanes until the first light orange-colored band (impurity band) was completely eluted out, and then with TBME to collect the following dark-orange colored band (product band) until no colored filtrate was eluted out. The dark-orange colored filtrate was initially concentrated using a rotary evaporator until most of the solvent was evaporated, and then under a high vacuum to yield an orange oil (5g) which was confirmed by ³¹P-NMR (>95% purity, 0.37ppm). The material at this stage was used as is for next step.

[0107] Pd(OAc)₂ (100 mg, 0.4 mmol), D'PPF (1,1'-bis(diisopropylphosphino)ferrocene; 180 mg, 0.4 mmol), (1-diisopropylphosphino)-1'-bromoferrocene (5.0 g, 0.013 mol), diadamantylphosphine (Ad₂PH, 4.20 g, 0.014 mol) and NaO*t*Bu (1.4 g, 0.015 mol) were placed in a 250 mL Schlenk flask, followed by adding 100 mL anhydrous toluene. The reaction mixture was stirred at room temperature for 10 minutes, and then heated to reflux for 20 hours, at which point the

reaction was deemed complete on the basis of ^{31}P NMR data obtained from a withdrawn aliquot. The reaction mixture was then allowed to cool and passed through a plug of silica, and the plug was then washed with CH_2Cl_2 until all the orange solution was collected. The combined eluent was collected, and the solvent was removed in vacuo to obtain an orange solid, which was slurry washed with 50 mL Et_2O to obtain an orange solid. The solid was filtered and washed with Et_2O (2 X 10 mL) and dried under vacuum to yield 6.3g, (80%) orange solid. ^1H NMR (CD_2Cl_2): $\delta=4.35$ (m, 2 H; Fc-H), 4.32 (m, 2 H; Fc-H), 4.23 (m, 2 H; Fc-H), 4.15 (m, 2 H; Fc-H), 2.09 (m, 6 H), 1.96 – 1.85 (m, 14 H; 1-Ad), 1.72 (s, 12 H; 1-Ad), 1.12 – 1.07 (m, 12 H, CH_3); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): $\delta=25.39$ ($\underline{PAd}_2$), -0.03 ($\underline{PPr}_2$).

[0108] Other ligands described herein were synthesized similarly.

[0109] Example 2. (1-diphenylphosphino)-(1'-diadamantylphosphino)ferrocene (I-a): The general procedure for compound I-c was used, except with the replacement of chlorodiisopropylphosphine with chlorodiphenylphosphine (3.53 g, 0.016 mol). The resulting compound was an orange solid. ^1H NMR (CD_2Cl_2): $\delta=7.50$ – 7.33 (m, 10H, Ar-H), 4.42 (m, 2 H; Fc-H), 4.29 (m, 2 H; Fc-H), 4.15 (m, 2 H; Fc-H), 4.08 (m, 2 H; Fc-H), 2.01 – 1.97 (m, 6 H, 1-Ad), 1.91 – 1.87 (m, 6 H; 1-Ad), 1.84 – 1.80 (m, 6 H; 1-Ad), 1.68 (s, 12 H, 1-Ad); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): $\delta=25.66$ ($\underline{PAd}_2$), 17.05 ($\underline{PPh}_2$).

[0110] Example 3. (1-dicyclohexylphosphino)-(1'-diadamantylphosphino)ferrocene (I-b): The general procedure for compound I-c was used, except with the replacement of chlorodiisopropylphosphine with chlorodicyclohexylphosphine (3.72 g, 0.016 mol). The resulting compound was an orange solid. ^1H NMR (CD_2Cl_2): $\delta=4.33$ (m, 2 H; Fc-H), 4.30 (m, 2 H; Fc-H), 4.21 (m, 2 H; Fc-H), 4.13 (m, 2 H; Fc-H), 2.10 – 2.06 (m, 6 H), 1.95 – 1.70 (m, 37 H), 1.35 – 1.20 (m, 9 H); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): $\delta=25.18$ ($\underline{PAd}_2$), -8.15 ($\underline{PCy}_2$).

[0111] Example 4. (1-di-t-butylphosphino)-(1'-diadamantylphosphino)ferrocene (I-d): The general procedure for compound I-c was used, except with the replacement of chlorodiisopropylphosphine with chlorodi-t-butylphosphine (2.89 g, 0.016 mol). The resulting compound was an orange solid. ^1H NMR (CD_2Cl_2): $\delta=4.38$ – 4.35 (m, 4 H; Fc-H), 4.20 – 4.18 (m, 4 H; Fc-H), 2.09 – 2.05 (m, 6 H, 1-Ad), 1.95 – 1.84 (m, 12 H; 1-Ad), 1.70 (s, 12 H; 1-Ad), 1.18 (d, 18 H, ^tBu -H); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): $\delta=27.07$

(*P*^{*t*}Bu₂), 25.31 (*P*Ad₂).

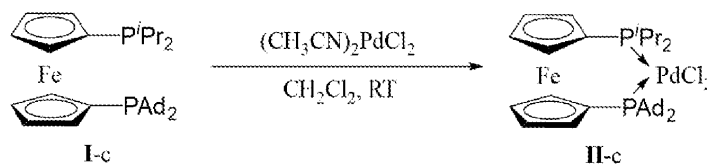
[0112] Example 5. (1-diisopropylphosphino)-(1'-di-*t*-butylphosphino)ferrocene (I-e): Under nitrogen, 1, 1'-Dibromoferrocene (5g, 0.013 mol) was placed in a 250 mL Schlenk flask and dissolved in 50 mL anhydrous THF. This solution was then cooled to -78 °C using dry ice / acetone bath. *n*BuLi (2.5M in hexanes, 6 mL, 0.015 mol) was slowly added dropwise into the reaction solution at -78 °C. The result orange reaction solution was stirred at -78 °C for about 1 hour. Chlorodiisopropylphosphine (CIP^{*i*}Pr₂, 2.5 mL, 0.016 mol) was slowly added dropwise using a syringe at -78 °C. The reaction mixture was slowly warmed up to room temperature and stirred at room temperature for about 3 hours. Methanol (2 mL) was added into the reaction mixture to quench the reaction. Solvent was removed on a rotary evaporator, and the residue was dissolved in 20 mL hexanes and filtered through a plug of silica. The plug was washed with hexanes until the first light orange-colored band (impurity band) was completely eluted out, and then with TBME to collect the following dark-orange colored band (product band) until no colored filtrate was eluted out. The dark-orange colored filtrate was initially concentrated using a rotary evaporator until most of the solvent was evaporated, and then under a high vacuum to yield an orange oil (5g) which was confirmed by ³¹P-NMR (>95% purity, 0.37ppm). The material at this stage was used as is for next step.

[0113] Under nitrogen, (1-diisopropylphosphino)-1'-bromoferrocene (5g, 0.013 mol) was placed in a 250 mL Schlenk flask and dissolved in 50 mL anhydrous THF. This solution was then cooled to -78 °C using dry ice / acetone bath. *n*BuLi (2.5M in hexanes, 6 mL, 0.015 mol) was slowly added dropwise into the reaction solution at -78 °C. The result orange reaction solution was stirred at -78 °C for about 1 hour. Chlorodi-*t*-butylphosphine (CIP^{*t*}Bu₂, 2.89 g, 0.016 mol) was slowly added dropwise using a syringe at -78 °C. The reaction mixture was slowly warmed up to room temperature and stirred at room temperature for about 3 hours. Methanol (2 mL) was added into the reaction mixture to quench the reaction. Solvent was removed on a rotary evaporator, and the residue was dissolved in 20 mL dichloromethane and filtered through a plug of silica. The plug was then washed with dichloromethane until the orange band was completely eluted out and collected. The filtrate was concentrated using a rotary evaporator, and the residue was dissolved in 20 mL

hexanes. The dark orange solution was cooled to $-20\text{ }^{\circ}\text{C}$ in a freezer overnight to yield the solid precipitation. The solid was collected and washed with cold hexanes (5 mL X 2) to obtain the orange solid (4.4 g, 75%). ^1H NMR (CD_2Cl_2): $\delta=4.35$ (m, 2 H; Fc-H), 4.32 (m, 2 H; Fc-H), 4.27 (m, 2 H; Fc-H), 4.19 (m, 2 H; Fc-H), 2.00 – 1.92 (m, 2 H, $\text{CH}(\text{CH}_3)_2$), 1.22 (d, 18 H; ^tBu), 1.15 – 1.05 (m, 12 H; $\text{CH}(\text{CH}_3)_2$); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): $\delta=27.06$ (P^tBu_2), -0.22 (P^tPr_2)

[0114] Synthesis of precatalysts of formula II.

