

Pd Nanoparticles as Efficient Catalysts for Suzuki and Stille Coupling Reactions of Aryl Halides in Ionic Liquids

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Pd-catalyzed Suzuki and Stille cross-couplings of aryl bromides and chlorides were carried out in quaternary ammonium salts as solvents under mild conditions and with the recycling of the catalyst.

Introduction

In the past three decades, palladium chemistry has emerged as one of the most powerful tools for the formation of carbon-carbon and carbon-heteroatom bonds. Special interest has been devoted to the palladium-catalyzed cross-couplings of aryl and vinyl halides with either olefins (Mizoroki-Heck reactions) or organometallic reagents (Suzuki, Stille, Sonogashira, Negishi, Kumada, Hiyama, etc. reactions), due to their tolerance toward a wide range of functional groups, which permits them to synthesize highly complex molecules.¹

Despite the synthetic elegance, these processes suffer from two serious limitations that have precluded a wide use in industry: (i) the need for the use of toxic and/or expensive phosphine ligands, which are necessary to stabilize the catalytically active Pd(0) species, and (ii) the very low reactivity of aryl chlorides, which are arguably the most useful class of substrates, because of their lower cost and the wider variety of available compounds in comparison with the more reactive iodides and bromides.²

More recently, palladium-centered catalysis in ionic liquids (ILs) has gained considerable importance, since

this methodology allows us to achieve simultaneously the advantages of the elimination of highly toxic solvents, the ease of workup, and the possibility of recycling the catalyst.³ In addition, it has been widely demonstrated that ILs can play a greater role than merely solubilizing the reagents, as their ability to affect the nature of the catalytically active species was shown to be dependent on the structure of both cation and anion.⁴

In this context, during the past few years we reported a series of highly efficient Pd-catalyzed Heck arylations of mono- and disubstituted olefins by using a tetraalkylammonium salt as the solvent and phosphane-free catalysts in both homogeneous⁵ and heterogeneous conditions.⁶ In particular, while searching for a Pd-catalyzed

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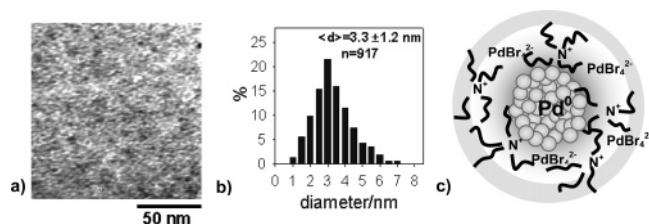


FIGURE 1. (a) TEM characterization of a palladium colloidal dispersion synthesized as described in the text. (b) Histogram representing size distribution of the palladium nanoparticle core. (c) Core-shell structure representation of a nanoparticle.

regio- and stereoselective Heck arylation of cinnamates⁷ and methacrylates⁸ in ILs, we found that by dissolving palladium acetate in melt tetrabutylammonium bromide (TBAB) and using tetrabutylammonium acetate (TBAA) as base, the rapidly formed dark suspension of Pd nanoparticles (Pd NPs) efficiently catalyzed the reaction of aryl bromides and chlorides.

Reactions occurred at the surface of the monodisperse nanoparticles, formed by chemical reduction of Pd(OAc)₂ by TBAA,⁹ whose structure, defined “core-shell”, is composed of a metallic core (~3.3 nm in size) surrounded by a stabilizing shell containing tetrabutylammonium cations and Br⁻ and [PdBr₄]²⁻ species (Figure 1).

Although the effectiveness of these nanosized catalysts has been widely demonstrated in the Heck couplings, the use of ILs as reaction media for other Pd NP-catalyzed coupling reactions is a relatively unexplored area.

We report here the applications of free Pd nanoparticles as catalyst for the *Suzuki* and *Stille* cross-coupling reactions of aryl bromides and chlorides carried out in ILs under mild conditions, with the recycling of the catalyst for aryl bromides.

