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Hydroxyapatite supported palladium catalysts for Suzuki–Miyaura cross-coupling reaction in aqueous medium†

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Supported palladium catalyst **1** has been prepared by the immobilisation of [Pd(COD)Cl₂] (COD = 1,5-cyclooctadiene) on hydroxyapatite. Catalyst **2** has been prepared by subsequent reduction of catalyst **1** with sodium borohydride in ethanol. Under similar reaction conditions, catalyst **1** with Pd²⁺, is found to be almost five times more active than **2**. Using **1** as the catalyst and water as the solvent, reaction conditions for Suzuki–Miyaura cross-coupling reactions have been optimised under aerobic conditions. The best catalytic activities are observed in the presence of potassium carbonate as the base and tetrabutylammonium bromide as a promoter. Catalyst **1** has been tested for catalytic cross-coupling reactions with sixteen different, electronically neutral, electron rich, electron poor and sterically hindered aryl boronic acids, and several different aryl halides including aryl chlorides. More than thousand turnovers and high selectivities to the hetero-coupled products have been observed in most cases. For many substrates the turnovers with **1** are notably more than what has been reported with other supported catalysts in water. The recyclability and scale-up potential of catalyst **1** have been tested and found to be satisfactory. A negligible drop in activity is observed over ten recycles with an accumulated turnover number of ~30 000.

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Introduction

The versatility and industrial applicability of palladium catalysed Suzuki–Miyaura cross-coupling (SMCC) reactions of aryl boronic acids and aryl halides have been intensively investigated over the last two decades.^{1–7} SMCC reactions are routinely used in the pharmaceutical industry, and their viability for the large scale synthesis of drug candidates is well established.^{8,9} Two issues related to sustainable, environment friendly applications of SMCC reactions however need special attention.^{8,10} First, palladium and the ligand must be completely purged from the active pharmaceutical ingredient to meet the stringent specifications of clinical testing. Secondly, it is desirable to have water rather than an organic solvent as the reaction medium because water is non-toxic, non-corrosive, non-flammable, abundantly available, and cheap.^{11,12} On the other hand, activation of the electronically deactivated and sterically hindered aryl boronic acids and aryl halides is important

for the new materials synthesis.^{1–3} In this respect, activation of the aryl chlorides requires special attention compared to the aryl bromides and iodides from the economical point of view.³

Immobilisation of the catalyst on an insoluble support without any added ligand is a promising strategy to address the first concern. Such a catalyst could be easily separated by filtration and reused. Furthermore by using such a catalyst in water, the use of organic solvents could be avoided. However, the catalyst must be shown to be recyclable, give good turnovers under aerobic conditions for a wide range of substrates, and the metal must not leach out.

With this background a variety of solid supports like activated carbon,¹³ oxides,^{14,15} functionalised silica,^{16,17} organic polymers,¹² nanomaterials,¹⁸ and calcium hydroxyapatite^{19,20} have been used for the immobilisation of palladium catalysts. However, success with this strategy so far has been modest because supported catalysts are generally less active than the corresponding homogeneous systems. Also the scope of substrates for supported catalysts is modest.²¹ Much effort into developing efficient water based, catalytic systems for the SMCC reactions has also been reported.^{11,12,22–34} Especially noteworthy in the context of the present work are the reports on the use of heterogenised catalysts in aqueous medium.^{19,20,32–34}

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† Electronic supplementary information (ESI) available: Powder XRD, EDX spectrum, X-ray mapping of the atomic distribution in catalyst, IR spectra and optimisation of the reaction conditions. See DOI: 10.1039/c3cy00160a

Use of calcium hydroxyapatite [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$] (HAP) as a support for Pd-catalysts has been reported earlier. Jamwal *et al.* treated HAP with $\text{Pd}(\text{OAc})_2$, and the resultant material after reduction with hydrazine hydrate, gave modest turnovers in SMCC reactions.¹⁹ Recently, $\text{Pd}(\text{NO}_3)_2$ supported on HAP has been used as the catalyst in the presence of PPh_3 to give turnovers ≤ 100 , and on recycling the catalytic activity was found to decrease.²⁰ In both these reports the SMCC reactions were limited to bromoarenes only.

