Green Chemistry

Cite this: Green Chem., 2012, 14, 317

www.rsc.org/greenchem

COMMUNICATION

Suzuki-Miyaura cross-coupling of arenediazonium salts catalyzed by alginate/gellan-stabilized palladium nanoparticles under aerobic conditions in water[†]

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Received 9th June 2011, Accepted 21st November 2011 DOI: 10.1039/c2gc15679b

The use of palladium nanoparticles stabilized by natural beads made of an alginate/gellan mixture in the Suzuki-Miyaura cross-coupling reaction of arenediazonium tetrafluoroborates with potassium aryltrifluoroborates (1:1 molar ratio) with loading as low as 0.01–0.002 mol% under aerobic, phosphine-, and base-free conditions in water is described. The catalyst system can be reused several times without significant loss of activity.

Since the pioneering studies reported by Matsuda *et al.* in 1977,¹ arenediazonium salts have emerged as an attractive alternative to aryl halides or triflates. This is due to their higher reactivity at room temperature or slightly higher temperature, their availability from anilines, considerably cheaper than most of the corresponding aryl halides or triflates, the use of aqueous conditions, and the absence of added bases and phopshine ligands in several applications. They have been used in a variety of palladium-catalyzed reactions² including the Suzuki-Miyaura cross-coupling,³ one of the most convenient and powerful tools in the arsenal of the practising organic chemist for the formation of carbon-carbon bonds.

Recently, Suzuki-Miyaura cross-couplings of arenediazonium salts with arylboronic acids have also been performed under heterogeneous conditions.⁴ Best results have been obtained using 0.1–0.9 mol% Pd/C in MeOH at 25 °C (the catalyst, however,

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could not be recycled).4b These studies are in line with the current trend of the modern sustainable chemistry, which requires to develop new processes that minimize pollution in chemical synthesis. In this context, heterogeneous catalysis is on the rise because of its potential in reducing contamination of the isolated products as well as in facilitating the removal, recovery, and reutilization of transition metals.5 Particularly, biodegradable natural polymers are attracting growing interest as substitutes for classical inorganic and petrochemical-based supports for environmentally friendly catalysts. Among them, widely diffused polysaccharides represent an attractive and promising material. Palladium/polysaccharides such as Pd/arabinogalactan,6 Pd/chitosan,⁷ and Pd/starch⁸ have been prepared. Recently, a heterogeneous catalyst based on palladium chelated in the framework of alginate biopolymer (a polymer of mannuronic and guluronic acids) has been shown to be active in the Suzuki-Miyaura cross-coupling reaction of iodobenzene or neutral and electron-poor aryl bromides with phenylboronic acid (DMF, K₂CO₃, 70 °C).⁹ High to excellent conversions and excellent selectivity was observed with the substrates investigated. The catalyst, tested for the reaction of bromobenzene, could be used three times. However, a decrease of the conversion from 95 to 70% was observed.

Herein, we report that palladium nanoparticles stabilized by an alginate/gellan mixture (Fig. 1) can be successfully used in the Suzuki-Miyaura cross-coupling reaction of arenediazonium tetrafluoroborates with potassium aryltrifluoroborates with a loading as low as 0.01–0.002 mol% in water. Potassium aryltrifluoroborates have been selected as coupling partners because they are known to circumvent many of the drawbacks associated with the use of arylboronic acids such as the tendency of the latter to give protodeborination¹⁰ or homocoupling in the Suzuki-Miyaura process¹¹ and to form trimeric anhydrides (boroxines), which creates difficulties in their purification and some structural ambiguity.¹²

Palladium nanoparticles stabilized by alginate (Pd_{np}/A) , prepared as described in literature,⁹ were initially tested when the study of the reaction of 4-acetyldiazobenzene tetrafluoroborate **1a** and potassium 4-methoxyphenyltrifluoroborate **2a** as the

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Fig. 1 Chemical structure of alginate (A) and gellan (G).

model system began. Reactions were performed using 1a and 2a in a 1:1 molar ratio and Pd_{np}/A (0.01 mol% palladium loading) in water at 40 °C for 24 h under aerobic conditions in the absence of bases. Under these conditions, 3a was isolated in a satisfactory 70% yield (Table 1, entry 1). Unfortunately, after the first run, the reused catalyst showed a significant deactivation leading to a modest yield of the desired cross-coupling product. Compound 3a was isolated in 60% yield. Most probably, the loss of activity is due to the leaching of palladium, in turn dependent on the instability of the alginate scaffold under the reaction conditions (shrinking of beads is clearly visible). Worse results were obtained switching to palladium nanoparticles stabilized by gellan, a natural polymer of glucose, rhamnose, and glucuronic acid. Using this catalyst system $(Pd_{nn}/G; 0.01)$ mol% palladium loading), prepared in the same manner,9 the cross-coupling product 3a was formed only in trace amounts (Table 1, entry 2). The reasons of this lack of activity are unclear at the moment. Interestingly, 3a was isolated in 62% yield when the same reaction was carried out in MeCN.

