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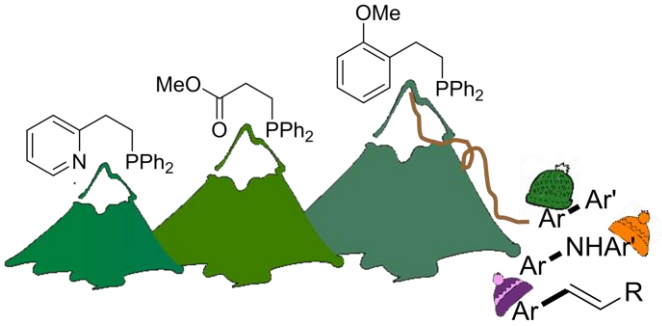

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Iron catalysis for the synthesis of ligands: exploring the products of hydrophosphination as ligands in cross-coupling

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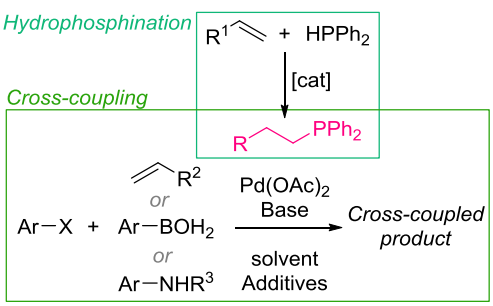
ABSTRACT

Catalytic hydrophosphination is a useful technique for the synthesis of phosphines, however, the phosphine products have been little exploited as ligands in catalysis. We have selected three phosphines prepared by iron catalyzed hydrophosphination and used them as ligands in a series of cross-coupling reactions: Heck, Suzuki-Miyaura and Buchwald-Hartwig. Rather than limit the chemistry to simple cross-coupling partners which are almost guaranteed to perform well in these transformations, industrially relevant substrates which are challenging from and electronic and/or steric perspective, along with substrates which contain several heteroatoms, were explored in order to gauge the true potential of these phosphine ligands.

1. Introduction

Phosphines, particularly when used as ligands in cross-coupling reactions for the synthesis of small organic motifs, form the bedrock of modern catalytic technologies.[1] Research into the development of novel phosphines plays a vital role in developing new catalytic reactions and the development of catalysis that implement ambitious substrates. This is particularly pertinent when considering the prevalence of phosphines in industrial transformations, not least in the pharmaceutical industry for the cross-coupling or organohalides and organometallic substrates.[2] With this in mind, hydrophosphination, the functionalization of an unsaturated bond with a primary or secondary phosphine, is an efficient method to make alkyl-phosphines.[3] The chemistry also benefits from high levels of functional group tolerance, allowing the synthesis of phosphines with a diverse range of groups including esters, halides and heterocycles, which is not always the case when implementing classical methodologies.[3g] Although hydrophosphination is an ideal methodology to make phosphines that could be used as ligands, there are limited studies of the applications of these structures in synthetic chemistry, in particular if we consider the hydrophosphination of activated alkenes, such as styrenes and acrylates, with diphenylphosphine, which are classic benchmarking substrates for catalytic hydrophosphination. Ethyldiphenylphosphines, the products of hydrophosphination of an alkene by diphenylphosphine, have been shown by Aguirre *et al*. to be effective ligands in methoxycarbonylation[4] and by Chou and Raines as reagents for use in chemical biology.[5] However, although the motifs can be prepared by hydrophosphination, in the aforementioned examples, classical synthetic methods were used. Our own research has shown that these ligand architectures can be easily prepared using room temperature hydrophosphination catalyzed by a low loading of a simple iron(III) complex, whilst Gaumont has used $FeCl_2$ at 30 mol% loading but in the absence of ligands.[6] The resulting phosphine products can be used in iron catalyzed Negishi cross-coupling.[7] Meanwhile Leung has shown that enantiopure cyclometalated phosphines prepared by palladium catalyzed hydrophosphination have potential as cancer therapeutics.[8] Leung and Pullarkat have elegantly shown that these cyclometalated phosphines can also be used to afford enantioselective hydrophosphination.[9] Beyond these limited examples, it is apparent that developing applications for hydrophosphination products remains an area of unmet need. We herein report the results of our investigations into the applicability of hydrophosphination products as ligands in catalysis, where a small selection of phosphines have been applied to palladium cross-coupling reactions involving challenging substrates (Scheme 1). We selected phosphines that we suspected would be suitable ligands in catalysis: phosphines with heteroatoms, which have the potential to stabilize the metal centre during catalysis.

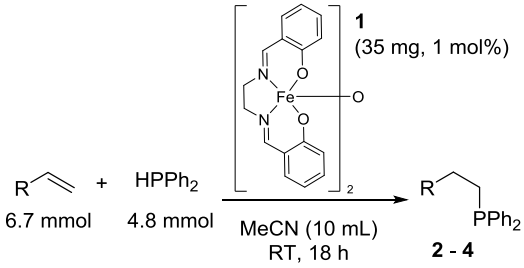


Scheme 1. Hydrophosphination and proposed use in cross-coupling.