We chose to evaluate HAP supported $[\text{Pd}(\text{COD})\text{Cl}_2]$ (COD: 1,5-cyclooctadiene) as a catalyst for SMCC reactions for the following reasons. First, the effectiveness of the supported catalyst must be established for a wide range of aryl boronic acids and aryl halides. Activations of aryl iodides and aryl bromides in SMCC reactions are known to be easier than aryl chlorides. The development of catalysts, that can utilise aryl chlorides as substrates in these reactions, is therefore also important.³⁵ Secondly, in view of the low turnovers and poor recyclability of many of the reported catalysts, we wanted to improve upon these two critical properties.

The complex $[\text{Pd}(\text{COD})\text{Cl}_2]$ was particularly appealing in view of the pioneering work by Mori *et al.*^{36,37} By using EXAFS and other techniques these researchers had conclusively shown that the treatment of $\text{PdCl}_2(\text{MeCN})_2$ with HAP leads to the formation of chemisorbed monomeric PdCl_2 species. The resultant material was investigated as an oxidation catalyst and also in typical Heck and SMCC reactions. However, the SMCC reactions were carried out in an organic solvent at a high temperature (120 °C), and were limited to three bromoarenes only.³⁶

From a mechanistic point of view, the loss of COD from $[\text{Pd}(\text{COD})\text{Cl}_2]$ on HAP is expected to be facile as it is weakly bound only through π -bonds. Also Cl^- , unlike the anions CH_3CO_2^- and NO_3^- cannot act as a bidentate ligand thereby ensuring sufficient coordinative unsaturation. Both these factors should result in generating catalytic sites with good activity. Thus, here we report the comparative performances $[\text{Pd}(\text{COD})\text{Cl}_2]$ supported on HAP before and after reductions *i.e.*, catalysts **1** and **2** respectively (Scheme 1).

We find **1** to be an excellent ligand-free catalyst for SMCC reactions in water, giving high turnovers and good selectivity with a wide range of aryl boronic acids and haloarene substrates. The catalyst has been recycled ten times with no observable loss of palladium and negligible loss in catalytic activity. We also find **1** to be a more active catalyst than **2** and many of the other supported catalysts.

Results and discussion

Syntheses and characterisation of the catalysts

Catalyst **1** has been synthesised by the reported cation exchange reaction where some of the Ca^{2+} ions of HAP are substituted

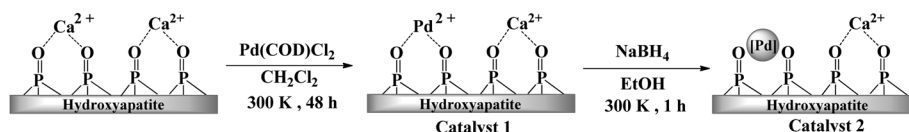
by Pd^{2+} . HAP is treated with $[\text{Pd}(\text{COD})\text{Cl}_2]$ for 48 h at room temperature in dichloromethane to give catalyst **1** as a yellow powder (Scheme 1 and Experimental Section). Reduction of **1** with sodium borohydride in ethanol produces **2** (Scheme 1 and Experimental Section).

Both **1** and **2** have been subjected to powder XRD, ICP-AES, and TEM analyses. As the catalytic performance of **1** is much better than **2** (see later), XPS and EDAX analyses have also been carried out on **1**. Powder XRD patterns of **1** and **2** are identical to that of parent HAP (Fig. S1, see ESI†). This suggests that Pd-loading does not change the bulk structure of HAP. In catalyst **2**, reduction of Pd^{2+} with NaBH_4 , is expected to generate palladium nanoclusters. However, very low concentration of the metallic clusters is not detected by powder XRD. ICP-AES analysis of the catalysts also indicates that the amount of palladium loading is similar (~ 0.3 wt% Pd) in **1** and **2**. Attenuated total reflectance (ATR) FTIR spectra of HAP and catalyst **1** are also identical (Fig. S2, see ESI†). No peak for the COD is detected after the immobilisation of $\text{Pd}(\text{COD})\text{Cl}_2$ on HAP. This probably indicates the facile loss of COD during immobilisation on the solid support, and suggests the structure of catalyst **1** to be as depicted in Scheme 1.

TEM images of both **1** and **2** show the presence of homogeneously distributed palladium nanoparticles on the HAP surface (Fig. 1). The sizes of the particles are in the range of 1.0 nm to 5 nm in **1**, and 2–5 nm in **2**. On the basis of previous literature reports the observation of Pd-nanoparticles after reduction, *i.e.*, in catalyst **2**, is expected. Such nanoparticles have been observed on both HAP supported $\text{Pd}(\text{OAc})_2$ and $\text{PdCl}_2(\text{MeCN})_2$ after reduction.^{19,37} However, in **1** where palladium is expected to be present as Pd^{2+} , observation of nanoparticles is surprising. Independent experimental verification of the palladium oxidation state by XPS and an explanation for clustering are therefore required.

