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Reactivity of Carbenes in Aqueous Nanomicelles Containing Palladium Nanoparticles

Uyen T. Duong,[†] Amol B. Gade,[†] Scott Plummer,[ǀ] Fabrice Gallou,[⊥] and Sachin Handa*[†]

[†]Department of Chemistry, University of Louisville, 2320 S. Brook St., Louisville, KY 40292, USA

[ǀ]Global Discovery Chemistry, Novartis Institutes for Biomedical Research, 250 Massachusetts Ave, Cambridge, MA 02139, USA

[⊥]Chemical & Analytical Development, Novartis Pharma AG, Basel 4056, Switzerland

Supporting Information Placeholder

ABSTRACT: Palladium nanoparticles ligated with inexpensive triphenylphosphine and amphiphile PS-750-M are suitable for exploring the reactivity of carbenes in aqueous nanomicelles. Nanocatalyst is highly selective for metal-carbene migratory insertion and micelles PS-750-M shields the in-situ generated carbene to prevent the dimerization. In addition to broad substrate scope, the nanocatalyst is thoroughly characterized by NMR, SEM, HRTEM, XPS, and TGA. The sustainability of the reaction system is demonstrated by the recyclability of both the catalyst and the micellar reaction medium at variable reaction scales. NMR and kinetics studies with the recycled catalyst revealed the retention of catalyst integrity. Control experiments including DLS study demonstrate the importance of PS-750-M.

KEYWORDS. *chemistry in water, cross-couplings, heterogeneous catalysis, micellar catalysis, sustainability*

Introduction. If appropriately used, water is arguably the most sustainable and green solvent for conducting organic synthesis.[1-6] Nevertheless, misperceptions that the use of water as a solvent in synthesis ultimately leads to an increase in waste generation and that water recycling is difficult continue to hinder its widespread adoption. As evinced by the promulgation of solvent selection guides such as Pfizer's,[7-9] which designates water as the most preferred solvent, attitudes are increasingly changing, but water has yet to attain the popularity it deserves. It is an ideal solvent for chemist safety,[10,11] process safety,[8] and environmental safety.[12,13] Contributions from Kobayashi,[14,15] Lipshutz,[16] Uozumi,[17,18] Ackermann,[19,20] and our group[21,22] have set the foundation to explore chemistry in water for highly selective reaction pathways, especially for industrial applications.[23,24] Very recently, our group developed an environmentally benign proline-based amphiphile, PS-750-M,[25,26] that when dissolved in water instantaneously forms nanomicelles with increased inner polarity, distinguishing it from other well-established amphiphiles.[27,28] The rationale behind the design of PS-750-M is that the inclusion of a *tert*-amide functionality inside the micelle allows it to mimic DMF, DMAc, NMP, and other toxic polar-aprotic solvents (Figure 1). The *tert*-amide group in these solvents imparts polarity and also participates in secondary interactions in some catalytic pathways.[29] PS-750-M has been explored on a variety of transformations including those which traditionally require toxic polar-aprotic solvents.[24,25] One such transformation, the monofluorination of indoles, is not even possible to cleanly achieve in any organic solvent, but is readily accomplished in aqueous PS-750-M.[30]

Despite such advances in micellar catalysis, there is a lack of knowledge on the behavior of reaction intermediates in micellar media. For example, do carbenes or carbenoids exist in the micelle; would such species react with the amphiphile; would such a reaction impact micellization? While exploring the reactivity of carbenes in micellar media, another unaddressed question is the stability and catalytic activity of palladium (Pd) nanoparticles (NPs) stabilized only by the non-biaryl inexpensive phosphine ligand and PS-750-M. The catalytic activity of Pd NPs stabilized by the biaryl ligands SPhos and XPhos is well documented.[31] Similarly, we recently documented the enhanced stability of Ni(0)Pd(0) NPs ligated with *N*,*N*-type bidentate ligand in the microballs formed with the aid of our engineered amphiphile PS-750-M.[21] The amphiphile played a crucial role to the stability of these NPs. Therefore, such enhanced stability and recyclability of Pd NPs ligated with inexpensive triphenylphosphine (PPh_3) and capped by PS-750-M is anticipated.

