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Palladium nano-particles supported on agarose as efficient catalyst and bioorganic ligand for C—C bond formation *via* solventless Mizoroki–Heck reaction and Sonogashira–Hagihara reaction in polyethylene glycol (PEG 400)

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ABSTRACT

In this study, abundant naturally occurring agarose has been used as a support and ligand for palladium nanoparticles. In the presence of this catalytic system, Mizoroki–Heck and Sonogashira–Hagihara coupling reactions were performed successfully. The catalyst exhibits high activity in Mizoroki–Heck reaction under phosphane and solvent-free conditions for the reaction of iodo- and bromoarenes with butyl acrylate and styrene. This catalytic system also showed high catalytic activity for Sonogashira–Hagihara coupling reaction of various aryl halides (I, Br, Cl) under copper and ligand-free conditions in polyethylene glycol (PEG 400) as an ecofriendly and non-poisonous media. The catalyst can be separated from the reaction mixture and reused for the similar batches of the reaction. High efficiency of the catalyst along with its recycling ability and the rather low Pd-loading which are demonstrated in both Mizoroki–Heck and Sonogashira–Hagihara reactions are the merits of the presented catalyst system.

1. Introduction

Carbon—carbon bond formation reactions have been under attention since the early attempts for introduction of protocols regarding the transformation of easily available, cheap, simple and small organic molecules to the more valuable complex molecules [1–4]. Some of the most exciting protocols for this achievement are the reactions catalyzed by palladium, an important topic which has been recognized with the Nobel Prize for Chemistry 2010 [5]. These reactions are commonly catalyzed by soluble palladium phosphane complexes. However, the soluble palladium phosphane complex catalysts suffer from problems associated with the separation, recovery, and instability at high temperatures. Moreover, most of phosphane ligands are expensive, not easily available and toxic which are associated with particular environmental and economic concerns, especially when large-scale operations are of consideration [6–8]. Palladium maintained on different supports may offer solutions for some of the associated troubles as mentioned [9]. Consequently, much attention has been focused on improving the reactions by synthesis and application of supports such as polymers [10], carbon nanofiber [11], clay [12], montmorillonite [13], silica and magnetic mesoporous silica [14], zeolite [15], metal oxides [16], and silica-starch [17].

In our recent reports, bioorganic polymers such as gelatin and agarose as ecofriendly degradable materials and abundant in nature have been used as the support and ligand for the reactions leading to C—C bond formation through a Pd-catalyzed reaction [18].

Agarose is a polysaccharide that is found extensively in nature [19]. It is a linear polymer, made up of the repeating monomeric unit of agarobiose. Agarobiose is a disaccharide made up of D-galactose and 3,6-anhydro-L-galactopyranose as presented in Fig. 1. Properties of agarose, such as flexibility, non-toxicity, low cost, freely soluble in hot water, carrying freely available hydroxy groups, make this material an ideal candidate for numerous practices in different areas of science [20]. It produces a gel network through its available hydroxy groups, which are formed by the presence of water molecules bound inside the double helical cavity. Moreover, a moderate reduction of Pd(II) to Pd(0) can occur on the backbone of agarose molecules by the available free hydroxy groups. This slow-rate reduction causes the formation of 10–30 nm of well distributed nano particles of palladium on the surface of the agarose molecules which are also stabilized by ligation with agarose hydroxy groups.

Palladium nanoparticles are employed in variety of catalytic reactions including Mizoroki–Heck, Suzuki–Miyaura, Stille and Sonogashira–Hagihara reactions. Using transition metal salts are

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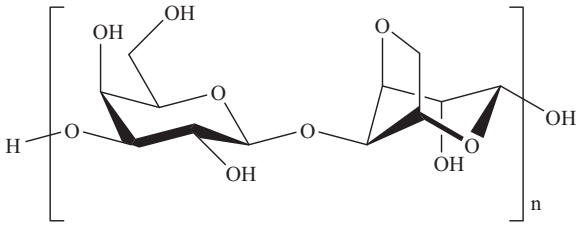


Fig. 1. The structure of agarose monomeric unit (agarobiose) composed of D-galactose and 3,6-anhydro-L-galactopyranose.

the most available and convenient way to deposit the metallic nanoparticles onto supports by reduction [21–23,12,24,25].