As shown in Fig. 2, both fresh and used **1** were subjected to normal and grazing angle XPS analyses. Normal angle XPS analyses of fresh **1** show conclusively that palladium is present in the 2+ oxidation state. The $3d_{5/2}$ core level of Pd^{2+} is observed at the characteristic binding energy of 337.7 ± 0.1 eV. No significant change in the spectrum pattern is observed by changing the X-ray incidence angle from normal to grazing. In light of the XPS data we suggest that formation of Pd-nanoparticles in **1**, as observed by TEM, is induced by the electron beam. Such TEM induced agglomeration of discrete molecular species has previously been reported in other organo-metallic derived catalytic systems.^{38,39}

As Mori *et al.* did not observe any nanoparticles by TEM, a plausible explanation for the difference between the TEM data of our sample and that reported by Mori *et al.* is required.



Scheme 1 Synthetic outlines for the preparation of the catalysts **1** and **2**.

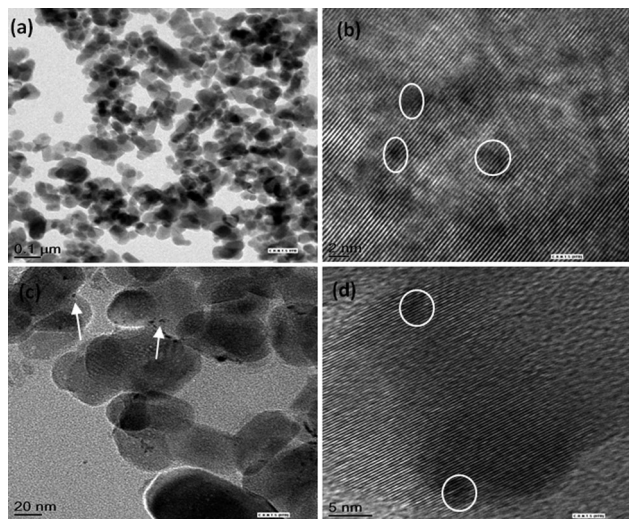


Fig. 1 FETEM image of the catalysts (a) **1** at 0.1 μm resolution, (b) **1** at 2 nm resolution, (c) **2** at 20 nm resolution and (d) **2** at 5 nm resolution.

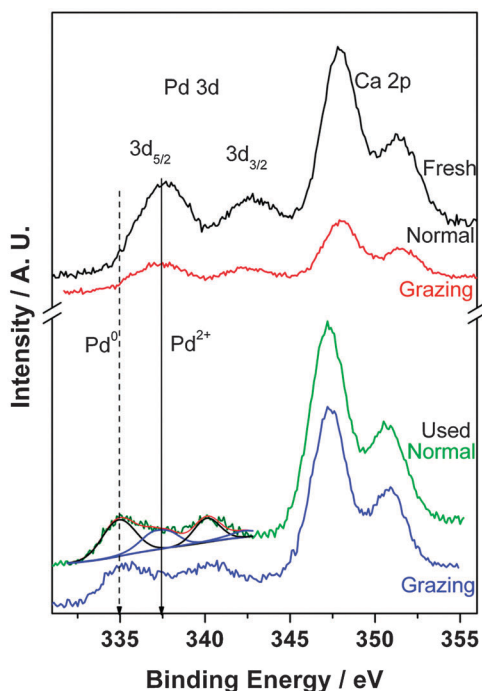


Fig. 2 Normal and grazing angle XPS spectra of Pd 3d and Ca 2p core levels of fresh and used **1**.

The extent of agglomeration caused by TEM is known to be dependent on various experimental conditions such as the specific molecular precursor, the energy of the electron beam *etc.* The differences between the TEM data is probably due to the fact that in our case the precursor was $\text{Pd}(\text{COD})\text{Cl}_2$, while Mori *et al.* had used $\text{PdCl}_2(\text{MeCN})_2$ as the precursor. Acetonitrile is a monodentate ligand capable of significant σ -donation while COD is a bidentate chelate where π -back-donation plays an important role.

