Copper- and Amine-free Sonogashira Cross-Coupling catalysed by HAP-Pd(0) in water

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Abstract : Hydroxyapatite [$Ca_5(PO_4)_3(OH)$: HAP] supported Pd (0) catalyst has been employed as an efficient and reusable heterogeneous catalyst for Sonogashira coupling reaction under copper and phosphine free conditions The catalyst HAP-Pd(0) was found to be very effective and stable under the reaction conditions and it can be easily recovered and recycled. The work-up procedure is simple and the corresponding acetylenes were obtained in good to excellent yields. Moreover the use of water as reaction medium is both economical as well as environmentally benign in accordance with the concept of green chemistry.

IndexTerms **- Hydroxyapatite [$Ca_5(PO_4)_3(OH)$: HAP], Heterogeneous, Recyclablility, Sonogashira coupling, Water.**

I. INTRODUCTION

The Sonogashira coupling reaction is an efficient approach to build C-C bonds between activated C_{sp2} and C_{sp} of terminal alkyneswhich plays an important role in the synthesis of pharmaceuticals, agrochemicals and functional materials[1-7]. *K. Sonogashira*, *Y. Tohda*, and *N. Hagihara* were the first to report the Sonogashira cross-coupling in 1975[1]. The Sonogashira reaction is usually performed by the use of a palladium-phosphane ligand complex as catalyst in the presence of a catalytic quantity of a copper(I) salt and an amine (as a solvent or in large excess) under homogeneous conditions.. The traditionally used catalysts are triphenylphosphane-related complexes, $Pd(PPh_3)_4$, with the more stable and soluble $Pd(PPh_3)_2Cl_2$ being the most common, although catalysts with bidentate ligands such as $Pd(dppe)Cl_2$, $Pd\text{-}(dppp)Cl_2$, or $Pd(dppf)Cl_2$ have also been employed. Most frequently, rather high loadings of palladium (usually up to 5 mol%) and larger amounts of the copper(I) salt are required[6].Pd(II) is often employed as a pre-catalyst since it exhibits greater stability than Pd(0) over an extended period of time and can be stored under normal laboratory conditions for months[8]. The Pd (II) catalyst is reduced to Pd(0) in the reaction mixture by either an amine, a phosphine, or a reactant, allowing the reaction to proceed[9]. The oxidation of triphenylphosphine to triphenylphosphine oxide can also lead to the formation of Pd(0) *in situ* when catalysts such as bis(triphenylphosphine)palladium(II) chloride are used.The use of copper as co-catalyst, although beneficial in terms of increasing the reactivity of the system, has some drawbacks such as the formation of alkyne homocoupling through a copper-mediated Hay/Glaser reaction[10]. To address such a problem, copper was eliminated in the so-called 'copper-free'*Sonogashira reaction*. In this case, the process could easily be termed as *Heck-Cassar reaction, Heck alkynylation* or perhaps *Sonogashira-Heck-Cassar coupling*. The term' *Sonogashira reaction'* however, is now-a-days a blanket description applied to the palladium(0)-catalysed coupling of a sp^2 (or even sp^3) halide or triflate with a terminal alkyne, regardless of whether copper(I) salts are present or not. The *Sonogashira reaction* has reached impressive records[11]and many efforts have been made to develop ligand-free, co-catalyst-free, and additive-free conditions, using a recyclable Pd catalyst[12]. In spite of recent advances in Sonogashira reaction protocols, there is still a great deal of challenge to get all the necessary conditions (such as aerobic, amine-free, ligand-free, co-catalyst-free, additive-free, innocuous solvent, low Pd loadings and recyclability of Pd) simultaneously. Recently, Sonogashira reaction in water has attracted much attention[13-25] as water is an ideal alternative for organic synthesis due to its non-toxicity, incombustibility as well as inexpensiveness.

