PAPER

NJC
www.rsc.org/njc

Catalytic investigations of carbon–carbon bond-forming reactions by a hydroxyapatite-bound palladium complex

Kohsuke Mori, Takayoshi Hara, Michitaka Oshiba, Tomoo Mizugaki, Kohki Ebitani and Kiyotomi Kaneda*

Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka, 560-8531, Japan.
E-mail: kaneda@cheng.es.osaka-u.ac.jp; Fax: +81-6-6850-6260; Tel: +81-6-6850-6260

Received (in Montpellier, France) 3rd May 2005, Accepted 24th June 2005
First published as an Advance Article on the web 19th July 2005

A new type of hydroxyapatite-bound palladium complex (PdHAP-1) was synthesized by treatment of a nonstoichiometric Ca-deficient hydroxyapatite, $Ca_9(HPO_4)(PO_4)_5(OH)$, with $PdCl_2(PhCN)_2$ in acetone solution. Characterization by means of physicochemical methods revealed that a monomeric Pd^{II} phosphate complex could be generated at a Ca-deficient site, which displayed outstanding catalytic activities for the Mizoroki–Heck reaction and Suzuki–Miyaura coupling reaction of aryl bromides. The remarkably high catalytic activity of the hydroxyapatite catalyst is ascribed to the exceptionally robust monomeric Pd structure, in which Pd is surrounded by anionic phosphate ligands, as confirmed by XAFS analysis. It is also proven that, upon adjustment of the solvent system, the PdHAP-1 was able to catalyze the Suzuki–Miyaura coupling of activated aryl chlorides in the presence of TBAB. Under such conditions, the *in situ* generated Pd nanocluster on the surface of hydroxyapatite was effective as a catalytically active species.

Introduction

Palladium is one of the most versatile and efficient catalyst metals in organic synthesis because of its unique catalytic performance for a wide range of functional group transformations and for carbon–carbon bond-forming reactions.[1] In modern palladium chemistry, various forms of Pd reagents have been explored as catalysts, *e.g.* simple Pd salts such as $PdCl_2$ and $Pd(OAc)_2$, mononuclear organopalladium complexes, molecular clusters, and colloidal particles. Generally, the precise architectures of the Pd species play a crucial role in designing highly functionalized Pd catalyst systems that are responsible for the target organic transformations. In particular, transition metal complexes, in which both steric and electronic properties can be tuned up by varying the active metal center and/or organic ligands, have been developed. Unfortunately, such complexes are faced with a number of disadvantages such as thermal instability and difficulties in catalyst separation and recovery. Alternatively, the use of a solid surface as a macroligand has proved a powerful protocol to create stable active sites, which has the advantages of being operationally simple, as well as enabling unprecedented reactions reflected by synergistic effects between the catalytically active species and the support.[2]

Palladium-mediated cross-coupling reactions between aryl halides and nucleophiles, such as the Mizoroki–Heck and Suzuki–Miyaura coupling reactions, have received considerable attention due to their enormous synthetic potential to form new carbon–carbon bonds.[3] New classes of Pd^{II} complexes having Pd–carbon σ bonds, *e.g.* palladacycle complexes,[4] PCP pincer-type complexes,[5] and *N*-heterocyclic carbenes (NHCs),[6] have led to significant breakthroughs in this area. More recently, Pd complexes based on electron-rich and sterically hindered tertiary phosphines have been demonstrated to enable the smooth reaction of traditionally sluggish aryl chlorides.[7] From practical and economical considerations, however, the demand for phosphine-free heterogeneous systems is still extremely high in order to circumvent the previously mentioned drawbacks imposed by homogeneous complexes. Although most effort has been directed toward the anchoring of efficient soluble systems onto insoluble matrices,[8] these hybrid catalysts have been inadequate due to: (i) inferior activities, as compared to their homogeneous analogues, (ii) tedious multi-step preparations, and (iii) leaching of the active components.

Hydroxyapatites possess Ca^{2+} sites surrounded by PO_4^{3-} tetrahedra parallel to the hexagonal axis, which are of considerable interest in many areas owing to their multiple functionalities.[9,10] The chemical composition of HAPs can be modified from the stoichiometric form, $Ca_{10}(PO_4)_6(OH)_2$ ($Ca/P = 1.67$), to the nonstoichiometric Ca-deficient form, $Ca_{10-z}(HPO_4)_z(PO_4)_{6-z}(OH)_{2-z}$ ($0 < z \leq 1$, $1.5 \leq Ca/P < 1.67$).[9] We have recently demonstrated that a monomeric $PdCl_2$ species grafted by chemisorption on the surface of the stoichiometric HAP (PdHAP-0) was readily transformed into Pd nanoclusters having a narrow size distribution in the presence of reducing reagents, *e.g.*, alcohols and molecular hydrogen. Such nanostructured Pd species could effectively promote the aerobic oxidation of alcohols,[11,12] indoline dehydrogenation,[13] and deprotection of Z-groups[14] as well as dehalogenation of haloarenes[15] with molecular hydrogen. Unfortunately, our preliminary experiments revealed that the PdHAP-0 failed to catalyze the Mizoroki–Heck reaction of bromobenzene with styrene, where the catalyst encountered severe deactivation due to the undesired irreversible agglomeration of the Pd metals.[11]

We envisioned that the introduction of Pd species into the Ca-deficient site of the apatite framework, which acts as a promising macroligand for catalytically active centers, could generate a robust heterogeneous Pd catalyst for carbon–carbon bond-forming reactions. The present work reports the synthesis of a novel hydroxyapatite-bound Pd complex using nonstoichiometric Ca-deficient HAP and describes its unprecedented catalytic activity for the Mizoroki–Heck and

DOI: 10.1039/b506129f

Suzuki–Miyaura coupling reactions of aryl bromides. The unique catalytic performance is related to the structure of the active palladium species and the work is further extended to the activation of aryl chlorides.

Results and discussion

Preparation and characterization of the catalyst

Ca-deficient hydroxyapatite, $Ca_9(HPO_4)(PO_4)_5(OH)$ (HAP-1; $z = 1$, Ca/P = 1.50), was synthesized according to the literature procedure from $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2HPO_4$ by adjusting the Ca/P molar ratio to 1.50 in the precipitation sequence.[16] The prepared HAP-1 was identified using powder X-ray diffraction (XRD), infrared spectroscopy (IR), and elemental analysis. The Brunauer–Emmett–Teller (BET) surface area of this sample was found to be 48.4 $m^2\ g^{-1}$. It is well known that the crystallographic structure of the Ca-deficient HAP is identical to that of the stoichiometric one, and that its charge deficiency due to the lack of Ca^{2+} in the lattice is compensated by the introduction of H^+ into the PO_4^{3-} ion and the removal of OH^- from the parent unit cell. Immobilization of the palladium precursor on the HAP-1 was achieved by the impregnation method in organic solvents. Treatment of the HAP-1 with an acetone solution of $PdCl_2(PhCN)_2$ for 3 h at room temperature yielded PdHAP-1 (Pd content: 0.015 mmol g^{-1}) as a white powder. The BET surface area of PdHAP-1 was slightly decreased after the immobilization process from 48.4 $m^2\ g^{-1}$ to 45.2 $m^2\ g^{-1}$. This observation suggests that the Pd species might be incorporated into the quite limited space available in the hydroxyapatite.