Palladium-catalyzed Mizoroki–Heck coupling reaction is a powerful and versatile method for arylation and vinylation of olefins [26–28]. Total synthesis of complex organic molecules has benefited enormously from the Mizoroki–Heck reaction. In this reaction, aryl, heteroaryl, alkenyl, and benzyl halides are coupled with alkenes in the presence of palladium catalysts to give the corresponding substituted alkenes [3,29]. However, organic solvents [30], ionic liquids [31], and water [32] as the media have been extensively used in these methods. On the other hand, similar reactions conducted under solvent-free conditions received less attention [33]. Solvent-free palladium catalyzed reactions are of significant interest due to their potential of environmental and economic benefits [34]. Very recently, we have reported a solvent-free Mizoroki–Heck reaction in the presence of palladium nanoparticles supported on aminopropyl-functionalized clay as an efficient catalyst for the reaction of iodo- and bromoarenes with butyl acrylate and styrene [35].

Also, in recent years, the Sonogashira–Hagihara reaction has come into view as one of the most general, reliable, and effective methods for the synthesis of substituted alkynes [36]. The Sonogashira–Hagihara protocol in which copper salts are used as co-catalysts has contributed greatly to the straightforward and facile construction of alkynyles. However, using copper salts as co-catalysts sometimes lead to the homocoupling reaction of terminal alkynes (Glaser-type reaction) upon exposure of the copper–acetylide intermediate to the air or other oxidizing agents [37–39]. Very recently, we have reported a copper-free Sonogashira–Hagihara reaction for coupling of various aryl iodides, bromides and chlorides and also β-bromo styrene with phenyl acetylene using Pd nanoparticles supported on gelatin [18a].

In our previous work [18b,c] we have demonstrated that agarose can be used as an effective bioorganic ligand, support and reducing agent for generation and entrapment of the *in situ* generated Pd(0) nanoparticles. This supported catalyst has been applied successfully for Suzuki–Miyaura reaction in aqueous media [18a]. Moreover, Pd-supported agarose has been applied for C—C bond formation *via* homocoupling reactions in water by our research group [18c].

Now in this article, we report the use of agarose supported Pd nanoparticles for Mizoroki–Heck reaction under solvent-free conditions without using phosphorus ligands. We have also presented the use of this catalyst for Sonogashira–Hagihara reaction under ligand and amine-free conditions in polyethylene glycol (PEG 400) as a green media.

2. Experimental

2.1. General

NMR spectra were recorded on a Bruker Avance DPX-250 spectrometer (^{1}H NMR 250 MHz and ^{13}C NMR 62.9 MHz) in $CDCl_3$ and TMS as the internal standard. UV-Vis spectra were recorded on Perkin-Elmer, Lambda 25, UV-Vis spectrometer which shows the conversion of Pd(II) to Pd(0). Scanning electron micrographs (SEM) were obtained (SEM, XL-30 FEG SEM, Philips, at 20 kV). X-ray diffraction spectra of the catalyst were obtained by XRD, D_8, Advance, Bruker, axs. Inductively Coupled Plasma (ICP) technique (Varian, Vista-pro) was employed for the determination of the amount of palladium nanoparticles supported on agarose.

2.2. Gram-scale preparation of palladium nano-particles supported on agarose

Agarose (1 g) was dissolved in water (100 mL) at 80 °C. To this solution, a solution of $Pd(OAc)_2$ (100 mL, 1 mM) was added and diluted with water (100 mL). To the resulting solution, a solution of citric acid (20 mL, 4 mM) was added dropwise upon which a grayish-brown color was developed. Refluxing of the obtained reaction mixture was continued for 1 h. Upon cooling the resulting mixture to room temperature, a grayish-brown mass of the agarose hydrogel catalyst was formed which was dried by the flow of the air over night and under vacuum for 24 h to produce the black powder catalyst.

2.3. General procedure for the Mizoroki–Heck reaction of aryl halides and styrene in the presences of Pd nano-particles supported on agarose under solvent-free conditions

Et_3N (2 mmol, 0.27 mL) was added to a flask containing the powder of agarose supported Pd nanoparticles [0.05 g, containing 55×10^{-5} g, 0.0052 mmol of Pd (ICP)]. To the resulting mixture, aryl halide (1 mmol) and styrene (2 mmol, 0.22 mL) were added and heated (for aryl iodides at 100 °C and for aryl bromides at 120 °C in an oil bath). After 1–16 h, the reactions were completed (TLC and GC). The mixture was cooled to the room temperature and extracted with Et_2O (3 mL × 5 mL). Evaporation of the ethereal solvent followed by chromatography on silica gel eluted with *n*-hexane/EtOAc afforded the desired coupled products in 60–91% yields (Table 2).

