Metal–Micelle Cooperativity: Phosphine Ligand-Free Ultrasmall Palladium(II) Nanoparticles for Oxidative Mizoroki–Heck-type Couplings in Water at Room Temperature

Tharique N. Ansari, Jacek B. Jasinski, David K. Leahy,* and Sachin Handa*

**ABSTRACT:** The amphiphile PS-750-M generates stable, phosphine ligand-free, and catalytically active ultrasmall Pd(II) nanoparticles (NPs) from Pd(OAc)₂, preventing their precipitation, polymerization, and oxidation state changes. PS-750-M directly interacts with Pd(II) NP surfaces, as confirmed by high-resolution mass spectrometry and IR spectroscopy, resulting in their high stability. The Pd cations in NPs are most likely held together by hydroxides and acetate ions. The NPs were characterized by HRTEM, revealing their morphology and particle size distribution, and by HRMS and IR, providing evidence for NP–amphiphile interaction. The NP catalytic activity was examined in the context of oxidative Mizoroki–Heck-type couplings in water at room temperature. Hot filtration, hot extraction, and three-phase tests indicate heterogeneous catalysis occurring at the micellar interface rather than homogeneous catalysis occurring in the solution. NMR studies indicate that the catalytic activity stems from metal cation−π interactions of the styrene along with transmetalation by the arylboronic acid, followed by insertion and β-H elimination to furnish the coupled product along with the reoxidation of Pd by benzoquinone to complete the catalytic cycle. This method is very mild and sustainable, both in terms of NP synthesis and subsequent catalysis, and shows broad substrate scope while circumventing the need for organic solvents for this important class of couplings.

**KEYWORDS:** micellar catalysis, chemistry in water, cross-couplings, nanoparticle catalysis, olefination

**INTRODUCTION**

Water is a safe, stable, inexpensive, and naturally abundant solvent. However, in organic synthesis, it is predominantly used for reaction work-ups rather than as an alternative solvent. Nonetheless, it has many exciting features to offer better and cleaner chemistry for green chemical synthesis. The very forward-thinking statement by Sheldon more than a decade ago, “the best solvent is no solvent, but if a solvent is needed, then water has a lot to recommend it,” has experimentally been proven correct for many areas of chemistry. For example, micellar catalysis, a significant enabler of chemistry in water, has been applied to many diverse classes of organic chemistry reactions, often with improved reactivity and/or selectivity compared to their organic solvent enabled counterparts.

Reactive intermediates and catalytically active ultrasmall metal nanoparticles (NPs) are generally unstable in aqueous environment. We have recently reported that reactive intermediates such as carbanions and carbenes can be stabilized in aqueous media under the shielding effect of micelles, thus fundamentally advancing the area of micellar catalysis. The in situ formed reactive intermediates in water are only of practical use if the highly active catalytic sites are immediately available in the same micellar environment, and we have demonstrated that ultrasmall NPs of palladium (Pd) do satisfy this requirement. However, σ-donor ligands are required for the stability and excellent catalytic activity of such NPs under aqueous environment; e.g., ligated Pd(0) NPs displayed excellent stability and catalytic activity due to the presence of stabilizing phosphine ligands. However, such phosphine ligands often present their own challenges in terms of cost, stability, environmental impact, and removal which is often overlooked. It follows that phosphine ligand-free aqueous micellar NP catalysis for C−C bond formation could be regarded as the next step in sustainable catalysis.

Normally, ligand-free NPs are unstable in aqueous environments likely due to energetically favored clumping of metal atoms or ions, resulting in poor-to-no catalytic activity unless strong π-donor alkynes or ammonium salts are ligated to the surface of the NPs. Due to the smaller size of metal cations compared to their corresponding metal atom, the degree of
clumping or aggregation becomes even more significant.\textsuperscript{42} Besides aggregation, another challenge associated with the synthesis of Pd(II) NPs is polymerization of Pd(II) precursors.\textsuperscript{43,44} To address these challenges and investigate the behavior of phosphine ligand-free Pd(II) NPs, we harness the structural features of our amphiphile PS-750-M, which is designed to mimic dipolar aprotic solvents. Its micelle possesses multiple tertiary amide groups that provide a polar environment to the micellar interior,\textsuperscript{45,46} causing dissolution of large aggregates of Pd(II) and \textit{in situ} release of primary or ultrasmall Pd(II) NPs that can be accommodated and stabilized by the micellar environment of PS-750-M (Figure 1). In these NPs, Pd cations are potentially held together by either OH\textsuperscript{−} or AcO\textsuperscript{−} anions, forming X-Pd-X-Pd-type NPs.