In used **1** peaks for both $\text{Pd}(0)$ and Pd^{2+} are observed at normal angle and grazing angle spectra. The valley observed

between Pd 3d_{5/2} and 3d_{3/2} components in the fresh catalyst cannot be seen on the used catalyst. This observation suggests the presence of mixed oxidation state of Pd in the used catalyst. Deconvolution carried out on the used catalyst clearly demonstrates the presence of both metallic Pd^0 and Pd^{2+} ionic species.⁴⁰ Slow and incomplete reduction of Pd^{2+} is therefore brought about by conditions under which the catalytic runs are carried out. Thus, comparative XPS data of fresh and used **1** also strongly support the suggestion that in fresh **1** monomeric Pd^{2+} species are present.

The elemental composition of the surface of fresh and used **1** has been analysed by EDX (Fig. S3, see ESI[†]). Atomic mapping of fresh **1** exhibits the homogeneous distribution of palladium and calcium atoms on the surface of **1** (Fig. S4, see ESI[†]). The atom percentage ratio of palladium and chloride in fresh and used **1** are approximately 1:1 and 1.4:1, respectively.

By EXAFS analyses Mori *et al.* had shown that HAP supported Pd^{2+} had two different ligand environments.^{36,37} In one the coordination sites were occupied by two Cl^- and two oxygens of the surface PO_4^{3-} groups, while in the other all the four were occupied by four oxygens of two PO_4^{3-} . The observed 1:1 ratio of Pd:Cl suggests that in fresh **1** these two coordination environments are present in approximately equal proportion. The increased Pd:Cl ratio in used **1** indicates partial removal of Cl^- ligand from the coordination environment probably due to the following reaction: $\text{Pd}^{2+} + \text{Cl}^- + \text{H}_2\text{O} = \text{Pd}^0 + \text{H}^+ + \text{HOCl}$. This explanation is consistent with the XPS data which show some reduction of Pd^{2+} during a catalytic run. Formation of the Pd^0 can also be explained by the double transmetalation of Pd^{2+} species with aryl boronic acids followed by reductive elimination during the coupling reaction. Double transmetalation is responsible for the formation of the homo-coupled product in the SMC reaction. Detection of 1–5% of the homo-coupled products with different substrates can be correlated with the double transmetalation and consequent formation of Pd^0 .

Optimisation of the reaction conditions for Suzuki–Miyaura coupling

The reaction conditions for the SMCC reactions with **1** as the catalyst were first optimised keeping experimental convenience and good catalytic activity in mind. Reaction of 4-methylphenylboronic acid with iodobenzene was performed under aerobic conditions and parameters such as the type and quantity of base and phase-transfer agent was varied (see ESI[†], Table S1: entries 1–18). In all the cases selectivity of desired hetero-coupled product was determined. The amounts (<5%) of homo-coupled products were negligible in almost all the cases.

The choice of base in Suzuki coupling reaction is known to be important for maximum efficiency.⁴¹ In the present case K_2CO_3 is found to be the most effective one. The activity and selectivity drop significantly in the presence of a strong base such as NaOH. Even though the reaction takes place in the absence of any base, there is a notable reduction in the turnover numbers (see ESI[†], Table S1: entries 5, 12 and 14).

The promoting effects of surfactants or a phase-transfer catalyst such as tetrabutylammonium bromide (TBAB) in SMCC

reactions are well known.^{34,42–45} In ligand-free coupling reactions the essential role of such salts is to stabilise the active catalytic intermediates.⁴⁶ While the reaction between 4-methylphenylboronic acid and iodobenzene proceeds satisfactorily even in the absence of TBAB, in its presence there is a significant increase in turnovers (see ESI,† Table S1: entries 3 and 5).

Under the optimised molar ratios of substrates, base and TBAB, the catalytic activity of **2** in water is about one fifth of that of **1**. Similar relative activities are also observed in toluene. The much higher activity of **1** in both water and toluene is further confirmed in the reaction of 4-bromoacetophenone with phenylboronic acid (see ESI,† Table S1: entries, 1–2, 5–6, 15–18).

SMCC of aryl iodides and boronic acids

SMCC reactions of 16 different arylboronic acids with iodobenzene have been studied under the optimised conditions (Table 1). Electron rich, electron neutral and electron deficient arylboronic acids all give cross-coupled biaryls with high turnovers and good to excellent selectivity.

