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Simple tricyclohexylphosphine–palladium complexes as efficient catalysts for the Stille coupling of deactivated aryl chlorides

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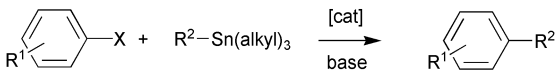
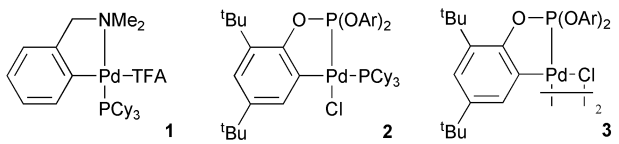
Simple, inexpensive tricyclohexylphosphine adducts of palladium show the highest activity yet observed in the Stille coupling of non-activated and deactivated aryl chlorides.

The Stille coupling of aryl halides (Scheme 1) is a very useful method for the synthesis of new carbon–carbon bonds which has enjoyed wide application due to the air and moisture stability of the organostannane reagents and the good functional group tolerance of the reaction.[1] A major limitation with this procedure is that it is usually necessary to use comparatively expensive aryl iodide or bromide substrates. The ideal substrates are aryl chlorides as they are much cheaper and more readily available. Unfortunately they are far more difficult to activate than their bromide or iodide counterparts, due to the comparatively high C–Cl bond strength.[2]



Scheme 1 The Stille coupling of aryl halides, R^2 = aryl, vinyl.

While there has been much effort expended on the search for new catalysts that are able to mediate the related Suzuki couplings of aryl chlorides,[3] very little progress has been made with the Stille reaction. Indeed, as far as we are aware, only two catalyst systems have been developed that show any real activity in the coupling of deactivated (electron-rich) substrates. These are one based on Pd–P^{t}Bu$_3$ developed by Fu and coworkers,[4] and a Pd–imidazolium salt-based system reported by Grasa and Nolan.[5] We have recently found that the PCy$_3$-containing complexes **1** and **2**, the latter of which is typically formed *in situ* from **3** and PCy$_3$, show good and excellent activity respectively in the Suzuki coupling of aryl chlorides.[6] We now find that not only the PCy$_3$ complexes shown, but also simple systems formed *in situ* from palladium acetate give, to the best of our knowledge, the highest activity yet reported in the Stille coupling of deactivated and non-activated aryl chlorides.



Ar = C$_6$H$_3$2,4-^{t}Bu$_2$

4-Chloroanisole was chosen as the test substrate for the optimisation studies in the coupling with PhSnBu$_3$ as it is electronically deactivated and thus resistant to oxidative addition and consequently very reluctant to enter a catalytic manifold. Therefore any catalyst that can activate this challenging substrate would be expected to be active with a broad spectrum of aryl chlorides. The solvents investigated were toluene and 1,4-dioxane while the bases studied were K_2CO_3, K_3PO_4, KF, K_3PO_4/KF (1:1), Cs_2CO_3 and CsF. The catalysts investigated were the preformed complex **1** and the catalyst formed *in situ* from complex **3** and tricyclohexylphosphine, both at 0.5 mol% Pd loading. The results of the solvent and base optimisation are shown in Fig. 1.

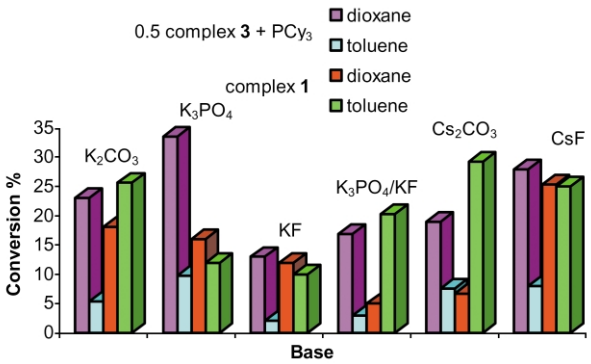


Fig. 1 Solvent and base optimisation. *Reagents and conditions*: 4-chloroanisole (1.0 mmol), PhSnBu$_3$ (1.1 mmol), base (2 mmol), catalyst (0.5 mol% Pd), solvent (5 ml), 120 °C (bath temperature), 18 h.

As can be seen, the best activity observed was when **3**/PCy$_3$ mixtures were used in dioxane with the inexpensive base K_3PO_4. Having established the optimum conditions we next examined the use of the catalysts formed *in situ* from one or two equivalents of PCy$_3$ and either complex **3** or palladium acetate and the results from this study are summarised in Table 1. The catalyst formed *in situ* from complex **3** and one equiv. of PCy$_3$ shows good activity, with complete conversion obtained within 48 h. However when two equivalents of PCy$_3$ per Pd are used then much higher activity results, with complete conversion observed within 18 h. Even more impressive is the observation that almost identical activity is seen when palladium acetate is used as the palladium source with one equiv. of PCy$_3$ (entry 5). By contrast the same reaction catalysed by a Pd–P^{t}Bu$_3$ system requires a 3 mol% Pd loading, the use of the far more expensive base CsF and a 48 h reaction time for comparable conversion.[4] In addition the PCy$_3$ systems offer the advantages that this ligand is considerably cheaper than P^{t}Bu$_3$ and far easier to handle. The closely related coupling of 4-chloroanisole with PhSnMe$_3$ catalysed by 3 mol% of a Pd–imidazolium salt-based system is reported to give only 35% conversion after 48 h.[5]