2. Results and Discussion

2.1. Ligands

Using the air stable iron(III) complex **1**, three ligands that can easily be prepared on a large scale that we postulated would have interesting electronic and coordinating properties, were synthesized (pro-ligands **2**, **3**, **4**, Scheme 2). In this case, all the ligands were isolated in high yield (at least 1 g of each material was prepared). The reagents used to prepare these phosphines are all commercially available and, although Schlenk techniques were employed in this particular synthesis, we have already shown that iron catalyzed hydrophosphination can be performed in a round bottom flask with a balloon of N_2, with $HPPh_2$ dispensed from a commercially available Sure/Seal™ bottle.[6c] Once isolated using silica gel column chromatography on the bench, these ligands are stable in air in the solid state for several weeks. As previously stated, pro-ligand **3** has been used in methoxycarbonylation chemistry[4] and analogues of **4** have been used as reagents in synthesis,[5] but **2** to **4** have not been exploited in cross-coupling.



Scheme 2. Ligands prepared using iron catalyzed hydrophosphination.

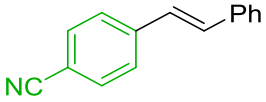
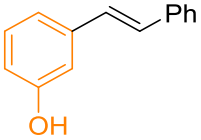
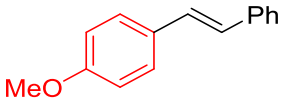
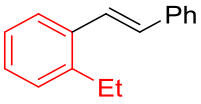
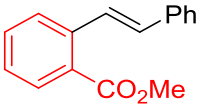
2.2. Cross-coupling methodology

Our approach is to use a general set of reaction conditions that can be applied to each class of cross-coupling. This builds upon previous studies of this type[10] and uses reagents, solvents and additives that are not only commercially available, but that are, as realistically as possible, close to industrial conditions that can be reproduced on a small scale (1 mmol) in a research laboratory.[11] The substrates chosen test a range of parameters which are necessary when considering 'real-life' examples of cross-coupling on scale.[12,10a,10b,10d,10e] This includes strongly electron withdrawing and donating groups, unprotected alcohols, amides, unmasked aldehydes, sterically encumbered substrates, fluoro- and heterocycle-containing substrates. Both coupling partners (aryl halide and organometallic reagent) were tested under these limiting conditions. We decided to benchmark our ligands against PPh_3, which, although it does not have the potential for chelating stability *via* a heteroatom, it is the simplest and most inexpensive mono-phosphine which can be readily employed by industry.

2.2.1. Heck reactions

Investigations were initiated by studying the proficiency of the pro-ligands in Heck cross-coupling.[13] Rather than select simple substrates, a range of sterically and electronically onerous aryl bromides were employed. 4-Bromobenzonitrile is the most facile coupling partner to bench-mark the reactivity (Table 1, Entry 1), followed by 3-bromophenol, which is perceived to be a moderately challenging substrate for electronic reasons, not least due to the presence of the free hydroxyl (Entry 2). Electron rich 4-bomoanisole (Entry 3), sterically encumbered 1-bromo-2-ethylbenzene (Entry 4) and methyl-2-bromobenzoate, which is problematic from both steric and electronic standpoints (Entry 5), were cross-coupled with styrene (a relatively simple alkene as an entry point into Heck chemistry). It is clear that phosphine **3** is not a good ligand, surpassed by PPh_3 and phosphines **2** and **4**. Phosphinoester **4**, matches the reactivity of PPh_3 for the simplest Heck reaction (Table 1, Entry 1) and when using the most challenging aryl bromide (Table 1, Entry 5). The phenol coupling partner performs best with **2** (Entry 2) and in all cases the yield of the 2-ethyl substituted product is poor (Entry 4). However, the proficiency of **4** surpasses that of all the other pro-ligands when cross-coupling is performed with the electron rich aryl bromide (Entry 3).

Table 1. Aryl bromide substrate scope cross-coupling with styrene.

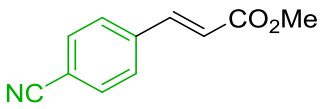
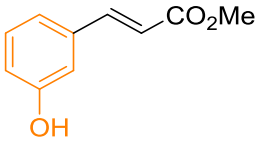
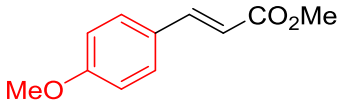
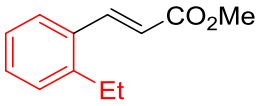
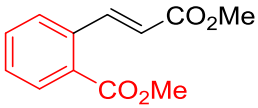
Entry	Product	Phosphine PPh_3	**2**	**3**	**4**
1		**92**	11	64	**95**
2		45	**58**	7	23
3		13	27	13	**42**
4		18	16	7	10
5		**66**	36	53	**65**