2.4. General procedure for the Mizoroki–Heck reaction of aryl halides and butyl acrylate in the presences of Pd nanoparticles supported on agarose in solvent-free conditions

Et_3N (2 mmol, 0.27 mL) was added to a flask containing the powder of agarose supported Pd nanoparticles [0.05 g, containing 55×10^{-5} g, 0.0052 mmol of Pd (ICP)]. The flask was placed in an oil bath at 100 °C for aryl iodides and at 120 °C for aryl bromides and stirred for 15 min. Then the aryl halide (1 mmol) and butyl acrylate (2 mmol, 0.28 mL) were added to the mixture. Completion of the reactions (1–24 h) was detected by TLC and GC. The resulting mixture was cooled to room temperature and extracted with diethyl ether (3 mL × 5 mL). Evaporation of the ethereal solution followed by chromatography on a short column of silica eluted with *n*-hexane/EtOAc afforded the coupled products in 59–90% yield (Table 3).

2.5. Recycling of the catalyst in Mizoroki–Heck reaction

Recycling of the catalyst was performed upon the reaction of iodobenzene with butyl acrylate under the condition discussed in the preceeding sections. After completion of the reaction in the first run, the mixture was washed with diethyl ether (3 mL × 5 mL) and decanted. The resulting solid mass was reused for another batch of the similar reaction. This process was repeated for four runs. As the reaction was performed from the first run to the fifth, the required time for the completion of the reaction was elongated from 1.5 to

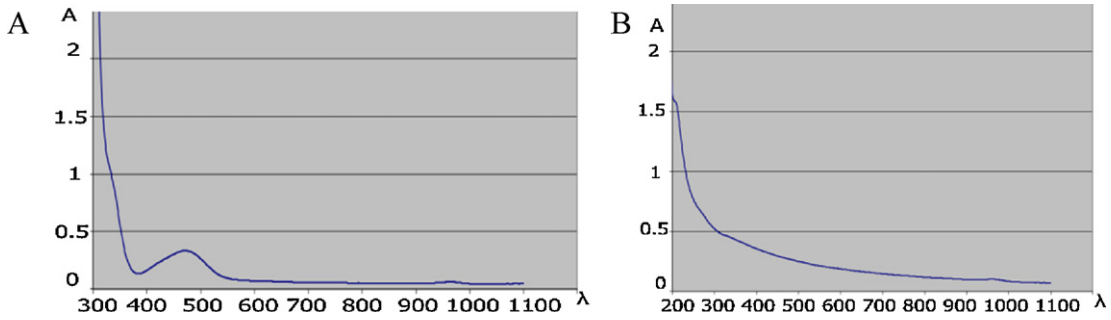


Fig. 2. (A) Pd(II) in the presence of agarose at room temperature before reduction and (B) UV-Vis spectra of Pd(0) supported on agarose generated by citric acid reduction.

5 h, which indicates that the activity of the catalyst was decreased as the number of the runs was increased.

2.6. General procedure for Sonogashira–Hagihara reaction of aryl halides catalyzed by palladium nanoparticles supported on agarose in PEG 400

Aryl halide (1 mmol) and phenyl acetylene (1.5 mmol, 0.16 mL) were added to a flask containing the powder of agarose supported Pd nanoparticles [0.05 g, containing 55×10^{-5} g, 0.0052 mmol of Pd (ICP)] and KOAc (1.5 mmol, 0.15 g) in PEG 400 (2 mL). The resulting mixture was stirred at 90 °C in the air for the appropriate reaction time. After completion of the reaction (TLC or GC), the reaction mixture was cooled to room temperature and extracted with Et_2O (3 mL × 5 mL). The ethereal solution was evaporated to afford the desired product in an almost pure state. Further purification, if it was necessary, has been performed by using silica gel column chromatography eluted with *n*-hexane/EtOAc to give the pure biphenyl products in high to excellent yields.

