Letter

Ultrasmall Pd Nanoparticles in Aqueous Micelles for Scalable #-Arylation of Nitriles: Surprising Formation of Carbanions

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Ultrasmall Pd Nanoparticles in Aqueous Micelles for Scalable α-Arylation of Nitriles: Surprising Formation of Carbanions

Manisha Bihani, [†,‡] Tharique N. Ansari,[†,‡] Lucie Finck,[†] Pranjal P. Bora,[†] Jacek B. Jasinski,[‖] Bhavana Pavuluri,[†] David K. Leahy,[*#] Sachin Handa[*†]

[†]Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States

[‖]Materials Characterization, Conn Center for Renewable Energy Research, University of Louisville, Louisville, KY, 40292, USA

[#]Process Chemistry Development, Takeda Pharmaceuticals International, Cambridge, Massachusetts 02139, USA

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ABSTRACT: A scalable synthetic method is described for both the preparation of ultrasmall palladium nanoparticles and their subsequent use in catalyzing an α-arylation reaction of nitriles in aqueous micelles. This method involves the intermediacy of carbanions or keteniminates which are presumably stabilized by the micellar environment rather than being quenched with water. These Pd nanoparticles are thoroughly characterized. Mechanistic studies using ^{31}P NMR spectroscopy revealed the binding of phosphine ligand with the Pd surface and control experiment confirmed the zero-oxidation state of palladium. The scope of the transformation is demonstrated over 35 examples, including one at 50 g scale.

Despite many misperceptions on the use of water as a solvent in organic synthesis hindering its widespread adoption,[1] chemistry in water is slowly gaining the popularity, especially amongst process chemists in the pharmaceutical industry where its value is multi-fold.[2-5] The increase in the number of publications, [6-11] and organization of various symposia on this topic[12-14] evidence the growth of this field of chemistry. Water is by far the greenest, safe, and sustainable solvent.[15] Key contributions from Kobayashi,[16,17] Lipshutz,[18-20] Uozumi,[21,22] others,[23-26] and our group[27-29] have demonstrated the advantages of choosing water as gross reaction medium, not only from an environmental perspective, but also due to the different reactivity often achieved through the use of micellar catalysis.

Micellar catalysis is a fundamental enabler of aqueous chemistry.[1,3] A micelle's broad range of size distribution, dynamic nature, and exchange processes assist in mimicking a variety of polar aprotic solvents with aqueous micelles of a single amphiphile.[27,30] In matching the solvent polarity index of extremely useful but toxic polar-aprotic solvents, our group has recently devised the amphiphile PS-750-M.[27] It has a tertiary amide functional group connecting a polar mPEG chain with the non-polar hydrocarbon chain via a proline linker (Figure 1a). Upon dissolution in water in an appropriate concentration, it instantaneously forms micelles containing the tertiary amide group in the micellar core, which assists in matching its activity with polar-aprotic solvents. Under mild conditions, the micelles of PS-750-M were proven effective for selective sulfonylation of perfluoroarenes,[29] extremely selective monofluorination of indoles and arenes,[31] selective Cbz cleavage,[32] and a variety of cross-coupling reactions. [27,28,33,34] Although many transformations are achieved in water with the use of various amphiphiles, there are still many unaddressed fundamental questions which pose limitations to their applications on more challenging and new transformations. For example, can carbanion- and keteniminate-type species[35-37] exist in the micelles under aqueous conditions? To generate carbanion- and keteniminate-type species in a reaction mixture, strong base is normally required to deprotonate the acidic proton. In water, such type of anionic species would instantaneously be quenched (Figure 1b), which prevents the further possible applications of these anionic species in aqueous chemistry and nanocatalysis. Should the micellar environment stabilize or protect the carbanion or keteniminate species within its hydrophobic core, new reactivity could be unlocked.