[0115] Example 6. Synthesis of [(1-diisopropylphosphino)(1'-diadamantylphosphino)ferrocene]dichloro palladium (II-c):



[0116] Under nitrogen, (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene (603 mg, 1.0 mmol) and $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (259 mg, 1.0 mmol) were placed in a 100 mL Schlenk flask and dissolved in 50 mL anhydrous dichloromethane. The reaction mixture was stirred at room temperature for 2 hours, followed by the solvent removal to yield a brown solid. The solid was slurried with 50 mL hexanes for 30 minutes, to obtain a reddish brown solid, which was filtered and dried under vacuum to yield the pure product (750 mg, 96%). Slow diffusion of pentane into a dichloromethane solution of the product yielded single crystals suitable for X-Ray diffraction studies. ^1H NMR (CD_2Cl_2): $\delta=4.77$ (m, 2 H; Fc-H), 4.59 (s, 2 H; Fc-H), 4.52 (s, 2 H; Fc-H), 4.50 (m, 2 H; Fc-H), 3.31 – 3.23 (m, 2 H; $\text{CH}(\text{CH}_3)_2$), 2.75 (br, 6H), 2.38 (br, 6H), 2.06 (s, br, 6H), 1.84 – 1.60 (m, 18H), 1.35 – 1.22 (m, 6H); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): $\delta=68.50$ (d), 58.10 (d).

[0117] Other metal complexes described herein were synthesized similarly.

[0118] Example 7. [(1-diphenylphosphino)(1'-diadamantylphosphino)ferrocene]dichloro palladium (II-a): The general procedure for compound II-c was used, except with the replacement of (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene with (1-diphenylphosphino)-(1'-

diadamantylphosphino)ferrocene (671 mg, 1.0 mmol). The resulting product was a brown solid. ^1H NMR (CD_2Cl_2): δ =8.10 (br, 4H, Ph-H), 7.60 – 7.50 (m, 6H, Ph-H), 4.96 (m, 2 H, Fc-H), 4.57 (m, 2H, Fc-H), 4.33 (m, 2H, Fc-H), 3.91 (m, 2H, Fc-H), 3.20 – 2.05 (br, 12H, Ad-H), 2.02 (m, 6H, Ad-H), 1.90 – 1.75 (m, 12H, Ad-H); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ =75.10 (d), 38.25 (d).

[0119] Example 8. [(1-dicyclohexylphosphino)(1'-diadamantylphosphino)ferrocene]dichloro palladium (II-b): The general procedure for compound II-c was used, except with the replacement of (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene with (1-dicyclohexylphosphino)-(1'-diadamantylphosphino)ferrocene (683 mg, 1.0 mmol). The resulting product was a brown solid. ^1H NMR (CD_2Cl_2): δ = 4.72 (m, 2 H, Fc-H), 4.57 (m, 2H, Fc-H), 4.55 – 4.45 (m, 4H, Fc-H), 3.10 – 2.20 (br, 18H), 2.20 – 1.60 (m, 18H), 1.55 – 1.20 (m, 16H); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ =75.10 (d), 38.25 (d).

[0120] Example 9. [(1-di-t-butylphosphino)(1'-diadamantylphosphino)ferrocene]dichloro palladium (II-d): The general procedure for compound II-c was used, except with the replacement of (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene with (1-di-t-butylphosphino)-(1'-diadamantylphosphino)ferrocene (631 mg, 1.0 mmol). The resulting product was a brown solid. $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ =66.66 (d), 60.00 (d).

[0121] Example 10. [(1-diisopropylphosphino)(1'-di-t-butylphosphino)ferrocene]dichloro palladium (II-e): The general procedure for compound II-c was used, except with the replacement of (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene with (1-diisopropylphosphino)-(1'-di-t-butylphosphino)ferrocene (446 mg, 1.0 mmol). The resulting product was a brown solid. $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ =74.37 (d), 58.80 (d).

[0122] Synthesis of precatalysts of formula III.

[0123] Example 11. Synthesis of [(1-diisopropylphosphino)(1'-diadamantylphosphino)ferrocene][2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (III-c): Under nitrogen, (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene (603 mg, 1.0 mmol) and Di- μ -mesylbis[2'-(amino-N)[1,1'-biphenyl]-2-yl-C]dipalladium(II) (370 mg, 0.5 mmol) were placed in a 100

mL Schlenk flask and dissolved in 50 mL anhydrous dichloromethane. The reaction mixture was stirred at room temperature for 2 hours, followed by the solvent removal to yield a brown solid. The solid was slurried with 50 mL hexanes for 30 minutes, to obtain a reddish brown solid, which was filtered and dried under vacuum to yield the pure product (875 mg, 90%). ^1H NMR (CD_2Cl_2): δ =7.65 – 7.55 (m, 2H, Ar-H), 7.35 – 7.25 (m, 6H, Ar-H), 4.65 – 4.55 (m, 3H, Fc-H), 4.51 (m, 1H, Fc-H), 4.48 (m, 1H, Fc-H), 4.39 (m, 1H, Fc-H), 4.37 (m, 1H, Fc-H), 4.34 (m, 1H, Fc-H) 2.97 (br, 3H), 2.77 (br, 3H), 2.40 (br, 2H), 2.25 (s, 3H), 2.20 – 1.70 (m, 26H), 1.35 – 1.20 (m, 6H), 0.65 – 0.50 (m, 6H); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ =38.94 (d), 38.65 (d).

[0124] Other metal complexes III described herein were synthesized similarly.

[0125] Example 12. [(1-diphenylphosphino)(1'-diadamantylphosphino)ferrocene][2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (III-a): Brown solid. The general procedure for compound II-c was used, except with the replacement of (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene with (1-diphenylphosphino)-(1'-diadamantylphosphino) ferrocene (671 mg, 1.0 mmol). ^1H NMR (CD_2Cl_2): δ = 7.80 – 7.65 (m, 3H, Ar-H), 7.48 -7.40 (m, 2H, Ar-H), 7.38 – 7.30 (m, 3H, Ar-H), 7.25 – 7.00 (m, 4H, Ar-H), 6.90 -6.75 (m, 3H, Ar-H), 6.60 – 6.50 (m, 1H, Ar-H), 6.45 – 6.30 (m, 2H, Ar-H), 6.20 (d, 2H), 4.85 (m, 1H, Fc-H), 4.77 (m, 1H, Fc-H), 4.59 (m, 1H, Fc-H), 4.48 (m, 1H, Fc-H), 4.42 (m, 1H, Fc-H), 4.23 (m, 1H, Fc-H), 4.19 (m, 1H, Fc-H), 3.89 (m, 1H, Fc-H), 2.79 (s, 3H), 2.38 (s, 3H), 2.25 (m, 2H), 2.20 – 1.55 (m, 25H); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ =34.89 (d), 25.78 (d).

[0126] [(1-dicyclohexylphosphino)(1'-diadamantylphosphino)ferrocene][2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (III-b): The general procedure for compound II-c was used, except with the replacement of (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene with (1-dicyclohexylphosphino)-(1'-diadamantylphosphino) ferrocene (683 mg, 1.0 mmol). The resulting product was a brown solid. ^1H NMR (CD_2Cl_2): δ = 7.70 – 7.65 (m, 1H, Ar-H), 7.60 – 7.50 (m, 1H, Ar-H), 7.45 – 7.40 (m, 1H, Ar-H), 7.38 – 7.30 (m, 3H, Ar-H), 7.30 – 7.25 (m, 2H, Ar-H), 4.62 (m, 2H, Fc-H), 4.58 (m, 1H, Fc-H), 4.50 (m, 2H, Fc-H), 4.36 (m, 2H, Fc-H), 4.28 (m, 1H, Fc-H), 2.95 (br, 3H), 2.78 (br, 3H), 2.36 (s, 3H), 2.25 (s, 2H), 2.20 – 0.75 (m, 46H); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ =38.93 (d), 25.97

(d).

[0127] Example 13. [(1-diisopropylphosphino)(1'-di-t-butylphosphino)ferrocene][2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (III-e): The general procedure for compound II-c was used, except with the replacement of (1-diisopropylphosphino)-(1'-diadamantylphosphino)ferrocene with (1-diisopropylphosphino)-(1'-di-t-butylphosphino)ferrocene (446 mg, 1.0 mmol). The resulting product was a brown solid. ^1H NMR (CD_2Cl_2): δ = 7.65 – 7.60 (m, 1H, Ar-H), 7.58 – 7.50 (m, 1H, Ar-H), 7.40 – 7.25 (m, 6H, Ar-H), 4.59 (m, 2H, Fc-H), 4.55 (m, 2H, Fc-H), 4.51 (m, 1H, Fc-H), 4.38 (m, 3H, Fc-H), 2.35 (s, 3H), 2.25 – 2.15 (br, 3H), 1.94 (d, 9H), 1.40 – 1.22 (m, 16H), 0.70 – 0.50 (m, 6H), $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ = 47.08 (d), 39.07 (d).

[0128] Synthesis of precatalysts of formula IV.

[0129] Example 14. Synthesis of $\text{Pd}(\text{Crotyl})[\text{Fc}(\text{PAd}_2)(\text{PPh}_2)]\text{Cl}$ (IV-c): Under nitrogen, (1-diphenylphosphino)-(1'-diadamantylphosphino)ferrocene (671 mg, 1.0 mmol) and (2-Butenyl)chloropalladium dimer (197 mg, 0.5 mmol) were placed in a 100 mL Schlenk flask and dissolved in 50 mL anhydrous THF. The reaction mixture was stirred at room temperature for 2 hours, followed by the solvent removal to yield a brown solid. The solid was slurried with 50 mL hexanes for 30 minutes, to obtain a reddish brown solid, which was filtered and dried under vacuum to yield the pure product (747 mg, 86%). $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ = 75.70 (d), 38.90 (d).

[0130] Other metal complexes IV described herein were synthesized similarly.