General reaction conditions: aryl bromide (1 mmol), alkene (1.2 mmol), $Pd(OAc)_2$ (2 mol%), phosphine (4 mol%), tetrabutylammonium chloride (10 mol%), $CyNMe_2$ (1.5 eq), DMA (10 mL/g), 80 °C, 24 h. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an analytical standard.[14]

Increasing the complexity of the alkene coupling reagent starts to reveal a distinct improvement in reactivity when using hydrophosphination products (Table 2). 4-Bromobenzonitrile is

efficiently cross coupled using **3** and **4** (Entry 1), the phenol and 4-methoxy substrates perform best using **2** (Entries 2 and 3), whilst PPh_3 remains the most competent ligand for the ester (Entry 5). Although it is worth noting that **4** gives the desired product with less than a 10% deficit of yield compared to PPh_3. The sterically encumbered 2-ethyl substituted product forms in poor yield, irrespective of ligand (Entry 4).

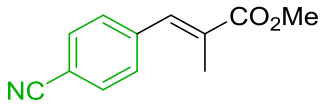
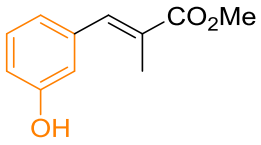
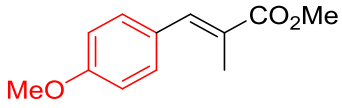
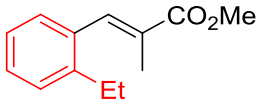
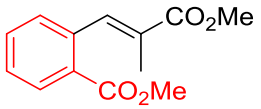
Table 2. Aryl bromide substrate scope cross-coupling with methylacrylate.

Entry	Product	Phosphine			
		PPh_3	2	3	4
1		53	24	**94**	**98**
2		36	**46**	7	26
3		18	**47**	17	31
4		8	13	0	15
5		**52**	45	16	43

General reaction conditions: aryl bromide (1 mmol), alkene (1.2 mmol), $Pd(OAc)_2$ (2 mol%), phosphine (4 mol%), tetrabutylammonium chloride (10 mol%), $CyNMe_2$ (1.5 eq), DMA (10 mL/g), 80 °C, 24 h. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an analytical standard.[15]

Next, methylmethacrylate was used, screening the same range of variety aryl bromides (Table 3). Surprisingly poor yields are achieved with 4-bromobenzonitrile (Entry 1) and PPh_3 substantially out-performs all the other ligands when 3-bromophenol is used in cross-coupling (Entry 2). Ligand **2** gives substantially higher yield when 4-bromoanisole is employed (Entry 3) and although the yield is very low, eight times the yield of the 2-ethylbenzene product is achieved with this ligand (Entry 4). Again, PPh_3 gives the best yield of diester product (Entry 5). It should be noted that for many of the examples (Tables 1 to 3), the spectroscopic yields obtained are competitive or in some cases surpass those reported with commercially available but expensive Pd(0) and Pd(II) pre-catalysts.[10c]

Table 3. Aryl bromide substrate scope cross-coupling with methylmethacrylate.

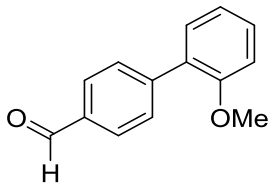
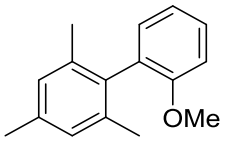
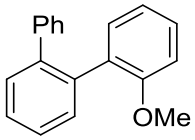
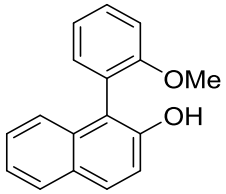
Entry	Product	Phosphine			
		PPh_3	**2**	**3**	**4**
1		20	7	25	**26**
2		**84**	36	2	52
3		16	**47**	9	13
4		2	**16**	10	7
5		**43**	7	25	22

General reaction conditions: aryl bromide (1 mmol), alkene (1.2 mmol), $Pd(OAc)_2$ (2 mol%), phosphine (4 mol%), tetrabutylammonium chloride (10 mol%), $CyNMe_2$ (1.5 eq), DMA (10 mL/g), 80 °C, 24 h. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an analytical standard.[16,10c]

2.2.2. Suzuki-Miyaura cross-coupling

We then investigated the proficiency of our pro-ligands in Suzuki-Miyaura cross-coupling.[17a-c,13d,17d] Once more, we do not want to study reactivity with simple substrates guaranteed to demonstrate exceptional reactivity irrespective of ligand system; we wish to use challenging substrates under industrially relevant conditions. Starting with a sterically and electronically demanding aryl boronic acid, 2-methoxyphenyl boronic acid, we carried out the cross-coupling with a selection of aryl bromides (Table 4). Use of the bromide allows for more facile cross-coupling, but the functionality selected provides an extra level of difficulty in synthesis: an aldehyde, 2,3,5-methyl, 2-phenyl, and naphthol substituted reagents were implemented in the reaction. In general, **2** out-performs the other ligands with the exception of PPh_3 in the cross-coupling of 4-bromobenzaldehyde (Entry 1). Overall **3** appears to be a poor ligand for this Suzuki-Miyaura cross-coupling.

