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A ligand-free Heck reaction catalyzed by the *in situ*-generated palladium nanoparticles in PEG-400

Wei Han, Ning Liu, Chun Liu^{*}, Zi Lin Jin

State Key Laboratory of Fine Chemicals, School of Chemical Engineering, Dalian University of Technology, Dalian 116012, China Received 1 April 2010

Abstract

A ligand-free Heck reaction catalyzed by *in situ*-generated palladium nanoparticles in PEG-400 has been developed. This catalytic system is a simple and active protocol for the Heck reaction of aryl halides under mild conditions. Comparative experiments demonstrated that the Heck reaction catalyzed by the palladium nanoparticles *in situ*-generated under the Heck reaction conditions was carried out much quicker than that by the *in ex situ*-generated ones.

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The palladium-catalyzed Heck reaction developed in the early 1970s was a milestone in modern organic chemistry, which opened a door to the construction of carbon–carbon bonds in a completely uncommon but practical manner [1–2]. Among the numerous achievements on this topic the development of "ligand-free" catalytic systems has been one of the most challenging fields in synthetic organic chemistry, because they are the simplest and cheapest systems in comparison to the ligand-promoted ones [1–8].

As an environmental benign and readily available solvent and good solubility to organic compounds, polyethylene glycol (PEG) has been widely used in the palladium-catalyzed ligand-free transformations in recent years [9–16]. The first example of the Heck reaction performed in PEG was reported in 2002 by Chandrasekhar et al., who used PEG-2000 as a solvent to carry out the Heck reaction of aryl bromides in high yields [9]. In 2005, Zhang and co-workers used the preformed palladium nanoparticles in PEG-2000 for the Heck reaction and found that PEGs with lower molecular weight resulted in difficulty in the formation of palladium nanoparticles [10]. Recently, Corma et al. prepared a PEG-anchored carbapalladacycle catalyst for the Heck reaction of 4-bromoacetophenone with styrene at 150 °C in PEG-6000 and observed the formation of palladium nanoparticles with an average size of 5.1 nm after the reaction [12]. Most recently, Lamaty et al. reported the formation of palladium nanoparticles after microwave irradiation of a mixture of palladium acetate, PEG-3400 and K₂CO₃ in the Heck reaction for the synthesis of benzazepines [17]. Generally, PEG enables the reduction of Pd(II) to Pd(0) while its hydroxyl groups are oxidized into aldehyde groups [10,18], which makes it possible to prepare palladium nanoparticles in many types of transformations due to its special molecular

* Corresponding author.

E-mail address: cliu@dlut.edu.cn (C. Liu).

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structure [10,12,17,19]. Therefore, it is possible to make use of the unique advantages of PEG to prepare palladium nanoparticles easily *in situ* for palladium-catalyzed transformations.

Based on this concept we have successfully demonstrated a ligand-free Suzuki coupling reaction [20,21]. In this paper, we report a ligand-free Heck reaction catalyzed by the *in situ*-generated palladium nanoparticles in PEG-400 (mp 4–8 °C) under mild conditions, a simple and active protocol for the Heck reaction. Moreover, comparative experiments have been designed for the first time to disclose the catalytic property differences between the *in situ*-generated palladium nanoparticles and the *in ex situ*-generated ones in the ligand-free Heck reaction.

1. Experimental

All chemicals were purchased from commercial sources and used without further purification. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Inova 400 spectrometer. Chemical shifts are reported in ppm relative to TMS. Transmission electron microscopy (TEM) was performed on a Tecnai 20 microscope operating at 200 kV. All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60–90 °C), unless otherwise noted. Compounds described in the literature were characterized by comparison of their melting points, ¹H NMR, and ¹³C NMR to the reported data.

In situ-formed palladium nanoparticles catalysis: A mixture of aryl halide (0.5 mmol), olefin (0.75 mmol), Pd(OAc)₂ (1 mol% or 2 mol%), CH₃COONa (1 mmol, 83 mg) and PEG-400 (4 g) was stirred at 80 °C. The reaction was monitored by GC or TLC.

Preprepared palladium nanocatalysis: $Pd(OAc)_2 \ 1 \ mol\%$ (2 mol% for 2-bromobenzonitril) was added into deoxygened PEG-400 (4 g) at 45 °C by magnetic stirring for 2 h under N₂. During the process the colour of the solution turned from light yellow to dark, indicating the formation of palladium nanoparticles.

2. Results and discussion

We first explored the scope and limitations of substrates for the Heck reaction under the optimized conditions of $1-2 \mod Pd(OAc)_2$ in PEG-400 and sodium acetate as a base at 80 °C. The results are illustrated in Table 1.