[0131] **Application Studies.** The ligands and catalysts described herein were used in two challenging and underrepresented class of reactions, namely $\text{C}_{\text{sp}2}\text{-C}_{\text{sp}3}$ coupling and P-C coupling. P-C coupling was chosen not only to demonstrate the proof of concept but also to generate some additional ligands such as adamantyl based phosphines such S-Phos, Ru-Phos, X-Phos, Amphos etc.

[0132] Example 15. $\text{C}_{\text{sp}2}\text{-C}_{\text{sp}3}$ Cross-coupling

[0133] Cross coupling involving $\text{sp}2\text{-sp}3$ coupling chemistry is one of the most challenging reactions in organic synthesis.¹⁹ While transition metal catalyzed cross-

coupling reactions involving sp^2 -hybridized carbon nucleophiles and aryl or vinyl halides have been extensively examined during the past three decades,¹⁸ studies on the chemistries with C_{sp^2} - C_{sp^3} couplings are very limited.¹⁹ Among them, Palladium and Nickel catalyzed cross-coupling reactions are two of the most extensively studied catalytic systems. Although there are some scattered reports in the literature with model substrates; major challenges, especially towards the scope of the reactions with different name reactions in cross-coupling, and especially the use of more complex drug-like molecules, remains underrepresented.¹⁹⁻²³ Late-stage functionalization on complex molecules has been and continues to be one of hot research areas for making this technology viable to real world applications.

[0134] The studies were initiated by evaluating a series of ferrocenyl based precatalysts with bromobenzene (PhBr) with methylmagnesium bromide (MeMgBr) using 1 mol % catalyst loading at ambient temperature in THF (Table 3). Pd(dppf)Cl₂, reported to be a very powerful catalyst for C_{sp^2} - C_{sp^3} coupling,³ gave poor conversion with methylmagnesium bromide. Further screening with other commercially available next generation precatalysts of ferrocenyl based bidentate ligands, namely Pd(dcyph)Cl₂, Pd(dippf)Cl₂, Pd(dtbpf)Cl₂, did not give satisfactory conversion either. However, Pd(dtbpf)Cl₂ gave moderate conversion (66%). In contrast, by incorporating Ad₂P moiety into ferrocenyl ligands, namely, Pd(L1-4)Cl₂, significantly increased the reactivity towards methylation *via* C_{sp^2} - C_{sp^3} couplings. Pd(L4)Cl₂, Pd4-a, gave almost quantitative conversion in 2 h at room temperature. Interestingly Stepnicka et.al's ligand, [Fc(P'Bu₂)(PPh₂)]PdCl₂, did not give satisfactory conversions either (8%, entry 10), suggesting the importance of Ad₂P moiety. As a baseline comparison, the reaction did not proceed at all without any catalyst addition (entry 1, Table 3).

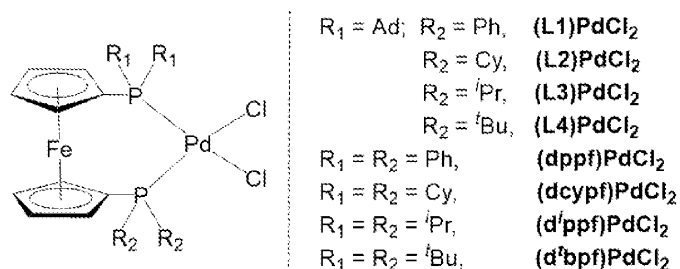


Table 3

Entry	Catalyst	Ph-Br, % ^b	Ph-Me, % ^b	Ph-H/Ph, % ^b
1	No Catalyst	100	0	0/0
2	(L1)PdCl ₂	95	5	0/0
3	(L2)PdCl ₂	18	80	1/2
4	(L3)PdCl ₂	35	65	0/0
5	(L4)PdCl ₂	0	97	2/1
6	(dppf)PdCl ₂	95	3	0/2
7	(dcypf)PdCl ₂	99	0	1/0
8	(d'ppf)PdCl ₂	90	8	1/1
9	(d'bpf)PdCl ₂	27	66	0/7
10	[Fc(PPh ₂)(P <i>t</i> Bu ₂)]PdCl ₂	86	8	6/0

1a , 97%	1b , 96% (75% from ArCl) ^c	1c , 96%	1d , 95%	1e , 91% ^{c, d}
1f , 85% ^{c, d}	1g , 87%	1h , 73%	1i , 88% ^d	

^aConditions: Ar-X (0.8 mmol), CH₃MgBr (1.6 mmol), catalyst (1 mol%), THF, room temperature or 50°C. ^bGC conversion. ^cReaction Temperature: 50°C. ^dIsolated yield.

[0135] With the preferred catalyst in hand, the cross-coupling reactions between

methylmagnesium bromide with various (hetero)aryl halides was examined. With relatively low catalyst loading, 1 mol% Pd(L4)Cl₂ (Pd4-a), very good yields were obtained for many substrates (Table 3). Both electron donating and electron withdrawing aryl bromides did not show any significant differences in terms of conversion/yield (>95% conversion). Reactions of sterically hindered aryl bromides (1e and 1f) required slightly higher temp (ca. 50°C) for obtaining >85% isolated yields. The substrates with nitrogen-containing hetero-cycles, *i.e.* pyridine (1g and 1h) and pyrimidine (1i), also gave very good results. Finally, coupling of Ar-Cl was also successful, with slightly elevated temperature (1b, 75% GC conversion at 50°C).

[0136] To further investigate the generality of this technology, various alkyl Grignard reagents were investigated (Table 5). Reagents with no β-hydrogen, such as CD₃-, TMSCH₂-, p-TolCH₂-, all worked well with high to excellent isolated yields (1l - p). The cyclic-alkyl reagents, such as cyclopropyl, cyclobutyl, cyclopentyl, also worked effectively (2a – s). However, reagents containing readily accessible β-hydrogen, e.g. Et-, ⁱPr-, ⁿBu-, ^sBu- etc. didn't work very well under these conditions using Pd(L4)Cl₂ (Pd4-a). Significant amounts of dehalogenated side products were observed, resulting in much lower yields (e.g., 30% GC conversion for 3a). In order to address this issue, a catalyst screening on a reaction (Table 4) of 4-Bromoanisole and ⁿBuMgCl with a catalyst of [Fc(Ad₂P)(R₂P)]PdCl₂ (R= Ph (Pd1-a), Cy (Pd2-a), ⁱPr (Pd3-a) and ^tBu (Pd4-a)), as well as (dppf)PdCl₂ was done. While Pd4-a gave only 30% GC yield, all the other catalysts tests gave excellent conversion. Surprisingly, despite the yields, all catalysts gave almost no isomerization product, namely 4-sec-butylanisole. The reactions with Pd4-a and (dppf)PdCl₂ were slower than others with Pd2-a, Pd3-a. Both reactions gave significant amount of unreacted starting material, 4-bromoanisole, even after 20 hrs at room temperature.

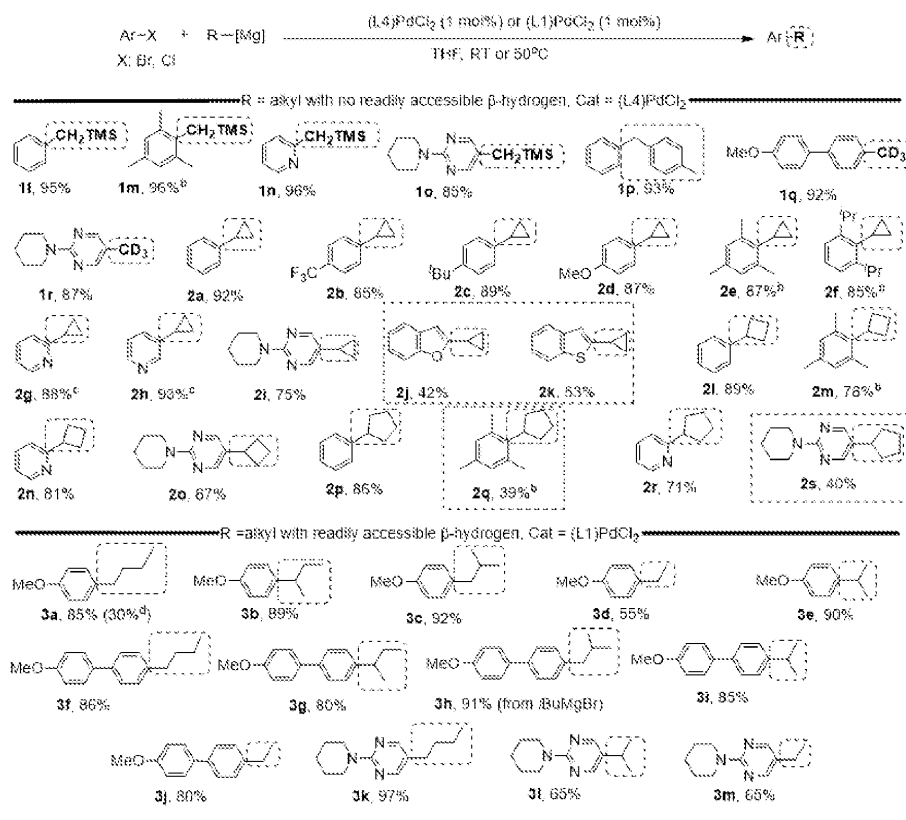
Table 4

Entry	Catalyst	Ar- ⁿ Bu, % ^a	Ar-Br, % ^a	3a/3b
2	(L1)PdCl ₂	93 (85 ^b)	0	100/0
3	(L2)PdCl ₂	86	0	100/0
4	(L3)PdCl ₂	92	0	100/0
5	(L4)PdCl ₂	30	37	100/0
6	(dppf)PdCl ₂	90	10	40/1

^aGC conversion; ^bIsolated yield.