Searching further for an efficient and reusable catalyst system based on a polysaccharide scaffold and with the idea of taking advantage of the synergic interactions described in the literature when mixing different biopolymers,¹³ we decided to investigate the activity of palladium nanoparticles stabilized by an alginate/gellan mixture ($Pd_{np}/A-G$). To our delight, this catalyst system (0.01 mol% palladium loading) could afford the desired coupling product 3a in 90% yield under the same conditions (Table 1, entry 3). More importantly, it could be reused several times without significant loss of activity (Table 2, entry 1). The cumulated turnover number[‡] (TON) over eight runs is 68 400. The recovery of the supported palladium involves filtration and washing with methanol in the presence of air, without any particular precaution. Further recycling studies were performed using lower palladium loading. With a palladium loading down to 0.002 mol%, the cumulated turnover number over five runs is 193 000 (Table 2, entry 2).

Palladium nanoparticles stabilized by alginate/gellan beads $(Pd_{np}/A-G; 0.00141\% \text{ palladium})$ were prepared dropping an alginate/gellan (50:50) solution into a CaCl₂ solution. Hydrogel beads were soaked for 48 h in a Na₂PdCl₄ solution and then dehydrated in a series of successive ethanol-water baths of increasing alcohol concentration. Reduction of palladium occurs during the dehydratation step with ethanol (Scheme 1, Fig. 2 and 3).



^{*a*} Reactions were carried out using 1 mmol of **1a** and 1 mmol of **2a** in 2 mL of solvent at 40 °C in the presence of Pd_{np} /polysaccharide (14 mg; 0.01 mol% palladium loading) for 24 h. ^{*b*} Yields are given for isolated products.

Table 2Recycling studies on the reaction of 4-acetyldiazobenzenetetrafluoroborate 1a with potassium 4-methoxyphenyltrifluoroborate 2ausing $Pd_{np}/A-G^a$

Entry	Pd loading	Yield % of $3a^b$	TON	
1	0.01 mol (%)	90, 85, 87, 83, 80, 84, 87, 88	68400	
2	0.002 mol (%)	85, 82, 80, 78, 61	193000	

^{*a*} Reactions were carried out at 40 °C under aerobic conditions in 2 mL of water using 1 mmol of **1a** and 1 mmol of **2a** in the presence of $Pd_{np}/A-G$ for 24 h. ^{*b*} Yields are given for isolated products.



Scheme 1 Preparation of $Pd_{np}/A-G$.

When observed under a stereomicroscope, hydrogel beads generally show a subspherical shape and a diameter of 1–3 mm (Fig. 2a). SEM analysis, performed prior to catalysis (Fig. 2b) demonstrate a homogeneously smooth surface of beads, which, at higher magnification, displays aggregated nanoparticles (Fig. 2c). FIB/SEM cross sections of the alginate/gellan beads, performed through the ion beam milling process (Fig. 2d), show several nanoparticles even under the superficial layer (Fig.



Fig. 2 (a) Stereomicrograph of hydrogel beads ($Pd_{np}/A-G$; 0.01 mol% palladium loading) showing homogeneous morphology. (b–f) FIB/SEM images of alginate/gellan beads, prior to catalysis. (b) External view of a representative bead showing regular shape and smooth surface. (c) Close-up of the external surface with aggregated nanoparticles. (d) View of the site of ion-beam milling process. (e, f) Details of cross sections, showing both outer and inner bead composition. Note the spongy appearance and the highly porous scaffold containing electron dense nanoparticles (whitish structures).

2e,f). This powerful procedure, avoiding artifact generation also allows study of the inner structure of hydrogel beads, which appear to contain a highly porous scaffold (Fig. 2d–f).

Transmission Electron Microscopy (TEM) measurements indicate that the catalyst system before use contains palladium spheroidal nanoparticles, whose average size is 3.4 ± 1.4 nm (Fig. 3a). The material recovered after 8 runs showed nanoparticles of about 3.6 ± 1.7 nm in diameter (Fig. 3b).

