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Suzuki cross-coupling reactions using reverse-phase glass beads in aqueous media

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Abstract—Reverse-phase glass beads have been employed in Suzuki reactions to provide, in aqueous media, a route to diverse polar substrates in good yield and with low levels of palladium leaching. © 2003 Elsevier Science Ltd. All rights reserved.

Controlled-pore glass beads have been used in supported liquid-phase catalysis for a variety of transition metal catalysed reactions.[1] Generally, the hydrophilic glass supports an aqueous film which contains a water-soluble catalyst.[2] However, straightforward derivatisation of the glass to provide a hydrophobic surface,[3] allows the support of non-polar solvents and conventional non-polar catalysts. It is therefore possible to use simple non-polar ligands such as PPh_3 using the reverse-phase glass bead methodology. We have previously reported the use of reverse-phase glass beads in Heck reactions and allylic substitution reactions.[4]

The Suzuki reaction is a versatile and powerful tool for the formation of C–C bonds, and has previously been reported using water-soluble palladium catalysts.[5,6] Herein, we wish to describe our results for the Suzuki cross-coupling of boronic acids **1** to **3** (Scheme 1) with various organohalides.

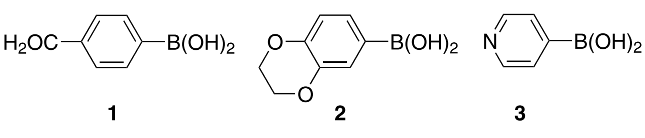
The derivatised glass beads were prepared by treatment of the beads with octyl trimethoxysilane, following the procedure reported previously.[3] The commercially available Davisil 500 Å beads were used as the silica support.

Scheme 2 illustrates the general conditions for the conversion of the reverse-phase glass bead into an active catalyst. After removal of excess solvent, the supported catalyst can be handled under a normal atmosphere. We assume that the catalyst is still mobile within a thin film of cyclohexane on the surface of the glass bead, and that reaction occurs at the solvent interface.[1]

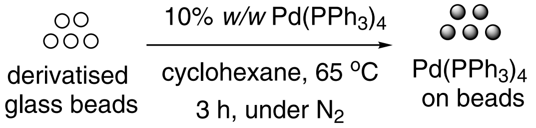
In a typical Suzuki reaction,[7] boronic acid **1**, 4-carboxyphenyl boronic acid, was coupled with 4-iodobenzoic acid (Table 1, entry 1). The reaction was carried out in water under the conditions indicated in Scheme 3.

After only 5 min, the coupled product was synthesised in good yield (86%) and with minimal palladium leaching (0.06%).[8]

The boronic acid **1** was also coupled with a variety of other aryl halides to provide the corresponding coupled



Scheme 1.



Scheme 2.

Keywords: glass bead technology; Suzuki cross-coupling; aqueous media; polar substrates.

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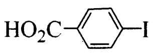
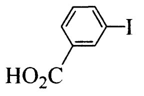
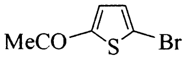
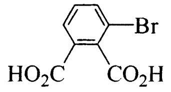
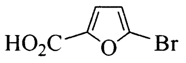
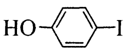
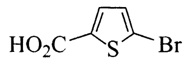
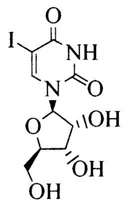
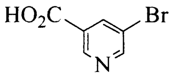
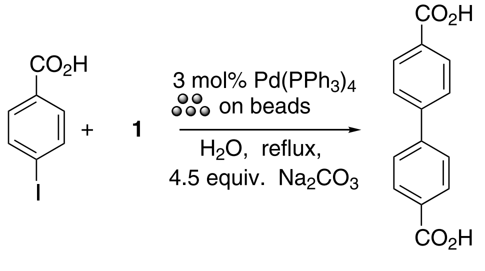
Table 1. Suzuki cross-coupling reactions of boronic acid **1** using the reverse-phase supported catalyst