[0137] For the sake of synthetic simplicity, (L1)PdCl₂ (Pd1-a) was selected as the model catalyst for application studies on C_{sp2}-C_{sp3} couplings with various alkyl Grignard reagents with readily accessible β-hydrogen (Table 5). Both primary alkyl Grignard reagents, such as EtMgBr, ^tBuMgBr, and secondary alkyl Grignard reagents, such as ⁿBuMgBr, ⁱPrMgBr, worked nicely with moderate to excellent yields. N-containing heteroaryl substrates also worked well.

Table 5



^aConditions: Ar-X (0.8 mmol), RMgX (2.0 equiv.), catalyst (1 mol%), THF, room temperature or 50°C. ^bReaction Temperature: 50°C. ^cIsolated as HCl salt. ^dGC conversion from the reaction using (L4)PdCl₂ as the catalyst. **2j**, **2k**, **2q** and **2s** were produced in higher yields under Negishi (Zn) or Suzuki-Miyaura (B) conditions (see Table 5).

[0138] With successfully demonstration on the C_{sp2}-C_{sp3} coupling using one of the challenging class of nucleophiles, namely Grignard reagents (Kumada-Corriu coupling), the generality of the coupling reactions with other commercially available C_{sp3}-hybridized organometallic reagents (nucleophiles), such as alkyl lithium (Murahashi-Feringa), alkyl Zinc (Negishi), and alkyl boronic acid (Suzuki-Miyaura) were also investigated for randomly selected examples (Table 6). Using similar strategy employed for alkyl Grignard reactions (*i.e.* balancing the steric and electronics of the ligands with that of the substrate), all name reactions investigated here gave good to excellent yields (see examples in Table 6). Owing to the lower nucleophilicity of alkyl zinc/boron reagents, the C_{sp2}-C_{sp3} couplings typically gave

better results in comparison to the alkyl Grignard reagents. For instance, product 2j was isolated with significantly higher yields from the reactions involving either cyclopropylzinc bromide or cyclopropylboronic acid, than that from the corresponding cyclopropylmagnesium bromide [(95% (B), 95% (Zn), 42% (Mg)]. Similar trend was also observed for product 2k (95% (B), 86% (Zn), 53% (Mg)).

[0139] Applying the same methodology to the organozinc reagents with various functional groups also proved to be very successful. Functional groups such as terminal alkene (4b, 83%; 4c, 81%, 4d, 94% and 4e, 79%), ester (4g, 89% and 4h, 75%), cyano (4f, 86% and 4i, 80%) were all well tolerated. Interestingly, reactions with the organozinc reagents containing strong electron-withdrawing groups close to the nucleophilic carbon center did require harsher reaction conditions. For instance, the reaction with $\text{EtOC(=O)CH}_2\text{CH}_2\text{ZnBr}$ required higher reaction temperature (e.g. 50°C) with longer reaction time (>20 h) vs the room temperature reaction ($<10\%$ of GC conversion). The electronic effects on the organozinc reagents seem to be diminishing with the increase of the chain length from the nucleophilic carbon center as products 4f and 4l have been isolated in excellent yields even at room temperature.

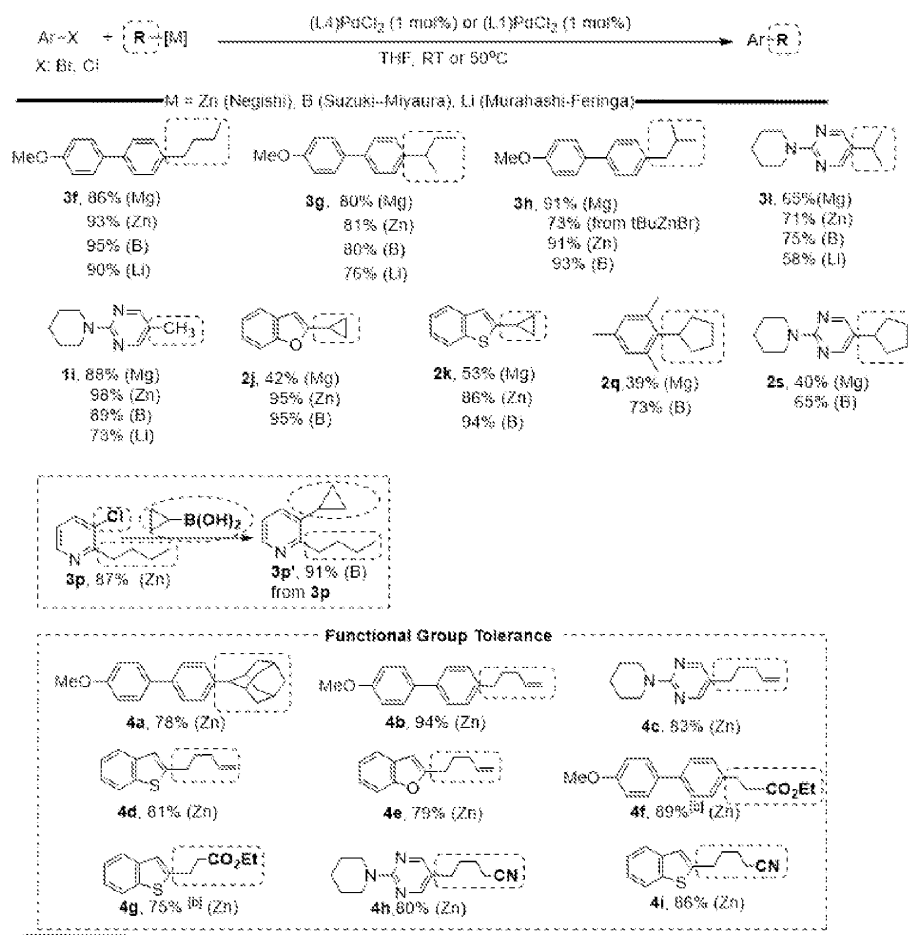
[0140] In addition to the reported isomerization and dehalogenation side-reactions for $\text{C}_{\text{sp}2}\text{-C}_{\text{sp}3}$ coupling with Li and Mg based nucleophiles, the coupling under Suzuki–Miyaura conditions with alkyl boronic acids also reported to suffer proto-deborylation from the corresponding alkyl boronic acid, especially at elevated temperature. To minimize the proto-deborylation side-reaction, Molandar, Hazari and Burk have been using BF_3K and MIDA boronates.²³ The direct use of alkyl boronic acids in $\text{C}_{\text{sp}2}\text{-C}_{\text{sp}3}$ coupling have been only demonstrated very recently in literature by Goosen et.al. with a few examples.^{23a}

[0141] With the success on $\text{C}_{\text{sp}2}\text{-C}_{\text{sp}3}$ coupling under Kumada–Corriu (Mg), Negishi (Zn), Suzuki–Miyaura (B) conditions, finally the one of the least explored coupling reactions namely: Murahashi–Feringa (Li) coupling, especially for $\text{C}_{\text{sp}3}$ -based Li nucleophiles where severe competitive halogen exchange reaction as well as the side reactions from isomerization were reported, were investigated. Because of these drawbacks, the Murahashi–Feringa coupling in general has been largely neglected for 30–40 years since its first discovery in 1970s. Until recently, Feringa group and Gessner group independently reported some significant development of Murahashi–

Feringa coupling with much improved substrate scope, functional group tolerance and reaction conditions. However, the catalyst system described herein, namely Pd(L1-4)Cl₂, for Murahashi-Feringa coupling (Table 6) was very effective under low catalyst loadings in comparison to the reported methods which uses up to 5% Pd loadings with O₂ for activation of catalyst and that some of the modern ligands are not scalable for any practical applications beyond R & D. Both simple aromatic substrates (3f and 3g) and nitrogen containing heterocycles (3i) gave good to excellent yields with alkyllithiums. Interestingly, reaction with MeLi didn't require either slow addition or dilution, presumably due to the slow Li/halogen exchange reaction rate under these conditions coupled with its stability in ether solvents (1i, 73%).

[0142] As mentioned earlier, the reactions for Kumada-Corriu and Negishi for Ar-Cl required heating (ca. 50°C), while those with Ar-Br typically proceeded at room temperature. This has been utilized for sequential C_{sp2}-C_{sp3} coupling of the substrates containing both Cl and Br groups to isolate the desired products in excellent selectivity and yield (e.g, 3p, 87% and 3p', 91% from 3p). The mono coupled product 3p was isolated in high yield by coupling 2-bromo-3-chloropyridine with ^tBuZnBr at room temperature, while keeping the chloro intact. Subsequent coupling of 3p (Ar-Cl) with cyclopropylboronic acid under Suzuki-Miyaura conditions at 100°C afforded 3p' in 91% isolated yield.