Results

Our investigations started with the study of *Suzuki*–*Myiaura* cross-coupling reaction, an extremely important methodology for the generation of new carbon–carbon bonds specially applied to the synthesis of biaryls.¹⁰ A typical procedure employs aryl halides as electrophiles and boronic acids as nucleophilic counterpart, these latter being widely available and air- and moisture-stable.

Concerning the *Suzuki* reaction carried out in ionic liquids, a number of articles have described the use of Pd catalysts based on phosphanes,¹¹ palladacycles,¹² carbenes,¹³ and N-donor¹⁴ ligands, dissolved in ILs derived from imidazolium cation. In some other cases, both ligand-free Pd catalysts and water solvents were used,

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but tetraalkylammonium salts were generally added as phase transfer agents.¹⁵

Pd nanoparticles were also used as a catalyst for the *Suzuki* reaction, but they were generally stabilized by incorporation into polymers, dendrimers, or inorganic supports.¹⁶ In most of these applications, iodo- and bromoarenes reacted, but only at elevated temperature, while aryl chlorides were almost unreactive. On the contrary, only a few articles reported the activation of bromides and chlorides by Pd NPs under mild conditions.¹⁷

With this aim, we tested the activity of the free monodisperse Pd nanoparticles in a biphasic medium consisting of an ionic liquid, generally a melt tetraalkylammonium bromide containing both reagents and catalyst, and an aqueous solution of a source of hydroxide anions (OH⁻), which are necessary to activate the boronic acid. Under these conditions, although the IL is water-soluble, it forms a biphasic system as already found by other groups.¹⁸

Of particular importance was the modality of preparation of Pd nanocolloids, carried out by adding to Pd(OAc)₂, dissolved in the IL, an excess of tetrabutylammonium acetate and heating the reaction mixture at 90 °C until a homogeneous dark red mixture was obtained (see Supporting Information).

The first experiments were devoted to investigating the efficiency of the catalytic system composed by Pd NPs, TBAB, and aqueous Na₂CO₃ on halobenzenes. At high temperatures, bromobenzene was rapidly converted into diphenyl (Table 1, entry 1), but the catalyst activity dropped fast when either the reaction temperature was lowered or the less reactive chlorobenzene was used as the substrate (entries 2 and 3). Ascribing this scarce

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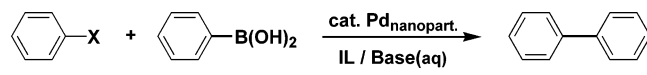
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TABLE 1. Screening of ILs and Bases in Pd NP-Catalyzed Cross-Coupling of Suzuki Reaction in ILs^a


entry	X	IL	base(aq)	T (°C)	t (h)	conv ^b (%)	yields ^c (%)
1	Br	TBAB	Na ₂ CO ₃	110	0.5	>99	95
2	Br	TBAB	Na ₂ CO ₃	60	16	<1	–
3	Cl	TBAB	Na ₂ CO ₃	140	16	15	–
4	Cl	TBAB	KOH	90	16	36	20
5	Cl	TBAB	NBu ₄ OH	90	3	93	86
6	Cl	THeptAB	NBu ₄ OH	90	3	98	92
7	Cl	TBAB	NBu ₄ OH	70	4.5	57	45
8	Cl	THeptAB	NBu ₄ OH	70	4.5	89	83
9	Cl	THeptAB	NBu ₄ OH	60	16	<1	–
10	Br	THeptAB	NBu ₄ OH	60	1.5	>99	93

^a Reaction conditions: IL (6 mmol), phenylboronic acid (1.1 mmol), aryl halide (1 mmol), base (2 mmol in 1.5 mL of H₂O), cat. Pd_{nanopart.} [2.5 mol % Pd(OAc)₂ + 12.5 mol % TBAA]. ^b Determined by GLC using dodecane as internal standard. ^c Isolated yields.

efficiency to a low OH[−] concentration in the IL phase, we replaced sodium carbonate with concentrate solutions of either KOH or tetrabutylammonium hydroxide. Excellent results were obtained only in the latter case, where the chlorobenzene was almost completely converted at 90 °C in only 3 h (entries 4 and 5).

