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Extremely high activity catalysts for the Suzuki coupling of aryl chlorides: the importance of catalyst longevity

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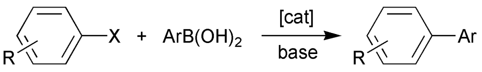
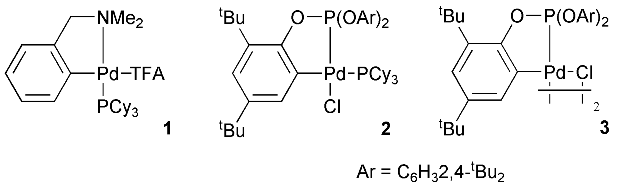
The incorporation of a new π-acidic, orthometallated phosphite ligand into a palladium pre-catalyst gives considerably enhanced catalyst longevity and thus extremely high activity in the Suzuki coupling of deactivated, activated and sterically hindered aryl chloride substrates.

The coupling of aryl halides with aryl boronic acids, the Suzuki reaction (Scheme 1), is one of the most powerful and versatile methods for the synthesis of biaryls.[1] There has recently been a considerable interest in the development of new catalysts that can couple aryl chlorides due to the lower cost and greater availability of these substrates compared with their bromide or iodide counterparts.[2] Unfortunately the comparatively high C–Cl bond strength makes aryl chlorides difficult to activate.[3] Consequently most catalysts that are able to catalyse aryl chloride coupling reactions still need to be used in relatively high loadings. Therefore the advantages associated with the use of aryl chlorides may be negated by the high cost of the catalyst systems.



Scheme 1 The Suzuki biaryl coupling reaction.

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.[2a,d] It was argued that the high activity obtained with the phosphite-containing catalyst is not necessarily due to any spectacular increase in rate, but rather to greater catalyst longevity which is conferred by the π-acidic nature of the phosphite ligand. Thus the catalyst was still active after one day, while the catalyst **1** shows no further activity after 2 h. If this explanation is correct, then it is reasonable to expect that increasing the π-acidity of the supporting ligand should lead to even greater longevity and therefore even higher total turn-over numbers (TONs, mol product/mol catalyst) should be achieved at low catalyst loadings. This indeed proves to be the case and the results of this study are reported below.



Ar = $C_6H_3$2,4-$^tBu_2$

In order to further increase the π-acidity of the orthopalladated ligand we decided to prepare a pre-catalyst related to **3**, but in which the two non-orthometallated aryloxide substituents were replaced by a single salicylate residue. In order to do this we first synthesised the new ligand **4** by reaction of commercially available 2-chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one, **5**, with 2,4-di-*tert*-butylphenol in the presence of triethylamine in toluene at reflux temperature for 18 h (Scheme 2). Reaction of the ligand **4** with $[PdCl_2(NCMe)_2]$ in toluene at reflux temperature for 18 h leads to the formation of the new dimeric complex **6** in good yield.

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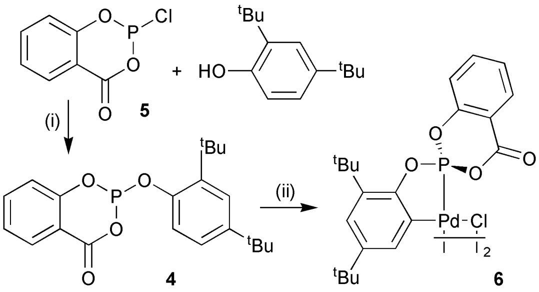


Scheme 2 *Reagents and conditions*: (i) NEt_3, toluene, Δ, 18 h; (ii) $[PdCl_2(NCMe)_2]$, toluene, Δ, 18 h.

Despite the fact that complex **6** could, in principle, exist in both *cis* and *trans* forms, in practice essentially only one isomer exists in solution, at least in chloroform, as evidenced by ^{31}P NMR spectroscopy which shows a very large peak at δ 124.4 with only a very small peak at δ 123.5 corresponding to the second isomer. This observation is also borne out by the ^1H and ^{13}C NMR spectra which again show essentially only one isomer present. This is in contrast with complex **3** which shows two peaks at δ 119.2 and 118.7 in the ^{31}P NMR spectrum in $CDCl_3$ in an approximately 2 : 1 ratio.