\section*{RESULTS AND DISCUSSION}

Herein, we report a convenient synthesis of ultrasmall Pd(II) NPs derived from palladium(II) acetate as well as studies on their characterization, reactivity, mechanistic investigations, and catalytic behavior. The NP synthesis is straightforward and does not require an inert atmosphere or organic solvents. The dispersion of palladium(II) acetate in 3 wt % aq PS-750-M with stirring (800 rpm) of the resulting aqueous suspension for 50 min at 45 °C affords 50–60 nm sized Pd(II) NPs, acting as aggregates of small NPs, which upon stirring at 1500 rpm (deaggregation) generates ultrasmall X-Pd-X-Pd\textsuperscript{−}-type NPs of an average size 2 nm (Scheme 1). The use of PS-750-M is key for the generation of NPs; otherwise, only catalytically inferior aggregates are formed. Notably, no visually dark-red or black colored insoluble polymeric Pd(OAc)\textsubscript{2} was observed as evidenced by complete solubility of the resulting NPs in the aqueous solution of PS-750-M. Furthermore, the resulting NPs are stable in the aqueous PS-750-M for at least 50 days.

Analysis by infrared (IR) spectroscopy revealed the interaction between NP and PS-750-M (Figure 2). The carbonyl stretches from the amide and ester of the Pd(II)-bound amphiphile are observed at 1635 and 1524 cm\textsuperscript{−1}, respectively (for details, see Supporting Information, page S3). These carbonyl stretches are different from the carbonyl stretches of amide (1694 cm\textsuperscript{−1}) and ester (1640 cm\textsuperscript{−1}) of an unbonded amphiphile. Likewise, the IR spectrum of pure Pd(OAc)\textsubscript{2} is significantly different from the NPs. The similarity of the spectra in the carbonyl regions (1600–1700 cm\textsuperscript{−1}) between free Pd(OAc)\textsubscript{2} and the NPs suggests that the two palladium cations are bridged by an acetate ion. Alternatively, two cations could also be bridged by a hydroxide ion. However, the presence of water in the analyte made the prediction uncertain.

Due to heat generated from X-rays during scanning electron microscopy (SEM)/high-resolution transmission electron microscopy (HRTEM) analysis, Pd(OAc)\textsubscript{2} can be decomposed, polymerized, or converted into metallic Pd rod-like structures. Likewise, it could be misleading if NPs are only being formed during SEM analysis via decomposition of Pd(OAc)\textsubscript{2}. Thus, we compared the SEM of commercially available Pd(OAc)\textsubscript{2} and Pd(OAc)\textsubscript{2} coated with PS-750-M (for details, see Supporting Information, page S4). SEM analysis reveals that no metallic Pd or its NPs are formed when Pd(OAc)\textsubscript{2} is coated with PS-750-M (Figure 3A), while in the absence of PS-750-M, Pd(OAc)\textsubscript{2} forms metallic rod-like structures during the SEM analysis (see Supporting Information, page S4). Therefore, structural changes in the presence of surfactant, other than those in the aggregation state brought on by stirring (vide infra), are less likely to occur. Next, the actual NPs suspended in aqueous PS-750-M (see Scheme 1) were analyzed for size, distribution, morphology, chemical composition, and oxidation state by HRTEM, scanning transmission electron microscopy-high-angle annular dark-field imaging (STEM-HAADF), energy dispersive X-ray analysis (EDAX), and X-ray photoelectron spectroscopy (XPS) (Figure 3, also see Supporting Information, pages S4, S7, S8). HRTEM

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Phosphine ligand-free X-Pd-X-Pd-type Pd(II) NPs for catalysis in the aqueous micelle of PS-750-M.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{IR probe for amphiphile–NP interaction.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Convenient Synthesis of X-Pd-X-Pd-type Pd(II) NPs}
\end{figure}
analysis reveals the formation of 50−60 nm sized aggregates of X-Pd-X-Pd-type NPs and their ultrasmall counterparts of average size 2 nm (B, C). These aggregates are most likely accommodated in aqueous micelles of PS-750-M. After vigorously stirring the aqueous solution containing these NPs aggregates for 5 min, ultrasmall NPs were formed as evidenced by HRTEM and STEM-HAADF (D, E). This process is reversible, and no catalytically dead Pd clumps were observed at any stage or after storing the sample for 50 days under ambient conditions. EDAX analysis confirms that the NP possesses Pd and C from the surfactant, while XPS analysis reveals the +2 oxidation state of Pd (see Supporting Information, pages S4, S7, S8).