Keeping in view of the importance of Sonogashira coupling in organic syntheses, and in continuation of our interest to explore the new catalytic activity of HAP-Pd(0), herein, we wish to report the use of HAP-Pd(0)as a heterogeneous recyclable catalyst for the copper- and phosphine-free Sonogashira coupling reaction between alkynes and aryl halides in water (Fig. 1).

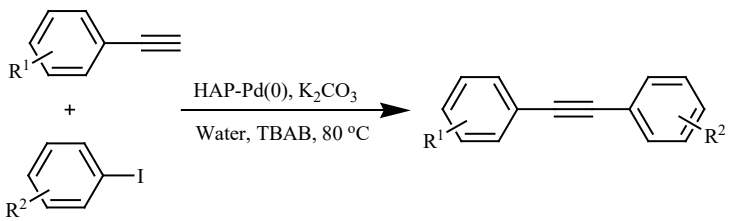


Fig. 1 Sonogashira coupling between phenyl acetylene and iodobenzene in water at 80 °C[a]

RESULTS AND DISCUSSION

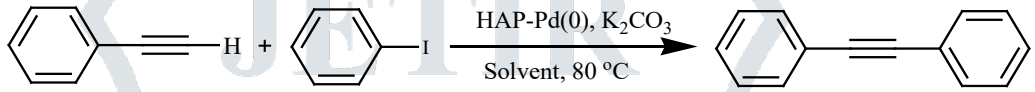
Hydroxyapatite used for the preparation of hydroxyapatite-supported Pd(0) catalyst [HAP-Pd(0)] was prepared according to the literature procedure with slight modification.[26] HAP-Pd(0) was prepared by stirring a mixture of hydroxyapatite and $Pd(OAc)_2$ in ethanol for 3 h, followed by dropwise addition of hydrazine hydrate (80%). To make the reaction medium completely heterogeneous, the catalyst was conditioned by refluxing for 6 h in ethanol, toluene, and acetonitrile (each for 2 h) to remove any physiosorbed palladium acetate. The conditioned catalyst was quite stable and could be used for several days. The

characterization of HAP-Pd)0)[27] was done by X-ray diffraction (XRD), atomic absorption spectrophotometry (AAS), scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Results have already been discussed in our previous communication[27].

OPTIMIZATION OF THE REACTION CONDITIONS

Sonogashira coupling was carried out by stirring a mixture of terminal alkyne and aryl iodide at 80 °C in the presence of HAP-Pd(0) as catalyst and K_2CO_3 as base in water in the presence of TBAB as PTC. We began our investigations using phenyl acetylene and iodobenzene as model substrates. The reaction conditions were screened to examine the effects of HAP-Pd (0) at 80 °C with different solvents (**Table 1**, acetonitrile, toluene, ethanol, methylene chloride and water). Results in **Table 1** clearly indicate that water is the suitable solvent leading to faster conversion and high yields of the products. It is pertinent to mention that in the absence of TBAB, the reaction rate was very slow due to the poor solubility of reactants in the aqueous medium.The reaction conditions were also screened for various temperatures (room temperature to 80 °C) and bases (K_2CO_3, triethyl amine, Na_2CO_3). The results were evaluated qualitatively through TLC. It was found that reaction was very slow at room temperature but got completed in just 4 h at 80 °C. Among various bases, K_2CO_3 was found to be most effective under the reaction conditions. The best conditionsemploy 0.03:1:1:2:0.5 mol ratios of HAP-Pd (0), phenyl acetylene, phenyl iodide, K_2CO_3 and TBAB at 80 °C for 4 h using water (5 mL) as solvent.

