DOI: 10.1002/adsc.200505229

# Palladium Nanoclusters in Sonogashira Cross-Coupling: A True Catalytic Species?

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Received: June 1, 2005; Accepted: September 5, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de or from the author.

**Abstract:** The question of whether palladium nanoclusters are the actual catalysts in the so-called 'cluster–catalyzed Sonogashira cross-coupling' is investigated, using the coupling of phenylacetylene with 4-bromobenzonitrile as a model reaction. By combining a detailed kinetic analysis with transmission electron microscopy (TEM), we show that a soluble species must be present in the system when Pd nanoclusters are used as catalysts. Various Pd clusters show similar kinetic profiles to that of a homogeneous Pd(dba)$_2$ complex. Most importantly, TEM analysis of samples taken before, during, and after the reaction shows that the cluster size decreases during the reaction. Based on these findings, we present a possible two-path mechanism for Sonogashira cross-coupling reactions in the presence of Pd nanoclusters.

**Keywords:** aryl halides; catalysis; kinetics; leaching; palladium; TEM

Nanometric palladium clusters can exhibit catalytic activities comparable to those of traditional Pd complexes in Heck, Suzuki and Sonogashira cross-coupling.[1,2] Several reports discuss the mechanisms for heterogeneous Pd catalysts,[3,4] but little is known about how cluster catalysts work in the liquid phase.[5–7] For palladium on a solid support, the Maitlis' filtration test[8] and ICP analysis of the filtrate can tell us whether Pd is leaching or not.[9] With nanoclusters, however, testing is difficult due to the small cluster size. El-Sayed et al.[10] and Bradley and co-workers[11] studied the cluster size effect in Suzuki and Heck reactions, and concluded that the reaction occurs at low coordination sites of the Pd cluster surface. Recently, we showed that Pd clusters, Cu clusters, and mixed metal clusters can catalyze the Sonogashira cross-coupling.[12] In this communication, we try to pinpoint the actual active species in the catalytic cycle. Does catalysis occur on the cluster surface or *via* leaching of Pd atoms/ions into solution? The answer to this question will help in future to design atom-economical and selective cluster catalysts.[13]

To try and answer this fundamental question, we studied the mechanism of the Sonogashira cross-coupling reaction,[14] catalyzed by Pd clusters at 50 °C.[15,16] We combined kinetic studies and transmission electron microscopy (TEM) analysis. The results indicate that a homogeneously catalyzed mechanism is likely.

Pd clusters were synthesized by reduction of Pd(NO$_3$)$_2$ with tetraoctylammonium glycolate in DMF.[17] In a typical reaction (Figure 1, top), phenylacetylene (**1**; 1.5 equivs.) was mixed with 4-bromobenzontrile (**2**; 1 equiv.), Pd clusters (0.01 equiv.) and tetrabutylammonium acetate (TBAA, 1.5 equivs.) as base. Quantitative yields of 1-cyano-4-phenylethynylbenzene (**3**) were obtained in 2 h. Diphenyldiacetylene (3–5%) from the homocoupling of excess **1** was also observed (see Supporting Information for full experimental details).

Cluster samples were taken for TEM analysis before, during, and after the reaction (Figure 1, *bottom*). Prior to reaction one can see separate Pd particles, with an average particle size of 14.5 nm (for 49 particles imaged). About 20% of the clusters are triangular, and the rest show an irregular morphology. Surprisingly, the samples taken during and after the reaction show smaller particles, *ca* 8.0 nm, compared to the sample before the reaction. In both cases, the particle size distribution was narrow and similar (±1.0 nm). This observation is contrary to the Oswald ripening process, where atoms detach from (thermodynamically unstable) smaller clusters and reattach to bigger clusters.[18,19] Such ripening usually leads to growth of the bigger clusters and eventual disappearance of the smaller ones. In

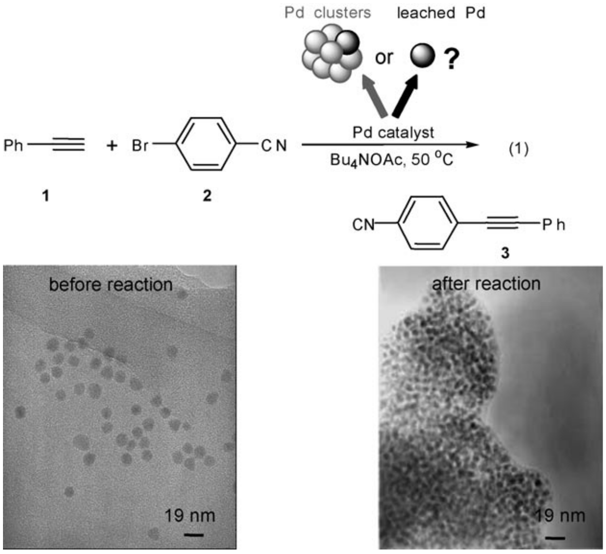

**Figure 1.** Sonogashira coupling of phenylacetylene with 4-bromobenzonitrile using Pd clusters as catalyst and TEM images before (*left*) and after (*right*) the reaction.