To gain further insight on the role of PS-750-M in NP stabilization, NPs were analyzed by high-resolution mass spectrometry (HRMS). The HRMS analysis also reveals the exact difference between Pd(OAc)$_2$ and NPs (Figure 4; for details, see Supporting Information, pages S8−S11). In the analyte containing only Pd(OAc)$_2$, the trimeric monocationic Pd species with mass 613.778 Da and formula C$_{10}$H$_{15}$O$_{10}$Pd$_3$Pd$_{108}$Pd was detected (Figure 4A). Other isotopes of Pd were also observed in the analysis (Figure 4B). The HRMS analysis of Pd(II) NPs in PS-750-M reveals the binding of PS-750-M with the Pd (Figure 4C). The monocationic fragment of NP with the formula C$_{50}$H$_{100}$NO$_2$Pd and mass 1156.582 Da suggests binding one molecule of PS-750-M with the one Pd cation (Figure, 4D). The fragment pattern and accurate mass also indicate a hydroxide ion and water molecule bound to the Pd, i.e., a fragment with accurate mass 1023.497 Da and formula C$_{44}$H$_{87}$NO$_{18}$Pd (Figure 4E). Therefore, different Pd cations in the NP are likely held together by hydroxide ions. Based on the HRTEM, STEM-HAADF, IR, and HRMS analysis, PS-750-M plays a critical role in the NP formation, holding the NP at the micellar inner-outer core interface through the proline unit, which potentially facilitates NP and substrate interaction at the interface, allowing catalysis to take place (vide infra).

Due to Pd−micelle interaction and the change in surface free energy of smaller NPs, an excellent reactivity was anticipated. Therefore, we performed control experiments to understand the NP’s interaction with arylboronic acids and to determine if reduction of Pd(II) to Pd(0) by the arylboronic acid is occurring via a homocoupling pathway (Figure 5). Likewise, hydration of styrenes is also possible in an aqueous environment.

Figure 3. (A) SEM of Pd(OAc)$_2$ coated with PS-750-M, (B−D) HRTEM, for particle size distribution, also see Supporting Information page S4, (E) STEM-HAADF, (F) EDAX analysis of X-Pd-X-Pd-type Pd(II) NPs.

Figure 4. High-resolution mass spectrometry analysis: (A) full spectrum of Pd(OAc)$_2$, (B) cation of Pd$_3$(OAc)$_3$ in Pd(OAc)$_2$, (C) full spectrum of NPs in PS-750-M showing NP-PS-750-M binding, (D) NP fragment PS-750-M bound monocationic Pd, (E) fragment of PS-750-M bound monocationic Pd.
environment. In the control experiments, interactions of the NP with both arylboronic acids and styrenes were observed. Mixing 1.0 mol equiv of arylboronic acid 1 with the NPs in aqueous PS-750-M results in the shift of $^{19}$F signal from $\text{106.4 to 114.5 ppm}$, indicating transmetalation by 1 on the NP surface (Figure 5A, B; for details, see Supporting Information pages S5, S6). The resulting intermediate was found to be stable, and no homocoupling of 1 was observed. In a separate control experiment, mixing 1.0 mol equiv of styrene 2 with the NPs suspended in aqueous PS-750-M results in the shift of the $^{19}$F signal of 2 from $\text{114.1 to 105.2 ppm}$, clearly revealing the interaction between 2 and the NP (Figure 5C, D). The mixing of the contents of both NMR tubes results in the formation of adduct 3 via a pathway involving reduction of Pd (Figure 5E). In the same NMR tube, addition of 1.0 mol equiv of an oxidant, i.e., benzoquinone (BQ), regenerates the Pd(II) NPs. Addition of 1.0 mol equiv of 1 and 2 to the regenerated Pd(II) NPs again forms an additional equivalent 3, meaning the NPs are catalytically active and stable in PS-750-M. Notably, all the events happen at room temperature (23 °C).

Because fast stirring causes the release of ultrasmall Pd NPs from 50 nm sized aggregates, the catalytic reaction rate should significantly depend on the stirring speed. Therefore, we performed the study to find the optimal stirring rate in revolutions per minute (rpm). Kinetic experiments at different stirring rates (50, 100, 500, 1000, and 1500 rpm; reaction vessel shape is cylindrical tube) were performed with the benchmark reaction between 4-(trifluoromethyl)phenylboronic acid 4 and styrene 5 (Scheme 2, also see Supporting Information, pages S12–S14). The reaction rate was slower at lower stirring rates (41 and 58% in 12 h at 50 and 100 rpm, respectively), whereas reaction was fast at higher stirring rates of 1000 and 1500 rpm. Notably, reaction kinetics were similar at 1000 and 1500 rpm. Similar trends were also observed in overhead stirring. These results indicate that the reaction rate is influenced by mass transfer effects. Therefore, we hypothesize that shear provided by stirring at 1000–1500 rpm breaks up the larger NP aggregates into the highly catalytically active primary particles (smaller NPs).