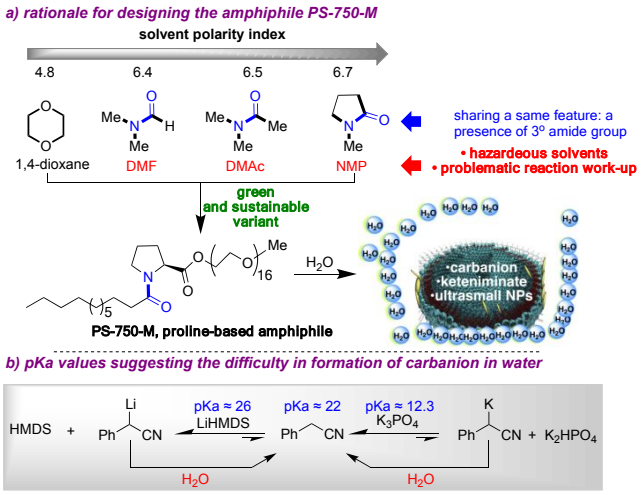
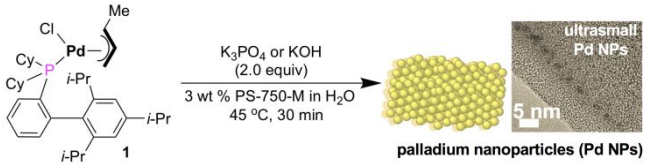


Figure 1. Design of PS-750-M and possibility of carbanion and keteniminate-type species in micelles.

Likewise, can ultrasmall metal nanoparticles (NPs)[38-41] be synthesized and remain stable in an aqueous quasi-homogeneous solution containing micelles? The activity of metal NPs as a catalyst can be enhanced, controlled, and fine-tuned by controlling the size and electronic properties, which causes a change in the surface free energy.[32,41,42] Enhancement of the catalytic activity with the decrease in NP size generally poses a problem of shifting the standard potential toward the negative, resulting in very rapid and facile oxidation or deactivation of the NP catalyst.[41] From a scalability prospective, synthesis of current ultrasmall NPs requiring costly and inconvenient procedures would limit their application in real world organic synthesis. Should ultrasmall NP prove manufacturable and stable in a micellar environment, this could open the door for manufacturing at the time of use, via a convenient one-pot process.

To address the aforementioned issues and gain answers of some fundamental questions, first we designed a sustainable and convenient method for the formation of stable ultrasmall palladium (Pd) NPs in the aqueous solution of PS-750-M without the use of any organic solvent, strong reductant, or harsh conditions. The rationale is to use a precursor that instantaneously generates Pd(0) after reductive elimination under mildly basic conditions. The fast generation and nucleation of the Pd(0) species could result in formation of ultrasmall NPs, assuming the ligand and amphiphile PS-750-M can stabilize the resulting NPs.



Scheme 1. Convenient synthesis of ultrasmall Pd NPs from **1**.

Suspending the Pd complex **1** (XPhosPd(crotyl)Cl) in a 3 wt % aqueous solution of PS-750-M containing 2.0 equivalents mild base (K_3PO_4 or KOH) followed by a gentle heating (45 °C) led to the formation of ultrasmall ligated Pd NPs after the fast-reductive elimination of crotyl chloride (Scheme 1). The choice of the bulky electron-rich XPhos ligand in the NPs was due to its anticipated role in enhancement of NP stability, its introduction of lipophilicity in the NP to interact with the micellar core, and its suitable reactivity for planned applications. Notably, Colacot's π-allyl complexes[43] were the only metal precursors which successfully formed NPs, while other phosphine-$PdCl_2$ or -$Pd(OAc)_2$ complexes were ineffective. The crotyl group was the key to the fast-reductive elimination and NP formation both in small (1 g) and large (20 g) scales. In contrast to other large-scale methods for NPs which are often tedious and difficult to reproduce, our synthetic procedure has proven very safe, convenient and scalable, while the resulting catalytic activity is reproducible (see Supplementary Information, page S2).

NPs were evaluated for composition, ligation, morphology, and size distribution using NMR spectroscopy, high-resolution transmission electron microscopy (HRTEM), scanning transmission electron microscopy-based high-angle annular dark-field imaging (STEM-HAADF), and energy-dispersive X-ray spectroscopy (EDX) mapping (Figure 2). The binding of the phosphine ligand with the NP is confirmed by ^{31}P NMR spectroscopy as the ^{31}P signal of the NP solution was detected at 43.1 ppm while the free XPhos signal appears at –12.9 ppm (Figure 2A). HRTEM analysis revealed the formation of ultrasmall NPs of average size 1.8 nm (Figures 2B, C). STEM-HAADF analysis of a dilute sample revealed the uniform distribution of NPs (Figure 2D). EDAX analysis and mapping confirmed the presence of phosphorus and from NPs and N from PS-750-M (Figures 2E-G, also see SI, page S17). Thus, these combined results evidenced the formation of ultrasmall Pd NPs without any leaching of phosphine ligand.