2.7. Large-scale Sonogashira–Hagihara reaction catalyzed by palladium nanoparticles supported on agarose in PEG 400

1-Bromo-4-nitrobenzene (5 mmol, 1 g) and phenyl acetylene (7.5 mmol, 0.82 mL) were added to a flask containing Pd-nanoparticles [0.5 g, containing 55×10^{-4} g, 0.0052 mmol of Pd (ICP)] and KOAc (7.5 mmol, 0.74 g) in PEG 400 (10 mL). The mixture was stirred at 90 °C for 3 h. After completion of the reaction (TLC or GC), the reaction mixture was cooled to room temperature and the mixture was extracted with Et_2O (5 mL × 10 mL). After vaporation of the ethereal solution, an almost pure product was obtained. Further purification was performed by silica gel column chromatography eluted with *n*-hexane/EtOAc to give the pure biphenyl product in excellent yield.

2.8. Selected ^{1}H- and ^{13}C-NMR spectra of the compounds

1b: ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm): 7.13 (d, 2 H), 7.31 (m, 6 H), 7.52 (m, 4 H).

3b: ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm): 2.32 (s, 3H), 6.89 (d, 1 H, J = 16.25), 7.06–7.29 (m, 7H), 7.40–7.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm): 19.99, 124.95,125.44, 126.28, 126.61, 126.63, 127.28, 127.62, 127.66, 128.75, 130.08, 130.47, 135.86, 136.47, 137.75.

7b: ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm): 6.98–7.57 (m, 9 H), 8.14 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 124.07, 124.95, 126.20, 126.93, 127.00, 128.08, 129.04, 129.93, 132.58, 133.25, 136.13, 143.82.

2c: ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm): 0.89 (t, 3 H, J = 7.5 Hz), 1.35 (sex, 2 H, J = 7.5 Hz), 1.61 (quint, 2 H, J = 5 Hz), 3.76 (s, 3 H), 4.13 (t, 2 H, J = 6.7), 6.24 (d, 1 H, J = 15 Hz), 6.83 (d, 1 H, J = 5 Hz), 7.40 (d, 2 H, J = 5 Hz), 7.56 (d, 1 H, J = 16 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm): 13.75, 19.20, 30.80, 55.35, 64.25, 114.28, 115.76, 129.67, 144.19, 161.30.

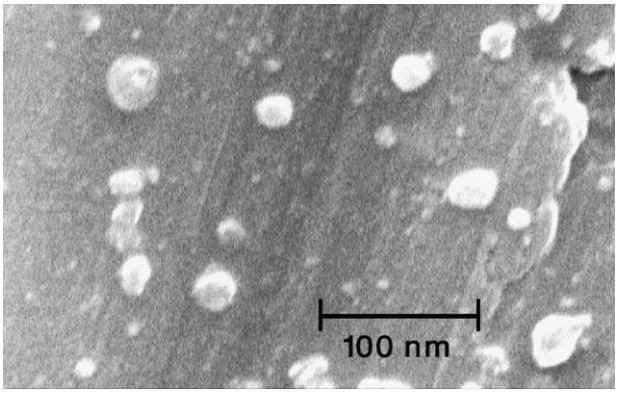


Fig. 3. SEM image of agarose supported Pd nanoparticles which shows the regular dispersion of the palladium nano-particles on the surface of the agarose.

3c: ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm): 0.85 (t, 3 H, J = 2.5 Hz), 1.32 (sex, 2 H), 1.57 (quint, 2 H), 2.30 (s, 3 H), 4.11 (t, 2H), 6.27 (dd, 1 H, J = 15.9 Hz, J' = 4.8 Hz), 7.11 (m, 3 H), 7.41 (m, 1H), 7.84 (dd, 1 H, J = 13.7 Hz, J' = 4.3 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm): 13.76, 18.96, 19.74, 30.79, 64.36, 119.26, 126.31, 129.94, 130.75, 133.40, 137.56, 142.20, 167.09.

3d: ^{1}H-NMR ($CDCl_3$, 250 MHz) δ (ppm): 2.3 (s, 3H), 7.06–7.17 (m, 2H), 7.24–7.46 (m, 7H); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ (ppm):

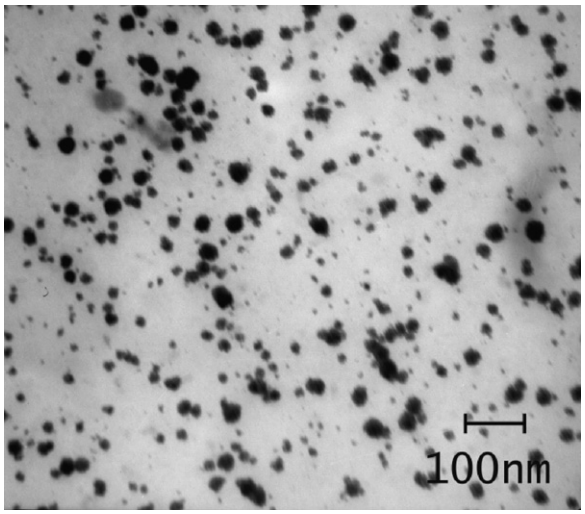
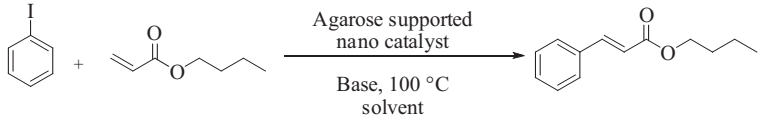