To ensure the formation of Pd NPs and their binding with the amphiphile PS-750-M, kinetic studies were also performed with fresh catalyst, catalyst recovered after hot filtration, and catalyst extracted with hot toluene (Figure 6; for details, see Supporting Information, pages S15, S16). To obtain NPs after hot filtration, fresh NPs were heated at 65 °C for 2 h and then filtered through fibrous glass filter. Likewise, fresh NPs were extracted with hot toluene and both the organic and aqueous layers were analyzed for their catalytic activities. Toluene was chosen for the hot extraction study due to its ability to solubilize and stabilize Pd(OAc)$_2$. For the catalytic reactions between boronic acid 4 and styrene 5, the NPs in aqueous solution of PS-750-M obtained after hot filtration and hot extraction retained catalytic activity, while no catalytic activity was observed with the use of toluene recovered from the hot extraction. Notably, the reaction rates in catalytic reactions in aqueous solution of NPs obtained from hot filtration and hot extraction were almost identical to the rates of the reactions catalyzed by fresh NPs. Therefore, this study confirms the catalysis by NPs, which are stable in aqueous PS-750-M. The above studies and ICP-MS analysis of toluene layer (residual Pd < 1 ppm) also reveal that no leaching of Pd from NPs occurs.

We expect that Pd NPs are evenly distributed in the aqueous micellar solution, and because the reaction happens at the micellar interface and not outside “in water” or “on water”, surface catalysis in bulk medium should not occur. To confirm this hypothesis, a three-phase test was also performed with the use of styrene bound to a REM resin (acryloyl Wang’s resin), 4-(trifluoromethyl)phenylboronic acid 4, and Pd NPs in aqueous PS-750-M (for details, see Supporting Information, page S17). No catalytic reaction was observed due to the lack of accommodation of the styrene bound to REM resin into the micelle, which confirms that it is a micellar catalysis, and not surface catalysis “in water” or “on water.”
We next set out to confirm the role of BQ and PS-750-M in the catalytic reaction (Table 1). BQ serves as a better oxidant compared to oxygen for the regeneration of Pd(II) NPs (entry 1). With oxygen as the oxidant, the conversion was significantly slower, and only 63% product was formed in 12 h (entry 2), likely due to low solubility of oxygen in PS-750-M. Similar results were obtained with air (entry 3). For catalytic activity, 1.5 equiv of BQ was optimal (entries 4, 5), where lower amounts led to diminished conversion. With the use of the same Pd(II) NPs, reactions in neat water or toluene were not as effective as in PS-750-M (entries 6, 7). Notably, state-of-the-art amphiphile TPGS-750-M was not effective, and only 40% conversion was observed.7,37,38,49,50

For synthetic convenience, we generated the Pd(II) NPs in situ and tested the catalytic activity all in a single-pot (Table 2).

Table 1. Role of Oxidant and PS-750-M

| entry | deviations from standard conditions | 6 (%) |
|-------|------------------------------------|-------|
| 1     | none                               | 98 (95) |
| 2     | oxygen balloon instead of BQ       | 63    |
| 3     | air balloon instead of BQ          | 70    |
| 4     | 1.5 equiv of BQ                    | 98    |
| 5     | 1.0 equiv of BQ                    | 81    |
| 6     | water instead of PS-750-M          | 46    |
| 7     | toluene instead of PS-750-M        | 15    |
| 8     | TPGS-750-M instead of PS-750-M     | 40    |

*Standard conditions: 4 (0.25 mmol), 5 (0.275 mmol), Pd(II) NPs (3 mol %), p-benzoquinone (0.5 mmol), 1 mL of 3 wt % aq PS-750-M, 23 °C, 12 h. GCMS yields using mesitylene (0.25 mmol) as an internal standard. Isolated yield. NPs were prepared in aq PS-750-M. Reaction vessel shape is cylindrical tube.

3, 6—32) to explore the scope of this transformation. Under neutral conditions at ambient temperature, NPs formed immediately in the aqueous solution of PS-750-M, then arylboronic acid, styrene, and BQ were added leading cleanly to the cross-coupling product. Notably, this reaction provides products typically obtained via Heck couplings under harsh conditions not compatible with perfluoro styrene or perfluoro bromoarenes, resulting in no desired reaction. Such adducts can be extremely valuable in the area of materials chemistry. With our technology, these substrates react cleanly to afford desired products due to the very mild conditions. This transformation is functional group tolerant and is compatible with nitro (10, 12, 17, 19, 31) and reactive fluoro groups (3, 18). The trifluoromethyl group was also well-tolerated (6, 9, 14, 21), as were substrates containing heterocyclic moieties, catalytic activity, 1.5 equiv of BQ was optimal (entries 4, 5), where lower amounts led to diminished conversion. With the use of the same Pd(II) NPs, reactions in neat water or toluene were not as effective as in PS-750-M (entries 6, 7). Notably, state-of-the-art amphiphile TPGS-750-M was not effective, and only 40% conversion was observed.7,37,38,49,50