Entry	R-Hal	Time	Conversion(%) Cross coupling product	Self-coupling product	Yield (%)	Palladium leaching[a] (%)
1		<5 min	100	0	86[b]	0.06
2		1.5 h	100	0	80[b]	0.30
3		3 h	100	0	78[b]	0.31
4		1.5 h	100	0	97[b]	0.16
5		1 h	93	7	91[c]	0.36
6		3 h	90	10	69[c]	0.63
7		3 h	100	0	85[b]	0.12
8		4 h	67	33	28[c]	0.40
9		2 h	75	25	84[c]	0.47

[a] The leaching level corresponds to the amount of palladium present as a percentage of the total palladium used.
[b] Isolated yields.
[c] Yields calculated from ^1H NMR from a mixture of cross and self-coupling products.



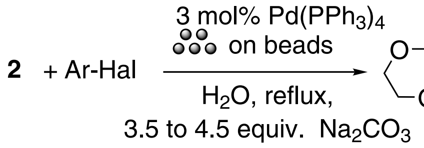
Scheme 3.

products (Table 1). In general, reactions were run for 1.5–4 h, although this is probably not a requirement. Small amounts of self-coupling products were also obtained in some cases. Moreno-Mañas et al. have reported the influence of an inert atmosphere on the formation of the homo-coupling product.[9] In their study, oxygen accelerates the reaction. However, we found that even with rigorous exclusion of oxygen, the self-coupling product was formed in similar yields.

We were pleased to find that the palladium leaching levels observed for all of the compounds were low, ranging from 0.06 to 0.63% of total palladium used. It is important to determine the percentage of metal contamination into the products, especially for possible pharmaceutical applications.

The recycling of the catalyst with boronic acid **1** has been briefly examined. Recycled catalyst was used in a repeat reaction without any appreciable loss of activity for entry 4. 97% then 94% of isolated yield of coupled product was achieved using 3 mol% of supported catalyst in water at reflux. The palladium leaching was below 1 ppm.

The presence of the glass beads has a strong influence on the rate of the reaction. Thus the reaction described in Scheme 3 was demonstrated to proceed to comple-



Scheme 4.

tion in less than 5 min using the supported catalyst, while the conventional catalyst $Pd(PPh_3)_4$ gave only 50% conversion after 7.5 h. The increased reaction rate can be attributed to the large contact area between the water and the organic phase when beads are present.

Other boronic acids (**2** and **3**) have been successfully coupled using the reverse-phase glass beads. Both reagents have lower water solubility than **1**, therefore a higher palladium leaching was expected in their final coupled products.

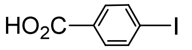
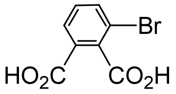
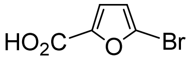
In particular, boronic acid **2** has been coupled with a selection of aryl halides under the conditions described in Scheme 4.

Although the solubility of boronic acid **2** is lower than boronic acid **1** in water, the isolated yields obtained are moderate to good (Table 2). In addition no self-coupling product has been observed for this boronic acid.

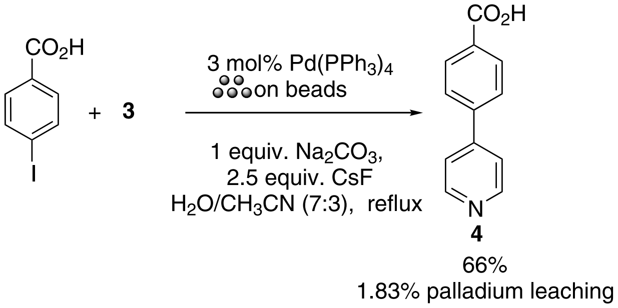
Whilst aryl iodides and aryl bromides were satisfactory coupling partners, only small amounts of coupled product (6%) were obtained when using 4-chlorobenzoic acid with boronic acid **2**, and no product formed at all with **1**. Alternative non-polar ligands for palladium have not been examined, although reverse-phase glass bead methodology could, in principle, be applied to other non-polar ligands.[10]

