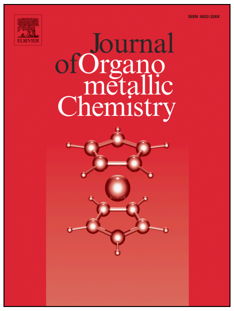

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Catalytic Specificity of Linear Polystyrene-Stabilized Pd Nanoparticles during Ullmann Coupling Reaction in Water and the Associated Mechanism

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1. Introduction

Biaryls are one of the most important classes of organic compounds, and are found in dyes [1-3], natural products [4], pharmaceutical compounds [5], advanced materials [6] and the backbones of some ligands [7,8] for metal catalysts. Over the past several decades, much effort has been devoted to the synthesis of biaryls *via* the coupling of aromatic compounds. The Pd-catalyzed Ullmann coupling reaction [9-11] is a versatile technique for the synthesis of biaryls, and many studies have focused on the Ullmann coupling reaction in water in conjunction with heterogeneous Pd catalysts [12,13]. Aryl iodides were initially used in such studies because the C-I bond is readily activated due to low dissociation energy of this bond compared with those of the C-Br and C-Cl bonds [14-18].

Metal nanoparticles immobilized by solid support generally exhibit improved catalytic activity compared to their bulk metal counterparts because they have high surface-to-volume ratios along with greater concentrations of available active catalytic sites per unit area. In many cases, however, the leaching of Pd species into the reaction medium occur during the reaction [19-21], and consequently metal nanoparticles tend to lose their catalytic activity during use because of decreasing the amount of catalyst or Ostwald ripening [22,23]. Our own group successfully developed linear polystyrene-stabilized metal nanoparticles with applications to several reactions in water [24-26] and a release-and-catch system for soluble Pd species in water using linear polystyrene as an efficient reservoir [27,28]. On the other hand, it has been thought that the metal nanoparticles catalyzed reaction proceed either in solution by leached species or on the surface of nanoparticles [19-21,29,30]. In the course of our research on the Hiyama coupling reaction catalyzed by linear polystyrene-stabilized PdO nanoparticles (PS-PdONPs), we determined that both reactions in solution and on the surface of nanoparticles were involved in the catalytic cycle and that the reaction sequence was different from the conventional mechanism [31]. Our continuing interest in the reaction mechanism of the catalytic reaction in water with linear polystyrene-stabilized metal nanoparticles as a catalyst led us to examine the Ullmann coupling reaction using PS-PdNPs in the present work. This study demonstrated that PS-PdNPs exhibit unique reactivity for Ullmann coupling reaction in aqueous solutions.

2. Experimental

*2.1 Preparation of PS-PdNPs by reduction with 4-methylphenylboronic acid (**1a**)*

To a screw-capped vial with a stirring bar were added 13 mg of polystyrene (0.13 mmol of styrene unit), $Pd(OAc)_2$ 8.4 mg (37 μmol), 4-methylphenylboronic acid 0.012 g (88 μmol), and 1.5 $mol \cdot L^{-1}$ aqueous KOH solution (3 mL). After stirring at 90 °C for 5 h, the aqueous solution was decanted. Subsequently, the polystyrene stabilized Pd nanoparticles were washed with water (5 × 3.0 mL), MeOH (1 × 3.0 mL), and Et_2O (5 × 3.0 mL).

*2.2 Preparation of PS-PdNPs by reduction with $NaBH_4$ (**1b**)*

To a screw-capped vial with a stirring bar were added 13 mg of polystyrene (0.13 mmol of styrene unit), $Pd(OAc)_2$ 8.4 mg (37 μmol), and water (2 mL). After adding methanol solution of $NaBH_4$ (0.37 $mol \cdot L^{-1}$, 1 mL) dropwise, the mixture was stirring at 25 °C for 1 h, and then the aqueous solution was decanted. Subsequently, the polystyrene stabilized Pd nanoparticles were washed with water (5 × 3.0 mL), MeOH (1 × 3.0 mL), and Et_2O (5 × 3.0 mL).