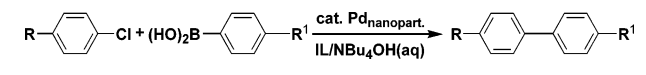
In addition to the high value of [OH[−]], this result could also be explained by the analogous high concentration of tetraalkylammonium cations realized into the water phase, which can contribute, by means of the partitioning equilibrium, to keeping constant the concentration of NR₄⁺ into the IL phase, thus preserving the protecting shell of nanoparticles.

However, as the presence of the aqueous phase seemed to accelerate the Pd NP aggregation, and consequently the catalyst inactivation, we thought to use a water-insoluble IL also possessing alkyl chains longer than TBAB. These chains should limit, by means of stronger hydrophobic interactions, the NPs growing into larger metal particles (the inactive “Pd black”). Among the various ILs investigated, tetraheptylammonium bromide (THeptAB) provided better performances than TBAB also at 70 °C (entries 5–8). When the reaction temperature was further lowered, the activity dropped again (entry 9), except with the more reactive bromobenzene, which was successfully converted also at 60 °C (entry 10).

We next applied the reaction to substituted chloroarenes to obtain unsymmetrical biphenyls. The better performances of THeptAB with respect to TBAB as stabilizing agent for Pd NPs were confirmed also in this case, as shown by the results reported in Table 2. Thus, *p*-chloroacetophenone was completely converted at 60 °C after 16 h (entries 1 and 2). These relatively mild conditions could successfully be applied to activated electron-poor chlorides (entries 3–5), while higher temperatures (at least 110 °C) were required in the case of deactivated electron-rich aryl chlorides (entries 6 and 7).

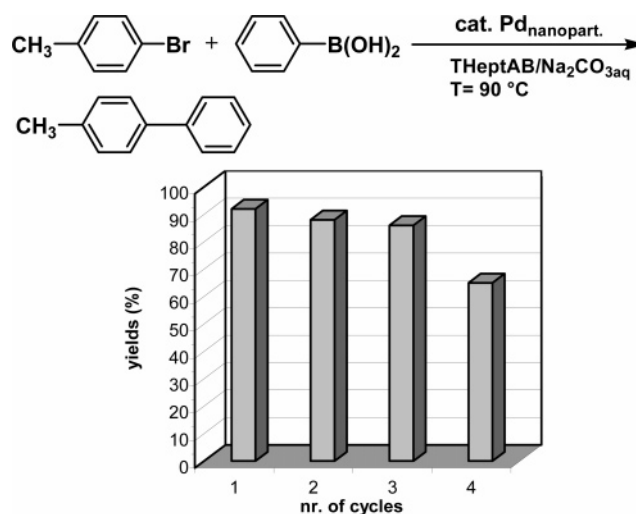
Recycling experiments, carried out on *p*-bromotoluene with Na₂CO₃ as base, showed that the catalytic system could be reused for three runs with a slight decrease in product yields (Figure 2).

To further expand the catalytic scope of Pd NPs, we investigated the Stille reaction, another very important

TABLE 2. Pd NP-Catalyzed Suzuki Reaction of Substituted Aryl Bromides and Chlorides in ILs^a


entry	R	R ¹	IL	T (°C)	t (h)	conv ^b (%)	yields ^b (%)
1	CH ₃ CO	H	TBAB	60	16	69	50
2	CH ₃ CO	H	THeptAB	60	16	>99	90
3	NO ₂	H	THeptAB	60	3	>99	90
4	CH ₃ CO	OCH ₃	THeptAB	60	5	>99	83
5	NO ₂	OCH ₃	THeptAB	60	5	>99	78
6	CH ₃ O	H	THeptAB	110	16	55	40
7	CH ₃	H	THeptAB	110	16	69	56

^a Reaction conditions: IL (6 mmol), phenylboronic acid (1.1 mmol), aryl halide (1 mmol), tetrabutylammonium hydroxide (2 mmol in 1.5 mL of H₂O), cat. Pd_{nanopart.} [2.5 mol % Pd(OAc)₂ + 12.5 mol % TBAA]. ^b Determined by GLC using dodecane as internal standard. ^c Isolated yields.