Table 1. Effect of solvent on the HAP-Pd (0)catalyzed Sonogashira-coupling between phenyl acetylene and iodobenzene at 80 °C[a]



Entry	Solvent	Time (h)	Yield (%)
1	Ethanol	10	70[b]
2	Methylene chloride	10	60[b]
3	Acetonitrile	10	65[b]
4	Toluene	10	50[c]
5	**Water**	**4**	**92[c]**

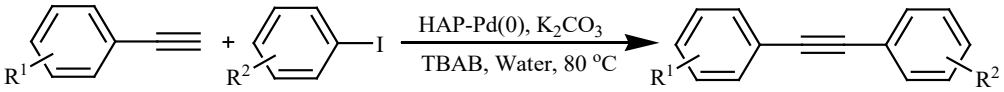
[a]Reaction conditions: Phenyl acetylene (0.102 g, 1 mmol), iodobenzene (0.204 g, 1 mmol), K_2CO_3 (0.276 g, 2 mmol), TBAB (0.161, 0.5 mmol, only in case of water), HAP-Pd(0)(0.3 g, 0.33 mol% Pd) at 80 °C in solvent (5 mL).

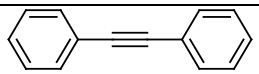
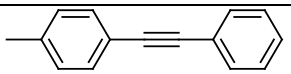
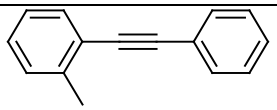
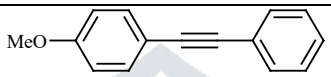
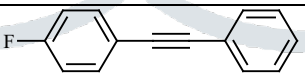
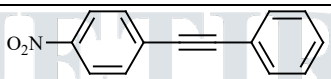
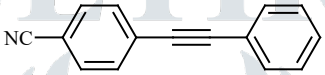
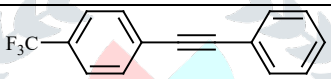
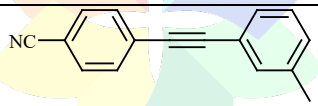
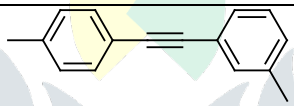
[b]Column chromatography yield.

[c]Isolated yield.

Using these optimized conditions, the reaction of various terminal acetylenes with aryl halides was investigated. It was found that all the reactions proceeded smoothly to give the corresponding arylated acetylenes in high yields (**Table 2**), which clearly indicates the generality and scope of the reaction with respect to various terminal alkynes and aryl halides. The reaction was also carried out using phenyl boronic acid in place of aryl halide, but unfortunately very low conversion was observed (TLC).

Table 2. HAP-Pd (0) catalyzed the Sonogashira-coupling between phenyl acetylene and iodobenzene in water at 80 °C[a]



Entry	R^1	R^2	Product	Time (h)	Yield(%)[b]	m.p./Lit. m.p. (°C)
1	H	H		4	92	53-54/54-55[28]
2	4-CH_3	H		4	92	70-71/70-72[28]
3	2-CH_3	H		4.5	90	70-71/69-70[28]
4	4-OMe	H		4	90[c]	60-61/59-60[28]
5	4-F	H		5	90	108-109/109-110[28]
6	4-NO_2	H		6	85[c]	119-120/120-121[28]
7	4-NC	H		6	89	109-110/108-110[28]
8	4-F_3C	H		6.5	88[c]	102-103/102-104[28]
9	H	3-CH_3		4	90[c]	72-73/71-73[28]
10	-CN	3-CH_3		4.5	85[c]	106-106/106-107[28]
11	4-CH_3	3-CH_3		4.5	90[c]	82-83/83-84[28]

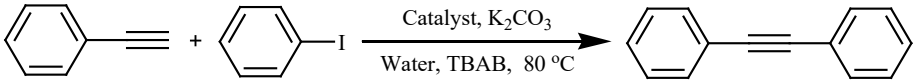
[a]Reaction conditions: Alkyne (1 mmol), halide (1 mmol), TBAB (0.5 mmol, 0.161 g), K_2CO_3 (0.276 g, 2 mmol), HAP-Pd(0)(0.3 g, 0.3 mol% Pd) at 80 °C in water (5 mL).

