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Suzuki Cross-Coupling Reactions Catalyzed by Palladium Nanoparticles in Aqueous Solution

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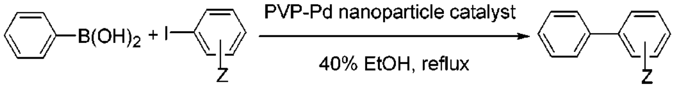
ABSTRACT



Palladium nanoparticles stabilized by poly(*N*-vinyl-2-pyrrolidone) (PVP) are efficient catalysts for the Suzuki reactions in aqueous medium. The time dependence of the fluorescence intensity of the biphenyl product in the reaction between iodobenzene and phenylboronic acid is used to determine the initial rate of the catalytic reaction. The initial rate depends linearly on the concentration of Pd catalyst, suggesting that the catalytic reaction occurs on the surface of the Pd nanoparticles.

The Suzuki cross-coupling reactions of arylboronic acids and aryl halides provide an effective synthetic route to biaryls.[1] The coupling reaction of arylboron derivatives with aryl halides in the presence of $Pd(PPh_3)_4$ and base to afford biaryls was first reported[2] in 1981. A number of modifications have appeared. These reactions are carried out in organic solvents and catalyzed by various Pd/ligand systems.[3] Phosphine-based palladium catalysts are generally used. A combination of $Pd(PPh_3)_4$ and aqueous Na_2CO_3 in dimethoxyethane (DME) works satisfactorily for most Suzuki cross-couplings.[4] However, in some cases the reactions can be catalyzed by using other palladium catalysts such as $Pd(OAc)_2$, $[(\eta^3\text{-}C_3H_5)\text{-}PdCl]_2$, and $Pd_2(dba)_3\ C_6H_6$.[5] Nevertheless, one serious problem in homogeneous metal catalysis is separation of the reaction products from the catalyst. To solve this problem, studies concerning coupling reactions in aqueous media using water-soluble phosphine ligands such as sulfonated analogues of triphenylphosphine[6] so that Pd partitions into the aqueous phase and the catalytic reaction proceeds in water have already been carried out. The use of water as a reaction medium for transition-metal-catalyzed reactions is very attractive for organic synthesis, due to environmental, economical, and safety reasons.

Colloidal metal particles are effective catalysts for chemical transformations due to their large surface area.[7] It has been shown that palladium colloids on the nanometer length scale are effective catalysts for the Heck reaction[8] (the reaction between aryl halides and olefins) and the Suzuki reaction[9] in organic solvents. In these experiments, no

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(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(2) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

(3) Suzuki, A. In *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Ed.; VCH: Weinheim, 1998; pp 49−97.

(4) Alo, B. I.; Kandil, A.; Patil P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, *56*, 3763−3768.

(5) (a) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034−5037. (b) Bumagin, N. A.; Bykov, V. V.; Beletskaya, I. P. *Dokl. Akad. Nauk. SSSR* **1990**, *315*, 1133−1136. (c) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277−3280.

(6) (a) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324−4330. (b) Genet, J. P.; Linquist, A.; Blart, E.; Mouries, V.; Savignac, M. *Tetrahedron Lett.* **1995**, *36*, 1443−1446. (c) Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305−317.

(7) Bradley J. S. In *Clusters and Colloids: From Theory to Applications*; Schmid, G., Ed.; VCH: Weinheim, 1994; pp 523−536.

(8) (a) Reetz, M. T.; Lohmer, G. *Chem. Commun.* **1996**, 1921−1922. (b) Beller, M.; Fischer, H.; Kuehlein, K.; Reisinger, C.-P.; Herrmann, W. A. *J. Organomet. Chem.* **1996**, *520*, 257−259. (c) Klingelhoefer, S.; Heitz, W.; Greiner, A.; Oestreich, S.; Foerster, S.; Antonietti, M. *J. Am. Chem. Soc.* **1997**, *119*, 10116−10120. (d) Le Bars, J.; Specht, U.; Bradley, J. S.; Blackmond, D. G. *Langmuir* **1999**, *15*, 7621−7625. (e) Ding, J. H.; Gin, D. L. *Chem. Mater.* **2000**, *12*, 22−24.