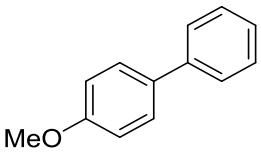
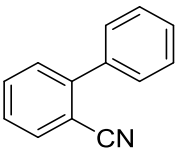
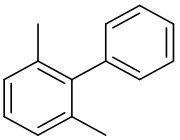
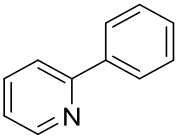
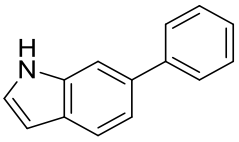
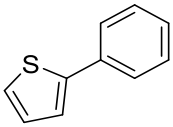
Table 4. Aryl bromide substrate scope cross-coupling with 2-methoxyphenyl boronic acid.

Entry	Product	Phosphine PPh$_3$	**2**	**3**	**4**
1		**94**	76	49	80
2		36	**44**	13	28
3		72	**87**	60	84
4		42	**50**	38	46

General reaction conditions: aryl bromide (1 mmol), aryl boronic acid (1.2 mmol), $Pd(OAc)_2$ (1 mol%), phosphine (2 mol%), K_2CO_3 (1.5 mmol), $MeCN/H_2O$ (2 mL, 1:1 v/v), 60 °C, 1 h. All yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an analytical standard.[18]

Aryl chlorides are highly desirable substrates for Suzuki-Miyaura cross-coupling due to the larger number of compounds that are commercially available. However, irrespective of functionality on the aryl ring, the aryl chloride bond does not undergo oxidative addition as readily as an aryl bromide bond making the aryl-aryl bond forming process overall more difficult. We tested aryl chlorides with a range of properties including heterocycles; vital functionality in the preparation of pharmaceutically relevant compounds (Table 5). These were cross coupled with phenylboronic acid. Across all substrates, the hydrophosphination products performed better than PPh_3; notably pro-ligand **2** furnishes almost double the yield of product compared to the other ligands when 2-chloropyridine and 2-chlorothiophene are employed (Entries 4 and 6), generating 61% and 62% respectively (compared to 28% and 25% when PPh_3 is used). 6-Chloroindole is a poor substrate, giving low yield of biaryl with all ligands. However, the hydrophosphination ligands generate a moderately higher yield compared to PPh_3, where the yield is negligible; the highest yield of 6-phenylindole (Entry 5) is achieved with **3**. We are pleased to report cross-coupling with 2-chlorothiophene, where the yield of product using ligand **2** is around double that achieved using the other ligands (Entry 6).

Table 5. Aryl chloride substrate scope cross-coupling with phenylboronic acid.

Entry	Product	Time (h)	Phosphine PPh$_3$	**2**	**3**	**4**
1		24	2	6	7	10
		48	38	**43**	12	31
2		24	0	18	14	17
		48	3	**22**	19	17
3		24	11	18	14	9
		48	14	**23**	20	22
4		24	23	33	34	26
		48	28	**61**	34	40
5		24	7	12	30	11
		48	9	19	**32**	17
6		24	12	48	22	25
		48	25	**62**	26	31

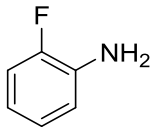
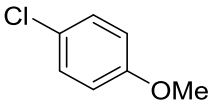
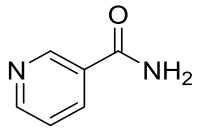
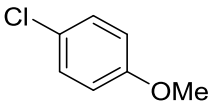
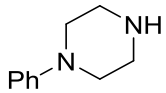
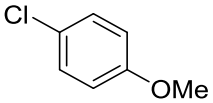
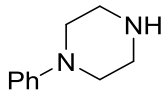
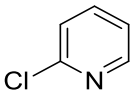
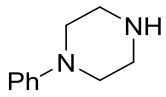
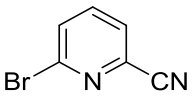
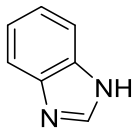
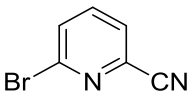
General reaction conditions: aryl chloride (1 mmol), phenylboronic acid (1.2 mmol), $Pd(OAc)_2$ (1 mol%), phosphine (2 mol%), K_2CO_3 (1.5 mmol), $MeCN/H_2O$ (2 mL, 1:1 v/v), 60 °C, 24/48 h. All yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an analytical standard.[19]

2.2.3. Buchwald-Hartwig cross-coupling

Finally, for Buchwald-Hartwig cross-coupling,[20] we initially targeted electron rich aryl chlorides; difficult both in terms of oxidative addition of the starting material and reductive elimination of the product. 4-Chloroanisole, gives poor yield of product irrespective of ligand and when a stronger base (NaO^tBu) is used in the reaction (Table 1, Entry 1, parentheses) there is no real increase in yield. Ligand **2** does give approximately double the amount of product, but this remains low at 35%. For comparison, changing to the aryl bromide (4-bromoanisole) would be envisioned to give higher yield due to the weaker aryl-halide bond, but this is not the case and only a moderate increase in yield is obtained. This result is in line with the anticipated difficulty associated with reductive elimination of such electron rich arenes.