The excellent activity is maintained in the coupling of a range of electronically deactivated, non-activated, activated and sterically encumbered aryl chlorides. Examining the data in Table 1 in more detail it is apparent that there is very little difference in activity between the systems formed *in situ* from palladium acetate or complex **3** and 1 equiv./Pd of PCy$_3$ for all of the biaryl coupling reactions. This implies that the orthometallated phosphite ligand plays little or no part in the activity. Indeed when one equivalent of the free ligand P(OC$_6$H$_3$-2,4-^{t}Bu$_2$)$_3$, **4**, is added to either of the catalysts formed *in situ* with one PCy$_3$ ligand, then activity is greatly diminished (entries 7 and 8).

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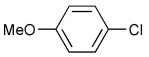
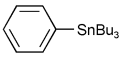
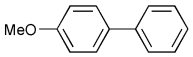
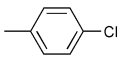
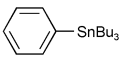
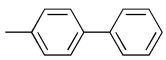
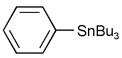
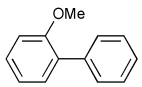
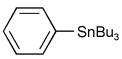
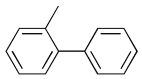
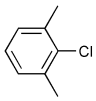
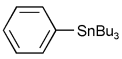
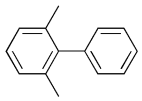
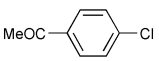
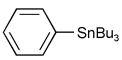
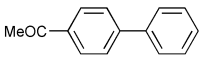
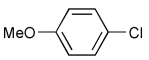
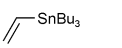
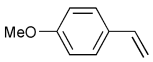
Table 1 Stille coupling of aryl chlorides.[a]

Entry	ArCl	$RSnBu_3$	Catalyst	Product	Conversion[b] (%)
1			0.5 **3** + PCy_3		56
2			0.5 **3** + PCy_3		72[c]
3			0.5 **3** + PCy_3		100[d]
4			0.5 **3** + 2 PCy_3		100
5			$Pd(OAc)_2$ + PCy_3		97
6			$Pd(OAc)_2$ + 2 PCy_3		100
7			0.5 **3** + PCy_3 + **4**		12.5
8			$Pd(OAc)_2$ + PCy_3 + **4**		19
9			$Pd(OAc)_2$ + PCy_3		74
10			0.5 **3** + PCy_3		70
11			0.5 **3** + 2 PCy_3		98
12			$Pd(OAc)_2$ + 2 PCy_3		96.5
13			$Pd(OAc)_2$ + PCy_3		72
14			0.5 **3** + PCy_3		65
15			0.5 **3** + 2 PCy_3		91
16			$Pd(OAc)_2$ + 2 PCy_3		94
17			$Pd(OAc)_2$ + PCy_3		71
18			0.5 **3** + PCy_3		74
19			0.5 **3** + 2 PCy_3		97
20			$Pd(OAc)_2$ + 2 PCy_3		93
21			$Pd(OAc)_2$ + PCy_3		78
22			0.5 **3** + PCy_3		76
23			0.5 **3** + 2 PCy_3		95
24			$Pd(OAc)_2$ + 2 PCy_3		92
25			$Pd(OAc)_2$ + PCy_3		76
26			0.5 **3** + PCy_3		71
27			0.5 **3** + 2 PCy_3		100
28			$Pd(OAc)_2$ + 2 PCy_3		100
29			$Pd(OAc)_2$ + PCy_3		56
30			0.5 **3** + PCy_3		32
31			0.5 **3** + 2 PCy_3		70

[a] *Reaction conditions*: aryl chloride (1.0 mmol), organostannane (1.1 mmol), K_3PO_4 (2 mmol), catalyst (1 mol% Pd), 1,4-dioxane (5 ml), 100 °C, 18 h. [b] Conversion to Stille-coupled biaryl product determined by GC (hexadecane standard). [c] 24 h. [d] 48 h.

In all cases activity increases when the ratio of PCy_3:Pd is increased from 1:1 to 2:1, with excellent yields of the biaryl products obtained within 18 h. Again there seems to be little difference in activity on changing the palladium source. The high activity is not limited to the formation of biaryls, but is also seen in the formation of a substituted styrene from vinyltributyltin (entries 29–32).

It is interesting to note that there is very little change in catalyst performance on changing from deactivated to more activated aryl chlorides, or from smaller to more sterically hindered chlorides. This is in stark contrast with the results obtained from the use of PCy_3-based catalysts in the Suzuki coupling of aryl chlorides.[3d,4] This suggests that here the rate determining step may not be oxidative addition of the aryl chloride but rather either transmetallation by the tin reagent or reductive elimination of the coupled product. It is unlikely to be the latter process as essentially the same intermediates should be involved in this step as in the Suzuki reaction. Therefore it is very probable that transmetallation is the rate-determining step. Indeed it has previously been observed that the rate of transmetallation of [PdCl(Ar)(P_2)] complexes with organostannanes is very slow.[7]

In summary, simple palladium complexes of the inexpensive, easily handled tricyclohexylphosphine ligand are excellent catalysts for the Stille coupling of aryl chlorides under mild conditions.

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Notes and references

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