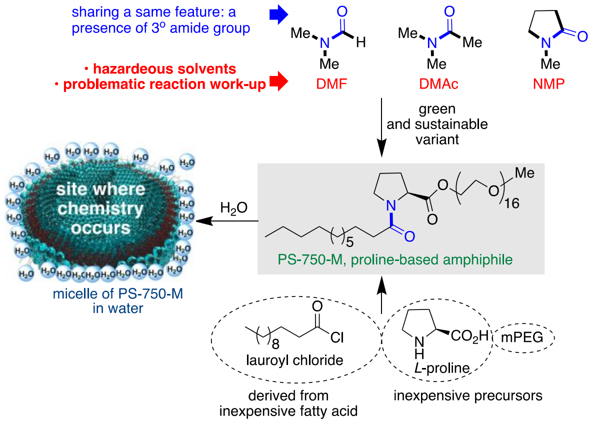
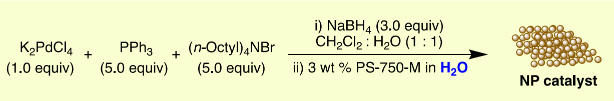


Figure 1. Rationale behind the design of PS-750-M.

If carbene molecules exist in a nanomicelle, it could be easily employed in the sustainable synthesis of highly useful intermediates. Cross-couplings comprising metal–carbene migratory insertion have aroused significant interest during the past decade which is likely due to noteworthy applications of resulting products in medicinal chemistry and material science.[32-34] However, most of these reactions involve the use of toxic solvents such as 1,4-dioxane, DMF, and benzene under harsh conditions. Due to the involvement of reactive Pd-carbene intermediates,[35] the achievement of such transformations in aqueous micellar media might be expected to be challenging and perhaps has hence remained elusive.

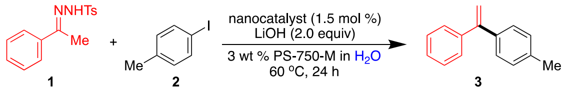
Results and Discussion. Herein, we report a nanotechnology which enables facile access to terminal olefins from *N*-tosylhydrazone in aqueous micelles of PS-750-M. The reaction mechanism involves a carbene intermediate, allowing for the investigation of micellar carbene behavior. Our technology uses a minimal amount of Pd in a recyclable fashion, inexpensive PPh_3 ligand, PS-750-M as both surfactant and capping agent for the generation of highly active Pd NPs, and water as the gross reaction medium. The hypothesis behind the design of our nanotechnology is: (i) stabilization of extremely small NPs of Pd by ligation with PPh_3 and PS-750-M via its proline fragment; (ii) presence of nanocatalyst near the proline fragment, which, when dissolved in water, resides in the micellar interface region or interior; (iii) shielding effect of micelle that protect the carbene intermediate and nanocatalyst from water and oxygen for desired catalytic activity and reaction pathway.[30]



Scheme 1. Synthesis of nanoparticle catalyst.

The synthesis of the NP catalyst (see Supporting Information, page S6) is straightforward and involves pre-complexation of K_2PdCl_4 with PPh_3 in a 1:5 ratio in a water/CH_2Cl_2 solvent system in the presence of tetraocotylammonium bromide followed by reduction of the Pd complex with $NaBH_4$ and capping the resulting NPs with PS-750-M (Scheme 1). Separation of the organic layer from the aqueous layer followed by removal of CH_2Cl_2 affords the desired NP catalyst. Upon use of these NPs as catalyst, we are able to access functionalized terminal olefins from *N*-tosylhydrazone by 1) stabilizing the reactive metal carbene intermediates under the aqueous micellar environment; 2) use of more economically viable NP catalyst and reagents; and 3) efficient recycling of reaction medium and catalyst. Our initial findings on the reactions of aryl halides with *N*-tosylhydrazone involving the formation of carbene in the presence of NP catalyst and base enables the first Pd-carbene in micellar media involving migratory insertion.