**FIGURE 2.** Recycling experiments for the Suzuki cross-coupling of Pd NPs in IL.

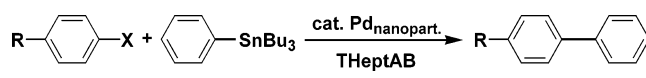
carbon–carbon bond-forming reaction used for the preparation of a wide variety of molecules ranging from biaryls and polyenes to aromatic carbonyl compounds.¹⁹ As for the Suzuki process, the organometallic coupling partner, an organostannane, is air- and moisture-stable, and thus it is compatible with IL media. In addition, this process does not require bases or other additives; as a consequence, product separation and recycling of catalyst should be simplified.

A number of articles describing the use of ionic liquids as reaction media have been published,²⁰ but only in a few cases Pd nanoparticles have been employed as catalyst;²¹ in addition, very rarely these catalysts were able to activate chloroarenes.^{17b} Therefore, we applied our

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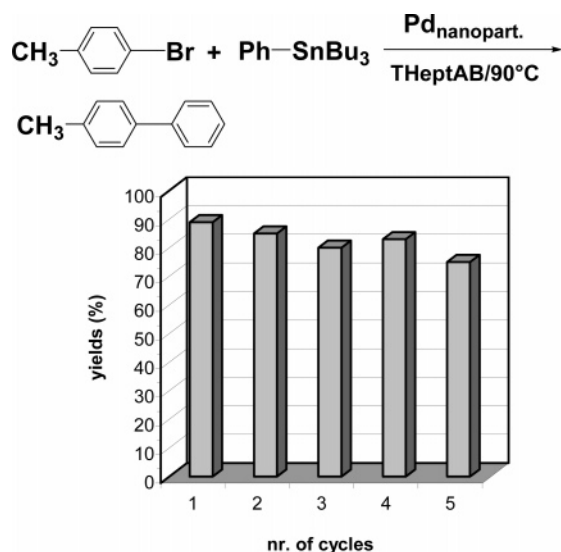
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TABLE 3. Stille Cross-Coupling Catalyzed by Pd_{nanopart.} in IL^a


entry	R	X	T (°C)	conv ^b (%)	yields ^c (%)
1	H	Br	90	97	86
2	CH ₃	Br	90	97	90
3	H	Cl	90	75	68
4	NO ₂	Cl	90	98	91
5	CH ₃ CO	Cl	90	70	52
6	CH ₃	Cl	110	27	10
7	CH ₃ O	Cl	130	57	40

^a Reaction conditions: IL (1 g), organostannane (1.2 mmol), aryl halide (1 mmol), cat. Pd_{nanopart.} [2.5 mol % Pd(OAc)₂ + 5% TBA].
^b Determined by GLC after 16 h by using dodecane as internal standard. ^c Isolated yields.

**FIGURE 3.** Recycling experiments for the Stille cross-coupling of Pd NPs in IL.

protocol using THeptAB as solvent in the Stille coupling between aryl bromides and chlorides and tributylphenyl stannane. Results are summarized in Table 3.

As in the case of the Suzuki reaction, the process afforded high product yields starting from aryl bromides, as well as simple or activated aryl chlorides. These substrates were in fact successfully converted at 90 °C for 16 h (entries 1–5), while deactivated electron-rich aryl chlorides turned out to be significantly less reactive and afforded modest yields of biaryls even working at 110–130 °C (entries 6 and 7).

Since the initial goal of this research effort was to develop a highly recyclable solvent/catalyst system, we further investigated the possibility to recycle the catalyst on the model reaction between *p*-bromotoluene and phenyltributylstannane. The results obtained show that the catalyst system can be used at least five times with little loss in activity (Figure 3).