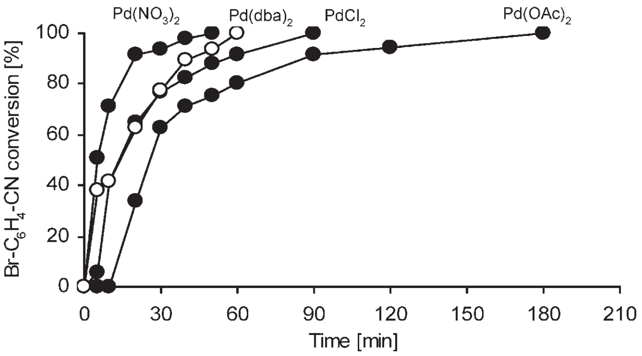

**Figure 2.** Sonogashira coupling of **1** with **2** catalyzed by homogeneous Pd(dba)$_2$ or by the Pd clusters prepared from various precursors. Reaction conditions: 1.5 mmol phenylacetylene, 1.5 mmol TBAA, 1 mol % catalyst (total Pd clusters relative to Br-C$_6$H$_4$-CN), 8 mL DMF, 50 °C, N$_2$ atmosphere.

our case, the decrease in the particle size during the reaction strongly indicates that Pd atoms and/or ions are leaching out of the clusters. The leached, "naked" Pd species may be the real catalysts,[20] instead of the defect sites on the clusters' surface.[20–23] When the substrate is consumed, these homogeneous species can re-cluster to form new (smaller) particles with the stabilizing influence of the TBAA.[24] We also investigated the catalytic activity of these smaller particles for the second cycle by adding another equivalent of the reactants and base to the reaction mixture of the first run.[25] We observed a drop in reaction rate and catalytic activity compared to the first run. These results further indicate that catalysis does not occur on the surface, as one would expect an increase in activity with the decrease in particle size.

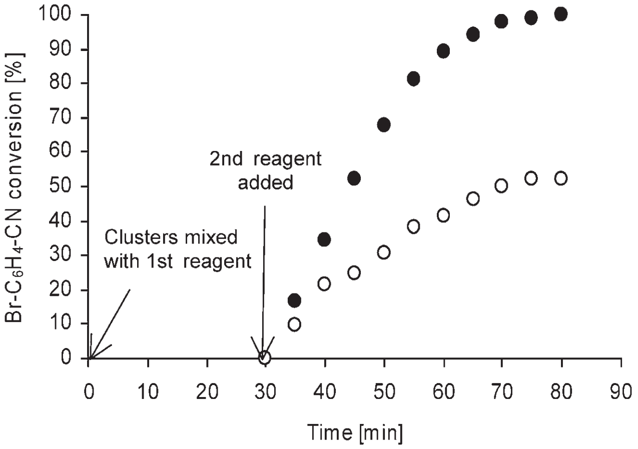

**Figure 3.** Time-resolved profiles showing the effect of mixing either 4-bromobenzonitrile **1** or phenylacetylene **2** with the Pd clusters prior to reaction. The '●' and '○' symbols denote {**1** + Pd} with **2** added after 30 min and *vice versa*, respectively.

We also studied the effect of various counteranions on the catalytic activity, using clusters prepared from Pd(NO$_3$)$_2$, PdCl$_2$ and Pd(OAc)$_2$. Cluster synthesis using different precursors yielded similar average particle sizes and size distributions (14–16 nm ± 1.0 nm in all cases). The activity decreased in the order $NO_3^- > Cl^- > OAc^-$ (Figure 2). Finke and Özkar[26,27] showed that the coordinating ability of anions to the cluster surface affects the cluster's stability. Acetate is a strong coordinating ion to Pd, while nitrate is a weak one.[28,29] This difference affects the stability, rendering the clusters more (or less) susceptible to leaching. Furthermore, clusters prepared from Pd(NO$_3$)$_2$ showed similar activity to that of a homogeneous Pd$^0$(dba)$_2$ complex. This may reflect the weaker coordination of $NO_3^-$ that increases the Pd leaching rate.