(9) Reetz, M. T.; Breinbauer, R.; Wanninger, K. *Tetrahedron Lett.* **1996**, *37*, 4499−4502.

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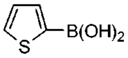
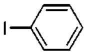
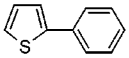
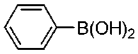
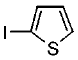
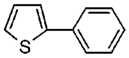
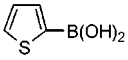
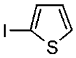
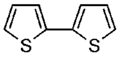
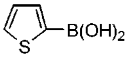
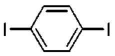
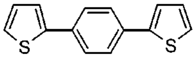
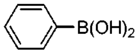
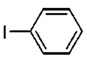
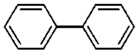
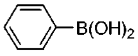
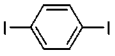
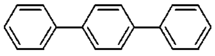
Table 1. Product Yields for Suzuki Coupling Reactions Catalyzed by PVP−Pd Nanoparticles (0.3 mol % of Metal) in 40% EtOH (base, 3.0 equiv of Na_3PO_4; temp, reflux)

arylboronic acid 1	aryl iodide 2	molar ratio 1:2	reflux time (h)	products	yield (isolated) (%)
		1.5	12		92%
		1.5	12		78%
		2.0	48		26%
		3.0	12		54%
		1.5	12		95%
		4.0	12		88%

evidence was given that the reactions were actually catalyzed on the surface of the nanoparticles used. Furthermore, the reactions were carried out in organic solvent. In this Letter, we report that palladium nanoparticles stabilized by PVP *in colloidal aqueous solution* are efficient catalysts for the Suzuki cross-couplings. By using fluorescence spectroscopy, it is found that the initial rate of the Suzuki coupling reactions depends linearly on the concentration of Pd catalyst, thus giving strong *evidence* that the catalysis *occurs on the surface of the Pd nanoparticles*.

The procedure reported by Miyake et al. was followed in preparing the Pd colloidal solution stabilized by PVP.[10] The solution thus prepared has a dark brown color and is stable for weeks at room temperature. Figure 1a shows UV−vis spectral changes during the formation of PVP−Pd nanoparticles. A peak at 235 nm due to the ligand-to-metal charge-transfer transition[10] of the $[PdCl_4]^{2-}$ ions disappears after heating a mixture of H_2PdCl_4 and PVP in 40% EtOH for 3 h, indicating that $[PdCl_4]^{2-}$ ions are completely reduced in the solution. The absorption in the visible region due to the band structure of metal nanoparticles increases, indicating that the Pd nanoparticles are formed. Transmission electron microscopy (TEM) shows that the PVP−Pd nanoparticles prepared in 40 vol % of ethanol at PVP/Pd = 10 have a mean diameter of 3.6 nm with a narrow size distribution (standard deviation = 0.73 nm, Figure 1b). The particles synthesized here are larger than those prepared by Miyake et al. (2.2 nm).[10]

The Suzuki cross-coupling reactions were carried out in 40% EtOH aqueous solution using PVP−Pd colloidal solution as catalyst.[11] Table 1 gives the reaction conditions and results for six couplings. It can be seen that the coupling of arylboronic acids with aryl iodides was successful in aqueous medium to afford reasonably high yields except for one reaction (the coupling of 2-thiopheneboronic acid with iodothiophene), which might be due to the poisoning of the Pd catalyst by sulfur-containing reactants. A small amount of PVP−Pd colloidal solution (0.3 mol %) is efficient at

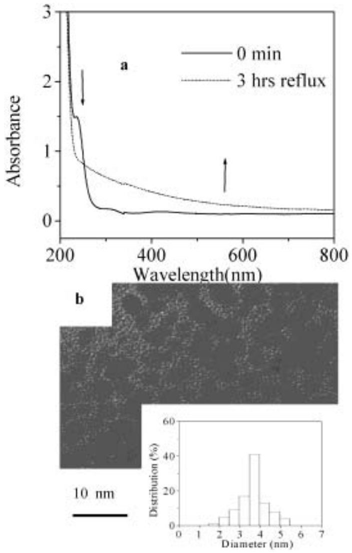


Figure 1. (a) UV−vis spectral changes during the formation of Pd nanoparticles. (b) TEM image of PVP−Pd nanoparticles. The inset shows the particle size distribution.