*2.3 Preparation of PS-PdNPs by reduction with benzyl alcohol (**1c**)*

To a screw-capped vial with a stirring bar were added 13 mg of polystyrene (0.13 mmol of styrene unit), $Pd(OAc)_2$ 8.4 mg (37 μmol), benzylalcohol 12 mg (0.11 mmol), and 1.5 $mol \cdot L^{-1}$ aqueous KOH solution (3 mL). After stirring at 90 °C for 24 h, the aqueous solution was decanted. Subsequently, the polystyrene stabilized Pd nanoparticles were washed with water (5 × 3.0 mL), MeOH (1 × 3.0 mL), and Et_2O (5 × 3.0 mL).

2.4 Determination of loading of the palladium

PS-PdNPs (**1a**-**1c**; 2.9 mg) was placed in a screw-capped vial and then added 13 M nitric acid (5 mL). The mixture was heated at 80 °C to dissolve completely. After cooled to room temperature, the solution was adjusted to 50 mL by water and then measured the amount of Pd metal by ICP-AES analysis (**1a**: 15.3 ppm, **1b**: 15.0 ppm, **1c**: 15.1 ppm).

2.5 Typical procedures for Ullmann coupling reaction

To a screw-capped vial with a stirring bar were added 4-bromotoluene (86.4 mg, 0.5 mmol), PS-PdNPs (2.9 mg, 1.5 mol% of Pd), and 1.5 mol·L^{-1} aqueous NaOH solution (1 mL). After stirring at 80 °C for 3 h, the reaction mixture was cooled to room temperature by immediately immersing the vial in water (~20 °C) for about 10 min. After separating the catalyst and the aqueous phase by centrifugation, the aqueous phase was decanted. Recovered catalyst was washed with H_2O (5 × 3.0 mL) and diethyl ether (5 × 3.0 mL), which were then added to the aqueous phase. The aqueous phase was extracted eight times with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The product was analyzed by ^{1}H NMR.

3. Results and discussion

Linear polystyrene-stabilized Pd nanoparticles (PS-PdNPs, **1a**-**1c**) [32] were prepared using 4-methylphenylboronic acid, $NaBH_4$, and benzyl alcohol as reductants. An X-ray photoelectron spectroscopy (XPS) analysis showed binding energy at 335.0 and 340.2 eV, which assigned to Pd 3d$_{5/2}$ and Pd3d$_{3/2}$ for palladium, respectively (Figure 1). Transmission electron microscopy (TEM) images showed Pd nanoparticles were dispersed on linear polystyrene with average particle size of 2.7 ± 0.3 nm for **1a** and 4.1 ± 0.7 nm for **1b**, respectively. In the case of **1c**, aggregates with 5 nm or more were observed (Figure 2).