In an effort to elucidate the structure of surface-bound Pd species on the catalyst, characterization using physicochemical methods was performed. XRD peaks for PdHAP-1 were similar to that of the parent Ca-deficient hydroxyapatite. The absence of chlorine in PdHAP-1 was confirmed by X-ray photoelectron spectroscopy (XPS) and energy-dispersive X-ray (EDX) spectroscopy. No signals assignable to the ν(CN) band could be observed in IR spectroscopy, suggesting that PhCN ligands arising from the Pd precursor were not present in the immobilized Pd species. The absence of carbon and nitrogen atoms in PdHAP-1 was also evidenced by CHN elemental analysis. Inductively coupled plasma (ICP) analysis revealed that no Ca was present in the filtrate after palladium loading. Therefore, an isomorphic substitution of Pd for Ca did not occur in the above preparation sequence utilizing organic solvents. Fig. 1 shows the Pd K-edge X-ray absorption near-edge structure (XANES) spectra of the PdHAP-1 along with those of Pd oxide and Pd foil as reference samples. The absorption edge varies with respect to the oxidation state of palladium, and the XANES spectrum of PdO has one broad peak at around 24 365 eV, while Pd foil showed two distinct peaks at around 24 360 and 24 384 eV, corresponding to the allowed 1s → 5p transition.[17] The shapes of the XANES spectra and the edge position in the PdHAP-1 (**A**) resembled those of Pd oxide (**D**) but differed from those of Pd foil (**E**), which reveals that all Pd species are in the +2 oxidation state. The Fourier transforms (FT) of k^3-weighted extended X-ray absorption fine structure (EXAFS) data are depicted in Fig. 2. No peaks due to Pd–Pd and Pd–O–Pd bonds in the second coordination sphere, detectable in those of Pd foil and Pd oxide at around 2.5 and 3.0 Å, were observed for the PdHAP-1 (**A** *versus* **D** and **E**). The best fit for the PdHAP-1 was achieved using only a Pd–O bond having an interatomic distance (R) of 2.01 Å and a coordination number (CN) of 4, respectively (Table 1). The distances from Pd to the nearest O atoms were essentially coincident with the values for the Pd–O bond in Pd oxide (R = 1.99 Å).[17] The second neighboring Pd–O bonds were assigned to the weak interaction between the Pd and PO_4^{3-} ions of hydroxyapatite. On the basis of these results, it is

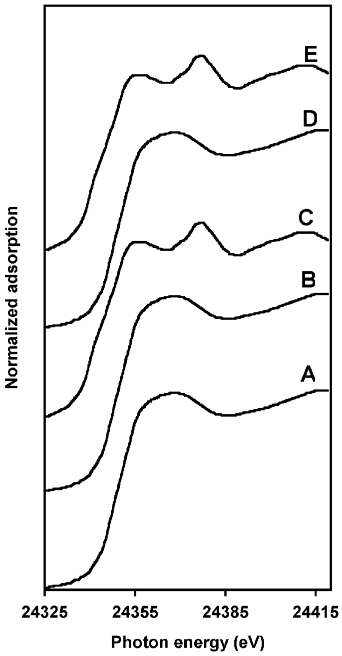


Fig. 1 Pd K-edge XANES spectra of (**A**) PdHAP-1, (**B**) recovered PdHAP-1 for the Mizoroki–Heck reaction of **1a** with **2a**, (**C**) recovered PdHAP-1 for the Suzuki–Miyaura coupling reaction of **4a** with **3a**, (**D**) PdO, and (**E**) Pd metal. Mizoroki–Heck reaction was conducted with PdHAP-1 (0.1 g, 0.075 mol% Pd based on **1a**), **1a** (2 mmol), **2a** (2.4 mmol), K_2CO_3 (2.4 mmol), and NMP (5 ml) at 130 °C for 2 h under an Ar atmosphere. Suzuki–Miyaura coupling reaction was conducted with PdHAP-1 (0.15 mol% of Pd based on **4a**), **4a** (1 mmol), **3** (1.5 mmol),

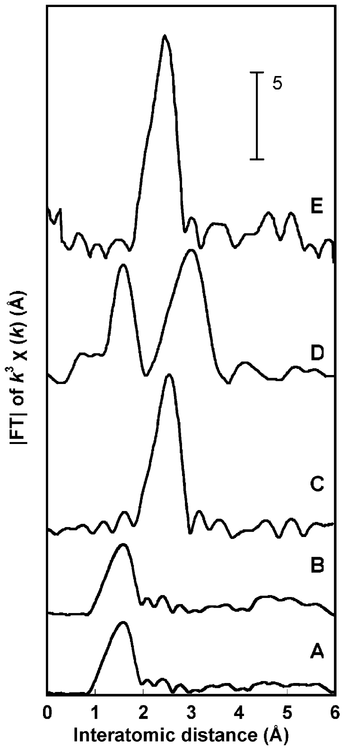


Fig. 2 Fourier-transforms of k^3-weighted Pd K-edge EXAFS experimental data for (**A**) PdHAP-1, (**B**) recovered PdHAP-1 for the Mizoroki–Heck reaction of **1a** with **2a**, (**C**) recovered PdHAP-1 for the Suzuki–Miyaura coupling reaction of **4a** with **3a**, (**D**) PdO, and (**E**) Pd metal. Phase shift was not corrected. Mizoroki–Heck reaction was conducted with PdHAP-1 (0.1 g, 0.075 mol% Pd based on **1a**), **1a** (2 mmol), **2a** (2.4 mmol), K_2CO_3 (2.4 mmol), and NMP (5 ml) at 130 °C for 2 h under an Ar atmosphere. Suzuki–Miyaura coupling reaction was conducted with PdHAP-1 (0.15 mol% of Pd based on **4a**), **4a** (1 mmol), **3** (1.5 mmol), DMF (5 ml), H_2O (0.1 ml), K_3PO_4 (2 mmol) and TBAB (0.1 mmol) at 130 °C for 1 h under an Ar atmosphere.