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(10) Teranishi, T.; Miyake, M. *Chem. Mater*. **1998**, *10*, 594−600. The Pd nanoparticles were prepared by the following procedure: H_2PdCl_4 aqueous solution (2.0 mM) was prepared by mixing 0.6 mmol of $PdCl_2$, 6.0 mL of 0.2 M HCl, and 294 mL of H_2O. A mixture of 15 mL of a 2.0 mM H_2PdCl_4 solution, 21 mL of H_2O, 14 mL of ethanol (40 vol %), and 0.0333 g of PVP (PVP/Pd (monomeric unit/metal ion) = 10, average MW of PVP = 40 000) was refluxed in a 100 mL flask for 3 h under air.

(11) In a typical procedure (e.g., cross-coupling of 2-thiopheneboronic acid with iodobenzene), 0.3% molar equiv of a PVP−Pd colloidal solution (15 mL) and 3 equiv (9 mmol) of $Na_3PO_4{\cdot}12H_2O$ were added to 100 mL of a 40% EtOH solution. The solution was heated until $Na_3PO_4{\cdot}12\ H_2O$ dissolved completely. Then 1 equiv (3 mmol) of iodobenzene and 1.5 equiv (4.5 mmol) of 2-thiopheneboronic acid were added to the solution. The mixture was heated at reflux and the extent of reaction was monitored by TLC (thin-layer chromatography) and ^1H NMR. After cooling to room temperature, the reaction mixture was extracted with petroleum ether, and the organic layers were combined and dried with anhydrous Na_2SO_4. Purification by column chromatography (silica gel/petroleum ether) gave the desired products which were confirmed by ^1H NMR. The other reactions followed the same procedure.

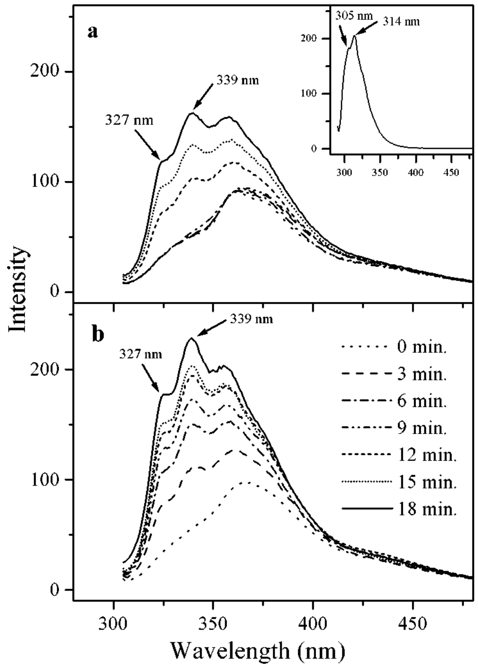

Figure 2. Time dependence of the emission spectra of reaction mixture at two different catalyst concentrations. (a) [Pd] = 0.06 mol %. (b) [Pd] = 0.15 mol %. The inset shows the emission spectrum of biphenyl in CH_3CN/H_2O solution.

catalyzing these reactions. Heating at reflux is required to drive these reactions to completion in a reasonable time.

It is worth noting that the Pd metal precipitated during the reaction. The catalytic activity of the Pd colloidal solution decreased during the reaction as the metal was precipitated. Similar observations were made by Herrmann and co-workers for the Heck reaction between aryl halides and styrene (or *n*-butyl acrylate) using palladium colloid as catalyst.[8b] This instability of the colloid might be due to the use of high temperatures. Antonietti and co-workers[8c] used block copolymer stabilized Pd colloid as a catalyst for the Heck reaction between aryl halides and styrene (or *n*-butyl acrylate). They claimed that there was no formation of Pd-black or any precipitate at the end of the reaction. Therefore, further improvements on the catalyst stability are necessary for practical applications.