We are particularly interested in maintaining a high level of activity in the presence of multiple heteroatoms, which decrease the efficacy of the catalyst and often necessitate higher catalyst loadings. Pleasingly, amination to form multiple-heteroatom containing products does work well with all ligands at 1 mol% $Pd(OAc)_2$ and 2 mol% ligand loading (Entries 4 to 6). But it is clear that, once again, **2** is a superior pro-ligand for this transformation, in particular note the much higher yield achieved when coupling *N*-phenylpiperazine to 2-chloropyridine (Entry 4).

Table 6. Aryl halide and amine cross-coupling substrate scope.

Entry	Amine	Halide	Phosphine PPh_3	**2**	**3**	**4**
1[a]			11 (16)	19 (**35**)	18 (12)	18 (15)
2			14	15	15	14
3[b]			15 (28)	24 (35)	21 (29)	18 (30)
4[b]			62	**92**	77	57
5[b]			77	**90**	84	76
6[b]			49	**60**	56	58

General reaction conditions: amine (1 mmol), aryl halide (1.2 mmol), $Pd(OAc)_2$ (1 mol%), phosphine (2 mol%), Cs_2CO_3 (1.4 mmol), tert-amyl alcohol (0.5 M), 110 °C, 18 h. All yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an analytical standard. [a]Result in parentheses depict change in reaction conditions: 4-bromoanisole (1 mmol), NaO^{t}Bu (1.4 eq), toluene. [b]Amine (1 mmol), aryl halide (1.2 mmol), $Pd(OAc)_2$ (1 mol%), phosphine (2 mol%), NaO^{t}Bu (1.4 mmol), toluene (0.5 M), 110 °C, 18 h. All yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an analytical standard.[21]

We assume that the benefits of using **2** lie in the enhanced electronic properties proffered by the electron donating methoxy group. We also postulated that the coordinating ability of the heteroatom may help to stabilize reactive intermediates. Complexation of two equivalents of **2** with $Pd(OAc)_2$ results in a centrosymmetric mononuclear complex (**5**, Figure 1) with the phosphines ligated in a *trans* geometry. In the solid state, no interactions between the metal centre and the methoxy groups are observed, however, we envisage that coordination could happen in solution and would not be restricted by ring strain of the resulting metallacycle.

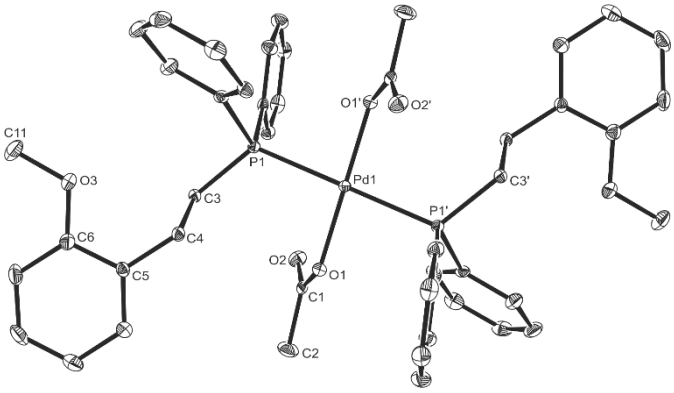


Figure 1. Complex **5** is formed when **2** is ligated to $Pd(OAc)_2$. Solvent and hydrogen atoms have been omitted for clarity. Ellipsoids are represented at 30% probability. Atoms with primed labels are related to those in the asymmetric unit by the 1-x, 1-y, -z symmetry operation.

3. Conclusions

Overall, 2-methoxy substituted phosphine ligand **2** has demonstrated itself to be a good ligand across a wide variety of cross-coupling reactions involving challenging substrates. In the vast majority of cases, it out-performs PPh_3. The phosphinoester ligand, **4**, also shows good reactivity that appears to be complementary to that of **2**, giving good yields in reactions which are otherwise poor with **2** or even PPh_3. Somewhat surprisingly, the 2-pyridyl ligand, **3**, is not a good ligand at facilitating the cross-coupling of troublesome substrates. We anticipated that transient coordination by the pyridyl group may help to stabilize intermediates during the catalytic cycle, thus making it a good ligand for catalysis. Unfortunately, this coordinating ability appears to be inconsequential for this particular ligand and, coupled with the solid state structure **5**, could indicate that electronics are more important. However, ethylphosphines prepared *via* hydrophosphination clearly have potential as ligands in chemical synthesis; this study has only just started to demonstrate their potential.