Table 1 Curve-fitting analysis for PdHAP-1 catalysts[a]

Sample	Shell	CN[b]	R/Å[c]	$\Delta\sigma$/Å^{2}[d]
PdHAP-1(**A**)	Pd–O(1)	4.2	2.01	0.0031
	Pd–O(2)	3.0	2.34	0.0342
Recovered PdHAP-1(**B**) (Mizoroki–Heck reaction of **1a**)	Pd–O(1)	4.1	2.01	0.0020
	Pd–O(2)	3.0	2.33	0.0233
Recovered PdHAP-1 (**C**) (Suzuki–Miyaura reaction; of **4a**)	Pd–Pd	10.6	2.76	0.0021

[a] Inverse Fourier transformations were performed for the regions of 0.9–2.0 Å in Fig. 2A, 0.9–2.0 Å in Fig. 2B, and 0.95–3.0 Å in Fig. 2C. [b] Coordination number. [c] Interatomic distance. [d] Difference between Debye–Waller factor of PdHAP and that of the reference sample.

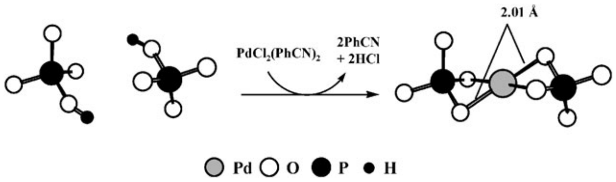


Fig. 3 A proposed surface reaction of $PdCl_2(PhCN)_2$ with Ca-deficient hydroxyapatite to generate monomeric Pd^{II} phosphate complex.

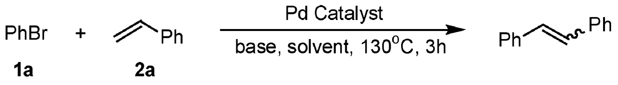
proposed that the most reasonable surface structure of PdHAP-1 is as illustrated in Fig. 3. This comprises a monomeric Pd^{II} phosphate complex surrounded by four oxygen atoms in square planar coordination, which is formed at the Ca-deficient site of the HAP-1 with the loss of 2 equivalents of PhCN and HCl. The proposed surface structure of PdHAP-1 is in sharp contrast to that of the Pd-grafted hydroxyapatite prepared previously by the same method using the stoichiometric HAP, in which a monomeric $PdCl_2$ species is chemisorbed on the HAP surface.[11,12] The present simple preparation method based on the precise control of the Ca/P ratios of the parent hydroxyapatites provides a powerful protocol to create two unique monomeric Pd species with intrinsically different surroundings on solid surfaces.

The calculated PO_4^{3-} ion coverage on the surface of hydroxyapatites is 5(PO_4^{3-}) nm^{-2},[18] which is estimated to be approximately 0.42 mmol g^{-1} for this surface area. However, the maximum Pd loadings for the PdHAP-1 only reached 0.015 mmol g^{-1}. This indicates that the Pd species may be located at specific sites of the hydroxyapatite surface, that is, at sites with the appropriate distances and arrangements between two adjacent PO_4^{3-} ions to allow the complexation of the Pd ions.

Catalysis results

To explore the potential catalytic activity of PdHAP-1, the Mizoroki–Heck reaction of bromobenzene (**1a**) with styrene (**2a**) was carried out using various Pd catalysts. The results are summarized in Table 2. PdHAP-1 displayed the highest catalytic activity to give stilbene in 97% yield after 3 h (entry 1). Neither an induction period nor a color change of the catalyst was observed during the above reaction. In the case of conventional Pd catalysts, *e.g.* Pd/C, Pd/Al_2O_3, and Pd/SiO_2, full conversion could not be achieved and the yields of stilbene were 12, 5, and 9%, respectively (entries 2–4). The use of the homogeneous Pd precursor $PdCl_2(PhCN)_2$ led to a significant decrease in catalytic activity, accompanied with the formation of inactive Pd black (entry 5). With respect to the solvents, NMP was the most effective among those examined, whereas DMF and DMA were substantially less effective (entries 6 and 7). DMSO and *p*-xylene gave no yields (entries 8 and 9). DMSO is thought to act as a strong coordination solvent for Pd and thereby blocks active sites. The choice of base also has a significant influence on the efficiency of the Mizoroki–Heck reaction; K_2CO_3 gave the best result. On the other hand, Na_2CO_3 was found to be a poor base (entry 11). The reactions using organic bases such as NEt_3 and N(n-Bu)$_3$ hardly occurred (entry 13 and 14). These results are in sharp contrast to those with the polymer supported palladium *N*-heterocyclic carbene complex, in which NEt_3 acts as a favorable base in the Mizoroki–Heck reaction.[8e]

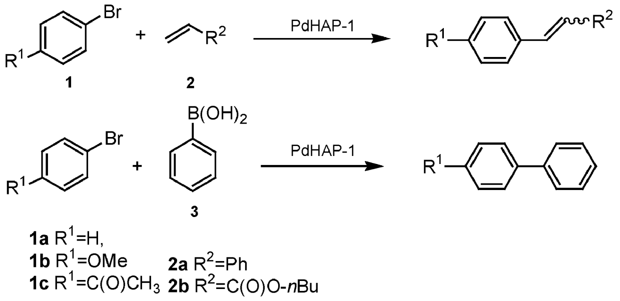
Table 2 Screening of the optimal reaction conditions for Mizoroki–Heck reaction of **1a** with **2a**[a]



Entry	Catalyst	Solvent	Base	Yield (%)[b]
1	PdHAP-1	NMP	K_2CO_3	97
2[c]	Pd/C	NMP	K_2CO_3	12
3[c]	Pd/Al_2O_3	NMP	K_2CO_3	5
4[c]	Pd/SiO_2	NMP	K_2CO_3	9
5	$PdCl_2$ $(PhCN)_2$	NMP	K_2CO_3	18
6	PdHAP-1	DMF	K_2CO_3	45
7	PdHAP-1	DMA	K_2CO_3	18
8	PdHAP-1	DMSO	K_2CO_3	0
9	PdHAP-1	*p*-Xylene	K_2CO_3	0
10	PdHAP-1	NMP	KOAc	51
11	PdHAP-1	NMP	Na_2CO_3	27
12	PdHAP-1	NMP	NaOAc	5
13	PdHAP-1	NMP	$N(Et)_3$	5
14	PdHAP-1	NMP	$N(Bu)_3$	2

[a] Reaction conditions: Pd catalyst (0.075 mol% based on **1a**), **1a** (2 mmol) **2a** (2.4 mmol), base (2.4 mmol), solvent (5 ml), 130 °C, Ar atmosphere, 3 h. [b] Yield = (mol of coupling product ($E + Z$))/(mol of initial **1a**). [c] 0.5 wt% of Pd. Purchased from N.E. Chemcat.

Table 3 Mizoroki–Heck and Suzuki–Miyaura coupling reactions catalyzed by PdHAP-1[a]



Entry	Aryl bromide	Acceptor	Time/h	Yield (%)[b]	TON
1	**1a**	**2a**	24	94	47 000
2	**1b**	**2a**	24	90	45 000
3	**1c**	**2a**	20	96	48 000
4	**1a**	**2b**	20	91	45 500
5	**1b**	**2b**	24	94	47 000
6	**1c**	**2b**	20	98	49 000
7[c]	**1a**	**3**	4	80	40 000
8[c]	**1b**	**3**	6	91	45 500
9[c]	**1c**	**3**	4	94	47 000

[a] Reaction conditions: aryl bromide (37.5 mmol), acceptor (45 mmol), PdHAP-1 (0.05 g, 2 × 10^{-3} mol% of Pd based on aryl bromide), K_2CO_3 (45 mmol), NMP (50 mL), 130 °C, Ar atmosphere. [b] Determined by GC analysis based on aryl bromide using an internal standard technique. [c] *o*-Xylene (50 mL) was used as solvent. 120 °C.