Table 6



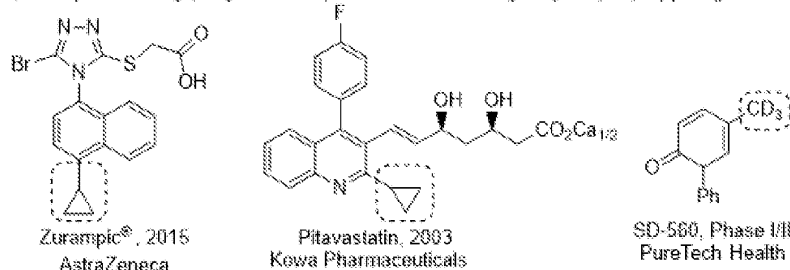
^aNegishi conditions (Zn): Ar-X (0.8 mmol), RZnX (2.0 equiv.), catalyst (1 mol%), THF, room temperature or 50°C. Suzuki-Miyaura conditions (B): Ar-X (0.8 mmol), RB(OH)₂ (2.0 equiv.), catalyst (1 mol%), K₃PO₄ (3 equiv.), Toluene/H₂O (10/1), 100°C. Murahashi-Feringa conditions (Li): Ar-X (0.8 mmol), RLi (1.2 equiv., diluted with Toluene to 0.2 M), catalyst (1 mol%), Toluene, room temperature. Slow addition using syringe pump for 2 hours. ^bReaction temperature: 50°C.

[0143] Deuterium labelled drugs (Table 7.1),²⁴ especially CD₃ based molecules are prominent due to the “magic methyl effect”, introducing a methyl group into pharmaceuticals could positively affect biological activities, and marked improvements to drug candidates related to absorption, distribution, and metabolism in organisms upon replacing the H atom(s) with deuterium (D). In addition, deuterium atoms can be used as tracer atoms to elucidate metabolic pathways in medicinal

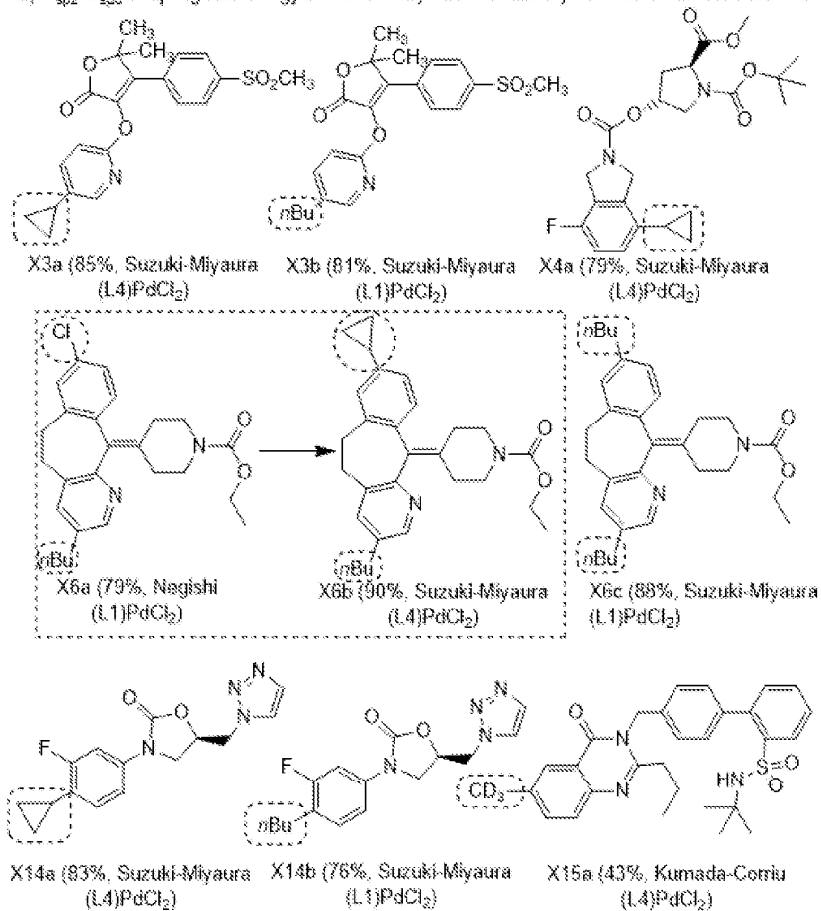
chemistry. Cyclopropane motif is also highly significant in drug synthesis as it is the 10th most frequently found ring system in small molecule drugs (Table 7.1).²⁵ With success on model substrates, grafting various “alkyl fragments” onto the “drug-like” molecules, i.e. “Chemistry Informer Libraries” developed by Merck & Co by extensive research to mimic “late stage functionalization” specially geared for various cross-coupling chemistries,²⁶ was attempted with excellent isolated yields for 9 examples (Table 7.2). Compounds X3a, X4a, X6b and X14a represent cyclopropane ring incorporated drug like molecules. The strategy of sequential Negishi and Suzuki C_{sp^2} - C_{sp^3} couplings on Cl/Br was also successfully achieved (X6a, 79% yield and X6b, 90% yield). Interestingly reaction of the same “Informer” substrate with $tBuB(OH)_2$ at elevated temperature (100°C) resulted in the double-coupling product X6c in excellent yields (88%). Finally, we also successfully incorporated CD_3 group on one of the “Informer” molecules (X15a) with moderate yield (43%). The lower yield of X15a is likely due to the strong nucleophilicity of Grignard reagent towards the functional groups. However, it is predicted that Negishi or Suzuki–Miyaura versions of the nucleophile might give better results in analogy with results on model substrates (currently these reagents are not commercially available).

Table 7

1) Examples for drug (drug candidate) molecules containing CD₃ or cyclopropyl fragment



2) C_{sp2}-C_{sp3} coupling technology on "Chemistry Informer Library" molecules as described herein

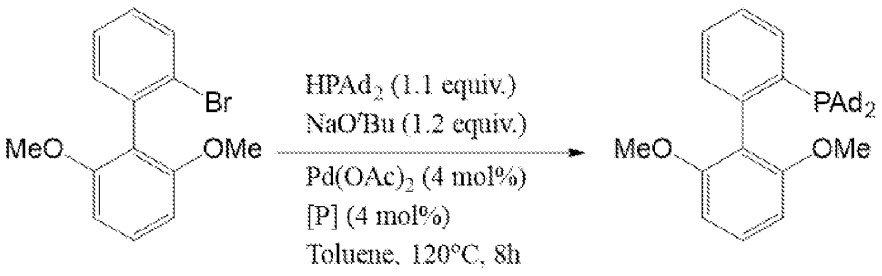


^aKumada-Corriu conditions (Mg): Ar-X (100 mg), RMgX (2.0 equiv.), catalyst (2 mol%) THF, room temperature or 50°C. Negishi conditions (Zn): Ar-X (100 mg), RZnX (2.0 equiv.), catalyst (2 mol%), THF, room temperature or 50°C. Suzuki-Miyaura conditions (B): Ar-X (100 mg), RB(OH)₂ (2.0 equiv.), catalyst (2 mol%), K₃PO₄ (3 equiv.), Toluene/H₂O (10/1), 100°C.

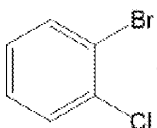
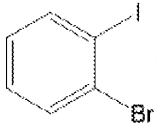
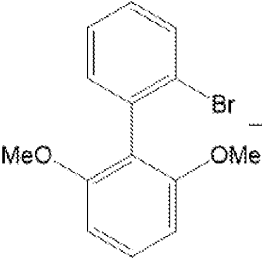
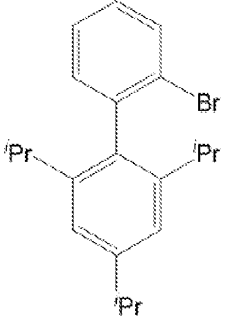
[0144] Example 16. P-C Coupling to Make New Ligands

[0145] To further understand the usefulness of the ligand/catalyst system described herein in other cross-coupling chemistries, the P-C couplings with a view to synthesize some new ligands as well as to demonstrate the practicality of P-C coupling was investigated. Following the similar protocol reported by Buchwald²⁷ and Stradiotto groups¹², screening reactions with the ligands described herein and various commercially available monodentate and bidentate ligands were tested (Table 8). The monodentate ligands screened in this work all gave less than 5% ¹H NMR conversion. On the other hand, bidentate ligands worked better in terms of ¹H NMR conversion, mostly giving more than 20% ¹H NMR conversion except dppe (<5%, entry 5) and Fc(PAd₂)(PPh₂) (8%, entry 9) giving less than 10% ¹H NMR conversion. Surprisingly, Fc(P'Pr₂)(P'Pr₂), dippf, reported to be an outstanding ligand for the P-C coupling, didn't work very well in the model reaction, only giving 24% yield (entry 7). More electron rich and bulky Fc(P'Bu₂)(P'Bu₂), dtbpf, did not give good conversion either (21% yield, entry 8). By replacing the ligands to the PAd₂ based ligands (L1-4) described herein improved the yields significantly. All gave good yields, except Fc(PAd₂)(PPh₂) (L1, 8%), while Fc(PAd₂)(P'Pr₂), L3, gave the highest yield (87%). Also noteworthy is that XantPhos gave an acceptable ¹H NMR conversion (45%, entry 6). The reaction without any phosphine ligand didn't proceed at all (entry 1).