Table 1

PEG-400/Pd(OAc)₂ catalyzed Heck reaction of aryl halides with olefins.^a



Entry	X	R^1	R^2	Time (h)	Isolated yield (%)
1	Ι	Н	Ph	1.5	93
2	Ι	Н	COOCH ₃	1.5	91
3	Ι	4-NO ₂	Ph	1.5	96
4	Ι	4-NO ₂	COOCH ₃	1.5	94
5	Ι	2-CH ₃	Ph	2.5	89
6	Ι	2-CH ₃	COOCH ₃	2.5	95
7	Br	4-NO ₂	Ph	3.0	94
8	Br	4-NO ₂	COOCH ₃	8.5	96
9	Br	4-CHO	Ph	6	92
10	Br	4-CHO	COOCH ₃	12	Trace
11	Br	2-CHO	Ph	9	92
12	Br	2-CHO	COOCH ₃	18	86
13	Br	2-CN	Ph	9	90
14	Br	2-CN	COOCH ₃	12	49
15	Br	Н	Ph	24	25
16	Br	Н	COOCH ₃	24	No reaction

^a Reaction conditions: aryl halide (0.5 mmol), olefin (0.75 mmol), Pd(OAc)₂ 1 mol% (1.12 mg) (2 mol% for aryl bromides except 4-nitrobromobenzene), base (1 mmol), PEG-400 (4 g), 80 °C (120 °C for entries 15 and 16). The reaction was monitored by TLC or GC.

Entry	X	R	Catalyst type	Time (h)	Isolated yield (%)
1a	Ι	2-CH ₃	in situ	2.5	89
1b	Ι	2-CH ₃	in ex situ	2.5	61
2a	Br	2-CN	in situ	9	90
2b	Br	2-CN	in ex situ	9	58
3a	Br	$4-NO_2$	in situ	3	94
3b	Br	$4-NO_2$	in ex situ	3	42

Comparative experiments of the in situ-generated and the in ex situ-generated palladium nanoparticles catalyzed Heck reaction in PEG-400.^a

Table 2

^a Reaction conditions: aryl halide (0.5 mmol), styrene (0.75 mmol), Pd(OAc)₂ 1 mol% (1.12 mg) (2 mol% for aryl bromides except 4-nitrobromobenzene), CH₃COONa (1 mmol), PEG-400 (4 g), 80 °C. The reaction was monitored by TLC.

A wide range of aryl iodides and bromides gave the cross-coupling products with good to excellent isolated yields in the system of PEG-400/Pd(OAc)₂. Moreover, different functional groups such as nitro, aldehyde, and cyano groups were tolerated in the reaction and not affected. The reaction system showed high reactivity for the Heck reaction of aryl iodides. The cross-couplings between aryl iodides with electron-withdrawing groups or electron-donating groups and styrene or acrylic acid methyl ester, respectively, were achieved in good yields using a 1 mol% palladium loading in short times (Table 1, entries 1–6). Compared to this, it took longer reaction time for completing the Heck reaction of aryl bromides with styrene or acrylic acid methyl ester. The results in Table 1 exhibit that the reaction system was active for the substituents in both *ortho* and *para* positions of aryl bromides. The reactivity of styrene was more reactive than that of acrylic acid methyl ester when using the same aryl bromide. Surprisingly, there was nearly no reaction occurred between 4-bromobenzaldehyde and acrylic acid methyl ester (Table 1, entry 10). However, an isolated yield of 86% was reached in 18 h using 2-bromobenzaldehyde (Table 1, entry 12). Unfortunately, this reaction system showed low reactivity for bromobenzene (Table 1, entries 15 and 16).

The isolated products are *E*-geometrical olefins according to 1 H NMR spectra. Probably, the PEG played a crucial role in the selectivity due to its special molecular structure [11,22,23].

To the best of our knowledge, the present work is the first example of the Heck reaction catalyzed *in situ* by palladium nanoparticles in PEG. To disclose the catalytic properties of the *in situ*-generated palladium nanoparticles under the Heck reaction conditions and the *in ex situ*-generated ones in the Heck reaction of aryl halides, comparative experiments were carried out under the same reaction conditions, respectively. The catalytic results are shown in Table 2 and the average sizes of the palladium nanoparticles were characterized by the transmission electron microscopy. As expected, the catalytic properties were quite different. The palladium nanoparticles generated under the Heck reaction conditions showed much more active than the *in ex situ*-generated ones (Table 2).

The results are consistent with the TEM micrographs (Fig. 1): the average diameters of the palladium nanoparticles generated under the Heck reaction conditions in the whole reaction process were *ca*. 2.5 nm, while the *in ex situ*-generated palladium nanoparticles were *ca*. 3.6 nm. It is known that nanoparticles have large surface to volume ratio



Fig. 1. TEM micrographs of Pd nanoparticles. (a) 30 min after reaction, (b) 180 min after reaction, (c) preprepared Pd nanoparticles (Pd(OAc)₂, 1 mol%) in PEG-400 at rt under N_2 .

leading to high energy surfaces and easy aggregation. In our manner, the formation of palladium nanoparticles *in situ* accompanied with the Heck reaction occurred immediately. And in view of the molecular collision theory, the reaction might be catalyzed by the palladium nanoparticles stabilized by PEGs once the formation of Pd(0).

In summary, we have presented a simple and effective ligand-free protocol for Heck reaction of aryl bromides and aryl iodides with olefins catalyzed by the *in situ*-generated palladium nanoparticles in PEG-400 under mild conditions. It was worth noting that the formation of the palladium nanoparticles and the catalysis were proceeded in one-pot. Moreover, the first example of comparative experiments illustrated that the reactivity of the palladium nanoparticles generated under the Heck reaction conditions was much higher than that of the *in ex situ*-generated ones. In this catalytic system, the PEG-400 played versatile roles: green solvent, reductant and stabilizer.

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