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In Situ Generation of Palladium Nanoparticles: A Simple and Highly Active Protocol for Oxygen-Promoted Ligand-Free Suzuki Coupling Reaction of Aryl Chlorides

Wei Han, Chun Liu,* and Zi-Lin Jin

State Key Lab of Fine Chemicals, Dalian University of Technology, Dalian 116012, China

chunliu70@yahoo.com

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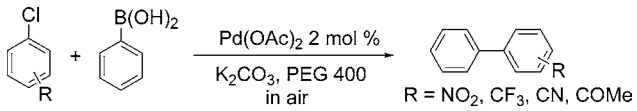
ABSTRACT



An oxygen-promoted ligand-free Suzuki coupling reaction catalyzed by in situ generated palladium nanoparticles in PEG-400 under aerobic conditions has been demonstrated. The reaction was highly efficient for coupling aryl chlorides with phenylboronic acid in short times under mild conditions.

The palladium-catalyzed Suzuki coupling reaction of aryl halides with arylboronic acids is one of the most important and powerful tools to form biaryls and has been extensively used in the synthesis of pharmaceuticals, herbicides, natural products, and advanced materials.[1]

Generally, the palladium-catalyzed Suzuki coupling reaction is performed under an inert atmosphere because the catalytic species are sensitive to oxygen or moisture.[2] Attempts have also been made to carry out Suzuki reactions under aerobic conditions by using a ligand-free or air-stable ligand system.[3] However, these aerobic systems showed moderate to high activity only for the coupling of aryl iodides or/and bromides with arylboronic acids but low activity for aryl chlorides.[3]

Slaughter et al. demonstrated that Suzuki reactions catalyzed over a palladium Chugaev carbene complex exhibited higher activity in nitrogen than in air.[3d] However, Corma et al. observed a positive effect of air on the Suzuki reaction of 4-bromoacetophenone and *o*-tolylboronic acid using a PEG-anchored carbapalladacycle catalyst.[3g] The influence of the air on the Suzuki coupling reaction has not been fully investigated. Therefore, developing an efficient and ligand-free reaction system for Suzuki coupling of aryl chloride under aerobic conditions is of great interest for chemists and

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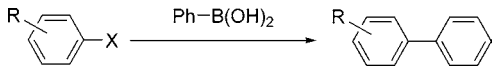
producers. Recently, polyethylene glycol (PEG) as a green and easily available solvent has been widely used in the Suzuki reaction.[3g,4] PEG enables the reduction of Pd(II) to Pd(0), and its hydroxyl groups are oxidized into aldehyde groups,[5] which makes it possible to prepare palladium nanoparticles easily in PEG in the absence of normally adopted reducing agents[6] such as hydrazine, hydrogen, sodium borohydride, etc. To our knowledge, no reactions catalyzed by the in situ generated palladium nanoparticles in PEG have been reported.

In this paper, we report a ligand-free Suzuki coupling reaction catalyzed by the in situ generated palladium nanoparticles in PEG-400 under aerobic conditions. A very simple and highly efficient approach for Suzuki coupling of aryl chlorides with phenylboronic acid, the TOF was reached up to 196 h^{-1} (Table 1, entry 9). Furthermore, the results showed

Table 1. Suzuki Coupling Reactions of Aryl Halides with Phenylboronic Acid in PEG-400 under Different Conditions[a]



entry	R	X	conditions	time	yield (%)[b]
1a	2-Me, 6-Me	Br	air	50 min	91
1b	2-Me, 6-Me	Br	N_2	6.5 h	92[c]
2a	4-CF_3	Cl	air	2 h	96
2b	4-CF_3	Cl	N_2	2 h	40[c]
3a	4-COMe	Cl	air	2 h	97
3b	4-COMe	Cl	N_2	2 h	54[c]
4a	2-CN	Cl	air	5 h	90
4b	2-CN	Cl	N_2	5 h	60[c]
5a	2-NO_2	Cl	air	1.5 h	96
5b	2-NO_2	Cl	N_2	4 h	88[c]
6	H	Cl	air	3 h	91
7	3-MeO	Cl	air	3 h	82
8	4-NO_2	Cl	air	20 min	96[d]
9	4-NO_2	Cl	air	1 h	98[e]

[a] Reaction conditions (not optimized): aryl halides (0.5 mmol), phenyl boronic acid (0.75 mmol), $Pd(OAc)_2$ (2 mol %) (1 mol % for entries 1a and 1b), K_2CO_3 (1 mmol), PEG (4 g), 45 °C (rt for entries 1a and 1b). The reactions were monitored by GC. [b] Isolated yields. [c] PEG-400 was degassed. [d] 1-Chloro-4-nitrobenzene (10 mmol), phenyl boronic acid (15 mmol), $Pd(OAc)_2$ (2 mol %), K_2CO_3 (20 mmol), PEG (50 g), rt. [e] $Pd(OAc)_2$ (0.5 mol %). Other conditions were the same as entry 8.

that this approach was oxygen-promoted (Tables 1 and 2).