There is controversy whether the Mizoroki–Heck reaction using solid Pd catalysts occurred on the catalyst surface or not.[19] In the Mizoroki–Heck reaction of **1a** with **2a**, the catalyst was removed after 50% conversion at the reaction temperature, followed by addition of K_2CO_3 to the filtrate and further reaction at 130 °C for 6 h (hot leaching test). The Mizoroki–Heck reaction hardly occurred after catalyst removal. ICP analysis of the filtrate confirmed that the Pd content was below the detection limit (<1 ppb). In a separate experiment, the used PdHAP-1 catalyst was found to be recyclable with retention of its high catalytic activity; yields of 95% could be attained in at least three recycling experiments for the reaction of **1a** with **2a**.

The practical applicability of the present synthetic protocol is highlighted by the reaction with low catalyst concentrations, as summarized in Table 3. In the case of **1a** with **2a** using 2 × 10^{-3} mol% Pd, the reaction was completed within 24 h, in which the turnover number (TON) based on Pd approached up to 47 000 (entry 1). Electronic variation of the *p*-substituted aryl bromides did not significantly affect the reaction rates and the corresponding coupling products were obtained in excellent yields (entries 2 and 3). *n*-Butyl acrylate (**2b**) also successfully reacted with a variety of aryl bromides (entries 4–6). Unfortunately, cyclohexene and 1-octene proved to be poor olefins; the reactions hardly occurred even when 0.1 mol% Pd catalyst was employed. The use of aryl bromides bearing electron-donating groups at the *ortho* position also remarkably retarded the reaction rates, presumably due to steric hindrance occurring at the solid surface.

The Pd-catalyzed Suzuki–Miyaura coupling reaction between aryl halides and aryl boronic acids is one of the most powerful and versatile methods for the construction of unsymmetrical biaryls.[20] It has been found that PdHAP-1 acts as an outstanding catalyst for the Suzuki–Miyaura coupling reaction. For example, the TON based on Pd reached 45 500 after 6 h for the reaction of deactivated 4-bromoanisole (**1b**) with phenylboronic acid (**3**) (entry 8). A preliminary screening of optimal reaction conditions showed that *o*-xylene was superior to aprotic polar solvents such as DMF, DMA, and NMP. Several other bases including KOAc, Na_2CO_3, and triethylamine were also examined but all gave inferior results in comparison to K_2CO_3.

To gain an insight into the structure of the recovered PdHAP-1 catalyst, characterization by means of XAFS analysis was performed. The XANES spectrum of the recovered PdHAP-1 after the Mizoroki–Heck reaction of **1a** with **2a** was identical to that of the fresh catalyst, revealing that electronic configuration of the Pd species did not change (Fig. 1B *versus* A). The lack of peaks assignable to the Pd–Pd and Pd–O–Pd bonds in the Fourier transform of k^3-weighted Pd K-edge EXAFS showed that the Pd species is monomeric (Fig. 2B). Curve fitting analysis of the inverse FT could be completed by using two Pd–O bonds with the same distance and coordination numbers as those of the fresh one (Table 1). Also from TEM examination, no formation of the Pd particles was determined after the reaction. It can be concluded that the high catalytic activity of the PdHAP-1, as compared with other conventional heterogeneous Pd catalysts, is ascribed to the exceptional stability of the monomeric Pd species under the reaction conditions. Electrostatic interaction between the anionic phosphate ligand (PO_4^{3-}) on the surface of the Ca-deficient HAP and the Pd species might be effective in suppressing the Pd leaching into the solution and the subsequent agglomeration of the metal.[21]

The use of hydroxyapatite as a macroligand is a promising protocol for the creation of stable monomeric active sites, which also provides unique catalytic functions when compared with a traditional homogeneous Pd complex. In the present PdHAP-1 catalytic system, the competitive Mizoroki–Heck reactions in an equimolar mixture of *p*-substituted iodobenzenes using **2a** gave a Hammett ρ value of 1.09, which differs from the value of 2.00 obtained with $Pd(PPh_3)_4$.[22] In a competitive reaction between **2a** and **2b** with iodobenzene, the PdHAP-1 gave a relatively high product ratio of 9.6 between *n*-butyl cinnamate and stilbene. This value significantly exceeds that of 4.1 observed with $Pd(PPh_3)_4$. The above phenomena associated with extremely high activity toward deactivated aryl bromides suggest that the rate-determining step in the Mizoroki–Heck reaction catalyzed by PdHAP-1 is not the oxidative addition but rather the insertion of the olefin into the aryl-palladium intermediate. This finding is also supported by kinetic studies of the reaction between **1a** and **2a**, where the reaction rate is zero order for **1a** and first order for **2a**. We consider that the acceleration of the oxidative addition could be ascribed to the electron-donating effect of the anionic phosphate ligand to Pd species.[23] Additionally, sterically hindered circumstances around the Pd center surrounded by the solid ligand may prohibit the agglomeration of the unstable Pd^0 intermediate into an inactive species under the reaction conditions. These are analogous concepts to those used to explain the promotion of the oxidative addition step by electron-donating and/or bulky phosphine ligands,[7] thus indicating that hydroxyapatite can serve as a powerful alternative to such organic ligands.

Suzuki coupling reactions of chloroarenes

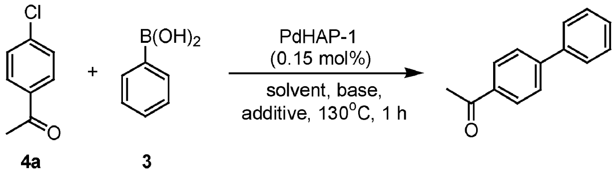
The utilization of readily available and inexpensive aryl chlorides in palladium-catalyzed cross-coupling reactions is a challenging task for industrial applications.[24] Since 1998, several research groups have described electron-rich and bulky ligands for homogeneous palladium complexes, in particular *N*-heterocyclic carbenes,[6] aryldialkyl phosphines,[7b,d] and P(*t*-Bu)$_3$,[7a,c,e] that exhibit high activities toward the activation of aryl chlorides. However, the cross coupling reactions of aryl chlorides using heterogeneous palladium catalysts have been relatively unexplored despite offering significant advantages from an environmental point of view.[25] As mentioned above, PdHAP-1 has proved to be an efficient heterogeneous catalyst for the Suzuki–Miyaura coupling reaction of aryl bromides. Unfortunately, the reaction of aryl chlorides hardly occurred under the standard conditions employed for the aryl bromides (*o*-xylene, K_2CO_3, 120 °C). Therefore, a further investigation was conducted to develop an effective heterogeneous catalyst system for the coupling reaction using *p*-chloroacetophenone (**4a**) as a model substrate with **3**.