4. Experimental

Phosphines were prepared using methods previously described.[6,7] Reaction conditions are as described in table footnotes. The reagents and analytical standard were weighed in air into sealable reaction vials and heated to the desired temperature for the stated reaction time in a pre-heated oil bath. Once the reaction mixture had cooled to room temperature a 30 µL aliquot was removed and the sample diluted with $CDCl_3$ and analyzed by ^{1}H NMR. Yields are based on the uptake of starting material and/or the formation of the known reaction product (all products are either commercially available or reported in the literature, see Tables 1 to 6 for references). See Supporting Information for crude NMR spectra.

(2-Methoxyphenethyl)diphenylphosphane (**2**)

White solid, 1.17 g (76%). ^{1}H NMR (300 MHz, 298 K, $CDCl_3$) δ 7.64 - 7.59 (m, 2H), 7.47 - 7.42 (m, 6H), 7.32 - 7.23 (m, 2H), 7.01 (app. td, 1H, J = 7.4, 1.0 Hz), 6.93 (d, 1H, J = 8.1 Hz) 3.88 (s, 3H), 2.94 - 2.86 (m, 2H), 2.52 - 2.47 (m, 2H); ^{13}C{^{1}H} NMR

(75 MHz, 298 K, $CDCl_3$) δ 157.3, 138.7 (d, J = 12.7 Hz), 132.8 (d, J = 18.3 Hz), 131.0 (d, J = 13.6 Hz), 129.6, 128.4 (d, J = 6.5 Hz), 127.4, 120.4, 110.2, 55.1, 28.4 (d, J = 12.1 Hz), 27.2 (d, J = 18.3 Hz); $^{31}P\{^1H\}$ NMR (121.5 MHz, 298 K, $CDCl_3$) δ −14.5; IR (solid) ν 3059, 2948, 2922, 2902, 2830, 1600, 1583, 1490, 1464, 1432, 852, 742, 696 cm^{-1}; HRMS (EI) $[M + H]^+$ 321.1403 (calcd.), 321.1404 (obs.); m.p. 67 °C.

2-(2-(Diphenylphosphanyl)ethyl)pyridine (**3**)

White solid, 1.17 g (84%). ^1H NMR (300 MHz, 298 K, $CDCl_3$) δ 8.56 (d, 1H, J = 4.1 Hz), 7.62 - 7.43 (m, 5H), 7.43 - 7.29 (m, 6H), 7.20 - 7.03 (m, 2H), 3.05-2.82 (m, 2H), 2.64 - 2.48 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, 298 K, $CDCl_3$) δ 161.9 (d, J = 13.3 Hz), 149.5, 138.5 (d, J = 13.0 Hz), 136.4, 132.9 (d, J = 18.6 Hz), 128.7, 128.6 (d, J = 6.8 Hz), 122.8, 121.3, 34.7 (d, J = 17.7 Hz), 28.1 (d, J = 12.4 Hz); $^{31}P\{^1H\}$ NMR (121.5 MHz, 298 K, $CDCl_3$) δ −14.6; IR (solid) ν 3046, 2920, 2949, 1590, 1567, 1470, 1479, 1433, 843, 781, 749, 735, 723, 697, cm^{-1}; HRMS (EI) $[M + H]^+$ 292.1250 (calcd.), 292.1249 (obs.); m.p. 68-69 °C.

Methyl 3-(diphenylphosphanyl)propanoate (**4**)

Colourless oil, 1.00 g (80%). ^1H NMR (300 MHz, 298 K, $CDCl_3$) δ 7.50 - 7.47 (m, 4H), 7.37 - 7.35 (m, 6H), 3.66 (s, 3H), 2.45 - 2.42 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, 298 K, $CDCl_3$) δ 173.5 (d, J = 14.9 Hz), 137.7 (d, J =12.1 Hz), 132.7 (d, J = 18.3 Hz), 128.8, 128.5 (d, J = 6.5 Hz), 51.7, 30.5 (d, J = 19.3 Hz), 22.9 (d, J = 11.5 Hz); $^{31}P\{^1H\}$ NMR (121.5 MHz, 298 K, $CDCl_3$) δ −14.9; IR (solid) ν 3054, 2950, 1735, 1585, 1481, 1433, 1354, 848, 736, 694 cm^{-1}; HRMS (EI) $[M + H]^+$ 273.1039 (calcd.), 273.1040 (obs.)

Complex **5**

Isolated as yellow plates. Crystal data for for $C_{48}H_{52}Cl_4O_6P_2Pd$, $2(C_1H_2Cl_2)$ (**5**, CCDC 1496173). M = 1035.03, λ = 0.71073 Å, monoclinic, space group P1 21/c1, a = 11.6809(5), b = 24.1157(9), c = 8.9898(4)Å, α = 90, β = 110.174(5), γ = 90°, U = 2376.99(18) $Å^3$, Z = 2, D_c = 1.446 g cm^{-3}, μ = 0.730 mm^{-1}, F(000) = 1064. Crystal size = 0.516 × 0.482 × 0.11 mm, unique reflections = 5441 [$R_{(int)}$ = 0.0324], observed reflections [I>2σ(I)] = 4910, data/restraints/parameters = 1064.0/0/279. Observed data; R1 = 0.0422, wR2 = 0.0814. All data; R1 = 0.0490, wR2 = 0.0798. Max peak/hole = 0.439 and −0.693 $eÅ^{-3}$, respectively.

