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The Suzuki coupling of aryl chlorides in TBAB–water mixtures

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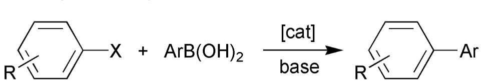
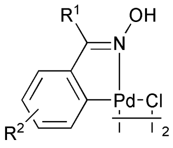
Palladium acetate in a mixture of TBAB and water can be used as an effective catalyst for the Suzuki coupling of deactivated aryl chloride substrates.

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 is 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] Many of the approaches to the activation of aryl chlorides in the Suzuki reaction rely on the development of either new ligand sets or new pre-catalysts types, both of which require a substantial degree of synthetic elaboration.



Scheme 1 The Suzuki biaryl coupling reaction.

There have recently been reports on the use of the orthopalladated oxime-containing catalysts **1** in the Suzuki coupling of aryl chlorides.[3] These reactions only proceed in the presence of water and the 'additive' tetrabutylammonium bromide (TBAB). Previously Herrmann and co-workers demonstrated that the performance of a phosphine-based palladacyclic catalyst in the Heck coupling of aryl chlorides could be substantially enhanced in the presence of TBAB or the phosphonium salt [Ph_4P]Cl.[4] TBAB is known to be able to stabilise colloidal palladium nanoparticles that act as catalysts in the Suzuki coupling of aryl bromides[5] and we wondered whether such species may also be the true active catalysts when complexes of the type **1** are employed in the coupling of aryl chlorides. Given that the closely related imine and amine palladacycles **2** and **3** undergo facile reductive processes in the presence of arylboronic acids,[6] it seems highly likely that complexes of the type **1** also undergo such reductions, thus allowing the formation of colloids in the presence of TBAB.[7] If this is true it should be possible to design a very simple catalyst system supported only by TBAB, *in the absence of added ligands*, that gives activity in the coupling of aryl chlorides.



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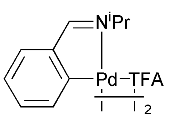

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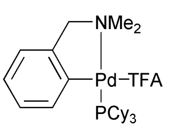

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We find that 'ligand-free' TBAB-Pd systems are indeed capable of showing good activity in the Suzuki coupling of aryl chlorides, even of electronically deactivated examples, providing the reactions are performed in the presence of water. The findings of this study are presented below.[8]

The initial optimisation studies were performed in the coupling of the electronically deactivated aryl bromide substrate, 4-bromoanisole, using pure molten TBAB as the solvent, palladium acetate as the palladium source (1.32 mol% Pd) and potassium carbonate as the base. The initial results were not promising with virtually no coupling observed, but the addition of incremental amounts of water led to a very rapid increase in activity until, at 33% w/w water, 93% conversion was obtained (Fig. 1). It is possible that in neat TBAB, any colloidal palladium that forms is overly stabilised and that the substrates are unable to compete effectively with the TBAB. The addition of water may lead to a competition between water and TBAB that opens up active sites on the catalyst surface. The addition of water meant that the reaction temperature was lowered with respect to that with neat TBAB and by 33% w/w water content the recorded reaction temperature was *ca.* 108 °C.

Encouraged by these results we decided to see whether the catalyst system was able to activate aryl chlorides. We initially concentrated on the coupling of the electronically challenging substrate, 4-chloroanisole. We were delighted to find that species formed from $Pd(OAc)_2$ in TBAB–water mixtures are indeed capable of catalysing this process. The plot of conversion against amount of water added (Fig. 1) is somewhat different to that for 4-bromoanisole, a maximum is observed at 0.5 mL of water. This was the first indication that simple extrapolation of optimum conditions from one substrate type to another is not always viable.

Next we performed a base screen and the results of this study are summarised in Table 1, entries 1 to 5. As can be seen K_2CO_3 and KF proved to be poor bases for the reaction, however both Cs_2CO_3 and K_3PO_4 could be used to good effect. We chose to use K_3PO_4 for the remainder of the studies as it is much less expensive. In all cases a small amount of biphenyl is formed as a by-product from the homocoupling reaction of the phenylboronic acid. The highest level of biphenyl is seen when Cs_2CO_3 is employed as the base. The level of water present in the reaction mixture does not appear to play a large role in the amount of biphenyl formed with a range of 2.5 to 3.5% obtained in the water optimisation study (Fig. 1).

At 1.32 mol% Pd a good conversion (65.5%) to Suzuki coupled product is observed after 17 hours. We were interested to see what effect varying the catalyst loading would have on performance (entries 6 to 11). As can be seen, increasing the catalyst loading beyond 1.32 mol% Pd is detrimental to the performance of the catalyst as indicated by the drop-off in turn-

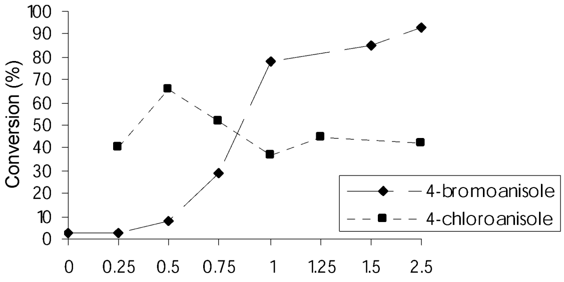

Fig. 1 Effect of water on the Suzuki coupling of 4-bromoanisole or 4-chloroanisole with phenylboronic acid in TBAB. Conditions: aryl halide (2.36 mmol), $PhB(OH)_2$ (3.00 mmol), base (4.00 mmol), $Pd(OAc)_2$ (1.32 mol%) TBAB (5.0 g), 125 °C (external), 17 h. Base = K_2CO_3, K_3PO_4 for 4-bromoanisole and 4-chloroanisole respectively.