As shown in Table 4, the catalytic activity of the PdHAP-1 was significantly improved in the presence of both TBAB ($Bu_4N^+Br^-$: 10 mol%) and a small amount of water (volumetric ratio: DMF : H_2O = 50 : 1), affording the corresponding 4-acetylbiphenyl in 92% yield for 1 h (entry 1 *vs.* 2–4). Addition of TBAI ($Bu_4N^+I^-$) led to a similar result (entry 5), but TBAC ($Bu_4N^+Cl^-$) retarded the reaction rate (entry 6). In the case of TEAB ($Et_4N^+Br^-$), a moderate yield of the coupling product was obtained (entry 7). The use of anionic (SDS; $CH_3(CH_2)_{10}CH_2OSO_3^-Na^+$) and nonionic surfactants (Span #80; sorbitan monooleate) did not influence the reaction rates (entries 8 and 9). Increasing the amount of TBAB up to 10 mol% relative to **4a** had a pronounced positive effect on the catalytic activity, but the yields of the coupling products gradually decreased at higher concentrations. It was also found that the optimal ratio of the solvent to water was determined to be 50 : 1, and further addition of water led to a considerable decrease in product yields. Among the solvents examined, DMF and NMP gave satisfactory yields (entries 1 and 10), whereas a non-polar solvent like *o*-xylene, which was the best solvent for aryl bromides, failed to promote the coupling reaction (entry 11). With respect to bases, K_3PO_4 and K_2CO_3 were found to be favorable (entries 1 and 12). Other bases such as KOH, K^{t}OBu, and NEt_3 were substantially less effective, and the use of Li_3PO_4 gave no product (entries 13–16).

The above optimal conditions are applicable to the Suzuki–Miyaura coupling reaction. Excellent yields of the cross-coupled products were obtained using various aryl chlorides bearing electron-withdrawing substituents, as summarized in Table 5. In all cases, the selectivities were almost 100% with no formation of the homo-coupled products. Under identical conditions, PdHAP-1 exhibited the highest catalytic activity when compared to other conventional heterogeneous catalysts, *e.g.* Pd/Carbon, Pd/Al_2O_3, and Pd/SiO_2 (entries 1–4). In the case of chlorobenzene, however, only a moderate yield of biphenyl was obtained (entry 8).

During the course of the reaction, the PdHAP-1 showed a quiet short induction period of a few minutes. Simultaneously, the color change of the catalyst from white to pale gray was observed. A TEM image of the isolated PdHAP-1 catalyst after the Suzuki–Miyaura coupling reaction of **4a** with **3** showed the presence of Pd^0 nanoparticles having a narrow size distribution

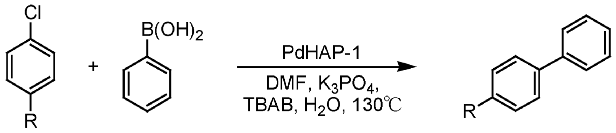
Table 4 Screening of the optimal reaction conditions for Suzuki-Miyaura coupling reaction of **4a** with **3**[a]



Entry	Solvent	Base	Additive	Yield (%)[b]
1	DMF : H_2O (50 : 1)	K_3PO_4	TBAB	92
2	DMF : H_2O (50 : 1)	K_3PO_4	—	34
3	DMF	K_3PO_4	TBAB	60
4	DMF	K_3PO_4	—	Trace
5	DMF : H_2O (50 : 1)	K_3PO_4	TBAI	90
6	DMF : H_2O (50 : 1)	K_3PO_4	TBAC	Trace
7	DMF : H_2O (50 : 1)	K_3PO_4	TEAB	60
8	DMF : H_2O (50 : 1)	K_3PO_4	SDS	29
9	DMF : H_2O (50 : 1)	K_3PO_4	Span 80	29
10	NMP : H_2O (50 : 1)	K_3PO_4	TBAB	90
11	*o*-xylene : H_2O (50 : 1)	K_3PO_4	TBAB	Trace
12	DMF : H_2O (50 : 1)	K_2CO_3	TBAB	82
13	DMF : H_2O (50 : 1)	NEt_3	TBAB	67
14	DMF : H_2O (50 : 1)	KOH	TBAB	63
15	DMF : H_2O (50 : 1)	KOtBu	TBAB	15
16	DMF : H_2O (50 : 1)	Li_3PO_4	TBAB	Trace

[a] Reaction conditions: **4a** (1.0 mmol), **3** (1.5 mmol), PdHAP-1 (0.15 mol% of Pd based on **4a**), solvent (5 ml), H_2O (0.1 ml), base (2 mmol), additive (0.1 mmol), 130 °C, Ar atmosphere. [b] Determined by GC analysis based on **4a** using and internal standard techniques.

Table 5 Suzuki–Miyaura coupling reaction of aryl chlorides[a]



Entry	Catalyst	R	Time/h	Yield (%)[b]
1	PdHAP-1	C(O)CH_3	1	92
2[c]	Pd/Carbon	C(O)CH_3	1	48
3[c]	Pd/Al_2O_3	C(O)CH_3	1	Trace
4[c]	Pd/SiO_2	C(O)CH_3	1	Trace
5	PdHAP-1	NO_2	1	>99
6[d]	PdHAP-1	CN	1	>99
7[e]	PdHAP-1	CHO	2	70
8[e]	PdHAP-1	H	5	30

[a] Reaction conditions: aryl chloride (1 mmol), **3** (1.5 mmol), PdHAP-1 (0.15 mol% of Pd based on aryl chloride), DMF (5 ml) H_2O (0.1 ml), K_3PO_4 (2 mmol), TBAB (0.1 mmol), 130 °C, Ar atmosphere. [b] Determined by GC analysis based on aryl chloride using an internal standard technique. [c] 0.5 wt% of Pd. Purchased from N.E. Chemcat. [d] Without H_2O. [e] Pd HAP-1 (0.3 mol % of Pd).