For synthetic convenience, we generated the Pd(II) NPs in situ and tested the catalytic activity all in a single-pot (Table 2).
including benzo furanyl (8, 24) and thiophenyl (11). Alkyl styrene was also well tolerated, and no isomerization or side products were observed when 4-phenylbutene was used as coupling partner (9). The combination of electron-deficient styrenes and aryloboric acids (10, 12, 14, 16, 17, 20, 21, 29–31), electron-deficient styrenes and electron-rich boronic acids (13, 15, 22–24), and electron-rich and electron-deficient aryloboric acids (9, 26, 28) can be found among many examples, illustrating the reaction’s flexibility with respect to electronic parameters. Methyl acrylate also displayed excellent reactivity with different boronic acids (29–31). The reaction was relatively fast when tert-butyl acrylate was used instead of methyl acrylate (32). Notably, no reaction was observed when acrylic acid was used as a coupling partner with 4-trifluoromethylphenyl boronic acid. The better reaction rate in the case of 32 and no reaction with acrylic acid suggests that reaction happens either at the micellar interface or interior.

The activity of the NP catalyst was tested on a multigram scale reaction with the use of only 1 mol % catalyst (Scheme 3a). Using 4-aryloboric acid 4 and styrene 5 as coupling partners, the reaction was carried out on 0.48 mol scale under standard conditions to furnish the desired product 6 (112.6 g) in a reproducible yield obtained in a small-scale reaction (see Table 2, vide supra). Notably, reversing the polarity in substrates using aged NPs (30 days) did not significantly affect the reaction outcome. As shown in Scheme 3b, a reaction between boronic acid 33 and styrene 34 cleanly afford product 17, although reaction rate is slightly different. The same yield of 17 was also obtained when one month old NPs were employed.

**CONCLUSIONS**

In summary, PS-750-M enables the formation of phosphine ligand-free NPs of Pd(II) in aqueous medium. Under the mild mechanical force of stirring, it in situ provides highly catalytically active Pd(II) NPs, which remained active for at least a month for useful oxidative Heck-type couplings. The syntheses of NPs as well as coupling products are scalable, reproducible on variable scales, and show a broad scope. The methodology provides access to compounds that are not possible with the use of traditional methods in a convenient and environmentally friendly fashion.

**EXPERIMENTAL PROCEDURES**

A. Synthesis and Isolation of Nanoparticles

In a 50 mL round-bottom flask containing a PTFE-coated stir bar, nanoparticle precursor palladium(II) acetate (85 mg, 0.38 mmol) was added. Later, 25 mL of 3 wt % aq PS-750-M was added, and the round-bottom flask was closed with a rubber septum. The reaction mixture was transferred to a pre-heated oil bath at 45 °C and stirred (800 rpm) for the next 50 min. The coloration of the suspension was changed from light brown to the darker brown. After 50 min, the reaction mixture was removed from the oil bath and allowed to cool to rt. The obtained dark brown suspension was used as the nanoparticle stock solution. These nanoparticles were characterized using IR spectroscopy, HRTEM, EDAX, SEM, and HRMS. The nanoparticles were stored without any notable precautions.

B. Optimized Procedure for Catalytic Couplings

A 4.0 mL reaction vial containing a PTFE-coated magnetic stir bar was charged with nanoparticle precursor palladium(II) acetate (1.7 mg, 0.0075 mmol). Later, 1 mL 3 wt % aq PS-750-M was added, and the vial was closed with a screw cap. Then, the reaction vial was transferred to a pre-heated stir plate at 45 °C and stirred (1500 rpm) for 50 min. After cooling to room temperature, the reaction vial was opened, and aryloboric acid (0.275 mmol), p-benzoquinone (108 mg, 0.375 mmol), and styrene (0.25 mmol) were added. The reaction vial was closed with a screw cap and then stirred (1500 rpm) at room temperature. After complete consumption of styrene as monitored by TLC or GCMS, the reaction vial was opened, and 1–2 mL ethyl acetate was added. The mixture was then gently stirred for 2 min at rt. Stiring was stopped, and the organic layer was separated using a pipet. This extraction was repeated for one more time. The combined organic layers were passed through a Celite-pad filled in the pipet. Volatiles were evaporated under reduced pressure to obtain the crude product, which was then purified by flash chromatography over silica gel using hexanes/ethyl acetate as eluent.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.0c00087.