These results, as well as those concerning the Suzuki process, confirm the superiority of tetraalkylammonium salts as reaction media for Pd NP-catalyzed processes. As anticipated, the nature of both cation and anion of the IL markedly influences the reaction outcome: on the one hand, the longer alkyl chains of cation ensure the

nanoparticles' stabilization, not only by protecting the metal core but also by sterically inhibiting its access; on the other hand, due to its nucleophilicity the bromide anion can play the double role of cocatalyst, by entering into the metal sphere and forming more active Pd(0) anionic species as already reported by us,^{4c} and also as accelerating agent, by assisting the transmetalation step as already shown by other authors^{20a} for the Stille reaction in imidazolium-based ILs.

Conclusions

The results of our study show that our ligand-free catalyst, composed of Pd NPs stabilized by tetraalkylammonium salts bearing long alkyl chains, behaves efficiently in important C–C bond-forming reactions such as the Suzuki and Stille cross-couplings. In the former process, the use of tetrabutylammonium hydroxide as base gets to a remarkable catalyst activity enhancement, permitting the reactions to proceed smoothly under relatively mild conditions (ranging from 60 °C for activated chlorides, to 90 °C for unreactive electron-rich chlorides). In addition, the catalytic system can be recycled a number of times, and the essential role of both anion and cation of the IL in determining the catalyst life and the reaction rate has been evidenced.

Experimental Section

Typical Procedure for the Pd NP-Catalyzed Suzuki Reaction. A 25-mL round-bottom flask, equipped with a magnetic bar, was charged with tetraalkylammonium bromide (6 mmol), Pd(OAc)₂ (5.6 mg, 0.025 mmol), and tetrabutylammonium acetate (38 mg, 0.125 mmol). The mixture was melted and stirred at 90 °C until a homogeneously dark red mixture was obtained (at least 15 min). The temperature was then set to the fixed value (see Tables 1 and 2), and the aryl halide (1 mmol), boronic acid (1.1 mmol), and a solution of the base (2 mmol in 1.5 mL of water) were added. Conversion of the substrate was monitored by GLC for a maximum of 16 h using dodecane as the internal standard. After cooling to room temperature, the reaction mixture was extracted with cyclohexane (5 × 10 mL). The extracted phases were collected and washed with dilute HCl to remove the trialkylamine deriving from the IL decomposition. After removal of the solvent in vacuo, the mixture was chromatographed on a silica pad using diethyl ether/petroleum ether in different ratios depending on the nature of the product to afford the diaryl derivatives in high purity as shown by ¹H NMR and reported in the Supporting Information.

Typical Procedure for the Pd NP-Catalyzed Stille Reaction. The preparation of the Pd NPs in the tetraalkylammonium salt was carried out following the procedure reported above. Then, aryl halide (1 mmol) and tributylphenylstannane (404 mg, 1.1 mmol) were added to the reaction mixture and stirred at the reaction temperature (see Table 3). Conversion of the substrate was monitored by GLC for a maximum of 16 h. Then, after cooling to room temperature, the reaction mixture was extracted with cyclohexane (5 × 10 mL). The extracted phases were collected and washed with dilute HCl to remove trialkylamine derived from the IL decomposition. After the solvent removal, in vacuo, the mixture was chromatographed on a silica pad, affording diaryl derivatives in high purity as shown by ¹H NMR and reported in the Supporting Information.

Procedure for the Catalyst Recycling of the Suzuki Coupling. After completion of the reaction and after cooling to room temperature, the products and the unreacted reagents were extracted with cyclohexane (5 × 10 mL). After removal

of the residual organic solvent under vacuum, the resulting biphasic mixture was charged with fresh reagents (aryl halide, boronic acid, and 2 equiv of solid Na_2CO_3) heated at the required temperature with stirring for the proper time (Table 2).

Procedure for the Catalyst Recycling of the Stille Coupling. After completion of the reaction and after cooling to room temperature, the products and the unreacted reagents were extracted with cyclohexane (5×10 mL). After removal of the residual organic solvent under vacuum, the resulting viscous mixture was charged with fresh reagents (aryl halide and tributylphenylstannane) and heated at the required temperature with stirring for the proper time (Table 3).

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Supporting Information Available: ^1H NMR spectra of the reaction products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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