(Fig. 4(a)). From high-resolution TEM analysis, the mean diameter was determined to be *ca.* 50 Å (Fig. 4(b)). These observations are in good agreement with the results of Pd K-edge XAFS analysis. The XANES spectrum of the recovered PdHAP-1 (**C**) was similar to that of Pd foil (**E**). The FT of k^3-weighted EXAFS exhibited a single peak at approximately 2.5 Å due to the contiguous Pd–Pd bond in the metallic form with a *R* of 2.76 Å and a CN of 10.6, as shown in Fig. 2C and Table 1. It can be concluded that the monomeric Pd species on the PdHAP-1 surface, which was extremely stable under the reaction conditions of aryl bromides, was transformed into Pd^0 nanoparticles during the reaction of aryl chlorides. It is well known that the chemical and electrochemical reduction of transition metal salts in the presence of ammonium salts leads to $R_4N^+X^-$-stabilized metal colloids.[26] Recent studies have also pointed out the involvement of intermediary Pd nanoparticles generated under the conditions in the Mizoroki–Heck and Suzuki–Miyaura coupling reactions.[27] Hence, it is likely that $Bu_4N^+Br^-$-stabilized Pd^0 nanoparticles are formed *in situ* and then function as the catalyst under the present reaction conditions. The increase in the catalytic activity of the PdHAP-1 toward the activation of aryl chlorides observed on the addition of TBAB might be ascribed to the generation of anionic $[Br–Pd^0–L]^-$ (L = ligand or neighboring Pd) species on the surface of Pd nanoparticles, which facilitate the oxidative addition of aryl chlorides as discussed in previous papers.[28] The effect of water might be explained by its role in increasing the concentration of both TBAB and inorganic bases on the hydrophilic surface of the PdHAP-1.[29] Water exists as a supported thin film at the interface between the catalyst and the organic phase to enhance the accessibility of these reagents.[30]

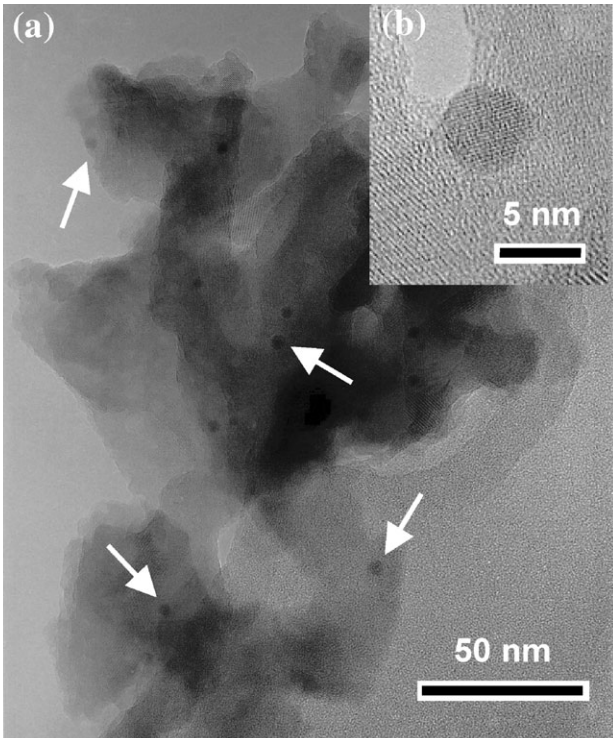


Fig. 4 (a) TEM image and (b) HR-TEM image of the Pd nanocluster for the recovered PdHAP-1 after Suzuki–Miyaura coupling reaction of **4a**. Reaction was conducted with **4a** (1 mmol), **3** (1.5 mmol), PdHAP-1 (0.15 mol% of Pd based on **4a**), DMF (5 ml), H_2O (0.1 ml), K_3PO_4 (2 mmol) and TBAB (0.1 mmol) at 130 °C for 1 h under an Ar atmosphere.

Conclusions

We have demonstrated a novel approach to catalyst design using hydroxyapatites and its excellent catalytic performances. Treatment of a nonstoichiometric Ca-deficient hydroxyapatite, $Ca_9(HPO_4)(PO_4)_5(OH)$, with $PdCl_2(PhCN)_2$ afforded a monomeric Pd phosphate complex surrounded by four oxygen atoms in square planar coordination. Such monomeric Pd species could effectively promote the Mizoroki–Heck and Suzuki–Miyaura coupling reactions of aryl bromides without any structural change around the Pd species. Moreover, the PdHAP-1 catalyst was also applicable to the Suzuki–Miyaura coupling reaction of aryl chlorides having electron-withdrawing substituents in the presence of TBAB and a small amount of water. No Pd leaching was observed for the above reactions and the catalysts were recyclable, making them highly suitable for large-scale operations and meeting the increasing demands for environmentally-inspired chemical processes.

Experimental

Materials

$PdCl_2$ was obtained from N. E. Chemcat Co. Ltd, and used without further purification. $(NH_4)_2HPO_4$ and $Ca(NO_3)_2 \cdot 4H_2O$ were purchased from Wako Pure Chemical Ind., Ltd. Solvents and all commercially available compounds were purified by standard procedures before use. All of the products are well known compounds and their identities were confirmed by comparison with IR, MS, and NMR spectra.

Synthesis of hydroxyapatite-bound palladium catalyst

$(NH_4)_2HPO_4$ (40.0 mmol) was dissolved in deionized water (150 mL) and the pH was adjusted to 11 with an aqueous NH_3 solution. To a solution of $Ca(NO_3)_2 \cdot 4H_2O$ (60.0 mmol) in deionized water (120 mL) adjusted to pH 11 with an aqueous NH_3 solution was added drop-wise over 30 min the above solution with vigorous stirring at room temperature, and then the resultant milky solution was heated at 90 °C for 10 min. The precipitate was filtered, washed with deionized water, and dried at 110 °C, giving nonstoichiometric Ca-deficient hydroxyapatite, $Ca_9(HPO_4)(PO_4)_5(OH)$ (HAP-1). HAP-1 (2.0 g) was stirred at 25 °C for 3 h in 150 mL of an acetone solution of $PdCl_2(PhCN)_2$ (2.67×10^{-4} M). The obtained slurry was filtered, washed with acetone and dried under vacuum, yielding 2.01 g of the PdHAP-0 (Pd content: 0.015 mmol g^{-1}).

Typical example for Mizoroki–Heck reaction

PdHAP-1 (0.05 g, Pd: 0.75 μmol) and K_2CO_3 (6.2 g, 45 mmol) were placed into a reaction vessel with a reflux condenser. Under an Ar atmosphere, *N*-methylpyrrolidone (NMP) (50 mL), bromobenzene (5.9 g, 37.5 mmol), and styrene (4.7 g, 45 mmol) were added, and then the resulting mixture was stirred at 130 °C. The progress of the reaction was monitored by GC analysis. After 24 h, 94% yield of stilbene ($E : Z = 15 : 1$) was obtained. The catalyst was removed by filtration, and the reaction mixture was poured into water (30 mL) to extract with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography on silica (eluent: hexane : ethyl acetate = 1 : 1) to give pure stilbene in a yield of 90% (6.1 g). For recycling experiments, a fresh reaction using bromobenzene (2 mmol), styrene (2.4 mmol), K_2CO_3 (2.4 mmol), NMP (5 mL), and PdHAP-1 (0.1 g, Pd: 1.5 μmol) was carried out at 130 °C under an Ar atmosphere. After 4 h, the reaction mixture was centrifuged and the liquid phase was decanted. The residual solid catalyst was again added to a fresh reaction solution and reacted under identical conditions. The first, the second, and the third runs gave stilbene in over 95% GC yields.