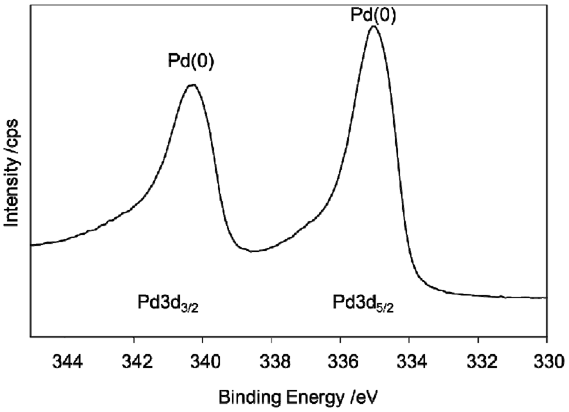
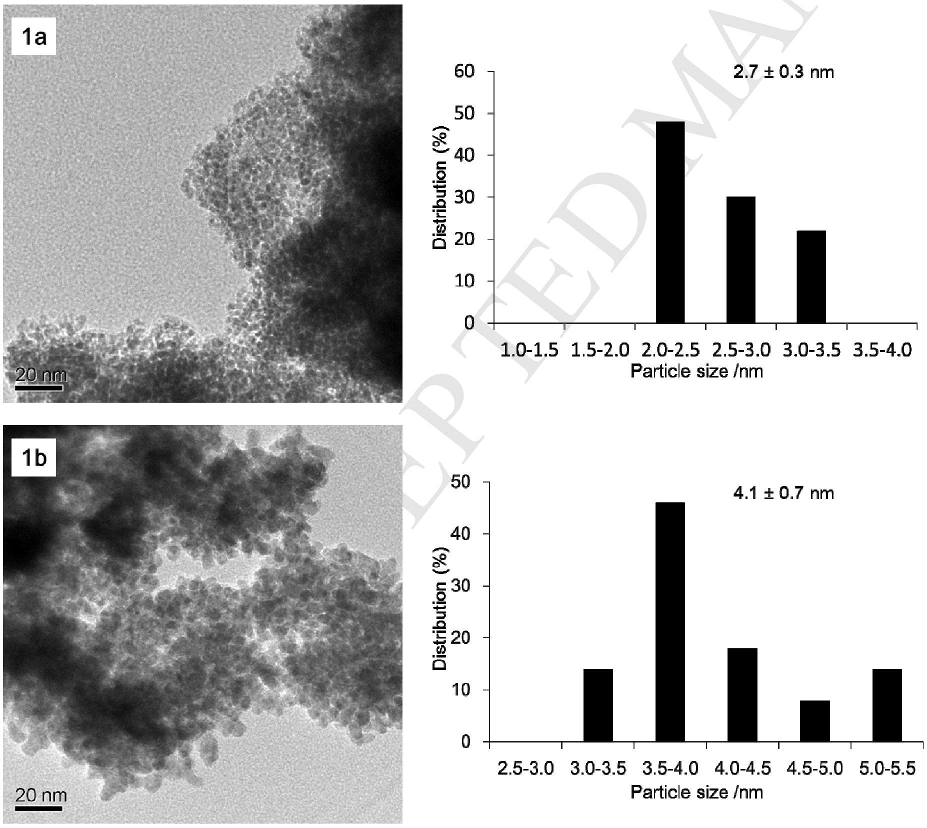


Figure 1 XPS spectrum of PS-PdNPs.



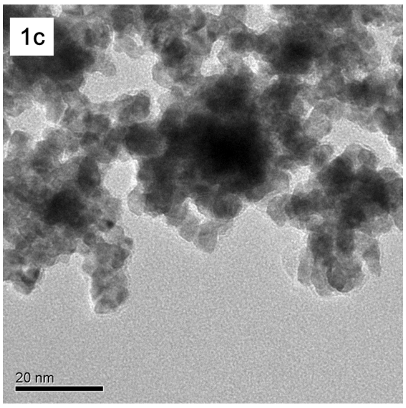
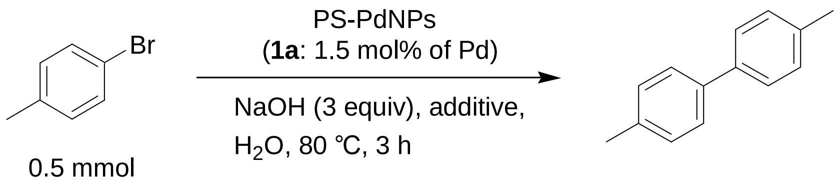


Figure 2 TEM micrographs and size distributions of **1a**-**1c** (scale bar = 20 nm).

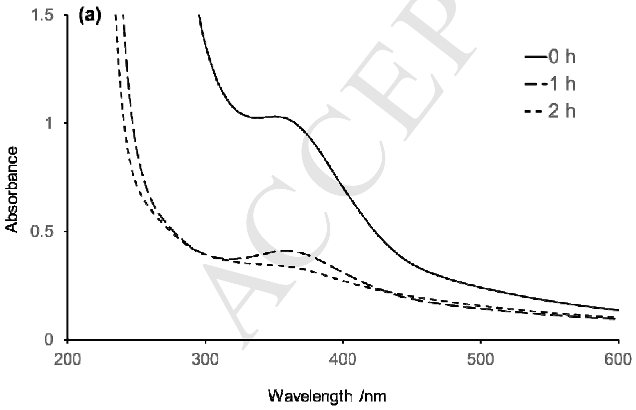
The effect of the Pd nanoparticle size was first examined by performing the Ullmann coupling reaction of 4-bromotoluene in a 1.5 mol·L^{-1} aqueous NaOH solution at 80 ºC for 3 h, using methanol as the external reductant. The desired coupling product was obtained efficiently only in the case of **1a**, indicating that the size of nanoparticles has a significant effect on the catalytic activity (Table 1, entries 1-3). In addition, the leaching of Pd into the reaction medium appears to be a challenge in this method, because the amount of leaching increased with increasing particle size [33,34]. Running the reaction with ethanol or 2-propanol as the external reductant lowered the yield of the desired product (entries 4 and 5), even though Zhang *et al.* has reported that 2-propanol is an excellent solvent and reductant [10]. To better understand the different performances of the reductants, the reduction of $PdBr_2$ by various alcohols in a 1.5 mol·L^{-1} aqueous NaOH solution at 80 °C was monitored by UV-vis spectroscopy. After heating a mixture of $PdBr_2$ and methanol (10 equiv), the disappearance of the peak at 368 nm corresponding to Pd$^{(II)}$ was observed within 2 h (Figure 3a), indicating the reduction of Pd$^{(II)}$ to Pd$^{(0)}$. In contrast, no reduction was observed when using ethanol or 2-propanol under the same conditions (Figures 3b and 3c).