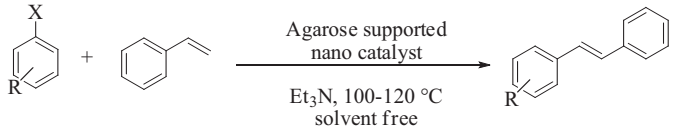
Fig. 4. TEM image of the agarose supported Pd nanoparticles which shows the size distribution of the particles to be around 10–30 nm.

Table 1
Comparison of the conditions used for the reaction of iodobenzene with butyl acrylate in the presence of palladium nanoparticles supported on agarose in the presence of different bases and solvents at 100 °C.

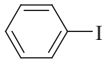
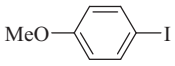
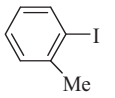
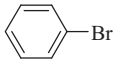
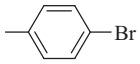
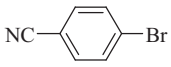
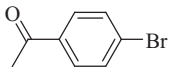
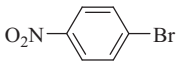
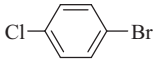
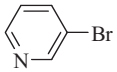
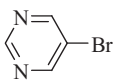


Entry	Solvent	Base	Time (h)	Isolated yield (%)
1	NMP	Et_3N	4	70
2	DMF	Et_3N	5	89
3	Toluene	Et_3N	7	70
4	EtOH	Et_3N	7	75
5	H_2O	Et_3N	5	62
6	None	Et_3N	2	90
7	None	$^nPr_3N$	3	83
8	None	Morpholine	7	80
9	None	K_2CO_3	5	50
10	None	Cs_2CO_3	5	49
11	None	KOAc	3	87
12	None	NaOH	5	10

Table 2
Reaction of different aryl halides (I, Br) with styrene in the presence of agarose supported Pd nano catalyst in solvent-free conditions.

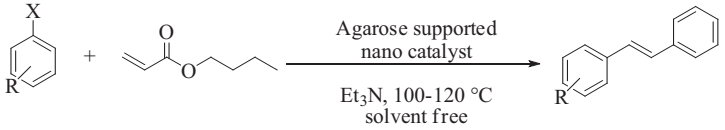


R= Me, OMe, CN
COMe, NO_2, Cl
X= Cl, Br, I

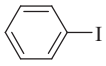
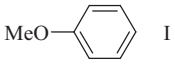
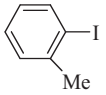
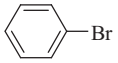
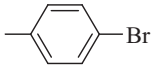
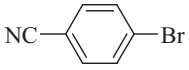
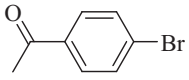
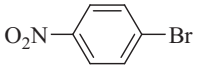
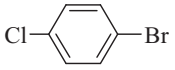
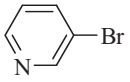
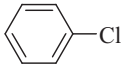
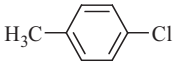
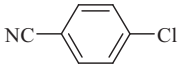
Entry	Ar-X	Product	Time (h)/temperature (°C)	Isolated yield (%)[a]	TON/TOF (h^{-1})
1		**1b**	2/100	90	173/86.5
2		**2b**	2.5/100	90	173/69
3		**3b**	4/100	84	161/40
4		**1b**	3/120	91	175/53
5		**4b**	3/120	89	171/57
6		**5b**	10/120	88	169/17
7		**6b**	10/120	72	138/14
8		**7b**	15/120	60	115/8
9		**8b**	10/120	87	167/17
10		**9b**	17/120	65	125/7
11		**10b**	12/120	76	146/12

[a]Reactions were performed with ArX (1 mmol), styrene (2 mmol), Et_3N (2 mmol) and catalyst (0.05 g containing 0.0052 mmol of Pd).