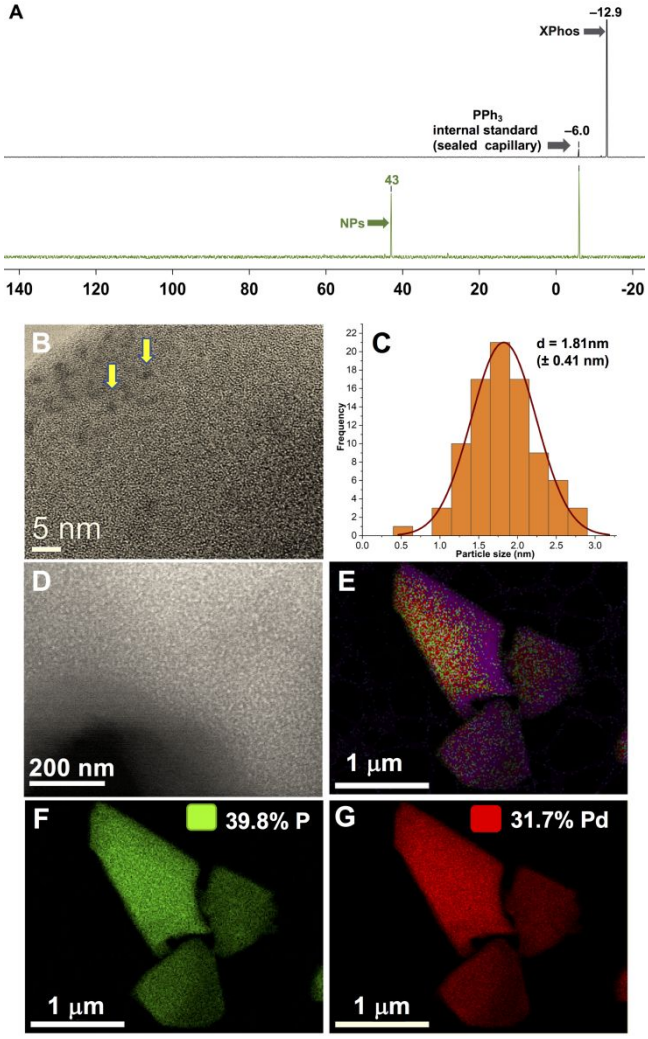
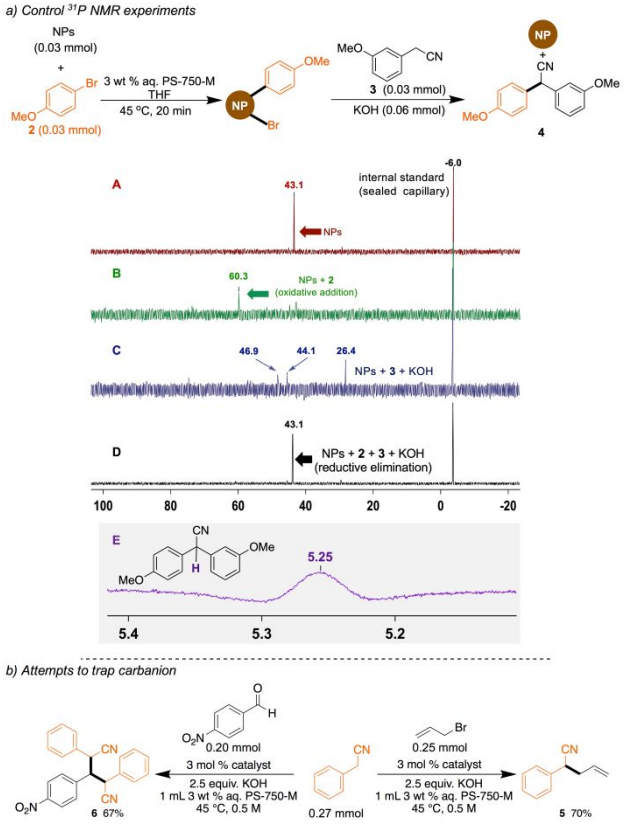


Figure 2. (**A**) ^{31}P NMR study, (**B**, **C**) HRTEM and particle size distribution, (**D-G**) STEM-HAADF and EDAX analysis of ultrasmall Pd NPs.