Table 8. Reaction screening on C-P coupling

		
Entry	[P]	Ar-PAd ₂ (¹ H NMR yield)
1	-	0%
2	P ^t Bu ₃	<5%
3	MorDalPhos	<5%
4	tBuBrettPhos	<5%
5	Ph ₂ PCH ₂ CH ₂ PPh ₂ (dppe)	< 5%
6	XantPhos	45%
7	Fc(P ^t Pr ₂)(P ^t Pr ₂), dippf	24%
8	Fc(P ^t Bu ₂)(P ^t Bu ₂), dtbpf	21%
9	Fc(PAd ₂)(PPh ₂), L1	8%
10	Fc(PAd ₂)(PCy ₂), L2	25%
11	Fc(PAd ₂)(P ^t Pr) ₂ , L3	87%
12	Fc(PAd ₂)(P ^t Bu ₂), L4	21%

With the optimized reaction condition and phosphine ligand in hand, this technology was further applied to synthesize various phosphine ligands. Several examples are shown below. Gratefully, several bulky Buchwald ligands were also synthesized using this P-C coupling with good to excellent isolated yields. Traditionally, these bulk Buchwald ligands are difficult to prepared, especially in industrial large scale.

Entry	Reaction	Isolated Yield
1		86%
2		91%
3		R = Ad, 82% R = ^t Bu, 85%
4		R = Ad, 93% R = ^t Bu, 86%

[0146] The examples provided herein are not meant to limit the scope of the invention as set forth in the claims.

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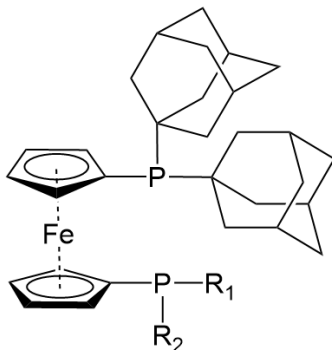
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CLAIMS

1. A compound of formula I



I

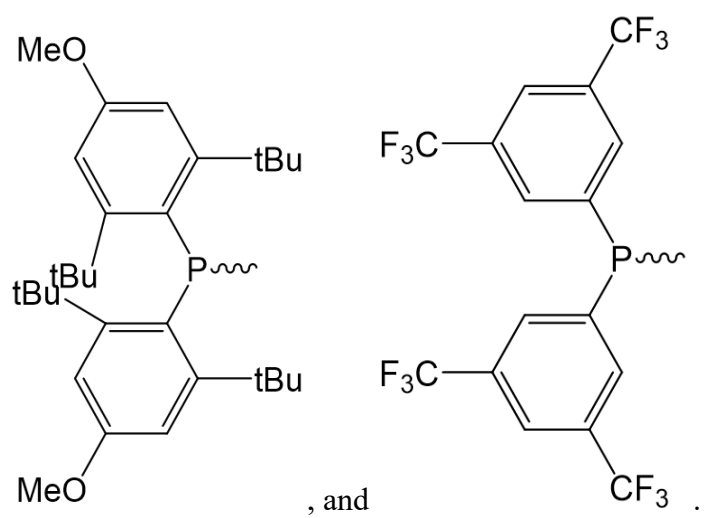
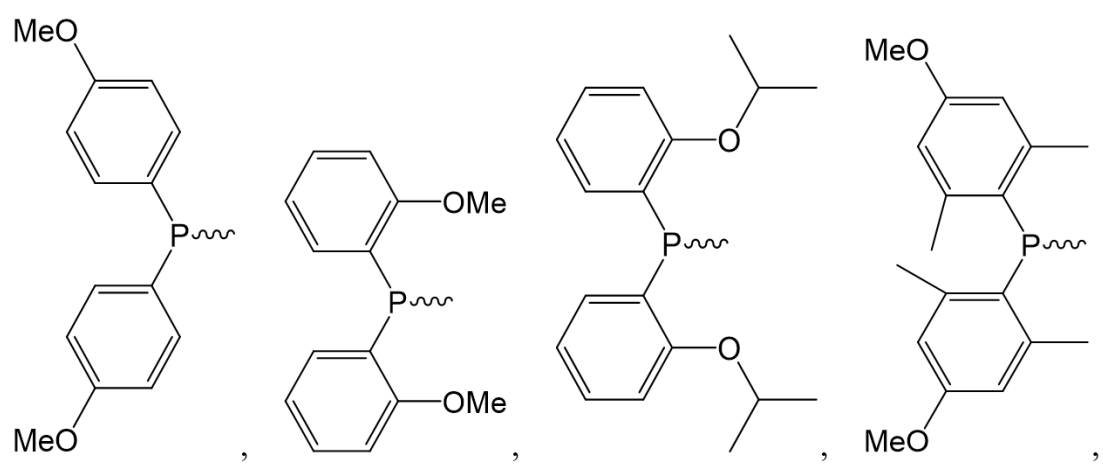
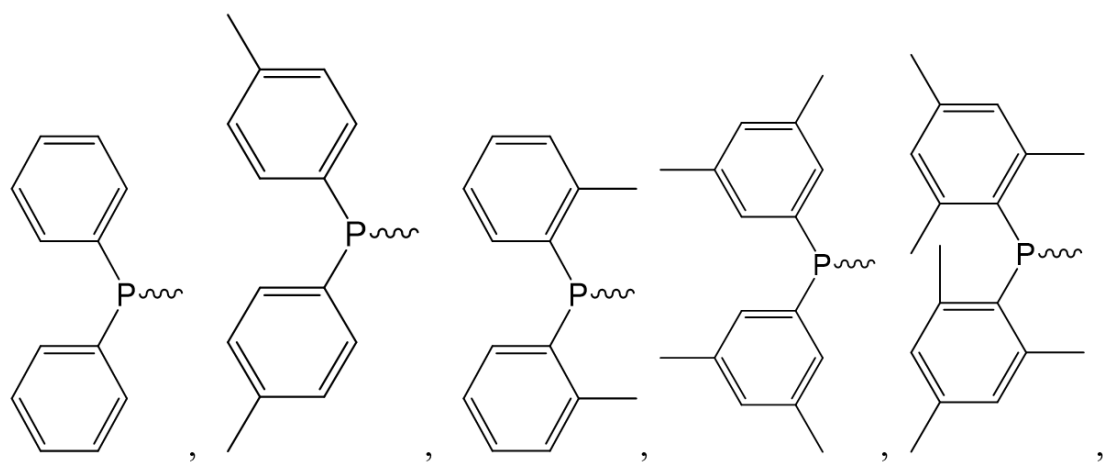
wherein

R_1 and R_2 are independently selected from the group consisting of C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl;

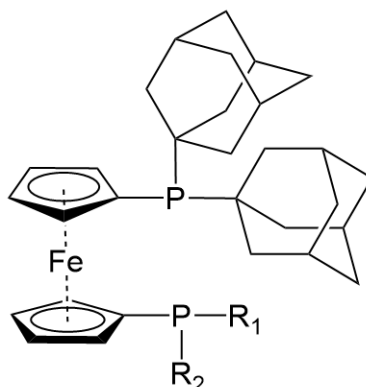
R_4 and R_5 are individually selected from the group consisting of H and C_1 - C_{12} alkyl, or R_4 and R_5 together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents; and

each optional substituent, when present, is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 haloalkyl and C_1 - C_4 alkoxy.

2. The compound according to claim 1 wherein R_1 and R_2 are independently selected from the group consisting of phenyl, optionally substituted phenyl, cyclohexyl, isopropyl and *tert*-butyl.
3. The compound according to either of claims 1 or 2 wherein R_1 and R_2 are each substituted phenyl.
4. The compound according to either of claims 1 or 2 wherein $-PR_1R_2$ is selected from the group consisting of



5. A ligand of formula I:



I

wherein

R₁ and R₂ are independently selected from the group consisting of C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, C₁-C₁₂ alkoxy, -NR₄R₅, and optionally substituted phenyl;