Table 3
Reaction of different aryl halides (I, Br, Cl) with butyl acrylate in the presence of agarose supported Pd nano-catalyst under solvent-free conditions.



R= Me, OMe, CN
COMe, NO_2, Cl
X= Cl, Br, I

Entry	Ar-X	Product	Time (h)/temperature (°C)	Isolated yield (%)[a]	TON/TOF (h^{-1})
1		**1c**	1.5/100	90	173/115
2		**2c**	2/100	89	171/85
3		**3c**	3/100	80	154/51
4		**1c**	3/120	87	167/56
5		**4c**	3/120	90	17358
6		**5c**	8/120	88	160/21
7		**6c**	10/120	69	13213
8		**7c**	10/120	59	113/11
9		**8c**	7/120	95	182/26
10		**9c**	15/120	60	115/8
11		**1c**	24/120	65	125/5
12		**4c**	24/120	57	110/5
13		**5c**	24/120	61	117/5

[a] Reactions were performed with ArX (1 mmol), butyl acrylate (2 mmol), Et_3N (2 mmol) and catalyst (0.05 g containing 0.0052 mmol of Pd).

21.52, 88.74, 89.58, 123.49, 128.08, 128.33, 128.46, 129.13, 131.56, 132.51, 138.39.

5d: ^{1}H-NMR ($CDCl_3$, 250 MHz) δ (ppm): 3.75 (s, 3H), 6.80 (d, 2H, J = 10 Hz), 7.18–7.46 (m, 7H); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ (ppm): 55.3, 89.2, 98.3, 113.9, 115.4, 123.6, 128.3, 128.8, 131.4, 133.0, 137.5.

7d: ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 7.13–7.25 (m, 3H), 7.33–7.43 (m, 6H); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ (ppm): 88.2, 90.3, 121.8, 122.9, 128.4, 128.5, 128.7, 131.6, 132.8, 134.2.

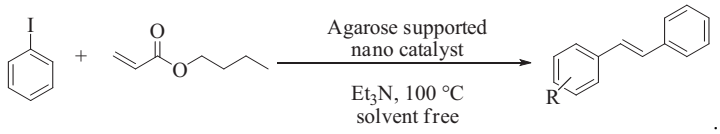
3. Results and discussion

The palladium nanoparticles supported on agarose were prepared by dissolving agarose in hot water to produce a homogeneous solution. To this solution, a solution of $Pd(OAc)_2$ in water was added. To the resulting solution, a solution of citric acid in water as a reducing agent was also added slowly and dropwise in order to reduce Pd(II) to Pd(0) in the reaction mixture. On cooling the mixture to room temperature, a grayish-brown hydrogel was appeared, which after drying in the air and under vacuum at room temperature, a black powder was obtained.

As discussed in our previously reported protocol [18b], the resulting black powder has been characterized by UV-Vis spectrum in which the complete conversion of Pd(II) to Pd(0) was confirmed by the absence of the peak at 420 nm (Fig. 2). The XRD of the black powder shows peaks at (1 1 1), (2 0 0), (2 2 0) and (3 1 1) crystallographic planes related to the formation of Pd(0).

Scanning electron microscopy (SEM) of the composite shows that the Pd particles are regularly deposited on the surface of

Table 4
Recycling of the catalyst for the reaction of iodobenzene with butyl acrylate in the presence of Et_3N and 0.05 g of the catalyst at 100 °C.



Run	Time (h)	Conversion%
1	1.5	100
2	1.5	100
3	2	100
4	3	100
5	5	100

agarose (Fig. 3). The TEM image indicates that the size of the palladium particles entrapped by agarose is in the range of 10–30 nm (Fig. 4).

The palladium content of the agarose composite was also obtained by inductively coupled plasma (ICP) to be 55×10^{-5} g, 0.0052 mmol of Pd per 0.05 g of the agarose support.

Application of the palladium nanoparticles supported on agarose as a catalyst in Mizoroki–Heck reaction of aryl halides with styrene and butyl acrylate under solvent and phosphane-free conditions:

In order to optimize the reaction conditions, first we studied the effect of media upon the reaction. For this purpose, the reaction of iodobenzene (1 mmol, 0.11 mL) with butyl acrylate (2 mmol, 0.28 mL) in the presence of the agarose supported palladium nanoparticles (0.05 g of the agarose composite contains 0.0052 mmol of Pd) in different solvents and bases at 100 °C (Table 1). Comparison of the results shows that the reaction in the absence of solvent proceeded much better than in solvents with an excellent yield and in a much shorter reaction time. Among the studied bases, Et_3N and KOAc were found to be more efficient for this reaction (Table 1). Therefore, Et_3N was chosen as the most suitable base under the optimized reaction conditions.