Table 1. Optimization study

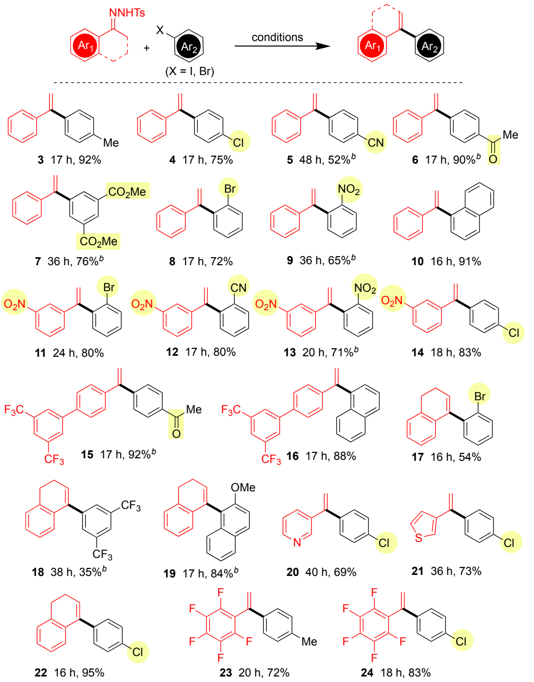


entry	deviation from standard conditions[a]	% yield[b]
1	none	99 (92)[c]
2	[5 mol % $Cu(PPh_3)_3Cl$][d] or Cu NPs	NR
3	[5 mol % $Pd(OAc)_2$][d]	trace
4	[5 mol % $Pd(OAc)_2$, 10 mol % XPhos][d]	60
5	[5 mol % $Pd(OAc)_2$, 10 mol % SPhos][d]	85 (78)[c]
6	[5 mol % $Pd(OAc)_2$, 10 mol % XantPhos][d]	74
7	[5 mol % $Pd(PPh_3)_2Cl_2$][d]	88
8	[5 mol % $Pd(PPh_3)_4$][d]	86
9	[5 mol % $Pd(dppf)Cl_2$][d]	83
10	K_2CO_3 instead of LiOH	44
11	*t*-BuOLi instead of LiOH	98 (92)[c]
12	Et_3N instead of LiOH	traces
13	water as reaction medium instead of aq. PS-750-M	traces

[a]Reaction conditions: 0.37 mmol **1**, 0.25 mmol **2**, 0.5 mmol LiOH, 1.5 mol% NP catalyst (12 mg), 3 wt % aq. PS-750-M (0.25 M), 60 °C, 24 h. [b]Yields based on GCMS with mesitylene as an internal standard. [c]Isolated yield. [d]NP catalyst was replaced with these molecular complexes.

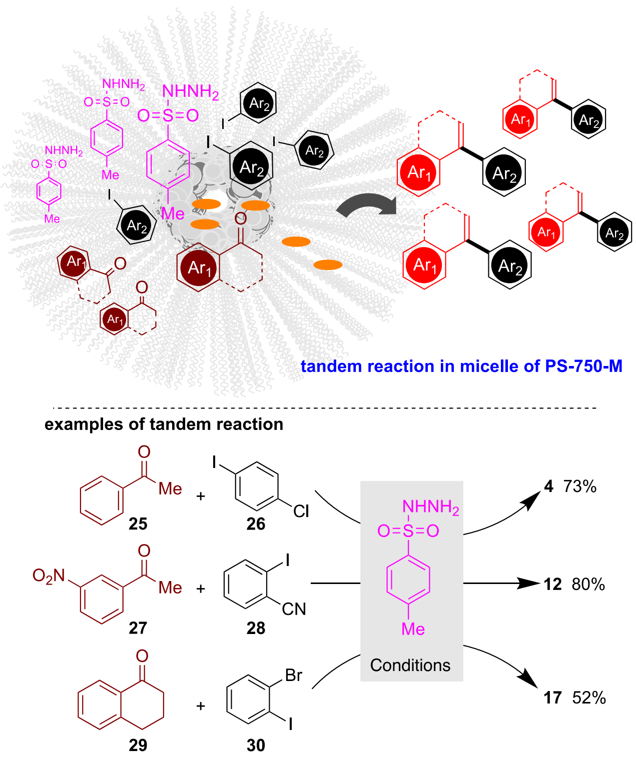
Using 1.5 mol % NP catalyst (weight determined by elemental analysis, see Supporting Information, page S6) in nanomicelles of PS-750-M, a reaction between *N*-tosylhydrazone **1** and aryl iodide **2** affords product **3** in an excellent isolated yield; notably, LiOH or *t*-BuOLi as a base was essential for the optimal catalytic activity (Table 1, entry 1, 11). No carbene dimerized product was observed in the reaction mixture. Optimization studies revealed the dependence of this transformation on choice of surfactant, catalyst, temperature, base, and global concentration. PS-750-M as a surfactant, our NPs as catalyst, 60-70 °C reaction temperature, *t*-BuOLi or LiOH as a base, and 0.25 M global concentration were the optimal reaction parameters (see Supporting Information, pages S3-S5). A nanocatalyst prepared with Cu instead of Pd and a phosphine-free molecular Pd catalyst provided unsatisfactory results (entries 2, 3). Although ligated molecular Pd complexes were somewhat catalytically active (entries 4–9), they were inferior to the nanocatalyst. Isolated Pd complexes afforded desired olefin **3** in good yields but not better than when NP catalyst was used (entries 7–9). Moreover, these complexes were not recyclable as Pd black is formed after reaction completion. Use of K_2CO_3 as the base affords low conversion (entry 10). The use of *t*-BuOLi was equally as effective as LiOH (entry 11). Therefore, inexpensive LiOH was chosen for further studies. Et_3N as a base inhibits the reaction, which may be due to binding of amine base on the surface of NP catalyst and occupying the catalytic sites (entry 12). Neat water as a reaction medium is detrimental, possibly due to destabilization of NP catalyst and instability of the carbene intermediate (entry 13). Furthermore, other state-of-the-art surfactants such as Nok (also called SPGS), TPGS-750-M, and SDS were found to be ineffective for this transformation (see Supporting Information, page S4).[27,28] This may be due to relatively extremely higher solubility of resulting product in their micelles containing highly lipophilic cores, while inner cores of micelles of PS-750-M are relatively polar, and anticipated relative solubility of product molecules is less. As Pd NPs showed an impressive reactivity and recyclability for coupling reactions in an aqueous medium, this system was selected for substrate scope and other detailed investigations.