The reaction with 4-pyridinylboronic acid **3** was examined (Scheme 5). The first attempt at cross coupling with 4-iodobenzoic acid in water did not provide any product. This was probably due to a poor solubility of the boronic acid. We reasoned that in order to achieve the best reactivity both reagents should be well solubilised. When the reaction was run exclusively in water, the reagents were solubilised by adding extra equivalents of base. Therefore it was important to find a system of solvents that would allow a good solubility of both reagents. Acetonitrile was chosen as a co-solvent, as it has been used in similar reactions.[11]

Table 2. Suzuki cross-coupling of **2** with organohalides using the reverse-phase supported catalyst

Ar-Hal	Time	Yield[a] (%)	Palladium leaching (%)
	3 h	96	3.30
	2 h	47	2.52
	2 h	85	2.75

[a]Isolated yield.

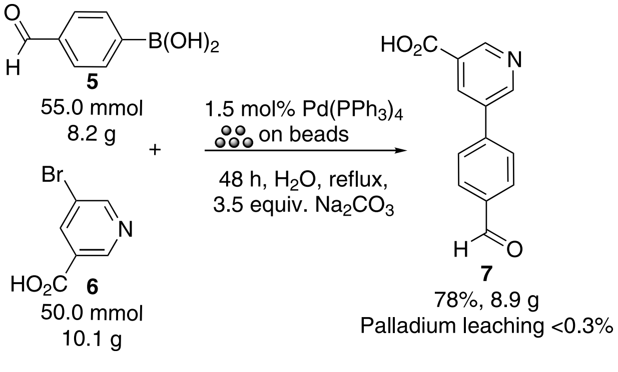


Scheme 5.

The most successful results were obtained using a water/acetonitrile (7:3) mixture as solvent, with Na_2CO_3 to deprotonate the carboxylic acid and CsF to promote the Suzuki reaction. It was interesting to note that the leaching level was higher than in earlier examples. We speculate that the pyridine may be able to act as a ligand to draw palladium into the aqueous layer. Additionally, the lower polarity of the water/acetonitrile solvent may have an effect on partitioning.

The majority of the reactions described in this communication were performed on a small scale, typically 0.5 mmol. We carried out one reaction on a larger scale. Compound **7** was produced in high yield and with low level of palladium leaching (Scheme 6).

In summary, a supported catalyst derived from $Pd(PPh_3)_4$ gave an efficient Suzuki cross coupling of boronic acids with several organohalides, in good yields and with low levels of palladium leaching, even though these levels are higher than for ordinary-phase glass beads.[4] In addition, the recycling of the reverse-phase glass beads has been investigated. Initial results showed that the catalyst could be recycled at least once without any loss of activity.



Scheme 6.

Acknowledgements

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7. *Typical procedure*: To a mixture of 4-iodophenyl carboxylic acid (130 mg, 0.50 mmol) in water (5 mL), was added Na_2CO_3 (2 M, 250 μL, 0.50 mmol) and supported catalyst (174 mg, 3 mol%). Then a solution of boronic acid (91.3 mg, 0.55 mmol) and Na_2CO_3 (260 μL, 0.55 mmol) in water (5 mL) was added. The solution was heated at reflux until completion of the reaction (<5 min). The supported catalyst was separated from the mixture by centrifugation and the remaining solution was acidified with concentrated HCl to give 4,4′-biphenyldicarboxylic acid (104.2 mg, 86%) as a white solid which was isolated after filtration under vacuum. δ_H (300 MHz, $(CD_3)_2SO$): 8.35 (4H, H_a, d, $J = 7.9$) and 7.85 (4H, H_b, d, $J = 7.9$).
8. Palladium leaching was determined by extraction of the product with 6 drops of aqua regia for 30 min. After addition of deionised water (5 mL), the solution was analysed on a Perkin–Elmer 1100B atomic absorption instrument in conjunction with a series of palladium standards.
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12. Boronic acids can be purchased from Maybridge plc, Trevillett, Tintagel, Cornwall, PL34 0HW, UK.