Next, the activity of the Pd NPs was evaluated in a stoichiometric reaction pathway involving carbanion- and keteniminate-type species (Scheme 2a). Upon treatment of Pd NPs with 1.0 molar equivalent of aryl bromide **2**, an oxidative addition product was observed by ^{31}P NMR spectroscopy, thus implying the initial oxidation state of the NPs as Pd(0). Oxidative addition of aryl bromide **2** results in the change in chemical shift of ^{31}P from 43.1 to 60.3 ppm (Scheme 2a, B). In a separate NMR tube, upon reaction between Pd NPs with 1.0 molar equivalent nitrile **3** and 1.0 equivalent KOH, the formation of a Pd complex with carbanion and corresponding

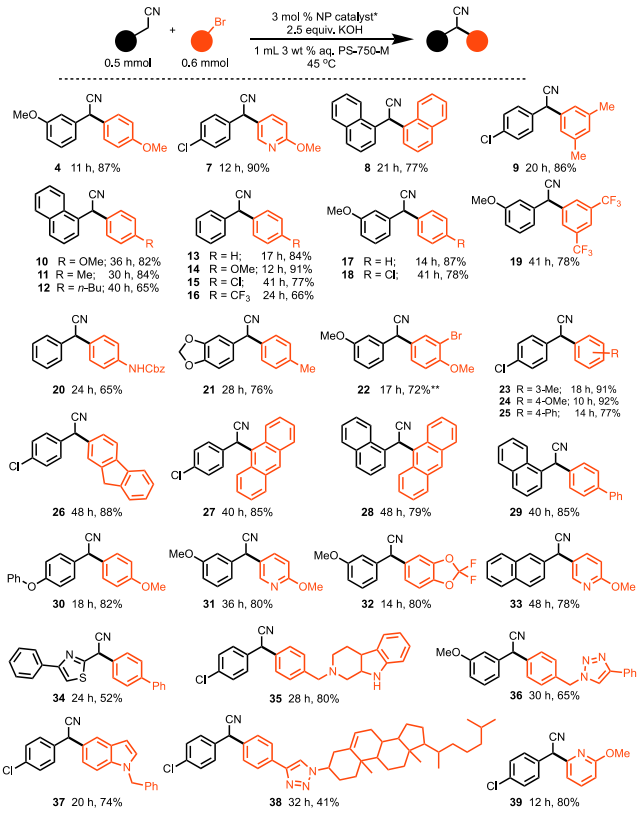
keteniminate complexes were observed, which show new ^{31}P signals at 46.9, 44.1, and 26.4 ppm (Scheme 2a, C). The multiple signals are most likely due to the presence of geometrical isomers of both the Pd-bound carbanion as well as keteniminate. However, upon mixing of these isomeric contents with the 1.0 molar equivalent of the contents from 2B results in formation of coupling product **4** and regeneration of active NPs evidenced by the reappearance of the ^{31}P signal at 43.1 ppm (Scheme 2a, D). The formation of product **4** was also detected by the appearance of benzylic proton at 5.25 ppm in ^{1}H NMR spectrum of the reaction mixture (Scheme 2a, E). To ensure that the NPs are catalytically competent, a second addition of aryl bromide **2** once again shows oxidative addition and appearance of a ^{31}P NMR signal at 60.3 ppm, which also disappears after a second addition of nitrile **3** and base. Again, the Pd(0) species is reformed along with product **4**. The continuation of the cycle shows that these NPs retains catalytic activity, and are stable in water. Notably, the above reactions were performed with the use of stochiometric Pd NPs. The NPs retained their morphology, composition, and catalytic activity after up to four weeks when prepared in bulk stored at 5 °C under argon atmosphere, as shown by HRTEM, EDAX, NMR, and catalytic activity analysis (see SI, pages S14-S20).



Scheme 2. a) Oxidative addition, transmetallation, and reductive elimination on the NP surface; b) trapping of carbanion.