There are very few reports on the copper-free version of the Sonogashira reaction, and the mechanism is not clear.[30–32] Using initial rate methods, we found that the reaction follows the rate law $v = k[\mathrm{Pd}][\mathbf{2}]$. Note that [Pd] represents the initial concentration of the Pd nanoparticles and not the leached Pd during the reaction. Moreover, we observed a decelerating effect of **1** on the oxidative addition of **2** (Figure 3). This may be due to the unreactive complex formed by the coordination of **1** with the leached Pd species, as observed by Amatore et al.[33]

Based on our results, we propose a mechanism for the Pd cluster-catalyzed Sonogashira cross-coupling. This mechanism includes two pathways (Figure 4): Path **A** involves the leaching of Pd$^0$ from defect sites on the cluster, that is then stabilized by the coordinating anions and the solvent, forming a homogeneous Pd$^0$ complex. Subsequent oxidative addition of the aryl bromide **2** gives a Pd$^{II}$ complex that enters the conventional catalytic cycle. Alternatively, in path **B**, **2** first attacks a defect site on the Pd cluster, releasing a Pd$^{II}$ complex into solution, that then enters the catalytic cycle, as sur-

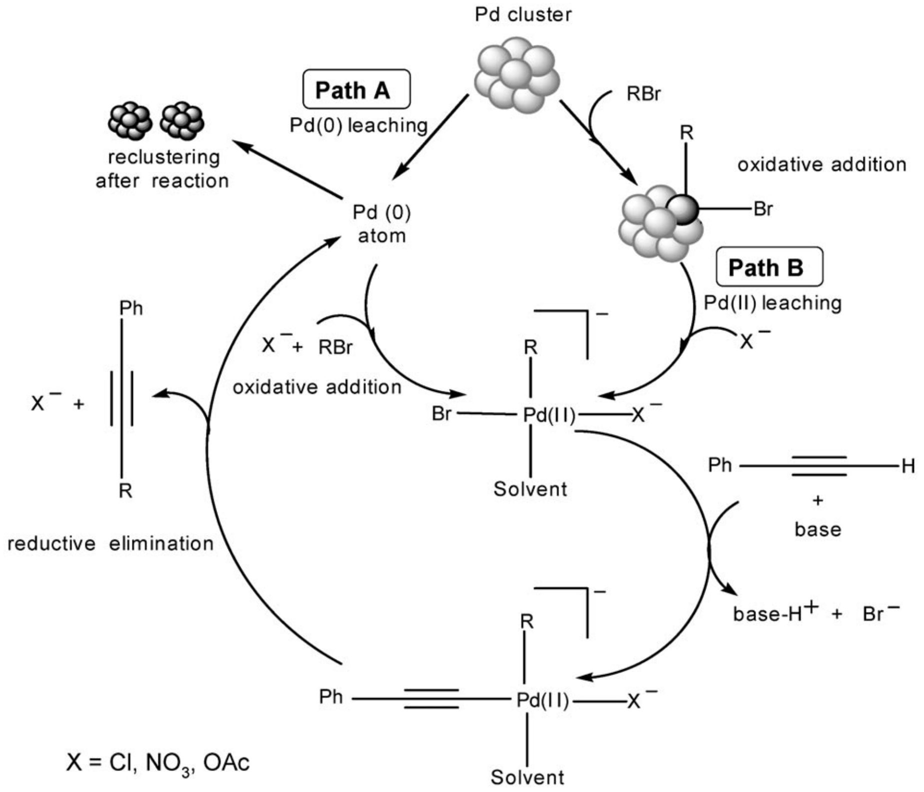

**Figure 4.** Proposed mechanism for the Pd cluster-catalyzed Sonogashira cross-coupling involving two possible pathways.

mised by Biffis et al.[21] based on the gathered evidence from the literature. The nucleophilic attack of **1** on the Aryl–Pd$^{II}$-Br(solvent)X complex takes place concomitant with the deprotonation of **1**. Finally, the dissolved Pd species can re-cluster, to form new (smaller) particles after the reductive elimination step. This mechanism is consistent with the results obtained from TEM analysis and kinetic studies, as well as with the one proposed by Hu and Liu for the analogous Suzuki cross-coupling.[7]

In summary, we show here that the cluster-catalyzed Sonogashira reaction probably proceeds *via* a soluble Pd species, and that the counteranions present in solution influence the leaching of the Pd ions/atoms. Further investigations into this mechanism will be the subject of future research in our laboratory.

## Experimental Section

Detailed synthesis and analysis procedures, including kinetic analysis, catalyst recycling experiments and additional TEM results are given in the Supporting Information.

### General Procedure for Cross-Coupling of Phenylacetylene with 4-Bromobenzonitrile using Pd Clusters

A Schlenk-type glass vessel equipped with a rubber septum and a magnetic stirrer was evacuated and refilled with $N_2$. The vessel was then charged with a Pd cluster suspension prepared in DMF (1.0 mL, 10.0 mM, 1.0 mol %), phenylacetylene (2 mL, 750 mM, 1.5 mmol), TBAA (2 mL, 750 mM, 1.50 mmol) and 3 mL of DMF. 4-Bromobenzonitrile (0.182 g, 1.00 mmol) was added and the mixture was stirred at 50 °C for 6 h under a slight overpressure of $N_2$. Reaction samples were taken at regular intervals and monitored by GC (pentadecane internal standard).

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