Table 1. Effect of size of Pd nanoparticles and external reductant.



entry	additive	yield (%)[a]
1	MeOH (3 equiv)	85
2[b]	MeOH (3 equiv)	<1
3[c]	MeOH (3 equiv)	<1
4	EtOH (3 equiv)	trace
5	*i*-PrOH (3 equiv)	trace

[a] NMR yield. [b] PS-PdNPs (**1b**) prepared by $NaBH_4$ was used as a catalyst. [c] PS-PdNPs (**1c**) prepared by BnOH was used as a catalyst.



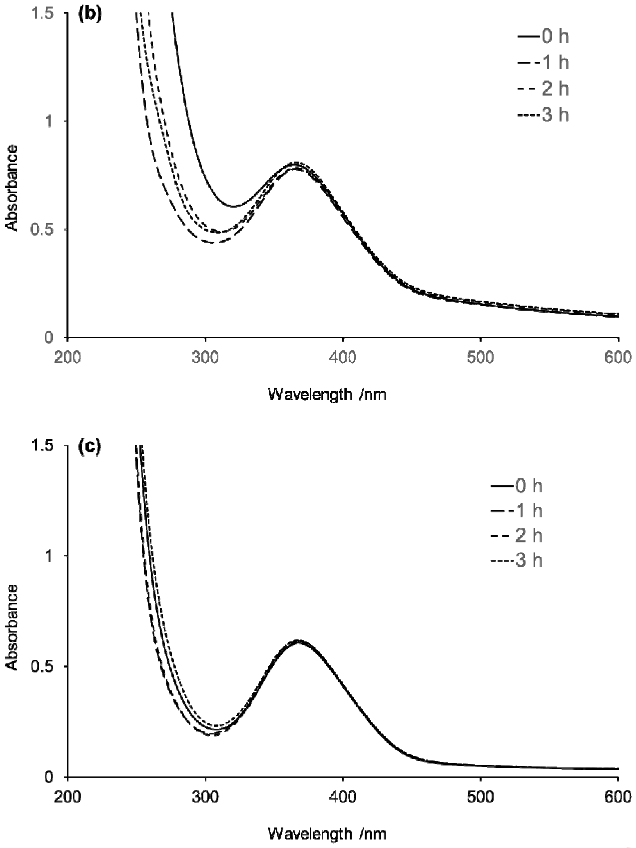


Figure 3. UV-vis spectra of $PdBr_2$ in a 1.5 mol/L aqueous NaOH solution at 80 °C: (a) in the presence of MeOH, (b) in the presence of EtOH, (c) in the presence of isopropanol.