The *in-situ* formation of carbanion-type species was also confirmed by trapping such species with either an aldehyde or allyl bromide (Scheme 2b). Upon addition of 1.0 molar equivalent of allyl bromide into an aqueous solution of PS-750-M containing the Pd NPs, phenylacetonitrile, and KOH, the formation of adduct **5** was observed with 70% isolated yield. Similarly, upon addition of 0.8 molar equivalent of *p*-nitrobenzaldehyde into the micellar medium containing the Pd NPs, phenylacetonitrile, and KOH, the formation of adduct was detected by GCMS which further formed the dinitrile **6** after the dehydration and addition of second phenylacetonitrile.

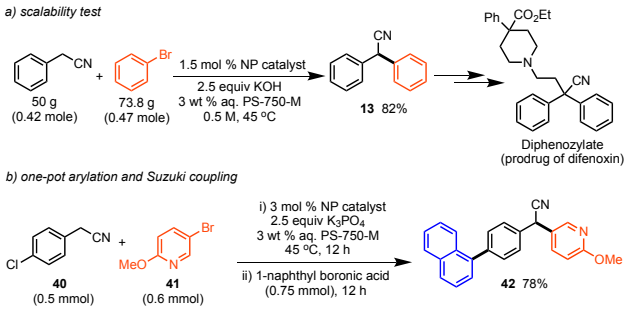
Table 1. Catalytic activity of in-situ formed NPs on a variety substrates[a]



[a]Conditions. (Hetero)arylacetonitrile (0.5 mmol), (hetero)aryl bromide (0.6 mmol), NP catalyst (3 mol %), KOH (1.25 mmol), 1 mL 3 wt % PS-750-M in H_2O, 45 °C. *NP catalyst was in-situ generated by adding 3 mol % **1** and 1 mg KOH in 1 mL 3 wt % PS-750-M in H_2O at 45 °C for 10 min. **aryl iodide was the coupling partner and reaction was carried at 35 °C. All reported yields are isolated.

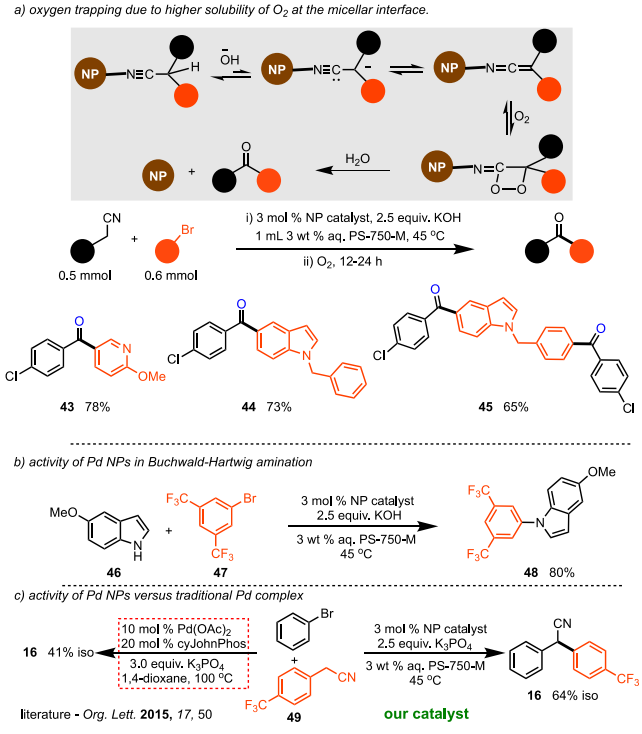
For synthetic convenience, we generated the ultrasmall Pd NPs *in-situ* and tested the catalytic activity all in a one-pot (Table 1). Under mildly basic conditions, NPs formed immediately in the aqueous solution of PS-750-M, then aryl bromide and nitrile were added (presumably forming a carbanion or keteniminate) leading directly to the desired *α*-arylation cross-coupling product. This reaction shows a broad substrate scope, tolerating a wide range of functional groups as well as steric, and electronic parameters. Heteroaromatics, including pyridyl (**7**, **31**, **33, 39**), thiazole (**34**), triazole (**36**), and indole (**37**) moieties as well as polycyclic (**26-28**, **35**) coupling partners were very well tolerated and provided *α*-arylated products in good-to-excellent yields. Notably, the fluorene residue in compound **26** did not affect the reactivity and no side-reaction on this residue was observed. Likewise, the free indole nitrogen in **35** which could potentially bind with the NPs and adversely affect the catalytic activity proved unproblematic. Common nitrogen and oxygen protecting groups such as Cbz (**20**) and benzyl (**37**) were tolerated in the reaction. Notably, chloro groups (**7**, **9**, **15**, **18**, **23-27**, **35**, **37-39**) did not participate in the reaction unless the reaction temperature was raised above 60 °C, thus allowing for a convenient synthetic handle for further functionalization. In addition, a second bromo group could be retained if reaction

is performed at 35 °C (**22**), the regiochemistry of oxidative addition presumably driven by sterics.