Table 2. Generality of the carbene-mediated reaction in water[a]



[a]Conditions: **1** (0.37 mmol), **2** (aryl iodide, 0.25 mmol), LiOH (0.5 mmol, 2.0 equiv), NP catalyst (1.5 mol%), 3 wt % PS-750-M in H_2O (1 mL), 70 °C; [b]aryl bromide is used as a coupling partner. All yields are isolated.

Using optimal reaction conditions, generality of the protocol is explored on the combination of different coupling partners. As illustrated in Table 2, irrespective of the steric bulk and electronic properties, the reaction is quite general with different combinations of aryl halide (bromide and iodide) and *N*-tosylhydrazone. Remarkable functional group tolerance is observed with retention of bromo (**8**, **11**, **17**), chloro (**4**, **14**, **20–22**, **24**), cyano (**5**, **12**), ester (**7**), ketone (**6**, **15**), and trifluoromethyl (**15**, **16**) functional groups. Reaction yields in all of these cases are good-to-excellent. No hydrodehalogenation is observed with dihaloarene coupling partners (**4**, **8**, **11**, **14**, **17**, **20-22**). In general, esters are hydrolyzed in aqueous basic conditions, especially when LiOH is used. However, no such hydrolysis is observed, and compound **7** is cleanly obtained in good yield. In this scope study, noteworthy steric congestion can be found in products **8-13** without affecting the yields. Pyridyl (**20**) and thiophenyl (**21**) moieties are also well tolerated. In examples **23** and **24**, the perflouoropheny coupling partner displays very good reactivity without any reduction in yield anticipated from competeing S_NAr pathway.[26] This methodology is also equally effective in obtaining cyclic olefins (**17-19**, **22**). These cyclic olefins are potentially useful for generation of biaryl compounds after further aromatization. Among all these examples, both the cyclic and acyclic hydrazones can be found as coupling partners.



Conditions. Aryl ketone (0.37 mmol), aryl iodide (0.25 mmol), tosylhydrazone (0.37 mmol), LiOH (0.5 mmol), NP catalyst (1.5 mol %), 1 mL 3 wt % PS-750-M in H_2O, 70 °C, 17 h; all yields are isolated.

Scheme 2. Access to olefins via tandem approach.

An intriguing feature of micellar catalysis is the high concentration and close contact between different coupling partners in the nanomicelles. Leveraging this feature, *in-situ* condensation (dehydration) between the carbonyl compound (**25**, **27**, **29**) and *N*-tosylhydrazide affords *N*-tosylhydrazone intermediate, which subsequently reacts with the aryl halide (**26**, **28**, **30**) already present in the same pot to afford final olefin. This tandem approach (Scheme 2) provides adducts **4**, **12**, and **17** in approximately same yields as obtained with the use of the corresponding isolated *N*-tosylhydrazones coupling partners (see Table 2). Notably, same tandem reactions in the organic solvent are either not possible or require two different solvents in a one-pot reaction, which clearly demonstrates another valuable aspect of micellar catalysis.