The scope of the reaction was subsequently studied, employing various aryl halides (Table 2). Both electron-rich and electron-deficient aryl bromides were found to be applicable, affording the desired coupling products in good yields (entries 1-4). When the reaction was performed at 50 °C, similar yields were obtained with either 4-bromobenzotrifluoride or bromobenzene. In contrast, the yield was decreased dramatically when using 4-bromotoluene or 4-bromoanisole, suggesting that the oxidative addition of the aryl halide is the rate-determining step. The Ullmann coupling reaction of

4-bromonitrobenzene proceeded with formation of the desired product in good yield only in the presence of TBAC (entry 5), likely due to the high melting point of 4-bromonitrobenzene (ca. 125 °C). In addition, steric hindrance associated with the substrate clearly retarded the Ullmann coupling reaction, such that 2-bromotoluene gave a low yield, while no product was obtained with either 1-bromo-*m*-xylene or 1-bromonaphthalene (entries 6-8). When 4-chlorotoluene was used as the substrate, the yield of the coupling product was low, as predicted, due to the difficulty of cleavage of C-Cl bond (entry 9). However, the yield obtained from the reaction of 4-iodotoluene was unexpectedly lower than that from 4-bromotoluene (entry 10) [35] in contrast to previous works by other researchers [9-13]. Given the ease of the cleavage of C-X bond, the difference in the yields obtained from 4-iodotoluene and 4-bromotoluene is attributed to variations in the rate of reduction to re-form $Pd^{(0)}$ species. Indeed, a quantitative yield was achieved when the Ullmann coupling reaction of 4-iodotoluene was performed in the absence of methanol using a large amount of PS-PdNPs (50 mol% of Pd). No coupling product was obtained from the reaction of 4-bromoanisole using PdI_2 as the catalyst, although the coupling proceeded, giving 4,4'-dimethoxybiphenyl in 20% yield, in the presence of $PdBr_2$ (entries 11 and 12). In addition, the reduction of $PdBr_2$ by methanol in a 1.5 mol·L^{-1} aqueous NaOH solution at 80 °C was confirmed by UV-vis spectroscopy, whereas little reduction occurred in the case of PdI_2 (Figure 3a and Figure 4).

Table 2. Ullmann coupling reaction of aryl halide in water.

$$\underset{\text{0.5 mmol}}{\text{Ar—X}} \xrightarrow[\substack{\text{NaOH (3 equiv),} \\ \text{MeOH (3 equiv),} \\ \text{H}_2\text{O, 80 ℃, 3 h}}]{\substack{\text{PS-PdNPs} \\ (\textbf{1a}\text{: 1.5 mol\% of Pd})}} \text{Ar—Ar}$$

entry	Ar	X	yield (%)[a]
1	phenyl	Br	71 (66)[b]
2	4-methylphenyl	Br	85 (8)[b]
3	4-methoxyphenyl	Br	63 (7)[b]
4	4-trifluoromethylphenyl	Br	75 (76)[b]
5	4-nitrophenyl	Br	44 (73)[c]
6	2-methylphenyl	Br	14
7	2,6-dimethylphenyl	Br	0
8	1-naphtyl	Br	0
9	4-methylphenyl	Cl	30
10	4-methylphenyl	I	9 (99)[d]
11[e]	4-methoxyphenyl	Br	20
12[f]	4-methoxyphenyl	Br	0

[a] NMR yield. [b] 50 ℃, 3 h. [c] In the presence of TBAC. [d] 50 mol% of Pd was used. [e] $PdBr_2$ was used as the catalyst. [f] PdI_2 was used as the catalyst.

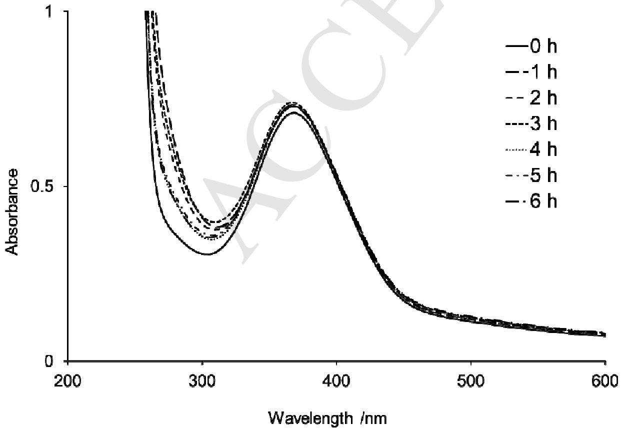


Figure 4. UV-vis spectra of PdI_2 in a 1.5 mol/L aqueous NaOH solution at 80 °C in the presence of MeOH.