Materials and methods, supplementary figures, supplementary tables, supplementary schemes, and analytical data (PDF)

**AUTHOR INFORMATION**

**Corresponding Authors**

Sachin Handa — Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States; was found among many examples, illustrating the reaction’s flexibility with respect to electronic parameters. Methyl acrylate also displayed excellent reactivity with different boronic acids (29–31). The reaction was relatively fast when tert-butyl acrylate was used instead of methyl acrylate (32). Notably, no reaction was observed when acrylic acid was used as a coupling partner with 4-trifluoromethylphenyl boronic acid. The better reaction rate in the case of 32 and no reaction with acrylic acid suggests that reaction happens either at the micellar interface or interior.

The activity of the NP catalyst was tested on a multigram scale reaction with the use of only 1 mol % catalyst (Scheme 3a). Using 4-aryloboric acid 4 and styrene 5 as coupling partners, the reaction was carried out on 0.48 mol scale under standard conditions to furnish the desired product 6 (112.6 g) in a reproducible yield obtained in a small-scale reaction (see Table 2, vide supra). Notably, reversing the polarity in substrates using aged NPs (30 days) did not significantly affect the reaction outcome. As shown in Scheme 3b, a reaction between boronic acid 33 and styrene 34 cleanly afford product 17, although reaction rate is slightly different. The same yield of 17 was also obtained when one month old NPs were employed.

**CONCLUSIONS**

In summary, PS-750-M enables the formation of phosphine ligand-free NPs of Pd(II) in aqueous medium. Under the mild mechanical force of stirring, it in situ provides highly catalytically active Pd(II) NPs, which remained active for at least a month for useful oxidative Heck-type couplings. The syntheses of NPs as well as coupling products are scalable, reproducible on variable scales, and show a broad scope. The methodology provides access to compounds that are not possible with the use of traditional methods in a convenient and environmentally friendly fashion.

**EXPERIMENTAL PROCEDURES**

A. Synthesis and Isolation of Nanoparticles

In a 50 mL round-bottom flask containing a PTFE-coated stir bar, nanoparticle precursor palladium(II) acetate (85 mg, 0.38 mmol) was added. Later, 25 mL of 3 wt % aq PS-750-M was added, and the round-bottom flask was closed with a rubber septum. The reaction mixture was transferred to a pre-heated oil bath at 45 °C and stirred (800 rpm) for the next 50 min. The coloration of the suspension was changed from light brown to the darker brown. After 50 min, the reaction mixture was removed from the oil bath and allowed to cool to rt. The obtained dark brown suspension was used as the nanoparticle stock solution. These nanoparticles were characterized using IR spectroscopy, HRTEM, EDAX, SEM, and HRMS. The nanoparticles were stored without any notable precautions.

B. Optimized Procedure for Catalytic Couplings

A 4.0 mL reaction vial containing a PTFE-coated magnetic stir bar was charged with nanoparticle precursor palladium(II) acetate (1.7 mg, 0.0075 mmol). Later, 1 mL 3 wt % aq PS-750-M was added, and the vial was closed with a screw cap. Then, the reaction vial was transferred to a pre-heated stir plate at 45 °C and stirred (1500 rpm) for 50 min. After cooling to room temperature, the reaction vial was opened, and aryloboric acid (0.275 mmol), p-benzoquinone (108 mg, 0.375 mmol), and styrene (0.25 mmol) were added. The reaction vial was closed with a screw cap and then stirred (1500 rpm) at room temperature. After complete consumption of styrene as monitored by TLC or GCMS, the reaction vial was opened, and 1–2 mL ethyl acetate was added. The mixture was then gently stirred for 2 min at rt. Stirring was stopped, and the organic layer was separated using a pipet. This extraction was repeated for one more time. The combined organic layers were passed through a Celite-pad filled in the pipet. Volatiles were evaporated under reduced pressure to obtain the crude product, which was then purified by flash chromatography over silica gel using hexanes/ethyl acetate as eluent.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.0c00087.

Materials and methods, supplementary figures, supplementary tables, supplementary schemes, and analytical data (PDF)

**AUTHOR INFORMATION**

**Corresponding Authors**

Sachin Handa — Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States; [orcid.org/0000-0002-7635-5794; Email: sachin.handa@louisville.edu]

David K. Leahy — Process Chemistry Development, Takeda Pharmaceuticals International, Cambridge, Massachusetts 02139, United States; Email: david.leahy@takeda.com

**Authors**

Tharique N. Ansari — Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States

Jacek B. Jasinski — Conn Center for Renewable Energy Research, University of Louisville, Louisville, Kentucky 40292, United States; [orcid.org/0000-0002-1297-6145]

Complete contact information is available at: https://pubs.acs.org/10.1021/jacsau.0c00087

**Funding**

We warmly acknowledge the financial support from Takeda Pharmaceuticals.