Other reaction conditions have also been tested. Investigation of the cross-coupling of 2-thiopheneboronic acid with iodobenzene shows that acetonitrile−water is also a good solvent system for coupling with catalytic amounts of colloidal palladium. Other bases such as triethylamine, diisopropylamine, or sodium acetate can be used for the coupling. A Pd colloidal solution prepared by a different method was also a good catalyst. For example, the Pd colloidal solution synthesized by the reduction of Na_2PdCl_4 by hydrogen using sodium polyphosphate as a stabilizer also catalyzes this coupling.

The initial rate of the PVP−Pd-catalyzed reaction between phenylboronic acid and iodobenzene using sodium acetate as base in CH_3CN/H_2O was determined by following the rate of appearance of the fluorescence of biphenyl. A mixture of 3 mmol of phenylboronic acid, 1 mmol of iodobenzene and 6 mmol of sodium acetate was added to a solution of CH_3CN/H_2O (3:1). The solution was brought to boiling with continuous stirring, and a designated amount of colloidal Pd solution was added. The total volume of the reaction mixture was always 150 mL. An aliquot was taken every 3 min and cooled to 0 °C to stop the reaction. The sample was warmed to room temperature for the fluorescence measurement. No precipitation of Pd nanoparticles after reaction was observed in this reaction system; however, the reaction was slower than that using 40% EtOH due to the lower reaction temperature in the solvent system.

The emission spectra of the reaction mixture at different times are shown in Figure 2. The emission at 0 min is due to both phenylboronic acid and iodobenzene. Compared to the emission spectrum of biphenyl in a 3:1 CH_3CN/H_2O solution (inset of Figure 2a), the emission bands at 327 and 339 nm which develop over time are assigned to biphenyl. They are shifted in the mixture due to overlapping fluorescence from phenylboronic acid. Figures 3b and 3c show that the intensity of the biphenyl fluorescence is quenched by iodobenzene and the Pd solution. It can be seen from Figure 3c that the quenching effect of the Pd solution is small in the Pd concentration range (0.04−0.15 mol %) used in the

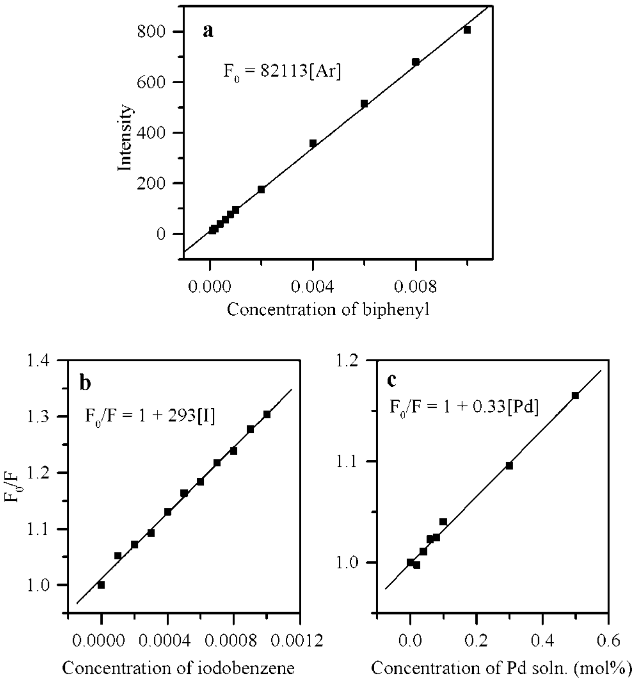

Figure 3. (a) Plot of the emission intensity of the peak maximum at 314 nm as a function of concentration of biphenyl in CH_3CN/H_2O solution. (b) Stern−Volmer plot of the ratio of the initial fluorescence intensity F_0 (emission at $\lambda_{\mathrm{max},\ 314\ \mathrm{nm}}$) to the intensity F in the presence of iodobenzene. (c) Stern−Volmer plot of the ratio of the initial fluorescence intensity F_0 (emission at $\lambda_{\mathrm{max},\ 314\ \mathrm{nm}}$) to the intensity F in the presence of a Pd solution.