Table 3. elemental analysis and ICP-MS of NP catalyst*

C 71.46%	H 7.73%	N 0.96%	P 11.28%
Pd 3.40%	Na 22 ppm	Cu 9 ppm	

*analysis was performed in duplicate by an independent laboratory.

The structure, chemical composition, and properties of the nanocatalyst have been elucidated by SEM, HRTEM, elemental analysis, ICP-MS, XPS, and TGA analysis. SEM imaging revealed the flower-like structure of the NP catalyst (Figure 2A).

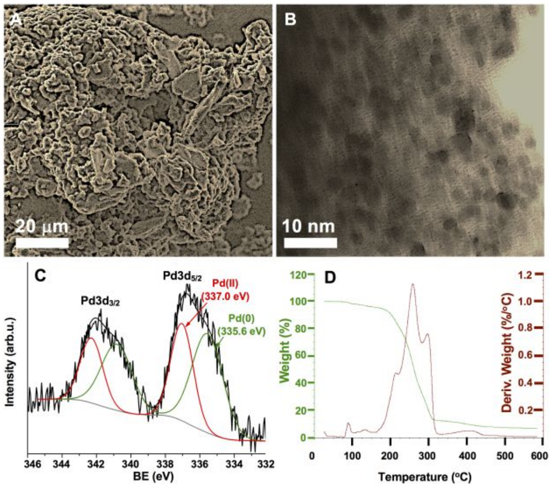


Figure 2. Detailed characterization of catalyst. A) SEM analysis; B) HRTEM analysis; C) XPS analysis; D) TGA analysis.

HRTEM analysis of finely-grounded nanoparticles revealed smaller sized NP of Pd embedded in the organic material containing surfactant (Figure 2B). No agglomeration of NP is observed in analysis. As found in XPS analysis, NPs exposed on the surface for a long time contain Pd in +2 oxidation state while those located inside of the material have Pd zero (Figure 2C). In the XPS analysis, the deconvolution of the Pd3d spectrum yields two species, i.e., one with the Pd3d5/2 line at 335.6 eV and the other at 337.0 eV, which correspond to Pd(0) and Pd(II), respectively. As evidenced by the surface mapping, only 0.43% of Pd can be found on the surface or periphery of NP catalyst (see Supporting Information, pages S10-S11). Most of the Pd is present in the interior as 3.4% Pd is detected in the elemental analysis of NP catalyst (Table 3, also see Supporting Information, page S6). From the elemental analysis study, the Pd:P ratio is ca. 2:7. The role of (*n*-octyl)$_4$NBr in the catalyst preparation was just as a phase-transfer catalyst, not capping agent, which was also evidenced by elemental analysis. The low abundance of nitrogen in the catalyst was due to use of small amount of PS-750-M as capping agent. Traces of sodium and copper were also detected in the ICP-MS analysis of NP catalyst. The copper impurity was inherited from the Pd source which was also confirmed by the ICP-MS analysis of K_2PdCl_4.

However, under catalytic conditions, oxidized Pd is easily reduced to Pd(0) as evidenced by NMR study (Figure 3). Catalyst is quite stable at elevated temperature as determined by thermogravimetric analysis (TGA) (Figure 2D). Upon heating the material up to 200 ^{o}C, only ca. 10% of total mass was lost due to loss of hydrocarbons from the surfactant. Between 200-300 ^{o}C, decomposition of PPh_3 is observed.

Catalytic activity of the aged NPs (30 days) was as same as the fresh NPs. However, NMR study (Figure 3A) revealed that the surface of the aged NPs has some Pd(II), which was also observed in XPS analysis. Exposing the NPs to the reaction conditions or basic conditions reduces the Pd(II) to Pd(0) NPs, which is clearly seen in the ^{31}P NMR study of NPs (Figure 3B). The signal at 33.3 ppm disappears and only signal at 29.4 ppm is observed, which is similar to the ^{31}P NMR of a fresh catalyst (Figure 3C). After the catalytic reaction and product extraction, NP catalyst stays in the aqueous nanomicelles of PS-750-M, and ^{31}P NMR of the recycled NPs did not show any change in chemical shift. Exposing the recycled NPs to the catalysis displayed efficient catalysis (see Supporting Information, pages S14-S17). Notably, the absence of signal when organic layer was analyzed for ^{31}P NMR indicates no loss of catalyst in the organic layer during product extraction with EtOAc (Figure 3E). This clearly indicates the association of NP catalyst with the nanomicelles of PS-750-M.