We have previously shown that the best conditions for the coupling of the challenging, electronically deactivated (electron rich) substrate 4-chloroanisole with aryl boronic acids are when Cs_2CO_3 is used as base and 1,4-dioxane is employed as the solvent and so these conditions were used for the initial studies. Fig. 1 shows a plot of conversion against time in the Suzuki coupling of 4-chloroanisole with phenylboronic acid catalysed by a range of catalysts formed *in situ* from tricyclohexylphosphine (one equiv. per Pd) and four differing palladacycles.

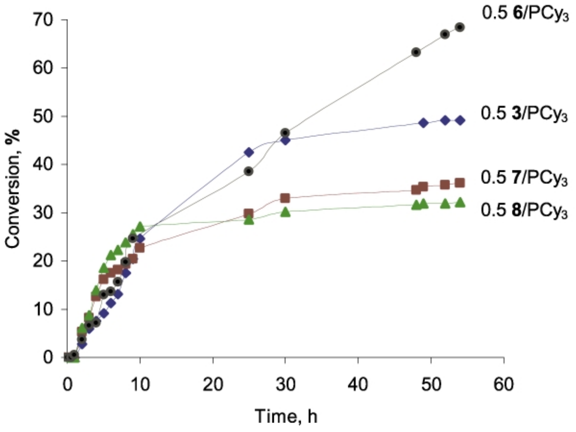
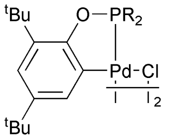


Fig. 1 Suzuki coupling of 4-chloroanisole with phenylboronic acid. *Reagents and conditions*: $MeOC_6H_4$-4-Cl (10.0 mmol), $PhB(OH)_2$ (15.0 mmol), Cs_2CO_3 (20.0 mmol), catalyst (0.001 mol% Pd), 1,4-dioxane (30 mL), hexadecane (internal standard, 0.204 mmol). Conversion to 4-methoxybiphenyl determined by GC.

As can be seen the catalyst formed *in situ* from **6** and PCy_3 shows considerably enhanced longevity compared with the analogous catalyst formed from **3**/PCy_3. Consequently, by 30 h **6**/PCy_3 gives higher conversion and the catalyst remains active even after 54 h. In order to verify that the increase in longevity is indeed a function of the π-acidity of the orthometallated co-ligand, the reactions catalysed by species formed *in situ* from PCy_3 and the palladacyles **7** and **8** were also studied. These complexes have been shown previously to give excellent activity in the coupling of aryl bromide substrates.[4] It is apparent that the catalyst longevity and hence overall performance falls in the order **6** > **3** > **7** > **8**. This trend is in line with decreasing π-acidity of the orthopalladated ligands. By comparison when no π-acidic co-ligand is used and the complex **1** is employed as a catalyst, then it has been found previously that no activity is observed after the first 2 h.[2a] These observations lend substantial weight to our previous supposition that the increase in longevity is due to a stabilisation of a palladium(0) 'resting state',[2a] since the more π-acidic the ligand, the better it would be expected to coordinate to such zerovalent species. Given that the rate-determining step is almost certainly oxidative addition of the aryl chloride to a Pd(0) active catalyst, then it is reasonable to suppose that the active catalyst spends most of its time 'resting' in the zerovalent state. Without the presence of additional stabilising ligands, such resting state species would be expected to be highly susceptible to catalyst decomposition by aggregation and subsequent precipitation of bulk metal.



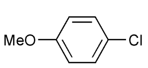
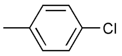
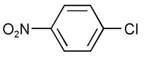
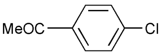
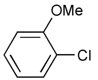
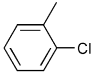
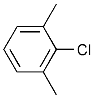
7: R = Ph
8: R = ^iPr

We next studied the performance of the catalyst formed *in situ* from complex **6** and PCy_3 (1 equiv. per Pd) in a range of aryl chloride Suzuki couplings and these results are summarised in Table 1.