Typical example for Suzuki–Miyaura coupling reaction

PdHAP-1 (0.05 g, Pd: 0.75 μmol), K_2CO_3 (6.2 g, 45 mmol), and phenylboronic acid (5.5 g, 45 mmol) were placed into a reaction vessel with a reflux condenser. Under an Ar atmosphere, *o*-xylene (50 mL) and 4-bromoanisole (7.0 g, 37.5 mmol) were added, and the resulting mixture was stirred at 120 °C. The progress of the reaction was monitored by GC analysis. After 6 h, 91% yield of 4-methoxybiphenyl was obtained. The catalyst was filtered, and the reaction mixture was poured into water (30 mL) to extract with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography on silica (eluent: hexane : ethyl acetate = 1 : 1) to give 88% (6.1 g) of pure 4-methoxybiphenyl.

Typical example for Suzuki–Miyaura coupling reaction of aryl chlorides

PdHAP-1 (0.1 g, Pd: 1.5 μmol), K_3PO_4 (0.42 g, 2 mmol), phenylboronic acid (0.24 g, 1.5 mmol), and TBAB (0.03 g, 0.1 mmol) were placed into a reaction vessel with a reflux condenser. Under an Ar atmosphere, DMF (5 mL), H_2O (0.1 mL), and 4-chloroacetophenone (0.15 g, 1.0 mmol) were added, and the resulting mixture was stirred at 120 °C. The progress of the reaction was monitored by GC analysis. After 1 h, 92% yield of 4-acetylbiphenyl was obtained.

Characterization

Powder X-ray diffraction patterns were recorded using Philips X'Pert-MPD with Cu Kα radiation. X-ray photoelectron spectroscopy was measured on a Shimadzu ESCA-KM using MgKα radiation. Energy-dispersive X-ray measurement was performed using a Philips EDAX DX-4 attached to a SEM. Infrared spectra were obtained with a JASCO FTIR-410. Elemental analysis was carried out using a Perkin Elmer 2400CHN. Inductively coupled plasma measurements were performed on a Nippon Jarrell-Ash ICAP-575 Mark II. X-Ray absorption spectra were recorded using a fluorescence-yield collection technique at the beam line 01B1 station with an attached Si (311) monochromator at SPring-8, JASRI, Harima, Japan (prop. No. 2001A0563-UX-np). Fluorescence-yield data were collected at room temperature using the 19-element solid-state detector. Data reductions were performed with a FACOM M-780 computer system of the Data Processing Center of Kyoto University. The detailed procedure for data analysis is described elsewhere.[31] HR-TEM micrographs were obtained with a Hitachi Hf-2000 FE-TEM equipped with a Kevex energy-dispersive X-ray detector operated at 200 kV.

Acknowledgements

This work is supported by the Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science, and Technology of Japan (16206078). We thank Dr Takashi Yamamoto (Tokyo Institute Technology) and Dr Tomoya Uruga (JASRI) for XAFS measurement, and Dr Tomoki Akita (Osaka National Research Institute AIST) for TEM measurement. T. H. thanks the JSPS Research Fellowships for Young Scientists.

References

1 (*a*) R. F. Heck, *Palladium Reagents in Organic Syntheses*, Academic Press, London, 1985; (*b*) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, 1995; (*c*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259; (*d*) *Applied Homogeneous Catalysis with Organometallic Compounds*, ed. B. Cornils and W. A. Herrmann, VCH, Weinheim, 1996; (*e*) M. Beller and T. H. Riermeir, in *Transition Metals for Organic Syntheses*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 1996; (*f*) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633.

2 (*a*) B. C. Gates, *Chem. Rev.*, 1995, **95**, 511; (*b*) J.-M. Basset, F. Lefebre and C. Santini, *Coord. Chem. Rev.*, 1998, **178–180**, 1703; (*c*) Y. Iwasawa, *Prep. Solid Catal.*, 1999, 427; (*d*) D. E. Bergbreiter, *Med. Res. Rev.*, 1999, **19**, 439; (*e*) R. Anwander, *Chem. Mater.*, 2001, **13**, 4419.

3 (*a*) E.-I. Negishi and F. Liu, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, 1998; (*b*) J. P. Wolfe, S. Wagaw, J.-F. Marcoux and S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805; (*c*) J. F. Hartwing, *Angew. Chem., Int. Ed.*, 1998, **37**, 2046; (*d*) B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125; (*e*) R. Sturmer, *Angew. Chem., Int. Ed.*, 1999, **38**, 3307; (*f*) V. Farina, *Adv. Synth. Catal.*, 2004, **346**, 1553.

4 (*a*) W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller and H. Fischer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1844; (*b*) W. A. Herrmann and V. P. W. Boehm, *J. Organomet. Chem.*, 1999, **576**, 23; (*c*) J. Dupont, M. Pfeffer and J. Osborn, *Eur. J. Inorg. Chem.*, 2001, 1917; (*d*) R. B. Bedford, *Chem. Commun.*, 2003, 1787.

5 M. Ohff, A. Ohff, M. E. van der Boom and D. Milstein, *J. Am. Chem. Soc.*, 1997, **119**, 11687.

6 (*a*) W. A. Herrmann, M. Elison, C. Ficher, C. Köcher and G. R. J. Artus, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2371; (*b*) W. A. Herrmann, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2371; (*c*) W. A. Herrmann, K. Ofele, D. Von Preysing and S. K. Schneider, *J. Organomet. Chem.*, 2002, **41**, 1291.

7 (*a*) A. F. Littke and G. C. Fu, *J. Org. Chem.*, 2001, **66**, 3820; (*b*) J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 9550; (*c*) A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020; (*d*) J. Yin, M. P. Rainka, X.-X. Zhang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 1162;

(*e*) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4177.

8 Recent reports on the heterogeneous catalyst consisting of the anchoring the Pd complexes onto insoluble supports: (*a*) T. Y. Zhang and M. J. Allen, *Tetrahedron Lett.*, 1999, **40**, 5813; (*b*) J. Schwarz, V. P. W. Böhm, M. G. Gardiner, M. Grosche, W. A. Herrmann, W. Hieringer and G. Raudaschl-Sieber, *Chem. Eur. J.*, 2000, **6**, 1773; (*c*) E. B. Mubofu, J. H. Clark and D. Macquarrie, *Green Chem.*, 2001, **3**, 23; (*d*) M. R. Buchmeiser, T. Schareina, R. Kempe and K. Wurst, *J. Organomet. Chem.*, 2001, **634**, 39; (*e*) C. Gonźalez-Arellano, A. Corma, M. Iglesias and F. Sánchez, *Adv. Synth. Catal.*, 2004, **346**, 1758; (*f*) C. Baleizáo, A. Corma, H. García and A. Leyva, *J. Org. Chem.*, 2004, **69**, 439; (*g*) C. Venkatesan and A. P. Singh, *J. Catal.*, 2004, **227**, 148; (*h*) P. G. Steel and C. W. T. Teasdale, *Tetrahedron Lett.*, 2004, **45**, 8977.