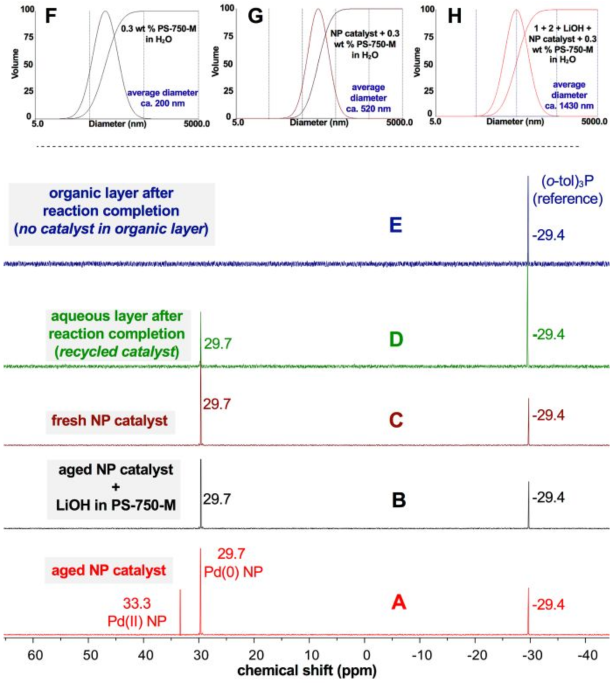
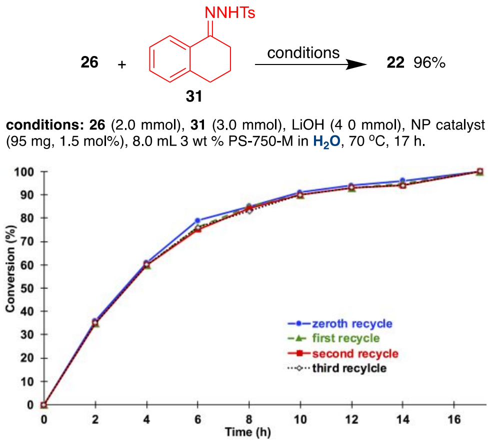


Figure 3. Control NMR study of NPs and DLS experiments.

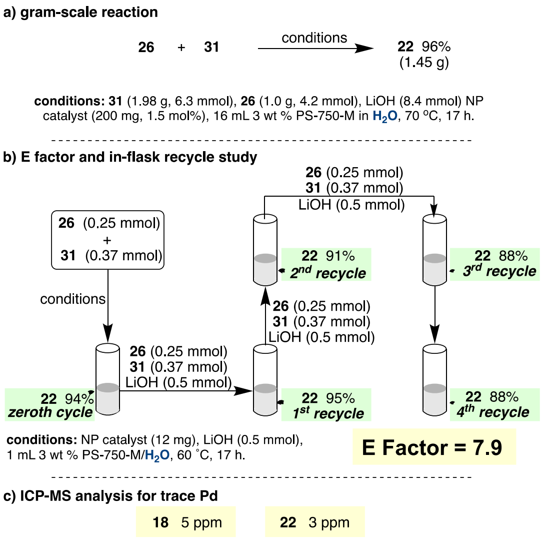
The role of nanomicelles is further confirmed by control dynamic light scattering (DLS) experiments. The average diameter of 0.3 wt % of solution of PS-750-M found to be *ca.* 200 nm (Figure 3F). Upon addition of NP catalyst to the aqueous solution of nanomicelle, the particle size increased to 520 nm, which is indicative of accommodation of NPs inside the micelles, especially when NPs are ligated with PPh_3 and inner core of the micelle of PS-750-M is relatively polar compared to the core of micelle of traditional surfactants (Figure 3G). Notably, addition of coupling partners results in the formation of enlarged NPs of average diameter 1430 nm (Figure 3H). This increase to the vesicle type particles was strong indication of accommodation of all the reaction components inside the micelles except LiOH.



conditions: 26 (2.0 mmol), **31** (3.0 mmol), LiOH (4 0 mmol), NP catalyst (95 mg, 1.5 mol%), 8.0 mL 3 wt % PS-750-M in H_2O, 70 ^{o}C, 17 h.

Figure 4. An assessment of catalyst stability: reaction rates with recycled catalyst.