When the reusability of the catalyst was examined, decreasing in yield was observed (Figure 5). Catalytic deactivation would be caused by decreasing of the catalyst amount because leaching of Pd [34] and slightly smaller Pd nanoparticle were confirmed by ICP-AES and TEM, respectively (Figure 6). Decrease in catalytic activity was also observed when the reaction time for the recycling trials was extended to 5 h. Although no palladium species in the reaction medium after the reaction was observed by ICP-AES analysis, TEM observation suggested Ostwald ripening occurred (Figure 7).

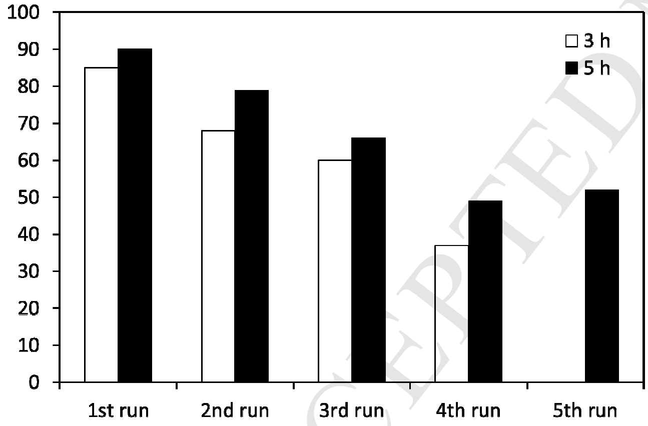


Figure 5. A recyclability test for PS-PdNPs in Ullmann coupling reaction of 4-bromotoluene in a 1.5 $mol \cdot L^{-1}$ aqueous NaOH solution at 80 °C in the presence of MeOH.

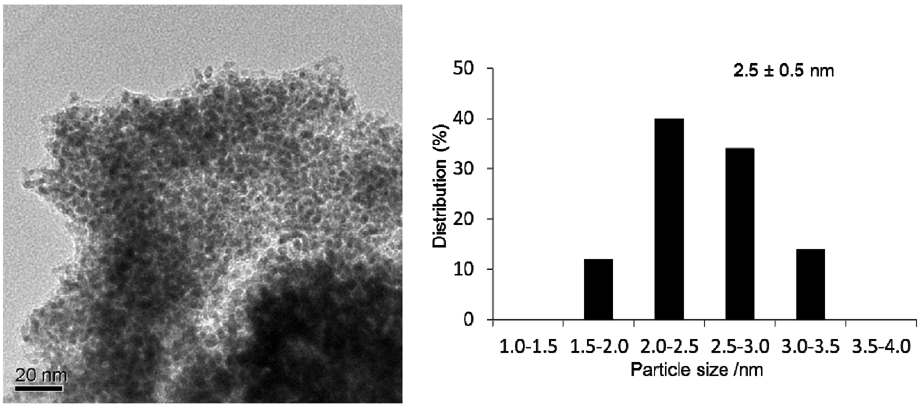


Figure 6 TEM micrographs and size distributions of the recovered catalyst after 4th run (reaction time = 3 h).