[b]Isolated yields.

[c]Column chromatography yields.

We further investigated the role of HAP-Pd (0) as a catalyst for the Sonogashira reaction (entry **1**, **Table 2**). The reaction was tested with $Pd(OAc)_2$ and HAP. It was also carried out in the absence and presence of HAP-Pd (0) under similar conditions. The results are summarized in **Table 3**, which indicate that HAP-Pd (0) catalyzes the reaction and the corresponding product was obtained in high yield.

Table 3 Effect of catalyst on the Sonogashira-coupling between phenyl acetylene and iodobenzene in water at 80 °C[a]



Entry	Catalyst	Time (h)	Yieldb (%)
1	No catalyst	15	Traces
2	HAP	15	Traces
3	$Pd(OAc)_2$	15	65[b]
4	HAP-Pd (0)	4	92[c]

[a]Reaction conditions: Phenyl acetylene (0.102 g, 1 mmol), iodobenzene (0.204 g, 1 mmol), TBAB (0.5 mmol, 0.161 g), HAP-Pd(0)(0.3 g) at 80 °C in water (5 mL) or HAP(0.3 g), $Pd(OAc)_2$ (0.1 g,) , water (5 mL) at 80 °C.
[b]Column chromatography yields.
[c]Isolated yield.

Deactivation and recyclability of HAP-Pd (0) has also been studied. For this, a series of 7 consecutive runs in case of entry **1** (**Table 2**) under the selected conditions were carried out with the same catalyst. The results are shown in **Fig. 1**. They demonstrate that there is no significant change in the activity of the catalyst upto 7th run.

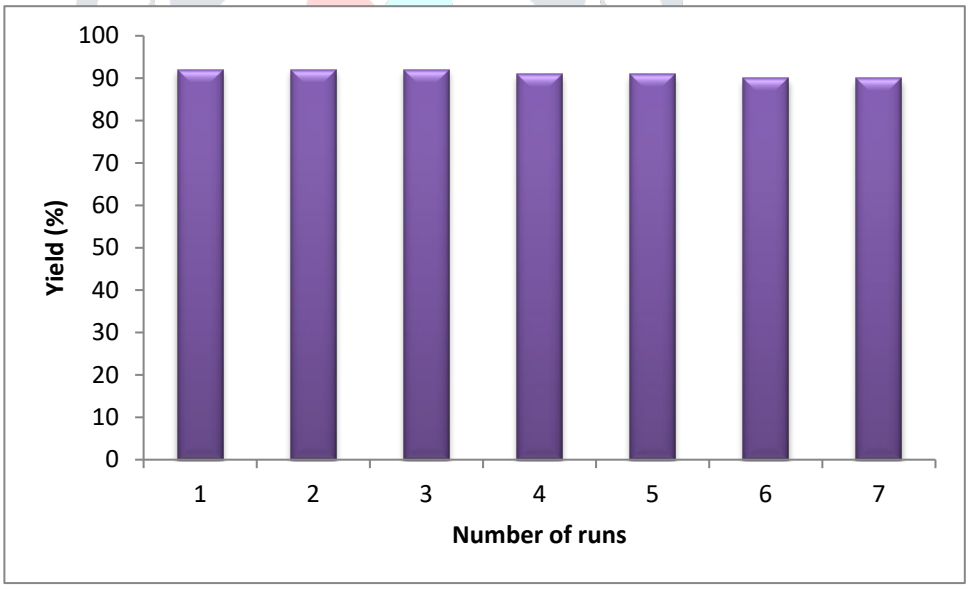


Fig. 2 Recylability of HAP-Pd (0). Reaction conditions: Alkyne (1 mmol), halide (1 mmol), K_2CO_3 (2 mmol), TBAB (0.5 mmol, 0.161 g), HAP-Pd(0)(0.3 g, 0.33 mol% Pd) at 80 °C in water (5 mL) for 2 h.