Under the optimized reaction conditions, 0.05 g of the catalyst (containing 55×10^{-5}g, 0.0052 mmol of Pd) and 2.0 mmol of Et_3N, the desired products were obtained in excellent yields for a wide array of aryl iodides at 100 °C and bromides with styrene at 120 °C (Table 2). The reaction of iodobenzene and 4-iodoanisole and 2-iodotoluene were performed smoothly within 2–4 h giving the desired products in 84–90% isolated yields. The results are tabulated in Table 2, Entries 1–3. This catalytic system was also applied to different aryl iodides and also hetero aryl bromides. A complete conversion was obtained for the reaction of bromobenzene and 4-bromotoluene with styrene after 3 h (Table 2, Entries 5, 6). For electron-deficient bromides, elongations of the reaction times along with the decrease of the yields of the products were observed. The low reactivity of 4-bromobenzonitrile, 4-bromoacetophenone, and 1-bromo-4-nitrobenzene is rather unexpected, which is most probably due to the less solubility of the above mentioned solid substrates in this solvent free system (Table 2, Entries 6–8). Also, 3-bromopyridine and 5-bromopyrimidine were reacted efficiently as hetero-aryl halides as illustrated in Table 2, Entries 10, 11.

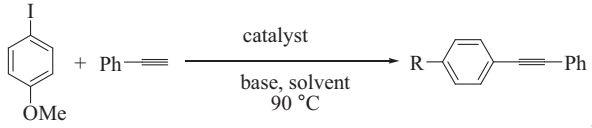
In an additional series of experiments, we have also studied the Mizoroki–Heck coupling reaction of aryl halides with butyl acrylate. The similar protocol as has been described for styrene was also employed for this purpose. The results of this study are presented in Table 3.

Afterwards, in order to investigate the recycling of the catalyst, the reaction of iodobenzene with butyl acrylate employing 0.05 g of the catalyst in the presence of Et_3N at 100 °C was tested. The first run reaction was carried out within 1.5 h. Similarly, the reaction for the repeated runs were conducted after separation of the organic compounds from the reaction mixture by extraction and the recovered catalyst was recycled for 5 successive runs with a rather sharp decrease in the catalytic activity from the 4th run (Table 4). The leaching of the catalyst into the reaction mixture was also determined by ICP analysis for the first run of recycling to be <2% after cooling the reaction mixture to room temperature.

Application of the palladium nanoparticles supported on agarose as a catalyst in Sonogashira–Hagihara reaction of aryl halides with phenyl acetylene in polyethylene glycol (PEG 400):

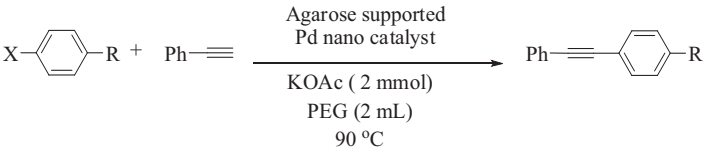
As a part of our ongoing project on application of new catalytic system in which $Pd(OAc)_2$ has been used as a pre-catalyst and agarose as a degradable bioorganic ligand, support and reductant, we decided to apply this system for Sonogashira–Hagihara reaction of aryl iodides, bromides and chlorides with phenyl acetylene. Preliminary screening to compare different conditions in the Sonogashira–Hagihara reaction were performed by using different solvents and bases upon the reaction of 1-bromo-4-nitrobenzene with phenyl acetylene as a benchmark at 90 °C. For this aim, two green solvents, water and polyethylene glycol (PEG 400) were used in the presence of KOAc. As shown in Table 5, PEG 400 was a better solvent for this reaction. Therefore, the rest of

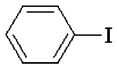
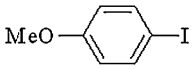
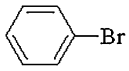
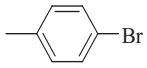
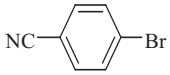
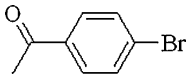
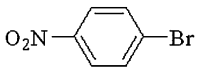
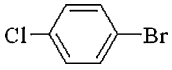
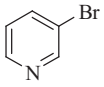
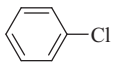
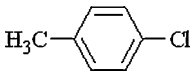
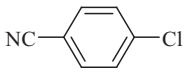
Table 5
Optimization studies for the Sonogashira–Hagihara reaction of 4-iodoanisole (0.234 g, 1 mmol) with phenyl acetylene (1.5 mmol) with respect to a few bases (1.5 mmol) and agarose supported Pd nanocatalyst at 90 °C.