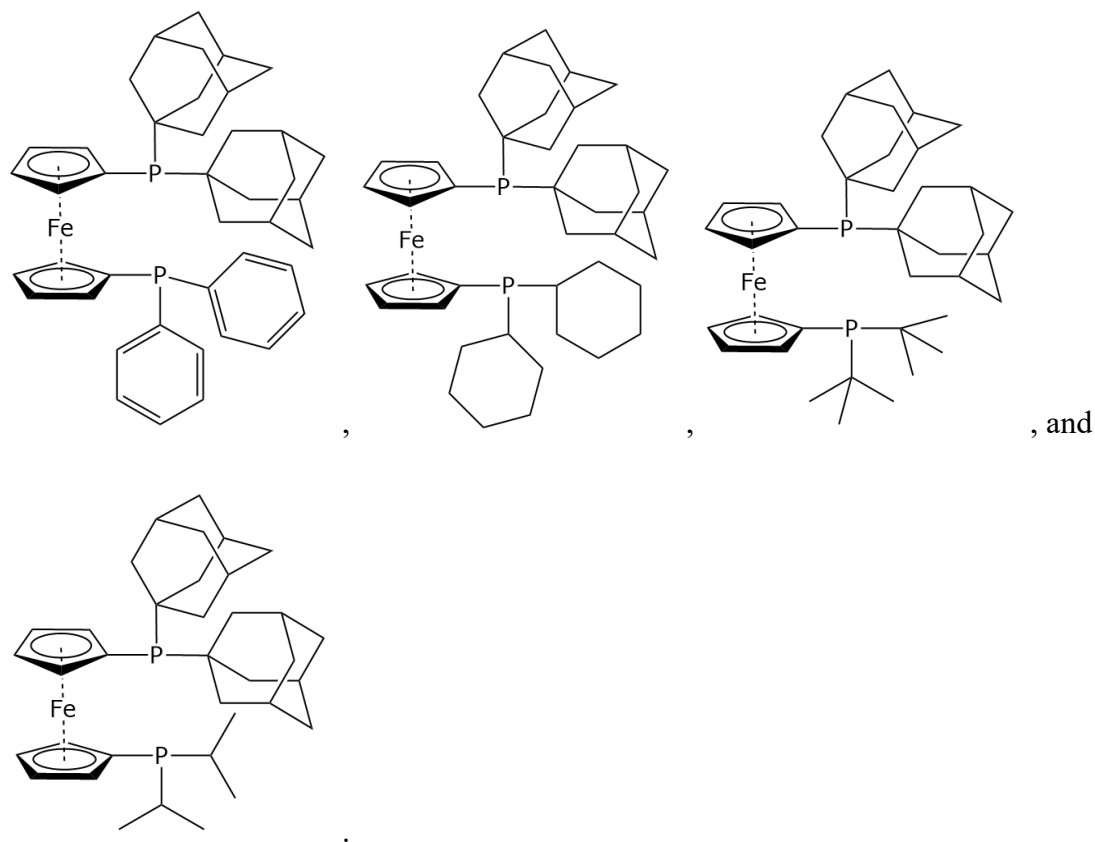
R₄ and R₅ are individually selected from the group consisting of H and C₁-C₁₂ alkyl, or R₄ and R₅ together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents; and

each optional substituent, when present, is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy.

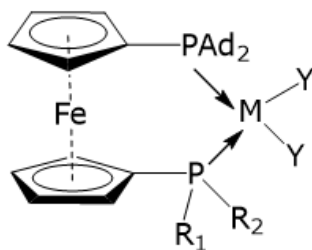
6. The ligand according to claim 5 wherein R₁ and R₂ are independently selected from the group consisting of phenyl, optionally substituted phenyl, cyclohexyl, isopropyl and *tert*-butyl.

7. The ligand according to either of claims 5 or 6 wherein R₁ and R₂ are each substituted phenyl.

8. A ligand according to either of claims 5 or 6, wherein the ligand is selected from the group consisting of



9. A precatalyst of formula II:



II

wherein

Ad is adamantyl;

R_1 and R_2 are independently selected from the group consisting of C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl;

R₄ and R₅ are individually selected from the group consisting of H and C₁-C₁₂ alkyl, or R₄ and R₅ together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents;

each optional substituent, when present, is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy;

M is a transition metal selected from Group 9 or Group 10; and

Y is halo.

10. The precatalyst according to claim 9 wherein R₁ and R₂ are independently selected from the group consisting of phenyl, optionally substituted phenyl, cyclohexyl, isopropyl and *tert*-butyl.

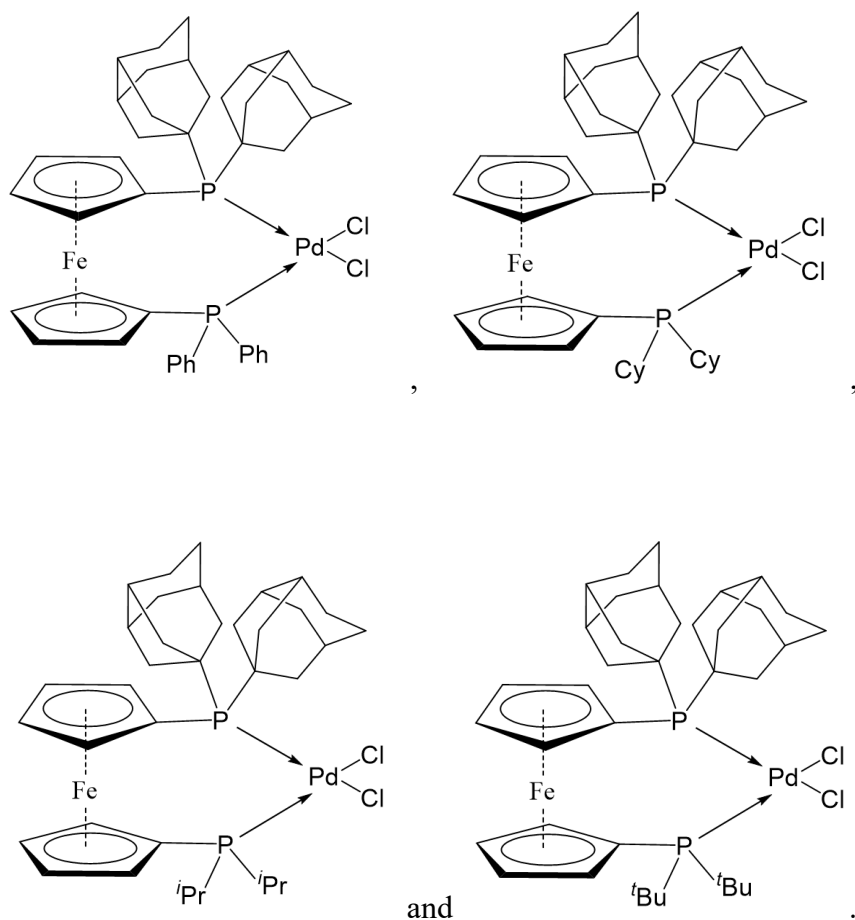
11. The precatalyst according to either of claims 9 or 10 wherein R₁ and R₂ are each substituted phenyl.

12. The precatalyst according to any of claims 9-11 wherein M is selected from the group consisting of Pd, Ni, Rh, Co, Ir and Pt.

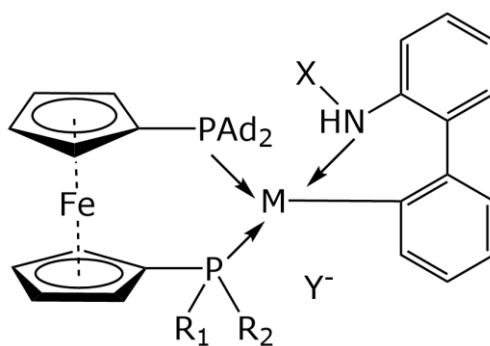
13. The precatalyst according to any of claims 9-12 wherein M is Pd.

14. The precatalyst according to any of claims 9-13 wherein Y is selected from chloro, bromo and iodo.

15. The precatalyst according to any of claims 9, 10 or 12-14 selected from the group consisting of



16. A precatalyst of Formula III:



III

wherein

Ad is adamantyl;

R_1 and R_2 are independently selected from the group consisting of C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, C_1 - C_{12} alkoxy, $-NR_4R_5$, and optionally substituted phenyl;

R₄ and R₅ are individually selected from the group consisting of H and C₁-C₁₂ alkyl, or R₄ and R₅ together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents;

each optional substituent, when present, is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy;

M is a transition metal selected from Group 9 or Group 10;

X is selected from the group consisting of H, C₁-C₄ alkyl and phenyl; and

Y⁻ is an anion selected from the group consisting of halide, triflate (OTf⁻), tetrafluoroborate (BF₄⁻), hexafluorophosphate (PF₆⁻), mesylate (OMs⁻), tosylate (OTs⁻), tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF⁻), hexafluoro antimonate (SbF₆⁻) and combinations thereof.

17. The precatalyst according to claim 16 wherein R₁ and R₂ are independently selected from the group consisting of phenyl, cyclohexyl, isopropyl and *tert*-butyl.