EXPERIMENTAL

MATERIALS

The chemicals used were purchased from Aldrich chemical company and Merck. The products were characterized by their spectral data and comparison of their physical data with those of known samples. The ^1H NMR data were recorded in $CDCl_3$ or $CDCl_3$+DMSO-d_6 on Bruker DPX 200 (200 MHz) spectrometer using TMS as an internal standard. . The IR spectra were recorded using KBr disc on Perkin-Elmer FTIR spectrophotometer. Mass spectral data were recorded on Esquire 3000 (ESI). Thermal analysis was carried out on DTG-60 Shimadzu make thermal analyzer with heating rate of 10 C/min. SEM was recorded using Jeol make T-300 Scanning Electron Microscope and Transmission Electron Microscope (TEM) on H7500 Hitachi. The amount of Palladium in HAP-Pd (0)was determined on double beam Atomic Absorption Spectrophotometer (AAS), GBC 932 AB manufactured in Australia. The catalyst was stirred in dil. HCl for 10 h and then subjected to AAS analysis.

General procedure for the preparation of hydroxyapatite-supported Pd(0) catalyst HAP-Pd(0)

Hydroxyapatite was prepared by stirring a solution of diammonium hydrogen phosphate (8 g) in double-distilled water (250 mL) at pH 12 and calcium nitrate [$Ca(NO_3)_2.4H_2O$] (25 g) in double-distilled water (150 mL) for 10 min. The suspension was then further stirred for 4 h at 115 °C, and the solid was filtered off, washed with double-distilled water (500 mL), and then dried in the oven at 95 °C for 5 h. The oven-dried hydroxyapatite was calcined in air at 750 °C for 30 min before use. HAP-Pd (0) was

prepared by stirring a mixture of hydroxyapatite (3 g) and $Pd(OAc)_2$ (0.05 g) in ethanol (25 mL) at room temperature for 2 h, followed by addition of hydrazine hydrate (80%, 1.5 mL) dropwise over a period of 20 min. It was further stirred at room temperature for 7 h. The color of the catalyst changed to dark grey, which indicated that Pd(II) was reduced to Pd(0). HAP-Pd(0) was filtered off and washed with ethanol (10 mL) and acetone (320 mL). To remove any physiosorbed$Pd(OAc)_2$, the catalyst was conditioned by refluxing for 6 h respectively in ethanol, toluene, and acetonitrile, each for 2 h. Finally, the HAP-Pd(0) was dried in the oven at 95 °C for 5 h and stored in a desiccator.

General procedure for the synthesis of diaryl alkynes by cross coupling between acetylenes and aryl halides at 100 °C

To a mixture of alkyne (1 mmol), aryl halide (1 mmol), K_2CO_3 (2 mmol) and HAP-Pd (0)(0.3 g, 0.33 mol% Pd) in a round-bottom flask (25 mL), TBAB (0.5 mmol), water (5 mL) was added. The reaction mixture was then stirred at 80 °C for an appropriate time (Table 2). After completion of the reaction (monitored by TLC), the reaction mixture was extracted with EtOAc (20 mL) and the HAP-Pd was filtered off. The organic layer was washed with water and dried over anhyd. Na_2SO_4. Finally, the product was obtained after removal of the solvent under reduced pressure followed by crystallization or column chromatography. The HAP-Pd was washed with distilled water (200 mL) followed by methylene chloride (3 × 15 mL) and dried at 110 °C for 2 h. It was used further for carrying out the reaction.

The structures of the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and comparison with authentic samples available commercially or prepared according to the literature methods.

CONCLUSION

In conclusion, a copper- and ligand-free condition has been developed for Sonogashira coupling between terminal alkynes and aryl halides using recyclable HAP-Pd (0) as catalyst in water at 80 °C. Since our catalytic system can be easily recovered easily by simple filteration, and work efficiently under water as the reaction medium which make our methodology an important addition to the existing protocols.

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