For the sake of comparison, the use of other solvents in the Suzuki-Miyaura cross-coupling was explored. No coupling product was formed in MeOH or EtOH (Table 1, entries 4 and 5) and MeCN or DMF led to the isolation of **3a** in lower yields (Table 1, entries 7 and 8). Furthermore, solubilization of the microbeads was observed in DMF. Only with H₂O/MeOH and H₂O/MeCN mixtures did the reaction afford **3a** in yields similar to those obtained in water (Table 1, entries 6 and 9). However, water is particularly attractive as reaction medium. It is inexpensive, nontoxic, and nonflammable, and is easily separated from organic products.¹⁴ Therefore, reactions were conducted in water when we next explored the efficiency of $Pd_{np}/A-G$ with other arenediazonium tetrafluoroborates and potassium aryltrifluoroborates. As shown in Table 3, good to high yields were obtained with arenediazonium tetrafluoroborates and potas-



Fig. 3 TEM image and particle size distribution of $Pd_{np}/A-G$ (0.01 mol% palladium loading) (particle size 3.4 ± 1.4 nm). (b) TEM image and particle size distribution of $Pd_{np}/A-G$ recovered after 8 runs (particle size 3.6 ± 1.7 nm). In these calculations only the isolated particles have been taken into account.

A	r ¹ N ₂ BF ₄ + KF ₃	$BAr^2 = \frac{Pd_{np}/A-G}{H_0O_{10}00}$		- $Ar^1 - Ar^2$	
	1 2	2	5, 10 0	3	
Entry	Ar ¹ 1	Ar ² 2	Time (h)	Yield % of 3^b	
1	4-MeCOC ₆ H ₄	4-MeOC ₆ H ₄	24	90	3a
2		$4-ClC_6H_4$	48	77	3b
3		$4-CF_3C_6H_4$	24	86	3c
4		$2-BrC_6H_4$	48	80	3d
5		Ph	48	66	3e
6	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	10	86	3f
7		$4-ClC_6H_4$	24	78	3g
8		$4-CF_3C_6H_4$	24	77	3ň
9		Ph	48	86	3i
10	4-CNC ₆ H ₄	4-MeOC ₆ H ₄	24	88	3j
11		$4-ClC_6H_4$	24	85	3ĸ
12		$4-CF_3C_6H_4$	24	83	31
13	Ph	4-MeOC ₆ H ₄	48	87	3i
14		$4-ClC_6H_4$	24	77	3m
15		$4-CF_3C_6H_4$	24	67	3n
16	2-Me. 4-MeOC ₆ H ₃	4-CF ₃ C ₆ H ₄	48	73 ^c	30
17	4-ClC ₆ H ₄	4-BrC ₆ H ₄	24	90	3p
18	4-ClC ₆ H ₄	$2-BrC_6H_4$	36	40	3q
19	2-ClC ₆ H ₄	$4-BrC_6H_4$	36	51	3r
20	$2-ClC_6H_4$	$2-BrC_6H_4$	48	traces	

^{*a*} Reactions were carried out in 2 mL of H₂O using 1 mmol of **1** and 1 mmol of **2** at 40 °C in the presence of $Pd_{np}/A-G$ (0.01 mol% palladium loading). ^{*b*} Yields are given for isolated products. ^{*c*} The homocoupling product derived from potassium aryl trifluoroborate was isolated in 23%.

sium aryltrifluoroborates containing both electron-donating and electron-withdrawing substituents. *ortho* substituents are tolerated in the arenediazonium tetrafluoroborate (Table 3, entry 16 and 19) or the potassium aryltrifluoroborate (Table 3, entry 4 and 18). However, a more severe steric congestion leads to trace amounts of the desired product (Table 3, entry 20).

In conclusion, we have shown that palladium nanoparticles stabilized by alginate/gellan aerogel beads can be successfully used in the Suzuki-Miyaura cross-coupling reaction of arenediazonium tetrafluoroborates with potassium aryltrifluoroborates under aerobic, phosphine-, and base-free conditions in water with loading as low as 0.01–0.002 mol%. The catalyst system can be reused several times without significant loss of activity.

Acknowledgements

Work carried out in the framework of the National Projects funded by Ministero dell'Università e della Ricerca Scientifica "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni".

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‡ Cumulated turnover number: cumulated overall yields divided by their catalyst loading.

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