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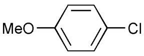
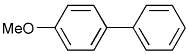
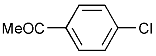
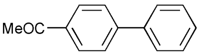
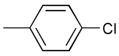
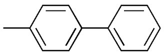
Table 1 Suzuki coupling of aryl chlorides in TBAB–water mixtures[a]

Entry	Aryl chloride	Catalyst loading (mol% Pd)	Base	Water added (mL)	Suzuki product, conversion (%)[b]	TON[c] (mol product per mol catalysts)	Conversion to biphenyl (%)[d]
							
1		1.32	K_2CO_3	2.5	6	4.5	2
2		1.32	KF	2.5	4	3	1
3		1.32	K_3PO_4	2.5	42	32	3
4		1.32	K_3PO_4/KF (1:1)	2.5	33.5	25	4.5
5		1.32	Cs_2CO_3	2.5	40.5	31	8
6		1.32	K_3PO_4	0.5	65.5	50	3
7		2.0	K_3PO_4	0.5	57	28.5	2.5
8		3.0	K_3PO_4	0.5	53.5	18	3
9		0.5	K_3PO_4	0.5	28	56	3
10		0.2	K_3PO_4	0.5	28	140	2.5
11		0.1	K_3PO_4	0.5	45	450	3.5
12		1.32	K_3PO_4	0.5	30[e]	23	2
13		1.32	K_3PO_4	0.5	41[f]	31	7
							
14		0.1	K_3PO_4	0.5	38	380	2
15		0.01	K_3PO_4	0.5	32	3200	3
16		0.8	K_3PO_4	2.5	87	109	6
17		0.08	K_3PO_4	2.5	94.5	1181	6.5
							
18		1.32	K_3PO_4	0.5	33.5	25	1.5
19		0.8	K_3PO_4	2.5	34.2	43	3.5

[a] Conditions: Aryl chloride (2.36 mmol), $PhB(OH)_2$ (3.0 mmol), base (4.0 mmol), TBAB (5.0 g), 125 °C (external temp.), 17 h. [b] Conversion to Suzuki coupled product, based on aryl chloride, determined by GC (hexadecane standard). [c] Conversion to biphenyl, based in $PhB(OH)_2$, determined by GC (hexadecane standard). [d] TON = turn-over number. [e] 2h reaction time. [f] Under air.

over number (TON, mol product per mol Pd), while lowering the loading is beneficial. An excellent TON of 450 is seen at 0.1 mol% Pd (entry 11). This would suggest that the conversion to product is limited by catalyst longevity. The main decomposition pathway is almost certainly aggregation of the active catalyst and precipitation of bulk metal. Reduction in catalyst loading would retard this process.

A shorter reaction time (entry 12) gives a somewhat lower conversion indicating that the catalyst is still active after 2 hours. Gratifyingly the catalyst seems to maintain most of its activity under aerobic conditions (entry 13).

When we investigated the coupling of the considerably more electronically activated substrate, 4-chloroacetophenone we found the results to be dependent on conditions. While good TONs are obtained with both 0.5 and 2.5 mL of added water (entries 15 and 17), much greater amounts of biphenyl impurity are observed at the lower water loading.

The performance of the catalyst system in the coupling of 4-chlorotoluene with phenylboronic acid seems to be anomalously low. Given that the rate-determining step is almost certainly oxidative addition, activity with this substrate should be in between that with 4-chloroanisole and 4-chloroacetophenone. One possible explanation for this is that the increased hydrophobicity of 4-chlorotoluene reduces its misciblity with the water–TBAB phase and thus limits its interaction with the catalyst surface.

In summary we have demonstrated that simple palladium catalysts formed *in situ* from palladium acetate in the presence of TBAB and water *and in the absence of added ligands* are effective in the Suzuki coupling of deactivated chlorides. It is highly likely that the true active catalysts are palladium colloids supported by the TBAB. We are currently working to demonstrate this conclusively and to optimise the use of such catalysts in a range of aryl chloride coupling reactions.

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Notes and references

1 For recent reviews, see: (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*b*) S. P. Stanforth, *Tetrahedron*, 1998, **54**, 263; (*c*) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147.

2 For leading references for the Suzuki coupling of aryl chlorides, see: R. B. Bedford, S. L. Hazelwood and M. E. Limmert, *Chem. Commun.*, 2002, 2610.

3 (*a*) D. A. Alonso, C. Nájera and M. C. Pacheco, *J. Org. Chem.*, 2002, **67**, 5588; (*b*) L. Botella and C. Nájera, *Angew. Chem., Int. Ed.*, 2002, **41**, 179.

4 W. A. Herrman, V. P. W. Böhm and C.-P. Reisinger, *J. Organomet. Chem.*, 1999, **576**, 23.

5 M. T. Reetz and E. Westermann, *Angew. Chem., Int. Ed.*, 2000, **39**, 165.

6 (*a*) R. B. Bedford, C. S. J. Cazin, M. B. Hursthouse, M. E. Light, K. J. Pike and S. Wimperis, *J. Orgamet. Chem.*, 2001, **633**, 173; (*b*) R. B. Bedford and C. S. J. Cazin, *Chem. Commun.*, 2001, 1540.

7 Nájera and co-workers explored the possibility that palladium acetate could be used as a source of active catalyst in their study and found that under the conditions employed it showed essentially no activity (see ref. 3). In view of our findings that catalyst activity is highly dependent on conditions it is perhaps not surprising that their system based on palladium acetate showed no activity.

8 Recently Leadbeater and Marco reported the microwave assisted Suzuki coupling of aryl chlorides in water-TBAB mixtures but much higher temperatures were required: N. E. Leadbeater and M. Marco, *Org. Letts.*, 2002, **4**, 2973.