**Notes**

The authors declare no competing financial interest.
Halides under Aqueous Micellar Conditions. J. Am. Chem. Soc. 2019, 141, 17117−17124.
(19) Carpenter, B. K.; Harvey, J. N.; Orr-Ewing, A. J. The Study of Reactive Intermediates in Condensed Phases. J. Am. Chem. Soc. 2016, 138, 4695−4705.
(20) Wei, Z.; Chen, Y.-Y.; Li, J.; Guo, W.; Wang, S.; Dong, M.; Qin, Z.; Wang, J.; Jiao, H.; Fan, W. Stability and Reactivity of Intermediates of Methanol Related Reactions and C–C Bond Formation over H-ZSM-5 Acidic Catalyst: A Computational Analysis. J. Phys. Chem. C 2016, 120, 6075−6087.
(21) Jagannadh, V. Carboxylation Lifetimes and Entropy of Water Addition to Carboxylates Depending on Their Stability. Proc. - Indian Acad. Sci., Chem. Sci. 2003, 115, 41−47.
(22) Sun, S.; Gebauer, D.; Cöllen, H. A General Strategy for Colloidal Stable Ultrasmall Amorphous Mineral Clusters in Organic Solvents. Chem. Sci. 2017, 8, 1400−1405.
(23) Jiang, X.; Du, B.; Huang, Y.; Zheng, J. Ultrasmall Noble Metal Nanoparticles: Breakthroughs and Biomedical Implications. Nano Today 2018, 21, 106−125.
(24) Kim, B. H.; Hackett, M. J.; Park, J.; Hyeon, T. Synthesis, Characterization, and Application of Ultrasmall Nanoparticles. Chem. Mater. 2014, 26, 59−71.
(25) Richard, J. P.; Amyes, T. L.; Toteva, M. M. Formation and Stability of Carboxylates and Carbanions in Water and Intrinsic Barriers to Their Reactions. Acc. Chem. Res. 2001, 34, 981−988.
(26) Bihani, M.; Ansari, T. N.; Finck, L.; Bora, P. P.; Jasinski, J. B.; Pavuluri, B.; Levy, D. K.; Han, S. Scalable α-Arylation of Nitriles in Aqueous Micelles Using Ultrasmall Pd Nanoparticles: Surprising Formation of Carbanions in Water. ACS Catal. 2020, 10, 6816−6821.
(27) Duong, U. T.; Gade, A. B.; Plummer, S.; Gallou, F.; Handa, S. Reactivity of Carbenes in Aqueous Nanomicelles Containing Palladium Nanoparticles. ACS Catal. 2019, 9, 10963−10970.
(28) Yang, G.; Zhou, L. Active Sites of M(IV)-Incorporated Zeolites (M = Sn, Ti, Ge, Zr). Sci. Rep. 2017, 7, 1−14.
(29) Foster, A. J.; Lobo, R. F. Identifying Reaction Intermediates and Catalytic Active Sites through in Situ Characterization Techniques. Chem. Soc. Rev. 2010, 39, 4783−4793.
(30) Chakrapani, V. Probing Active Sites and Reaction Intermediates of Electrocatalysis Through Confocal Near-Infrared Photoluminescence Spectroscopy: A Perspective. Front. Chem. 2020, 8, 327.
(31) Wardhan, H.; Verpoort, F. Metal-Organic Polyhedra: Catalysis and Reactive Intermediates. Adv. Synth. Catal. 2015, 357, 1351−1368.
(32) Shan, J.; Lei, Z.; Wu, W.; Tan, Y.; Cheng, N.; Sun, X. Highly Active and Durable Ultrasmall Pd Nanocatalyst Encapsulated in Ultrathin Silica Layers by Selective Deposition for Formic Acid Oxidation. ACS Appl. Mater. Interfaces 2019, 11, 43130−43137.
(33) Koh, K.; Seo, J. E.; Lee, J. H.; Goswami, A.; Yoon, C. W.; Asefa, T. Ultrasmall Palladium Nanoparticles Supported on Aminemodified SBA-15 Efficiently Catalyze Hydrogen Evolution from Formic Acid. J. Mater. Chem. A 2014, 2, 20444−20449.
(34) Sawai, K.; Tatumi, R.; Nakahodo, T.; Fujihara, H. Asymmetric Suzuki–Miyaura Coupling Reactions Catalyzed by Chiral Palladium Nanoparticles at Room Temperature. Angew. Chem., Int. Ed. 2008, 47, 6917−6919.
(35) Wang, Z.; Reddy, C. B.; Zhou, X.; Ibrahim, J. J.; Yang, Y. Phosphine-Built-in Porous Organic Cage for Stabilization and Boosting the Catalytic Performance of Palladium Nanoparticles in Cross-Coupling of Aryl Halides. ACS Appl. Mater. Interfaces 2020, 12, 53141.
(36) Yasukawa, T.; Kobayashi, S. Chiral Metal Nanoparticles for Asymmetric Catalysis BT - Nanoparticles in Catalysis; Kobayashi, S., Ed.; Springer International Publishing: Cham, 2020, pp 279−314.
(37) Handa, S.; Jin, B.; Bora, P. P.; Wang, Y.; Zhang, X.; Gallou, F.; Reilly, J.; Lipshutz, B. H. Sonogashira Couplings Catalyzed by Pd Nanoparticles Containing Ppm Levels of Reusable Pd, under Mild Aqueous Micellar Conditions. ACS Catal. 2019, 9, 2423−2431.
(38) Handa, S.; Wang, Y.; Gallou, F.; Lipshutz, B. H. Sustainable Fe–Ppm Pd Nanoparticle Catalysis of Suzuki-Miyaura Cross-Couplings in Water. Science 2015, 349, 1087−1091.
(39) Heuer-Jungemann, A.; Feliu, N.; Bakaimi, I.; Hamaly, M.; Alkilany, A.; Chakraborty, I.; Masood, A.; Casula, M. F.; Kostopoulou, A.; Oh, E.; Susumu, K.; Stewart, M. H.; Medintz, I. L.; Stratakis, E.; Parak, W. J.; Kanaras, A. G. The Role of Ligands in the Chemical Synthesis and Applications of Inorganic Nanoparticles. *Chem. Rev.* 2019, 119, 4819–4880.