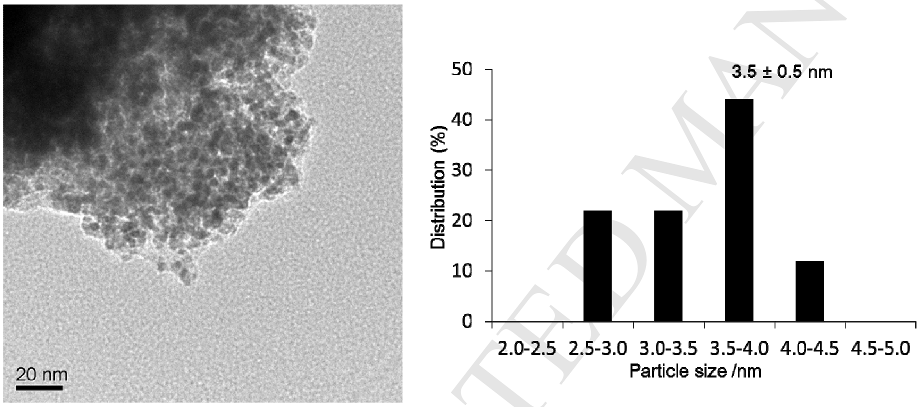
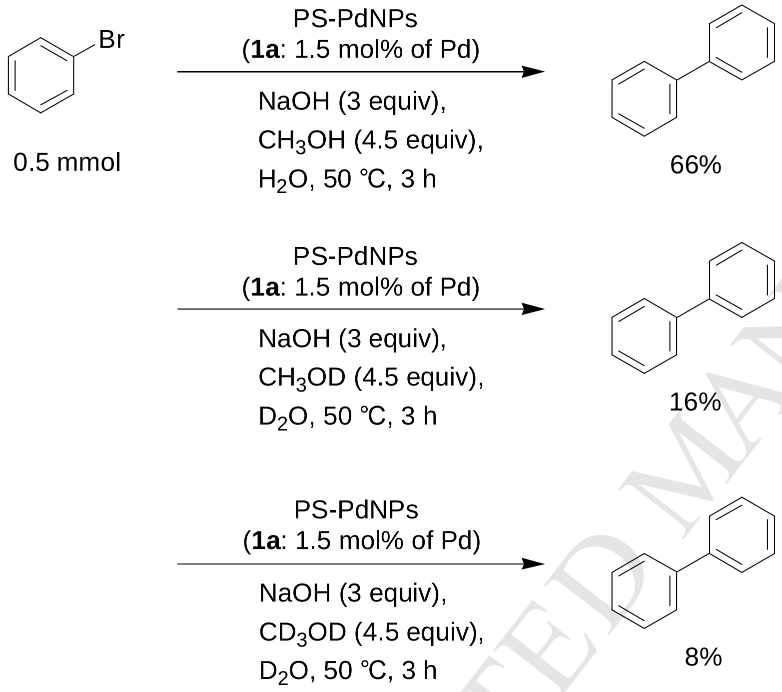


Figure 7 TEM micrographs and size distributions of the recovered catalyst after 5th run (reaction time = 5 h).

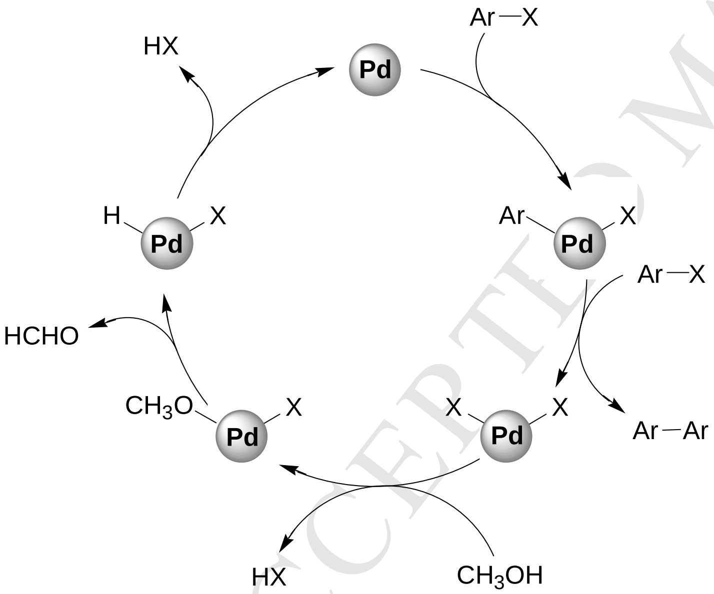
Deuterium labeling experiments were also conducted to obtain further mechanistic details (Scheme 1). The control reaction produced a 66% yield of coupling product, whereas reactions with CH_3OD or CD_3OD furnished the biphenyl in 16% or 8% yields, respectively. Because both the CH_3OD

and CD_3OD gave lower yields, it appears that both cleavage of C-H bond of methanol by *β*-H elimination and O-H bond such as oxidative addition to $Pd^{(II)}$ species [36] or deprotonation from methanol on the metal surface [37] include in the catalytic cycle.



Scheme 1. Deuterium labelling experiments.