Steric hindrance in the *ortho*-position of arylboronic acids is tolerated though the turnover number (TON) decreases with increasing crowding. Thus, the TON for 4-methylphenyl-, 2-methylphenyl- and 2,6-dimethylphenyl boronic acid are approximately in the ratio of 3:2:0.6 (Table 1, entries 2–4). Similarly, phenylboronic acids substituted in *ortho* position by methoxy-, phenoxy- and benzyloxy- substituted give reduced but good (>1000) TON (Table 1, entries 5, 7 and 8). It may be noted that in the reactions between iodobenzene and 2-methylphenyl or 2-methoxyphenyl boronic acids, with other supported catalysts, much lower TONs (~110) have been reported.⁴⁷ Electron donating group in the *para*-position of arylboronic acids does not change TONs to a large extent (Table 1, entries 2 and 6). Reaction of iodobenzene with 2-chloroboronic acid results in lower conversion than with 4-chloroboronic acid. Reaction of thiophene boronic acid with iodobenzene gives a TON of 1582 (Table 1, entry 14).

SMCC reactions of electron deficient arylboronic acids is particularly important.⁴⁸ Lower nucleophilicity of these compounds leads to slow transmetallation and consequently these compounds often show resistance toward SMCC reaction.⁴⁹ However, with catalyst **1**, boronic acid derivatives with electron withdrawing groups (–NO₂, –CF₃) at the *para*-positions, good turnovers (>1500) are obtained (Table 1, entries 12–13). It may be noted that in the reaction between iodobenzene and 4-CF₃ substituted boronic acid, the TON with **1** is about three times that of the literature reported TON with a supported catalyst in water.⁵⁰

Synthesis of polyaryls by SMCC reactions is important because such organic fragments find use in pharmaceuticals and materials.^{51–53} Reaction of α -naphthylboronic acid with iodobenzene is catalysed by **1** with good turnovers. The TON is about thirty times that of the literature reported TON in water with supported catalyst.⁴⁷ However, with the β -naphthylboronic acid the TON is about one third of that with the α -isomer (Table 1, entries 15–16).

Table 1 Suzuki–Miyaura cross-coupling reaction of iodobenzene and aryl boronic acids with **1**^a

Entry	ArB(OH) ₂	Product	TON ^b	Hetero-coupled product selectivity ^c
1			2941	100
2			2941	97
3			2243	87
4			522	97
5			1430	93
6			2941	99
7			1412	99
8			1176	97
9			1823	94
10			2265	84
11			2028	78
12			1617	91
13			1705	89
14			1587	88
15			2558	99
16			763	99

^a Reaction conditions: the catalytic reactions were carried out with 0.5 mmol iodobenzene, 0.6 mmol aryl boronic acid, 1.5 mmol K₂CO₃, 1.7 × 10^{−4} mmol Pd, 0.5 mmol TBAB, 5 mL water at 353 K for 24 h under atmospheric conditions. ^b Yield was determined by GC and TON was calculated from GC yield. ^c Determined by GC.

Reactions of 4-methyliodobenzene instead of iodobenzene with six different arylboronic acids reveal that the presence of a methyl group in the *para*-position increases the TON slightly for electron deficient arylboronic acids. Thus, for aryl boronic acids substituted in the 4-position of the phenyl ring by $-\text{NO}_2$, $-\text{CF}_3$ and $-\text{Cl}$ groups (Table 2, entries 3, 4 and 6) the increase in TON is approximately 7, 4 and 17%. The increase in TON is more notable for the sterically demanding 2,6-dimethylphenylboronic acid (Table 2, entry 2) where an increase of $\sim 68\%$ is observed.

Activation of aryl bromides

Reactions of six different aryl bromides with five different aryl boronic acids have been studied (Table 3). In most cases good turnover and high selectivity are obtained. Thus, even bromophenol, known to be a poor substrate in SMCC reaction, gives a moderate TON of 700 (Table 3, entry 3). With 4-bromoacetophenone good (>2500) TON (Table 3, entries 4–5) are obtained. It may be noted that for both bromophenol and 4-bromoacetophenone with previously reported HAP supported catalyst notably lower TONs (~ 250) were obtained.¹⁹ 1,4-dibromobenzene can be successfully activated to give polyaryl 4-phenylbiphenyl (Table 3, entry 6).

1-phenylnaphthalene has been obtained both by the reaction of α -naphthaleneboronic acid with bromobenzene, and by the reaction of phenylboronic acid with α -bromonaphthalene. With a supported catalyst such as **1**, due to diffusion constraints the activation of sterically hindered aryl halide is expected to be especially difficult. In accordance with such expectation, the TON for the former pair is about two and a half times more than that of the latter (Table 3, entries 7–8).