(40) Hamasaka, G.; Roy, D.; Tazawa, A.; Uozumi, Y. Arylation of Terminal Alkynes by Aryl Iodides Catalyzed by a Parts-per-Million Loading of Palladium Acetate. *ACS Catal.* 2019, 9, 11640–11646.

(41) Le Bras, J.; Mukherjee, D. K.; González, S.; Tristany, M.; Ganchev, B.; Moreno-Mañás, M.; Pleixats, R.; Hénin, F.; Muzart, J. Palladium Nanoparticles Obtained from Palladium Salts and Tributylamine in Molten Tetrabutylammonium Bromide: Their Use for Hydrogenolysis-Free Hydrogenation of Olefins. *New J. Chem.* 2004, 28, 1550–1553.

(42) Keller, A. A.; Wang, H.; Zhou, D.; Lenihan, H. S.; Cherr, G.; Cardinale, B. J.; Miller, R.; Ji, Z. Stability and Aggregation of Metal Oxide Nanoparticles in Natural Aqueous Matrices. *Environ. Sci. Technol.* 2010, 44, 1962–1967.

(43) Carole, W. A.; Bradley, J.; Sarwar, M.; Colacot, T. J. Can Palladium Acetate Lose Its “Saltiness”? Catalytic Activities of the Impurities in Palladium Acetate. *Org. Lett.* 2015, 17, 5472–5475.

(44) Carole, W. A.; Colacot, T. J. Understanding Palladium Acetate from a User Perspective. *Chem. - Eur. J.* 2016, 22, 7686–7695.

(45) Smith, J. D.; Ansari, T. N.; Andersson, M. P.; Yadagiri, D.; Ibrahim, F.; Liang, S.; Hammond, G. B.; Gallou, F.; Handa, S. Micelle-Enabled Clean and Selective Sulfonylation of Polyfluoroaromatics in Water under Mild Conditions. *Green Chem.* 2018, 20, 1784–1790.

(46) Sharma, S.; Buchbinder, N. W.; Braje, W. M.; Handa, S. Fast Amide Couplings in Water: Extraction, Column Chromatography, and Crystallization Not Required. *Org. Lett.* 2020, 22, 5737–5740.

(47) Ramezani-Dakhel, H.; Mirau, P. A.; Naik, R. R.; Knecht, M. R.; Heinz, H. Stability, Surface Features, and Atom Leaching of Palladium Nanoparticles: Toward Prediction of Catalytic Functionality. *Phys. Chem. Chem. Phys.* 2013, 15, 5488–5492.

(48) Pattadar, D. K.; Zamborini, F. P. Size Stability Study of Catalytically Active Sub-2 Nm Diameter Gold Nanoparticles Synthesized with Weak Stabilizers. *J. Am. Chem. Soc.* 2018, 140, 14126–14133.

(49) Thakore, R. R.; Takale, B. S.; Gallou, F.; Reilly, J.; Lipshutz, B. H. N. C-Disubstituted Biarylpalladacycles as Precatalysts for ppm Pd-Catalyzed Cross Couplings in Water under Mild Conditions. *ACS Catal.* 2019, 9, 11647–11657.

(50) Takale, B. S.; Thakore, R. R.; Handa, S.; Gallou, F.; Reilly, J.; Lipshutz, B. H. A New Substituted Palladacycle for Ppm Level Pd-Catalyzed Suzuki-Miyaura Cross Couplings in Water. *Chem. Sci.* 2019, 10, 8825–8831.