Good results are obtained when the cheaper bases K_3PO_4 or KF are employed, however the use of Cs_2CO_3 leads to astonishingly high turn-over numbers. Thus TONs of up to 128,000 are seen for the electronically deactivated substrate 4-chloroanisole. By contrast, to the best of our knowledge, the highest TON reported previously for this reaction was *ca.* 48,000 using **3**/PCy_3 mixtures for the same period of time and under the same conditions.[2a] High conversions are seen with this substrate at 0.001 mol% Pd catalyst loading. Despite the fact that 4-chlorotoluene is considered to be electronically deactivated, it was still coupled with TONs of up to 1.86 million. When the activated substrates 4-chloroacetophenone or 4-chloronitrobenzene are employed, then essentially quantitative conversions are seen at one two-millionth catalyst loadings. Very high TONs are also seen for the sterically hindered substrates 2-chloroanisole, 2-chorotoluene and 2-chloro-*m*-xylene. By contrast, to the best of our knowledge, the previous highest TON observed in the coupling of 2-chlorotoluene with phenylboronic acid was 100,000, again with a complex **3**/PCy_3 mixture acting as catalyst.[2a]

It can be seen that for all the reactions excellent TONs are obtained after 24 h, however it is also apparent that the catalyst is still active after this time and in all cases reactions run for 48 h lead to greater conversions. This highlights the importance of catalyst longevity and has major implications for industrial processes where catalyst stability is often of paramount importance.

Table 1 Suzuki coupling of aryl chloride substrates catalysed by complex **6**/PCy_3 2 : 1 mixtures.[a]

Entry	Aryl chloride	Pd loading (mol%)	Base	Time/h	Conv.[b] (%)	TON (mol product/mol Pd)
1		0.001	K_2CO_3	24	4	4,000
2		0.001	K_3PO_4	24	19.5	19,500
3		0.001	KF	24	20	20,000
4		0.001	KF/K_3PO_4 (1:1)	24	7	7,000
5		0.0005	Cs_2CO_3	24	43	86,000
6		0.0005	Cs_2CO_3	48	64	128,000
7		0.001	Cs_2CO_3	48	90	90,000
8		0.00005	Cs_2CO_3	24	65	1,300,000
9		0.00005	Cs_2CO_3	48	84	1,860,000
10		0.00005	Cs_2CO_3	24	98	1,960,000
11		0.00005	Cs_2CO_3	48	100	2,000,000
12		0.00005	Cs_2CO_3	24	85	1,700,000
13		0.00005	Cs_2CO_3	48	97	1,940,000
14		0.0005	Cs_2CO_3	24	62	124,000
15		0.0005	Cs_2CO_3	48	84	168,000
16		0.0005	Cs_2CO_3	24	71	142,500
17		0.0005	Cs_2CO_3	48	87	174,000
18		0.0005	Cs_2CO_3	24	41	82,000
19		0.0005	Cs_2CO_3	48	58	116,000

[a] *Reaction conditions*: ArCl (1.00 mmol), $PhB(OH)_2$ (1.50 mmol), base (2.00 mmol), 1,4-dioxane (5 mL), 100 °C, N_2. [b] Conversion to coupled product, determined by GC (hexadecane standard).

In summary a simple catalyst precursor made by the orthopalladation of a phosphite ligand containing a salicylate residue shows by far the best activity yet reported in the Suzuki coupling of deactivated, activated and sterically hindered aryl chlorides. The basis of this performance is the high stability and longevity of the active catalyst, which in turn is a function of the π-acidic nature of the co-ligand.

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Notes and references

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3 For a discussion, see: V. V. Grushin and H. Alper, *Chem. Rev.*, 1994, **94**, 1047.

4 R. B. Bedford and S. L. Welch, *Chem. Commun.*, 2001, 129.