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References

(1) For an overview see: a) Corbridge, D. E. C. *Phosphorus : an outline of its chemistry, biochemistry and technology*; 2nd ed. ed.; Elsevier: Amsterdam Oxford, 1980; b) *Phosphorus Compounds: Advanced Tools in Catalysis and Material Sciences*; Springer: Dordrecht, 2011; Vol. 37; c) Behr, A. *Applied homogeneous catalysis*; Wiley-VCH: Weinheim, 2012; d) Kamer, P. C. J.; Leeuwen, P. W. N. M. v. *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*; Wiley, 2012.

(2) *Applied Cross-Coupling Reactions*; Springer: Berlin, Heidelberg, 2013; Vol. 80.

(3) a) Delacroix, O.; Gaumont, A. C. *Curr. Org. Chem.* **2005**, *9*, 1851; b) Glueck, D. S. *Chemistry - A European Journal* **2008**, *14*, 7108; c) Glueck, D. S. In *C-X Bond Formation*; Vigalok, A., Ed. 2010; Vol. 31, p 65; d) Pullarkat, S. A.; Leung, P.-H. In *Hydrofunctionalization*; Ananikov, V. P., Tanaka, M., Eds. 2013; Vol. 43, p 145; e) Rosenberg, L. *ACS Catal.* **2013**, *3*, 2845; f) Koshti, V.; Gaikwad, S.; Chikkali, S. H. *Coord. Chem. Rev.* **2014**, *265*, 52; g) Wauters, I.; Debrouwer, W.; Stevens, C. V. *Beilstein J. Org. Chem.* **2014**, *10*, 1064; h) Rodriguez-Ruiz, V.; Carlino, R.; Bezzenine-Lafollee, S.; Gil, R.; Prim, D.; Schulz, E.; Hannedouche, J. *Dalton Trans.* **2015**, *44*, 12029; i) Pullarkat, S. A. *Synthesis* **2016**, *48*, 493.

(4) Aguirre, P. A.; Lagos, C. A.; Moya, S. A.; Zuniga, C.; Vera-Oyarce, C.; Sola, E.; Peris, G.; Bayon, J. C. *Dalton Trans.* **2007**, 5419-5426.

(5) Chou, H.-H.; Raines, R. T. *J. Am. Chem. Soc.* **2013**, *135*, 14936-14939.

(6) a) Routaboul, L.; Toulgoat, F.; Gatignol, J.; Lohier, J.-F.; Norah, B.; Delacroix, O.; Alayrac, C.; Taillefer, M.; Gaumont, A.-C. *Chem. Eur. J.* **2013**, *19*, 8760-8764; b) Gallagher, K. J.; Webster, R. L. *Chem. Commun.* **2014**, *50*, 12109-12111; c) Gallagher, K. J.; Espinal-Viguri, M.; Mahon, M. F.; Webster, R. L. *Adv. Synth. Catal.* **2016**, *358*, 2460-2468.

(7) Brown, C. A.; Nile, T. A.; Mahon, M. F.; Webster, R. L. *Dalton Trans.* **2015**, *44*, 12189-12195.

(8) a) Song, Y. C.; Vittal, J. J.; Srinivasan, N.; Chan, S. H.; Leung, P. H. *Tetrahedron: Asymmetry* **1999**, *10*, 1433-1436; b) Chew, R. J.; Sepp, K.; Li, B.-B.; Li, Y.; Zhu, P.-C.; Tan, N. S.; Leung, P.-H. *Adv. Synth. Catal.* **2015**, *357*, 3297-3302; c) Jia, Y.-X.; Chew, R. J.; Li, B.-B.; Zhu, P.; Li, Y.; Pullarkat, S. A.; Tan, N. S.; Leung, P.-H. *Dalton Trans.* **2015**, *44*, 17557-17564; d) Li, B.-B.; Jia, Y.-X.; Zhu, P.-C.; Chew, R. J.; Li, Y.; Tan, N. S.; Leung, P.-H. *Eur. J. Med. Chem.* **2015**, *98*, 250-255; e) Chew, R. J.; Leung, P.-H. *Chemical Record* **2016**, *16*, 141-158.

(9) a) Huang, Y.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Inorg. Chem.* **2012**, *51*, 2533-2540; b) Gan, K.; Sadeer, A.; Xu, C.; Li, Y.; Pullarkat, S. A. *Organometallics* **2014**, *33*, 5074-5076; c) Yang, X.-Y.; Gan, J. H.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Dalton Trans.* **2015**, *44*, 1258-1263; d) Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2015**, *34*, 1582-1588; e) Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Commun.* **2016**, *52*, 4211-4214.