Scheme 3. Scale up and two step one-pot reaction.

The activity of the NP catalyst was also tested on a multigram-scale reaction as well as one-pot arylation and Suzuki coupling. As demonstrated in Scheme 3a, the catalytic reaction between phenylacetontrile and bromobenzene on 50-gram scale affords the product **13** in good isolated yield, even with only 1.5 mol% catalyst loading. Notably, **13** is a key intermediate for the synthesis of diphenozylate, a prodrug of difenoxin.[44] Another key aspect of this nanocatalysis is the ability to achieve multiple complimentary reactions in one-pot without isolating the reaction intermediate while using the same catalyst (Scheme 3b). Hence, the α-arylation reaction was achieved by a coupling between arylnitrile **40** and aryl bromide **41**. Notably, **40** has two reaction handles, i.e., chloro and nitrile's α-CH_2. After α-arylation of **40** with **41**, a Suzuki coupling was achieved by the addition of 1-naphthylboronic acid in a same pot and raising the reaction temperature to 60 °C to obtain **42** in 78% yield.



Scheme 4. Tests for broader activity of ultrasmall Pd NPs.

Another important feature of the micellar catalysis with the aqueous PS-750-M is the higher solubility of oxygen in the interfacial region,[31] which allows molecular oxygen to be used in the reaction pathway depicted in Scheme 4 to generate diarylketones, which are highly important drug molecules in medicinal chemistry as many drug molecules contain biaryl ketones.[45,46] In a one-pot process, after the completion of the α-arylation, we exposed the same reaction mixture to an oxygen atmosphere to obtain biaryl ketones **43-45** in good isolated yields.

Notably, with these ultrasmall NPs, Buchwald-Hartwig amination[33] is also possible. As a proof-of-the-concept, a reaction between amine **46** and aryl bromide **47** affords the educt **48** in good isolated yield (Scheme 4b). A comparison between the current state-of-the-art α -arylation and our methodology is also depicted in Scheme 4c. Compared to the literature,[47] low palladium loading is required to obtain slightly better yield in the coupling of less reactive nitrile **49** with bromobenzene, i.e., 64% isolated yield of compound **16** compared to 41% reported in the literature.

In conclusion, an environmentally responsible α-arylation reaction of nitriles in aqueous medium was developed where the surfactant PS-750-M serves three critical roles: 1) allowing the generation and stabilization of ultrasmall Pd NPs via a fast-reductive elimination process, 2) stabilizing the carbanion/ketenimine intermediates inside its hydrophobic core preventing protonation by water, and 3) using water for larger scale reactions, removing the need for hazardous organic solvents. Our technology involves a convenient synthetic method of ultrasmall Pd NPs, without the need for organic solvent or harsh reductants and should find a myriad of uses across the chemical and pharmaceutical industries, which potentially opens new doorways to the applications of nanocatalysis in chemical synthesis, and having direct impacts on the environment, economy, and advancement of green chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Materials and methods, Supplementary Figures, Supplementary Tables, Supplementary Schemes, and Analytical Data.

AUTHOR INFORMATION

Corresponding Author

*sachin.handa@louisville.edu
david.leahy@takeda.com

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Notes

Any additional relevant notes should be placed here.

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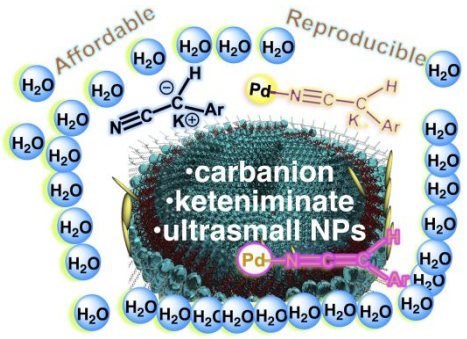

When micelle, water, and ultrasmall nanoparticles synergistically combine, transformation involving carbanion and keteniminate species can be achieved under aqueous conditions.