N-heteroaryl halides are generally considered as poor substrates for SMCC reactions. In water the uses of N-heteroaryl halides and N-heteroarylboronic acids for SMCC reactions have

recently been reported.^{54,55} Catalyst **1**, is found to be efficient enough to give more than a thousand turnovers in the reaction of 2-bromopyridine with 4-methylphenylboronic acid (Table 3, entry 9). Similarly, in the reaction of electron deficient 4-nitrophenylboronic acid with bromobenzene more than 1500 turnovers are obtained (Table 3, entry 10).

Activation of aryl chlorides

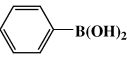
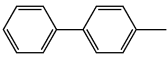
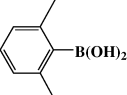
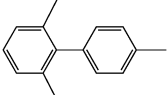
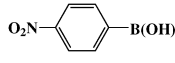
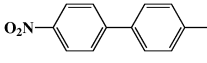
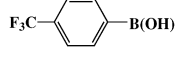
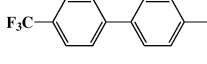
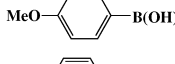
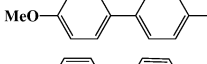
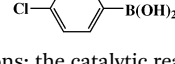
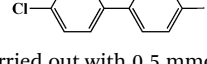
As mentioned earlier, one of the objectives of this work was to develop a supported catalyst for the activation of cheap and commercially available aryl chlorides in water.^{56–59} Reactions of three such aryl chlorides with five different aryl boronic acids using **1** as the catalyst have been studied under the optimised conditions. Both chlorobenzene and 4-chlorotoluene give good and notably higher TON than 4-chloronitrobenzene (Table 4, entries 1–3). However even with 4-chloronitrobenzene the TON is close to a thousand. It may be noted that for the SMCC reactions between 4-chloronitrobenzene and phenylboronic acid, TONs only in the range of 20–200 have been reported with other supported catalysts.^{59–61} Even with 4-bromonitrobenzene, a more reactive substrate, using Pd/C (10%) as the catalyst TONs ≤ 100 have been reported.⁶²

Successful couplings of electron deficient 4-nitrophenylboronic acid and sterically crowded 2,6-dimethylphenylboronic acid with chlorobenzene can also be achieved with **1** and the TONs are comparable to that of iodobenzene (Table 4, entries 4 and 5). Polyaryl 1-phenylnaphthalene is also produced with more than a thousand turnovers by the reaction of chlorobenzene and α -naphthylboronic acid (Table 4, entry 6).

Recycling experiment

Good recyclability of a supported catalyst ensures that over several batches the total accumulated TON is substantial. The catalyst **1** has been recycled 10 times in the SMCC reaction

Table 2 Suzuki–Miyaura cross-coupling reaction of 4-methyliodobenzene and aryl boronic acids with **1**^a

Entry	ArB(OH) ₂	Product	TON ^b	Hetero-coupled product selectivity ^c
1			2941	98
2			882	95
3			1735	94
4			1765	91
5			2941	96
6			2646	83

^a Reaction conditions: the catalytic reactions were carried out with 0.5 mmol 4-methyliodobenzene, 0.6 mmol aryl boronic acid, 1.5 mmol K₂CO₃, 1.7×10^{-4} mmol Pd, 0.5 mmol TBAB, 5 mL water at 353 K for 24 h under atmospheric conditions. ^b Yield was determined by GC and TON was calculated from GC yield. ^c Determined by GC.

Table 3 Activation of aryl bromides for the Suzuki–Miyaura cross-coupling reaction with **1**^a

Entry	ArB(OH) ₂	Ar'–Br	TON ^b	Hetero-coupled product selectivity ^c
1			2941	98
2			2941	97
3			705	81
4			2676	97
5			2823	92
6 ^d			2411	90
7			823	95
8			2176	94
9			1088	96
10			1559	92

^a Reaction conditions: the catalytic reactions were carried out with 0.5 mmol aryl bromide, 0.6 mmol aryl boronic acid, 1.5 mmol K₂CO₃, 1.7 × 10⁻⁴ mmol Pd, 0.5 mmol TBAB, 5 mL water at 353 K for 24 h under atmospheric conditions. ^b Yield was determined by GC and TON was calculated from GC yield. ^c Determined by GC. ^d 0.5 mmol aryl bromide, 1.5 mmol phenylboronic acid, 3 mmol K₂CO₃, 3.4 × 10⁻⁴ mmol Pd, 1 mmol TBAB, 8 mL water at 353 K for 24 h under atmospheric conditions.

of 4-methylphenylboronic acid and iodobenzene. As can be seen in Fig. 3, the drop in activity has been negligible and a total turnover of ~30 000 is achieved.