(10) a) Moseley, J. D.; Murray, P. M.; Turp, E. R.; Tyler, S. N. G.; Burn, R. T. *Tetrahedron* **2012**, *68*, 6010-6017; b) Murray, P. M.; Tyler, S. N. G.; Moseley, J. D. *Chimica Oggi-Chemistry Today* **2012**, *30*, 15-18; c) Murray, P. M.; Bower, J. F.; Cox, D. K.; Galbraith, E. K.; Parker, J. S.; Sweeney, J. B. *Org. Proc. Res. Dev.* **2013**, *17*, 397-405; d) Murray, P. M.; Tyler, S. N. G.; Moseley, J. D. *Org. Proc. Res. Dev.* **2013**, *17*, 40-46; e) Moseley, J. D.; Murray, P. M. *J. Chem. Technol. Biotechnol.* **2014**, *89*, 623-632.

(11) a) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027-3043; b) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825-1864; c) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177-2250; d) Biajoli, A. F. P.; Schwalm, C. S.; Limberger, J.; Claudino, T. S.; Monteiro, A. L. *J. Braz. Chem. Soc.* **2014**, *25*, 2186-2214.

(12) a) Ackermann, L. *Synlett* **2007**, 507-526; b) John, A.; Shaikh, M. M.; Butcher, R. J.; Ghosh, P. *Dalton Trans.* **2010**, *39*, 7353-7363; c) Lundgren, R. J.; Stradiotto, M. *Chem. Eur. J.* **2012**, *18*, 9758-9769.

(13) Introductory reviews: a) De Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed.* **1994**, *33*, 2379-2411; b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066; c) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651-2710; d) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609-679.

(14) a) Xiong, Z.; Wang, N.; Dai, M.; Li, A.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3337-3340; b) Lion, C. J.; Matthews, C. S.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2005**, *48*, 1292-1295; c) Tobisu, M.; Hyodo, I.; Onoe, M.; Chatani,

N. *Chem. Commun.* **2008**, 6013-6015; d) Alacid, E.; Nájera, C. *J. Org. Chem.* **2009**, *74*, 2321-2327; e) Shahzad, S. A.; Wirth, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 2588-2591.

(15) a) Gurtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107-3112; b) Tan, E. W.; Chan, B.; Blackman, A. G. *J. Am. Chem. Soc.* **2002**, *124*, 2078-2079; c) Zhang, Z.; Wang, Z. *J. Org. Chem.* **2006**, *71*, 7485-7487; d) Dai, M.; Sarlah, D.; Yu, M.; Danishefsky, S. J.; Jones, G. O.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 645-657; e) Huang, W.-J.; Chen, C.-C.; Chao, S.-W.; Lee, S.-S.; Hsu, F.-L.; Lu, Y.-L.; Hung, M.-F.; Chang, C.-I. *ChemMedChem* **2010**, *5*, 598-607.

(16) a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989-7000; b) Li, J.; Qian, W.; Zhang, Y. *Tetrahedron* **2004**, *60*, 5793-5798.

(17) Introductory reviews: a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168; b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633-9695; c) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419-2440; d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

(18) a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696; b) Zhang, G. *Synthesis* **2005**, 537-542; c) Dichiarante, V.; Fagnoni, M.; Albini, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 6495-6498; d) Tempesti, T. C.; Pierini, A. B.; Baumgartner, M. T. *New J. Chem.* **2009**, *33*, 1523-1528.

(19) a) Lerebours, R.; Wolf, C. *Synthesis* **2005**, 2287-2292; b) Moreno-Mañas, M.; Pleixats, R.; Serra-Muns, A. *Synlett* **2006**, 3001-3004; c) Yang, Q.; Ma, S.; Li, J.; Xiao, F.; Xiong, H. *Chem. Commun.* **2006**, 2495-2497; d) Alacid, E.; Nájera, C. *Org. Lett.* **2008**, *10*, 5011-5014; e) Ackermann, L.; Potukuchi, H. K.; Althammer, A.; Born, R.; Mayer, P. *Org. Lett.* **2010**, *12*, 1004-1007; f) Pascanu, V.; Hansen, P. R.; Bermejo Gómez, A.; Ayats, C.; Platero-Prats, A. E.; Johansson, M. J.; Pericàs, M. À.; Martín-Matute, B. *ChemSusChem* **2015**, *8*, 123-130.

(20) Introductory reviews: a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125-146; b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400-5449; c) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599-1626; d) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 5142-5148; e) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361; f) Fischer, C.; Koenig, B. *Beilstein J. Org. Chem.* **2011**, *7*, 59-74.

(21) a) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576-6583; b) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 2929-2932; c) Hoi, K. H.; Çalimsiz, S.; Froese, R. D. J.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2012**, *18*, 145-151.

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