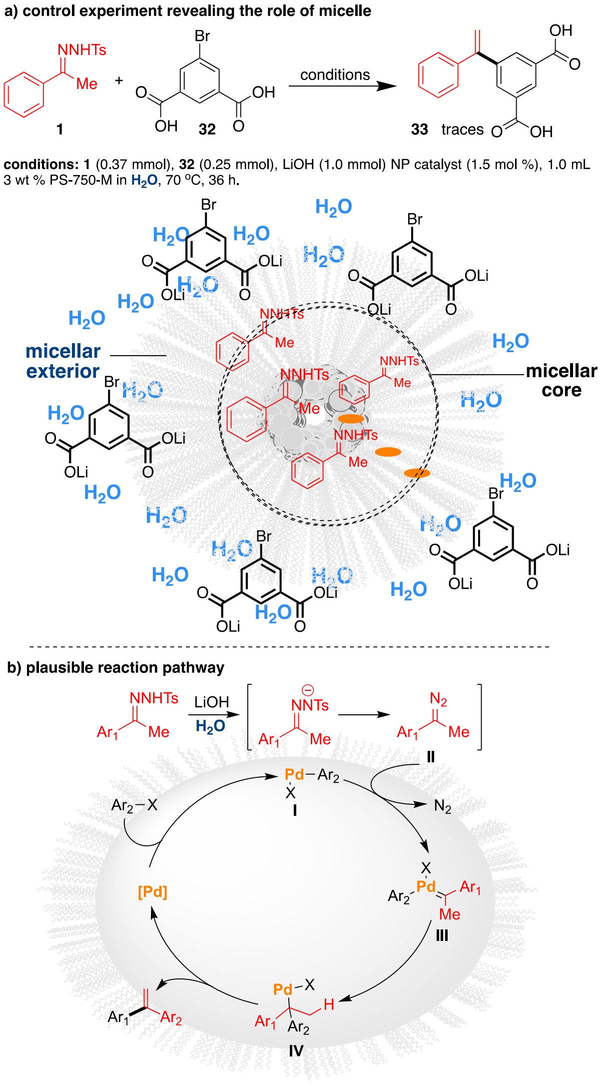
To validate the retention of catalytic activity of recycled catalyst,[36] reaction rates in each reaction cycle were recorded (Figure 4, also see Supporting Information, pages S15-S17). To avoid experimental error, the initial reaction between **26** and **31** was performed at the 2 mmol scale, and adduct **22** was obtained in 96% isolated yield. Kinetic study revealed that 50% product was formed in < 4 h, and remaining 50% of reaction was complete in next 13 h. This is likely due to the high solubility of product in the micelle, which keeps the micelles occupied and slows down the exchange process between individual micelles. After reaction completion, the product is extracted from the micellar core by adding a minimal amount of lipophilic solvents such as MTBE or EtOAc. The recycled catalyst displayed similar reaction kinetics up to three cycles. The same reaction rate is a strong evidence of catalyst stability and perpetuation of catalyst structure.



Scheme 3. Scalability test, E factor, and recycle study.

This technology is also applicable to gram-scale reaction. A reaction between coupling partners **26** and **31** affords product **22** in an excellent isolated yield (Scheme 3a). The catalyst was recovered and reused without noticing any loss of catalytic activity. Next, E factor and recycle study was performed (Scheme 3b). Catalyst was recycled up to four cycles without significant loss of activity. The calculated E factor in this study is 7.9, which meets the standards of the pharmaceutical industry. As determined by ICP-MS analysis, only up to 5 ppm of Pd is observed in the crude product, which also meets the USFDA standard for any active pharmaceutical ingredient (Scheme 3c).

Control experiments were performed to draw the plausible reaction pathway. Base is required to obtain desired product, although some homocoupling product from aryl halide is observed in the absence of base. Attempts to couple **1** with diacid **32** were unsuccessful (Scheme 4a). Under reaction conditions, diacid **32** forms dicarboxylate ion, which may have difficulty to enter in micelle, and thereby, stays in water. At the same time, catalyst and carbenoid precursor are likely to be inside the micelle. Location of coupling partners at two different sites prevent the desired coupling.



Scheme 4. Role of micelle of PS-750-M and plausible reaction pathway.