The TEM image of the used catalyst after 10th cycle is similar to that of the used catalyst after one batch. For successive batches after separation of **1**, no palladium could be detected in the aqueous filtrate (see Experimental Section). The fact that metal leaching does not take place is further confirmed by estimating the amount of palladium in used catalyst after the 10th cycle. No observable difference in palladium content is observed between fresh **1**, and used **1** recycled for ten times.

Heterogeneity of the catalytic systems has been further proved by hot filtration method. The reaction of 4-methylphenyl boronic acid with iodobenzene was carried out up to 6 h when 32% conversion was achieved. The catalyst was separated by centrifugation (5000 rpm, 5 min) at the hot condition and the reaction was again continued with the filtrate for 24 h. Only 4% increase in the conversion was detected. This experiment definitely proves that the catalysis is not done with partially dissolved Pd(COD)Cl₂ or other leached palladium species. Amount of the palladium in the solution after the

Table 4 Activation of aryl chlorides for the Suzuki–Miyaura cross-coupling reaction with **1**^a

Entry	ArB(OH) ₂	Ar'–Cl	TON ^b	Hetero-coupled product selectivity ^c
1			2234	82
2			941	94
3			2323	86
4			1352	89
5			471	92
6			1235	83

^a Reaction condition: the catalytic reactions were carried out with 0.5 mmol aryl chloride, 0.6 mmol aryl boronic acid, 1.5 mmol K₂CO₃, 1.7 × 10⁻⁴ mmol Pd, 0.5 mmol TBAB, 5 mL water at 353 K for 24 h under atmospheric conditions. ^b Yield was determined by GC and TON was calculated from GC yield. ^c Determined by GC.

reaction is also beyond the limit of detection of ICP-AES (see experimental).

Finally the scale up potential of the catalytic system has also been evaluated. The reaction has been carried out with 10 mmol of 4-bromoacetophenone and 12 mmol of phenylboronic acid with 100 mg of **1** in water. Reproducible data with turnovers close to 3000 is obtained with a slight drop in hetero-coupled product selectivity (97 to 93%).

Conclusions

In conclusion, the work demonstrates the synthesis of hydroxyapatite supported novel palladium catalyst and its application to the Suzuki–Miyaura cross-coupling reaction in water under atmospheric conditions. With **1** as the catalyst a wide variety of electronically neutral, electron rich, electron poor or sterically hindered aryl boronic acids and aryl halides are shown to undergo SMCC reactions with good turnovers. Catalyst **1** with Pd²⁺ exhibits much better catalytic activities compared to **2**. The TON and product yield towards hetero-coupled product in water are found to be comparable to those obtained in organic solvent and superior to that of many other literature reported supported catalysts. Similar results are also obtained with a range of aryl chlorides and boronic acids. Catalyst **1** has been recycled ten times without any metal leaching and with negligible drop in activity.

Experimental Section

Chemicals

Hydroxyapatite, 1,5-cyclooctadiene (COD) were purchased from Aldrich. Sodium borohydride, inorganic bases, hydrochloric

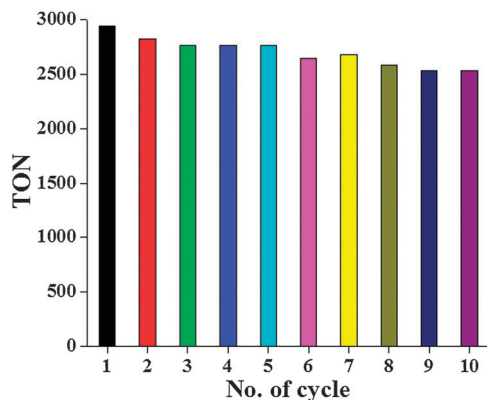


Fig. 3 Recycling experiment of the catalyst **1** in terms of TON during the reaction of 4-methylphenylboronic acid and iodobenzene in water.

acid and solvents were obtained from Merck India Limited, Mumbai, India. All the aryl halides and boronic acids were procured from Alfa Aesar or Fluka or Aldrich or Spectrochem Pvt. Ltd, India. Palladium chloride and tetrabutylammonium bromide (TBAB) were obtained from Spectrochem Pvt. Ltd, India. $[\text{Pd}(\text{COD})\text{Cl}_2]$ was prepared according to the literature reported procedure.⁶³ Double distilled water was used for the catalytic reactions in aqueous medium. Nitrogen cylinder was supplied by BOC India. Dry solvents were used for the reactions where necessary. All other reagents are of analytical grade and used as received without further purification.