9 J. C. Elliott, *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates*, Elsevier, Amsterdam, 1994.

10 (*a*) K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.*, 2000, **122**, 7144; (*b*) K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani and K. Kaneda, *Chem. Commun.*, 2001, 461; (*c*) K. Mori, M. Tano, T. Mizugaki, K. Ebitani and K. Kaneda, *New J. Chem.*, 2002, **26**, 1536; (*d*) K. Mori, T. Hara, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.*, 2003, **125**, 11460.

11 K. Mori, K. Yamaguchi, T. Hara, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.*, 2002, **124**, 11572.

12 K. Mori, T. Hara, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.*, 2004, **126**, 10657.

13 (*a*) T. Hara, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *Tetrahedron Lett.*, 2003, **44**, 6207; (*b*) M. Murata, T. Hara, K. Mori, M. Ooe, T. Mizugaki, K. Ebitani and K. Kaneda, *Tetrahedron Lett.*, 2003, **44**, 4981.

14 M. Murata, T. Hara, K. Mori, M. Ooe, T. Mizugaki, K. Ebitani and K. Kaneda, *Tetrahedron Lett.*, 2003, **44**, 4981.

15 T. Hara, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *Green Chem.*, 2004, **6**, 507.

16 S. Sugiyama, T. Minami, H. Hayashi, M. Tanaka, N. Shigemoto and J. B. Moffat, *J. Chem Soc., Faraday Trans.*, 1996, **92**, 293.

17 T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer and G. Wilkinson, *J. Chem. Soc.*, 1965, 3632.

18 H. Tanaka, A. Yasukawa, K. Kandori and T. Ishikawa, *Colloids Surf. A*, 1997, **125**, 53.

19 (*a*) F. Zhao, K. Murakami, M. Shirai and M. Arai, *J. Catal.*, 2000, **194**, 479; (*b*) I. W. Davies, L. Matty, D. L. Hughes and P. J. Reider, *J. Am. Chem. Soc.*, 2001, **123**, 10139; (*c*) K. Köhler, R. G. Heidenreich, J. G. E. Krauter and J. Pietsch, *Chem. Eur. J.*, 2002, **8**, 622; (*d*) S. S. Pröckl, W. Kleist, M. A. Gruber and K. Köhler, *Angew. Chem., Int. Ed.*, 2004, **43**, 1881.

20 (*a*) N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.*, 1979, **36**, 3437; (*b*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.

21 K. Shimizu, S. Koizumi, T. Hatamachi, H. Yoshida, S. Komai, T. Kodama and Y. Kitayama, *J. Catal.*, 2004, **228**, 141.

22 J.-F. Fauvarque and F. Pflüger, *J. Organomet. Chem.*, 1981, **208**, 419.

23 The anionic Pd^0 species, *i.e.* $[PO_4^{3-}–Pd^0]^-$, might be generated *in situ* by the dissociation of the other phosphate ligand at the reaction temperature (130 °C), which is originated from the diffusion of redox carriers, *e.g.* protons and electrons. After completion of the coupling reaction, cooling to the room temperature allows the Pd^0 species to be restabilized as a monomeric Pd^{II} species. We think that the high catalytic activity of the PdHAP-1 is also attributed to the participation of whole bulk of hydroxyapatite in the reduction-oxidation cycle of the Pd^{II} species. For the detailed diffusion mechanism of redox carriers in the hydroxyapatite matrix, see: S. Nakamura, H. Takeda and K. Yamashita, *J. Appl. Phys.*, 2001, **89**, 5386.

24 (*a*) V. V. Grushin and H. Alper, in *Activation of Unreactive Bonds and Organic Synthesis*, ed. S. Murai, Springer, Berlin, 1999; (*b*) V. V. Grushin and H. Alper, *Chem. Rev.*, 1994, **94**, 1047.

25 (*a*) K. Kaneda, M. Higuchi and T. Imanaka, *J. Mol. Catal.*, 1990, **63**, L33; (*b*) M. R. Buchmeiser and K. Wurst, *J. Am. Chem. Soc.*, 1999, **121**, 11101; (*c*) L. Djakovitch and K. Koehler, *J. Am. Chem. Soc.*, 2001, **123**, 5990; (*d*) C. R. LeBland, A. T. Andrews, Y. Sun and J. R. Sowa Jr., *Org. Lett.*, 2001, **3**, 1555; (*e*) B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam and B. Sreedhar, *J. Am. Chem. Soc.*, 2002, **124**, 14127; (*f*) H. Bulut, L. Artok and S. Yilmaz, *Tetrahedron Lett.*, 2003, **44**, 289.

26 (*a*) N. Toshima and T. Takahashi, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 400; (*b*) M. T. Reetz and S. A. Quaiser, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2240; (*c*) M. T. Reetz, W. Helbig, S. A. Quaiser, U. Stimming, N. Breuer and R. Vogel, *Science*, 1995, **267**, 367.

27 (*a*) M. T. Reetz, R. Breinbauer and K. Wanninger, *Tetrahedron Lett.*, 1996, **37**, 4499; (*b*) M. T. Reetz and E. Westermann, *Angew. Chem., Int. Ed.*, 2000, **39**, 165; (*c*) K. Okamoto, R. Akiyama, H. Yoshida, T. Yoshida and S. Kobayashi, *J. Am. Chem. Soc.*, 2005, **127**, 2125.

28 (*a*) C. Amatore and A. Jutand, *Acc. Chem. Res.*, 2000, **33**, 314; (*b*) G. T. Crip, *Chem. Soc. Rev.*, 1998, **27**, 427.

29 The hydrophilic properties of hydroxyapatite were evaluated by a simple adsorption technique. See: B. Mathew and V. N. R. Pillai, *Polym. Bull.*, 1991, **26**, 603. Hydroxyapatite (1.0 g) was dried at 573 K for 3 h, followed by exposure to air with high humidity. After 48 h, the hygroscopic degree (H) was calculated according to the following equation; $H = [(X_w - X_d)X_d] \times 100$ (X_w: weight of wet sample, X_d: weight of dried sample). The estimated hygroscopic degree of hydroxyapatite was 11.7.

30 It has been demonstrated that the apatitic tricalcium phosphate acts as a useful solid for the supported aqueous phase catalysis (SAPC) in hydroformylation reaction. See: M. Dessoudeix, U. J. Jáuregui-Haza, M. Heughebaert, A. M. Wilhelm, H. Delmas, A. Lebugle and Ph. Kalck, *Adv. Synth. Catal.*, 2002 **344**, 406.

31 T. Tanaka, H. Yamashita, R. Tsuchitani, T. Funabiki and S. Yoshida, *J. Chem. Soc., Faraday Trans. 1*, 1988, **84**, 2987.