Based on the above results, we propose a mechanism for the Ullmann coupling reaction in the presence of PS-PdNPs (Scheme 2). Following the successive oxidative addition of two aryl halides on the surface of the nanoparticles (as opposed to the solution phase), reductive elimination proceeds to form the coupling product [38]. And then the reduction by methanol occurs to regenerate $Pd^{(0)}$. The result obtained using 4-iodotoluene (Table 2, entry 10) is consistent with the proposed process, in which the successive oxidative addition of two aryl halides occurs prior to the reduction by methanol. There is only minimal reduction of dissolved Pd$^{(II)}$ species by methanol at 50 °C (Figure 8), the Ullmann coupling reaction of 4-bromobenzotrifluoride took place smoothly at 50 °C (entry 4 in Table 2), and only 4% of the corresponding product was obtained from the reaction of 4-bromobenzotrifluoride using a water-soluble palladium species, which was prepared by dissolving $PdBr_2$ in 1.5 mol·L^{-1} NaOH aqueous solution (eq 1). These results indicate that the leaching of Pd species into the reaction medium has a negative effect on the Ullmann coupling reaction.



Scheme 2. A plausible reaction mechanism for Ullmann coupling reaction.

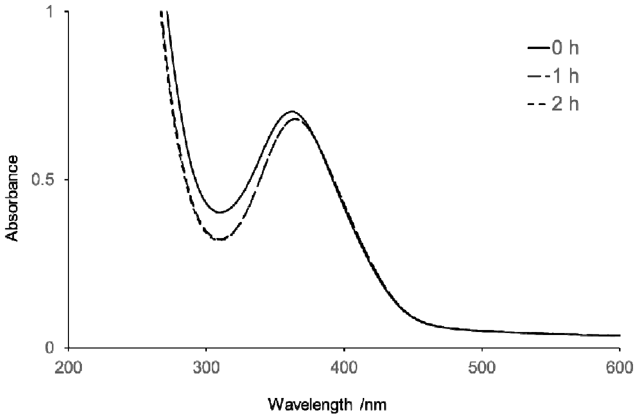
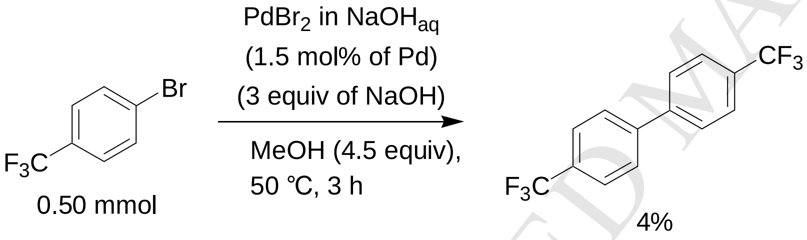


Figure 8. UV-vis spectra of $PdBr_2$ in a 1.5 mol/L aqueous NaOH solution at 50 °C in the presence of MeOH.



(1)

4. Conclusion

In summary, the Ullmann coupling reaction as catalyzed by polystyrene-stabilized Pd nanoparticles was investigated. This catalyst showed high catalytic activity and the catalytic activity was also found to be dependent on the size of nanoparticles. The reactivity order of aryl halides was Ar-Br > Ar-Cl > Ar-I, as a result of variations in the ease with which the C-X bond could be cleaved and with which $Pd^{(II)}$ could be reduced to $Pd^{(0)}$ by methanol. The reaction evidently starts with the successive oxidative addition of two aryl halides, with the reduction of Pd$^{(II)}$ species by methanol occurring after the formation of the coupling product. It was further determined that the reaction takes place on the surface of the Pd nanoparticles and that leaching of Pd into reaction medium impedes the reaction.

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Highlights

Catalytic Specificity of Linear Polystyrene-Stabilized Pd Nanoparticles during Ullmann Coupling Reaction in Water and the Associated Mechanism

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- Polystyrene-stabilized Pd nanoparticles showed high catalytic activity for Ullmann coupling reaction of aryl bromides in water.
- The reactivity order of aryl halides was Ar-Br > Ar-Cl > Ar-I.
- The size of nanoparticles has a significant effect on the catalytic activity.
- The reaction takes place on the surface of the Pd nanoparticles and that leaching of Pd into reaction medium impedes the reaction.