Entry	Base	Solvent	Time (h)	Conversion % (GC)
1	KOAc	H_2O	5	60
3	KOAc	PEG	2	100
12	NaOAc	PEG 400	6	83
13	Morpholine	PEG 400	6	74
14	Cs_2CO_3	PEG 400	5	79

Table 6
Reaction of different aryl halides (I, Br, Cl) with phenyl acetylene in the presence of agarose supported Pd nano catalyst in PEG 400.



Entry	Ar-X	Product	Time (h)	Isolated yield (%)[a]	TON/TOF (h^{-1})
1		**1d**	0.5	95	182/365
2		**2d**	2	90	173/86
3		**1d**	1.5	95	183/121
4		**3d**	1.5	89	171/114
5		**4d**	5	90	173/35
6		**5d**	5	88	169/34
7		**6d**	7	80	154/22
8		**7d**	7	90	173/25
9		**8d**	8	93	179/22
10		**1d**	14	70	135/10
11		**3d**	14	69	133/9
12		**4d**	14	75	144/10

[a]Reactions were performed with ArX (1 mmol), phenyl acetylene (1.5 mmol), KOAc (2 mmol) and catalyst (0.05 g containing 0.0052 mmol of Pd) in PEG (400) (2 mL).

this study was performed in PEG 400. We also investigated the effect of a few bases in this media upon the reaction. The results given in Table 5 show that KOAc was a suitable base for the reaction.

As shown in Table 6, a range of aryl iodides, bromides and chlorides reacted with phenyl acetylene to give the desired products in high yields. As expected, the reaction of aryliodides bearing electron donating groups went to completion in longer reaction times (Table 6, Entry 2). The coupling reaction of phenyl acetylene with both electron- releasing and electron withdrawing aryl bromides afforded the desired products in high yields. Heterocyclic bromides such as 3-bromopyridine led to the corresponding bi-functionalized acetylene in a desirable yield (Table 6, Entry 9). The catalytic system was also applied for the reaction of aryl chlorides with phenyl acetylene. In these cases, the prolonged reaction times to 24 h were required to give the expected products in good yields (Table 6, Entries 10–12). Moreover, we have also applied this catalyst for a gram-scale reaction. For this aim, 1-bromo-4-nitrobenzene (5 mmol) was reacted with phenyl acetylene (7.5 mmol) under similar optimized reaction conditions. The reaction proceeded well to produce the desired biphenyl compound in 80% isolated yield

In order to get some information about the active catalytic species at 90 °C, we have performed poisoning test by using poly(4-vinylpyridine) as poisoning additive [40]. For this purpose, poly(4-vinylpyridine) with respect to the catalyst was used in the ratio of 400: 1 for the reaction of 4-methoxyiodobenzene with phenyl acetylene at 90 °C in PEG 400. Analysis of the reaction mixture by GC showed the conversion to the desired product after 2 h to be around 42–50% whereas, similar reaction in the absence of poisoning additive was performed in 2 h with 90% isolated yield (Table 6, Entry 2). Therefore, we may conclude that the catalyst acts as a heterogeneous–homogeneous catalyst at 90 °C. The heterogeneous part of the catalyst is responsible for the above mentioned conversion whereas, the homogeneous part of the catalyst performs the rest of the reaction. However, by cooling the reaction mixture to room temperature, absorption of the homogeneous Pd species to the surface of agarose molecules can occur which after

separation of the agarose catalyst it can be used for another batch of the reaction.

4. Conclusion

In this study, we have applied agarose which is a non-toxic, cheap, degradable natural product which can be used for the entrapment and ligation with Pd(0) species for Mizoroki–Heck reaction under phosphane and solvent-free conditions. This catalytic system was also applied with success for Sonogashira–Hagihara reaction in PEG 400 as a green solvent under copper-free conditions. The catalyst was recyclable which has been shown upon the Mizoroki–Heck reaction. By a poisoning test, we have concluded that the catalyst acts as a heterogeneous–homogeneous catalyst at higher temperatures.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2012.02.006.

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