The first challenge was to generate palladium nanoparticles in situ under aerobic conditions in PEG-400 without additional ligands, reductants, and stabilizers. The transmission electron microscopy (TEM) micrograph showed that palladium nanoparticles with an average size of ca. 1.5 nm were formed within 5 min at room temperature or even at a lower temperature accompanying the Suzuki coupling reaction (Figure 1a). Whereas Zhang et al. reported a procedure for

Table 2. Control Experiments of Suzuki Coupling of 2-Bromo-*m*-xylene with Phenylboronic Acid in Different Conditions by Palladium Nanoparticles in PEG-400[a]

entry	conditions	time	isolated yield (%)
1	air	50 min	91
2	O_2	50 min	93
3	N_2	6.5 h	92[b]

[a] Reaction conditions (not optimized): 2-bromo-*m*-xylene (0.5 mmol), phenylboronic acid (0.75 mmol), $Pd(OAc)_2$ (1 mol %), K_2CO_3 (1 mmol), PEG (4 g), rt. The reactions were monitored by GC. [b] PEG-400 was degassed.

preparing palladium nanoparticles in more than 2 h at 80 °C in PEG with an average molecular weight range from 600 to 4000 g/mol for a Heck reaction,[5] Reetz and Westermann generated in situ nanosized palladium colloids, which needed an induction period of about 1 h.[7] This means in our case the formation of the palladium nanoparticles was much faster, which is supposed to be due to the reduction of phenylboronic acid.

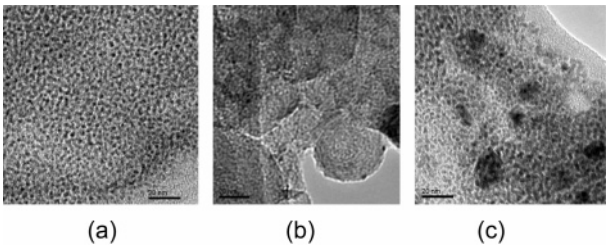


Figure 1. TEM micrographs showing the in situ generated palladium nanoparticles in PEG-400: (a) 5 min after reaction in air, (b) 75 min after reaction in air, and (c) 75 min after reaction in nitrogen. Reaction conditions: 4-chlorobenzotrifluoride (0.5 mmol), phenyl boronic acid (0.75 mmol), $Pd(AcO)_2$ (2 mol %), K_2CO_3 (1 mmol), PEG-400 (4 g), rt.

It was worth noting that the system possessed excellent catalytic activity for coupling aryl chlorides or unactivated aryl bromides with phenylboronic acid using low catalyst loadings in short times under mild conditions (Table 1, entries 2a, 3a, 4a, and 5a). Excitingly, the reactions performed in open air were much quicker than those in nitrogen (Table

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1). These results were consistent with what Corma et al. reported.[3g] To investigate the essence of the effect of the air on the Suzuki reaction, control experiments have been designed by performing the coupling reaction of 2-bromo-*m*-xylene with phenylboronic acid in air, oxygen, and nitrogen, respectively (Table 2). Obviously, the reactions carried out in air and oxygen had the same highly efficient catalytic activity. The substrates in both open air and pure oxygen systems were consumed in 50 min, which was analyzed by GC (Table 2, entries 1 and 2), whereas it took 6.5 h to complete the couplings in N_2 (Table 2, entry 3).

Thus, it could be concluded that it was the oxygen that promoted the Suzuki coupling reaction.

In principle, the catalytic activity in nanocatalysis is determined by the size of nanoparticles. The smaller the nanoparticle is, the more effective the catalytic activity. We further prepared in situ the palladium nanoparticles in both air and nitrogen when the Suzuki reactions were carried out for 75 min. The average sizes of the palladium nanoparticles prepared in this manner were characterized by TEM, respectively (Figure 1b,c). The TEM micrographs showed that the average diameters of palladium nanoparticles of ca. 1.5 nm in air were smaller than those of ca. 3.0 nm in nitrogen. Different sizes of the palladium nanoparticles could be the reason why the reaction took place much faster in open air than in nitrogen. Moreover, it could be seen clearly that there were partially aggregated particles in the micrograph of the in situ generated palladium nanoparticles in nitrogen (Figure 1c). However, the system of the in situ generated palladium nanoparticles in PEG-400 in air was stable for months; no palladium black was observed.

In 2000, Sheldon et al.[8] reported a zerovalent palladium peroxide intermediate in aerobic oxidation of alcohol. Recently, Amatore et al.[9] isolated a peroxo complex (η^2-O_2)Pd(PPh_3)$_2$ in the homocoupling of arylboronic acids. These reports prompted us to suppose that palladium nanoparticles could adsorb molecular oxygen on their surfaces in the presence of pure oxygen or air (Figure 2).

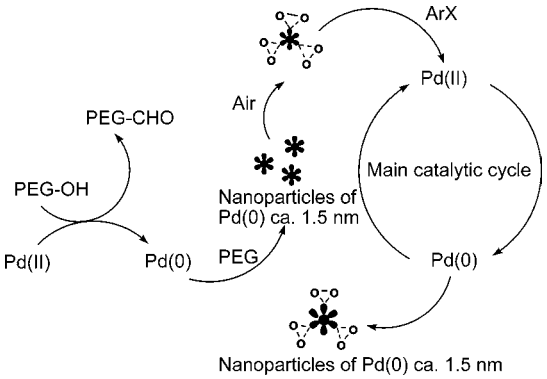

Figure 2. Proposed mechanism of an oxygen-promoted ligand-free Suzuki coupling reaction catalyzed by the in situ generated palladium nanoparticles under aerobic conditions in PEG-400.

As a result, the oxygen-adsorbed palladium nanoparticles were more stable against aggregation and maintained high catalytic activity.

In conclusion, a simple and highly efficient oxygen-promoted ligand-free protocol for Suzuki coupling of aryl chlorides with phenylboronic acid catalyzed by the in situ generated palladium nanoparticles in PEG-400 under aerobic conditions has been demonstrated. In addition, the PEG-400 played versatile roles: green reactive medium, reductant, and stabilizer. Further applications of the system in other coupling transformations are under investigation in our laboratory.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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