Based on the results obtained, nanoparticles reside inside the micelle where oxidative addition of aryl halide occurs to generate intermediate **I** (Scheme 4b). Deprotonation of *N*-tosylhydrazide by OH^- likely to occurs at the micellar interface to form *N*-tosylhydrazinide which immediately generate diazo species **II** to enters the micelle. Since the inner core of micelle of PS-750-M mimic polar-aprotic solvent, the solubility of **II** is potentially much more therein compared to water. Simultaneously, oxidative addition of aryl halide occurs in the micellar core to generate the intermediate **I**. The transfer of carbene to **I** generates the Pd-carbene intermediate **III**, which upon insertion generates the intermediate **IV.** β -Hydrogen elimination in **IV** releases the final product and regenerates the active catalyst for the next catalytic cycle. Except for the generation of diazo species, all the events are likely to happen inside the micelles, as evidenced by control experiments and DLS study.

Conclusions. Carbenoids and metal carbene species can be stabilized by the shielding effect of micelle, and further employed to access synthetically useful precursors. With the use of nanomicelles of PS-750-M, and nanopalladium as a catalyst, both the reaction medium and catalyst can be fully recycled. At the same time, this technology has a high potential to assist the process chemist to safely and sustainably employee carbene chemistry at large scale. NP catalyst used in this study is stable, recyclable, and requires inexpensive PPh_3 ligand. DLS data supports the existence of nanomicelles in the presence of carbenes. Further reports on the use of metal-carbenes in micellar media for enantioselective pathways will be reported in a due course.

EXPERIMENTAL METHODS.

Preparation of Nanocatalyst. To a vigorously stirred solution of K_2PdCl_4 (33 mg, 0.1 mmol) and *tetra*-n-octylammonium bromide (109 mg, 0.2 mmol) in 1:1 deionized water/CH_2Cl_2 (2 mL), a solution of PPh_3 (131 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was slowly added at room temperature (rt). The resulting mixture was stirred for 30 minutes at rt. To the reaction mixture, a solution of $NaBH_4$ (12 mg, 0.3 mmol) in deionized water (1 mL) was slowly added followed by addition of 0.1 mL 3 wt % PS-750-M in H_2O. Reaction mixture was stirred for additional 1 h at rt under inert atmosphere.

After 1 h additional stirring, CH_2Cl_2 (1 mL) was added to the reaction mixture and mixture was stirred for few minutes. Stirring was stopped and organic layer was allowed to separate from the aqueous. Organic layer was removed from the reaction mixture. Organic layer was dried over Na_2SO_4. Volatiles were removed under reduced pressure to obtain nanoparticles as yellow solid. To the solid material 1 mL pentane was added and material was tritiated for a minute. Pentane was removed under reduced pressure to obtain free-flowing yellow solid (132 mg).

Catalytic Reactions with Nanocatalyst. In a 4 mL reaction vial containing PTFE-coated stir bar, *N*-tosylhydrazone (0.37 mmol), aryl halide (0.25 mmol), Pd NPs (1.5 mol %, 12 mg), and LiOH (0.5 mmol, 12 mg) were added. The reaction vial was sealed with a rubber septum. 1.0 mL 3 wt % aq. PS-750-M was added to the reaction mixture and septum was wrapped with parafilm. The reaction mixture was stirred at 70 ˚C till complete consumption of starting material.

After complete consumption of starting material as monitored by TLC and GCMS, reaction mixture was cooled to rt. 1 mL EtOAc or MTBE was added to the reaction mixture and mixture was stirred for a minute at rt. Stirring was stopped and organic layer was allowed to separate from the aqueous layer. Organic layer was removed with the use of pipette. Similarly, additional extraction procedure was employed. Combined organic layers were dried over anhydrous Na_2SO_4. Volatiles were removed under reduced pressure to obtain semi-pure product, which was further purified by flash chromatography using EtOAc/hexanes as eluent. All organic solvents were recovered and reused.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Detailed reaction optimization, general catalytic procedure, characterization of nanomaterial, analytical data and NMRs of compounds.

AUTHOR INFORMATION

Corresponding Author.

*sachin.handa@louisville.edu

Author Contributions

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

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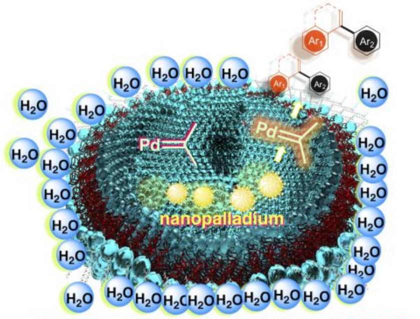

• carbenes on nanopalladium in micelles of PS-750-M
• facile and sustainable access to terminal olefins