present investigation, making it reasonable to ignore it. Considering only the quenching of the iodobenzene, the measured fluorescence intensity of the biphenyl is given by:

$$F = F_0/(1 + K_1[\mathrm{I}]) = K_2[\mathrm{Ar}]/\{1 + K_1([\mathrm{I}_0] - [\mathrm{Ar}])\} \quad (1)$$

where F_0 is the fluorescence intensity of biphenyl in the absence of quencher and [I], [I_0], and [Ar] are the concentration of iodobenzene, the initial concentration of the iodobenzene, and the concentration of biphenyl in the reaction mixture, respectively. K_1 is equal to $k_q\tau_0$ where k_q is the quenching rate constant and τ_0 is the mean lifetime of the excited state of biphenyl in the absence of quencher[12] (Figure 3b). K_2 is the slope of the straight-line dependence of the fluorescence intensity of biphenyl on its concentration (Figure 3a). Rearranging eq 1 gives:

$$[\mathrm{Ar}] = F(1 + K_1[\mathrm{I}_0])/(K_1F + K_2) \quad (2)$$

Thus, the concentration of product during the reaction can be obtained from eq 2. The measured fluorescence intensity, F, is determined by subtracting emission at $\lambda_{\max}$ 339 nm at 0 min from the emission at 339 nm (Figure 2), assuming that the concentration of reactants does not change at the beginning of reaction. In Figure 2a, no fluorescence of biphenyl could be observed before 9 min due to quenching of fluorescence by iodobenzene and the Pd solution. The initial reaction rate at different concentrations of Pd was determined by dividing the concentration of biphenyl by the time required to reach the first measurable fluorescence intensity. Each catalytic reaction was carried out three times to examine reproducibility. The initial reaction rate was also determined by using fluorescence intensity at 327 nm. From Figure 4, we can conclude that the reaction rate depends on the Pd concentration linearly in the Pd concentration range used (0.04−0.15 mol %). This suggests that the catalytic reaction occurs at the surface of the Pd nanoparticles.

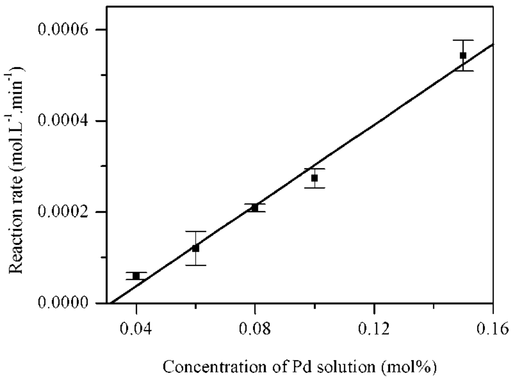

Figure 4. Initial reaction rate of iodobenzene and phenylboronic acid vs Pd concentration (mol %). The rate was determined by using the fluorescence intensity at both 339 and 327 nm, which are two characteristic peaks of biphenyl fluorescence.

In conclusion, we have demonstrated that a colloidal solution of Pd nanoparticles is an efficient catalyst for Suzuki cross-coupling reactions in aqueous solution. The initial reaction rate is linearly dependent on the Pd concentration, suggesting that the catalysis takes place on the nanoparticle surface. Compared to water-soluble palladium complexes, the colloidal solution is easily made and separated from reaction products. As such, it may be considered to be a ligand-free and water-soluble catalyst of great potential utility.

Acknowledgment. Y.L. and M.A.E. (Grant CHE-9727633) and X.M.H. and D.M.C. (Grant DMR-9501716) thank the NSF for support. We thank Mr. Chao Liu for assistance with the TEM images obtained for the Pd nanoparticles.

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[12] Sharma, A., Schulman, S. G., Ed. *Introduction to Fluorescence Spectroscopy*; John Wiley and Sons: 1999; pp 57−58.