Instrumentation

Bruker AV III 400 MHz FT-NMR and 400 MHz Varian FT-NMR spectrometer have been used for recording NMR. FTIR spectra in ATR mode was recorded in Nicolet Instruments Corporation, USA (Model: MAGNA 550). TEM images of fresh and used catalysts have been recorded in JEOL-JEM-2100F FEG-TEM transmission electron microscope. Powder XRD of the catalysts and HAp was recorded in Philips powder diffractometer PW3040/60 with Cu K α radiation. Palladium content of the catalysts and reaction mixture was determined by ICP-AES instrument (Arcos from M/s. Spectro, Germany, Detection limit: 1 $\mu\text{g L}^{-1}$ or ppb). Conversions and hetero-coupled product selectivity of the reactions were monitored by GC mass spectrometer GCD-HP1800A from Hewlett-Packard Company, USA, Shimadzu GC-2014 gas chromatograph with FID detector using a capillary column (Sigma Aldrich, Supelco, Astec, Chiraldex B-DM; length 50 m, inner diameter 0.25 mm, thickness 0.12 μm) and liquid chromatogram mass spectrometer from Varian Inc, USA (410 Prostar Binary LC with 500 MS IT PDA Detectors).

Syntheses of the catalysts

Synthetic procedure for the preparation of the catalysts is shown in Scheme 1.

Synthesis of catalyst 1. Finely powdered hydroxyapatite $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$ (251 mg, 0.5 mmol) was added to a solution of $[\text{Pd}(\text{COD})\text{Cl}_2]$ (28.5 mg, 0.1 mmol) in 10 mL of CH_2Cl_2 and stirred for 48 h at 300 K. The mixture was centrifuged at a speed

of 5000 rpm for 15 min. The supernatant liquid was decanted off and the residue was washed with CH_2Cl_2 (5×20 mL). The residue was collected and dried at 300 K in vacuum for 6 h. The amount of Pd was 3.4×10^{-2} mmol g^{-1} (determined by ICP-AES analysis).

Synthesis of catalyst 2. 100 mg of catalyst **1** was suspended in 10 mL of ethanol. Freshly prepared solution of NaBH_4 (38 mg, 1.00 mmol) in 10 mL ethanol was added to the mixture for 10 min with vigorous stirring. Immediate change in the colour of the solid from yellow to grey was observed. The mixture was stirred for 1 h at 300 K, centrifuged at 5000 rpm for 15 min and washed with ethanol (5×10 mL). The solid was collected and dried in vacuum. The amount of Pd was 3.1×10^{-2} mmol g^{-1} (determined by ICP-AES analysis).

Catalytic reaction

The catalytic reactions were performed in organic solvents or in aqueous medium. 0.5 mmol aryl halide, 0.6 mmol aryl boronic acid, 1.5 mmol base, 1.7×10^{-4} mmol Pd as catalyst and 5 mL of solvent were used for the Suzuki coupling reaction. Phase transfer reagent TBAB (0.5 mmol) was used for the reaction in aqueous medium. Reactants, catalyst, base and solvent were taken in a Schlenk tube, closed with a rubber septum and placed in the oil bath preheated at the desired temperature with stirring (1000 rpm). After completion of the reaction, the Schlenk tube was cooled to room temperature. Product mixture was extracted with diethyl ether or ethyl acetate (3×5 mL). The combined extracts were collected. Conversion and product yield were determined by gas chromatographic technique using naphthalene as an external standard. The products were characterised by comparing with standard samples in gas chromatographic technique/GCMS and ^1H NMR. The turn over number (TON) was described as the mmol of substrate converted to product by 1 mmol of palladium.

Recycling test

After extraction of the product, the same aqueous solution was used for the recycling experiment without recovering the catalyst. 0.5 mmol aryl halide, 0.6 mmol aryl boronic acid, 0.5 mmol base were added to the solution mixture and the reaction was continued for the next cycle.

Leaching test for palladium

To justify the stability of catalyst **1**, leaching of palladium in the reaction solution was tested. After completion of the reaction, product was extracted and the aqueous solution was centrifuged at 5000 rpm for 10 min. The supernatant liquid was collected, evaporated to dryness and treated with aqua regia. The amount of palladium in the solution, determined by ICP-AES, was beyond the limit of detection.

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