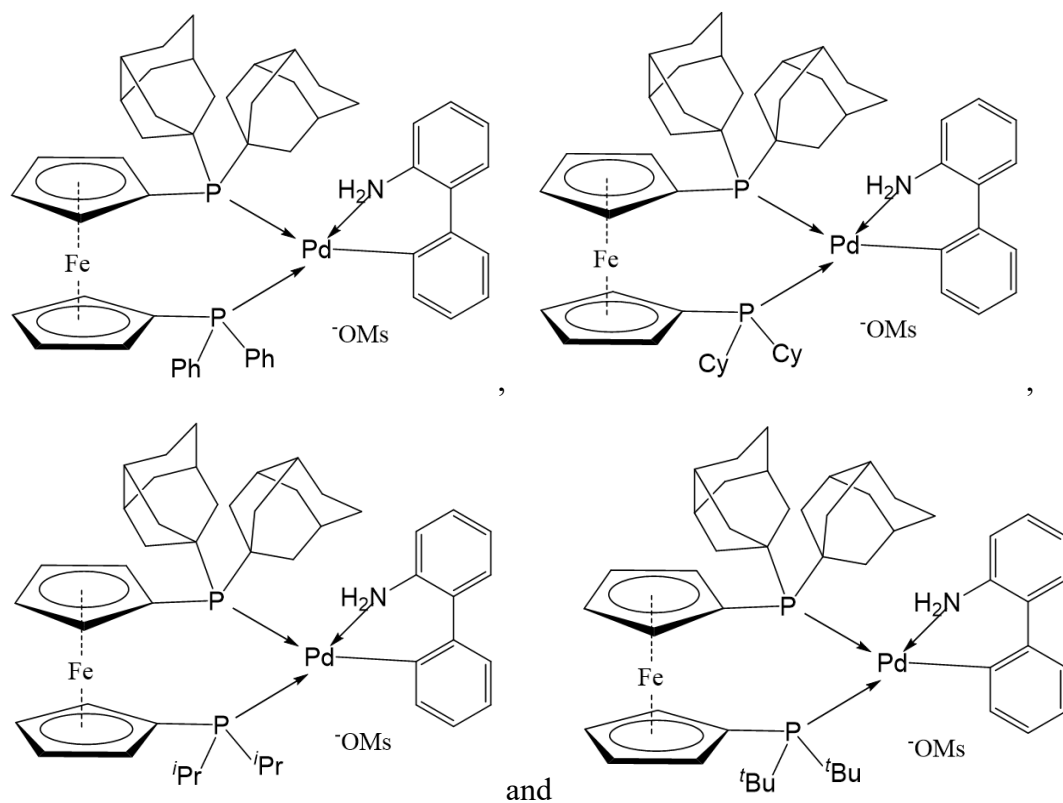
18. The precatalyst according to either of claims 16 or 17 wherein M is selected from the group consisting of Pd, Ni, Rh, Co, Ir and Pt.

19. The precatalyst according to any of claims 16-18 wherein M is Pd.

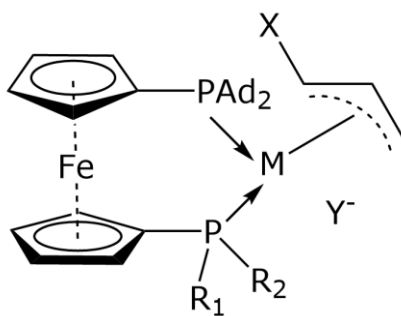
20. The precatalyst according to any of claims 16-19 wherein X is selected from the group consisting of H, methyl and phenyl.

21. The precatalyst according to any of claims 16-20 wherein Y⁻ is selected from the group consisting of Cl⁻, Br⁻, I⁻, OTf⁻, BF₄⁻, OMs⁻, OTs⁻, PF₆⁻, BArF⁻, and SbF₆⁻.

22. The precatalyst according to any of claims 16-21 selected from the group consisting of



23. A precatalyst of formula IV:



IV

wherein

Ad is adamantyl;

R₁ and R₂ are independently selected from the group consisting of C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, C₁-C₁₂ alkoxy, -NR₄R₅, and optionally substituted phenyl;

R₄ and R₅ are individually selected from the group consisting of H and C₁-C₁₂ alkyl, or R₄ and R₅ together can form a saturated or unsaturated 5- or 6-membered ring, the ring optionally including one or more additional heteroatoms selected from O, S and N, and one or more optional substituents;

wherein each optional substituent, when present, is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy;

M is a transition metal selected from Group 9 or Group 10;

X is selected from the group consisting of H, C₁-C₄ alkyl and phenyl; and

Y⁻ is an anion selected from the group consisting of halide, triflate (OTf⁻), tetrafluoroborate (BF₄⁻), hexafluorophosphate (PF₆⁻), mesylate (OMs⁻), tosylate (OTs⁻), tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF⁻), hexafluoro antimonate (SbF₆⁻) and combinations thereof.

24. The precatalyst according to claim 23 wherein R₁ and R₂ are independently selected from the group consisting of phenyl, cyclohexyl, isopropyl and *tert*-butyl.

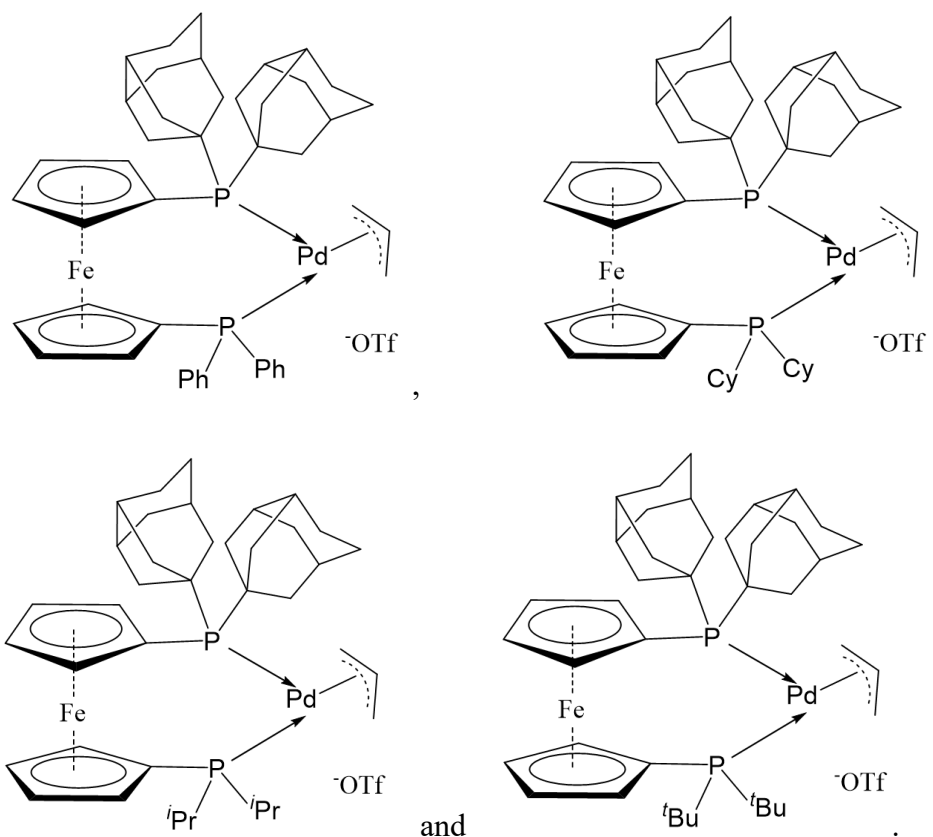
25. The precatalyst according to either of claims 23 or 24 wherein M is selected from the group consisting of Pd, Ni, Rh, Co, Ir and Pt.

26. The precatalyst according to any of claims 23-25 wherein M is Pd.

27. The precatalyst according to any of claims 23-26 wherein X is selected from the group consisting of H, methyl and phenyl.

28. The precatalyst according to any of claims 23-27 wherein Y⁻ is selected from the group consisting of Cl⁻, Br⁻, I⁻, OTf⁻, BF₄⁻, OMs⁻, OTs⁻, PF₆⁻, BArF⁻, and SbF₆⁻.

29. The precatalyst according to any of claims 23-28 selected from the group consisting of



30. A method for performing a metal-catalyzed P-C cross-coupling reaction comprising the steps of:

contacting a ligand according to any of claims 5-8 with a metal catalyst in the presence of an aromatic solvent and a base in a reaction vessel;

adding a first substrate of formula Ar-X', wherein Ar is aryl and X' is halo and a second substrate of formula R'₂PH, wherein R' is selected from the group consisting of C₁-C₁₀ alkyl and C₃-C₁₀ cycloalkyl, to the reaction vessel;

heating the reaction vessel to a temperature in the range from 100 °C to 200 °C for a time sufficient to form the carbon-phosphorous bond.

31. The method of claim 30 wherein the ligand is a ligand according to claim 8, the catalyst is a Pd catalyst.

32. A method for performing a metal-catalyzed C_{sp2} - C_{sp3} cross-coupling reaction comprising the steps of:

contacting a precatalyst of Formula II according to any of claims 9-15 with a first substrate and a second substrate in the presence of a solvent in a reaction vessel;

wherein the first substrate is of formula $Ar-X'$, wherein Ar is optionally substituted aryl or optionally substituted heteroaryl and X' is chloro or bromo or iodo;

wherein the second substrate is of formula $R'[M]$, wherein R' is selected from the group consisting of C_1 - C_{10} alkyl, C_1 - C_{10} fluoroalkyl and C_3 - C_{10} cycloalkyl, $[M]$ is selected from the group consisting of Li , MgX' , ZnX' and $B(OH)_2$ and related boron reagents, wherein X' is selected from the group consisting of chloro, bromo and iodo;

optionally, heating the reaction vessel and

allowing first substrate and the second substrate to react in the presence of the precatalyst for a time sufficient for the C_{sp2} - C_{sp3} cross-coupling to occur.

33. The method according to claim 32 wherein the first substrate is selected from the group consisting of optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thienyl, and optionally substituted furyl.

34. The method according to either of claims 32 or 33 wherein $[M]$ is Li , the solvent is toluene, and the reaction vessel is not heated.

35. The method according to either of claims 32 or 33 wherein $[M]$ is selected from MgX' and ZnX' , the solvent is tetrahydrofuran, and the reaction vessel is heated to $50^\circ C$.

36. The method according to either of claims 32 or 33 wherein $[M]$ is $B(OH)_2$, the solvent is toluene and the reaction vessel is heated to $100^\circ C$.