Aqueous Micellar Technology: An Alternative Beyond Organic Solvents

Journal:	*ChemComm*
Manuscript ID	CC-FEA-01-2023-000127.R2
Article Type:	Feature Article

ARTICLE

Aqueous Micellar Technology: An Alternative Beyond Organic Solvents

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Gaspard Hedouin[a], Deborah Ogulu,[a] Gaganpreet Kaur,[a] and Sachin Handa*[a]

Solvents are the major source of chemical waste from synthetic chemistry labs. Growing attention to more environmentally friendly sustainable processes demands novel technologies to substitute toxic or hazardous solvents. If not always, sometimes, water can be a suitable substitute for organic solvents, if used appropriately. However, the use of sole water as a solvent remains non-practical due to its incompatibility with organic reagents. Nonetheless, over the past few years, new additives have been disclosed to achieve chemistry in water that also includes aqueous micelles as nanoreactors. Although one cannot claim micellar catalysis a greener technology for every single transformation, it remains the sustainable or greener alternative for many reactions. Literature precedents support that the micellar technology has much more potential than just as a reaction medium, i.e., the role of amphiphile as a ligand obviating phosphine ligands in catalysis, shielding effect of micelles to protect water-sensitive reaction intermediates in catalysis, and compartmentalization effect. While compiling the powerful impact of micellar catalysis, this article highlights two diverse recent technologies: (i) the design and employment of surfactant PS-750-M in selective catalysis; (ii) semisynthetic HPMC polymer to enable ultrafast reactions in water.

Introduction

The overly used word “green” is generally very subjective in the field of synthesis. Unlike Nature, most likely, nothing is green in today’s organic synthesis. Furthermore, the processes which are somewhat called green today may not be considered green in the future because green and sustainable chemistry is a fast-evolving field. Thus, the term “greener” is more meaningful than “green.” It is a comparative word that implies the greenness comparison between the best processes. For example, Jessop allegiantly demonstrates which is greener, the use of a plastic bag or paper bag?[1] In the demonstration, the author considers the systems thinking and life-cycle assessment and concludes that plastic bags are greener than paper bags if used appropriately. Along the same lines, here we ask a question, which is greener, the chemistry in water or the chemistry in organic solvents? This may be a very difficult question to answer in a simple way. To answer this question, life cycle assessment, catalyst cost and efficiency, total solvent usages, operational simplicity, workers and process safety, and most importantly, understanding how chemistry in water occurs and its comparison with organic solvent counterpart is worthy.[2] At the end of this article, the readers can easily deduce under what conditions chemistry in water is greener and sustainable than the traditional chemistry in organic solvents. Not every reaction conducted in water can be considered green. In general, no solvent is better than any solvent. Although water has many exciting features to offer new chemistry,[3,4] this article focuses on situations where chemistry in water is greener or better, or at least more efficient than chemistry in traditional organic media and where micelles can act as more than solvents alternate. At first glance, chemistry in water seems problematic to entry-level chemists because most organic or organometallic compounds are insoluble in water, including the reactants, catalysts, and products. To enable chemistry in water, the solubility of reactants and the catalyst in the medium is more important than the product.[4,5] The latter’s insolubility in the medium can be leveraged for product isolation by simple filtration.[5,6] However, the solubility of reactants and the catalyst is the key to the reaction’s success. The self-assembled engineered micelles can accommodate reaction components, and based on literature, such aqueous nanostructures are a significant enabler of chemistry in water.[7] These micelles are dynamic and accommodate catalysts and substrates in themselves.

Design, Applications, and Insights into Micellar Technology

The dynamic nature of micelles allows for the exchange of substrate and sometimes catalyst between different micelles. The more time spent by the catalyst and substrate and the less time spent by the resulting product in these micelles, the better the reaction efficiency. Notably, the syntheses of engineered amphiphiles, the monomer of micelles, also involve organic solvents, including ethyl acetate, toluene, and ethanol. These are sustainable solvents compared to *N*,*N*-dimethylformamide

---

[a] *Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States. E-mail: sachin.handa@louisville.edu*

(DMF), *N*,*N*-dimethylacetamide (DMAc), *N*-methyl pyrrolidone (NMP), and 1,4-dioxane. If organic chemistry can be performed efficiently in ethyl acetate, toluene, and ethanol, chemistry in water may not be ideal; a more rigorous life-cycle assessment is needed in such cases.[8] However, if engineered micelles can replace DMF, DMAc, NMP, and 1,4-dioxane and their syntheses only involve greener and recyclable solvents, micellar catalysis may be a viable option. Inspired by the Lipshutz chemistry[9,10] and to provide greener alternatives to the reactions requiring toxic DMF, DMAc, NMP, and 1,4-dioxane, our lab has rationally designed a simple proline-based amphiphile and showcased its applications to achieve completely organic solvent-free chemistry, and often, ligand-free catalysis.[5,11-15] Besides, we have also demonstrated that the chemistry achieved in these aqueous micelles cannot be cleanly and efficiently achieved in traditional organic solvents.[16] In this way, aqueous micellar catalysis significantly contributes to sustainable chemistry.

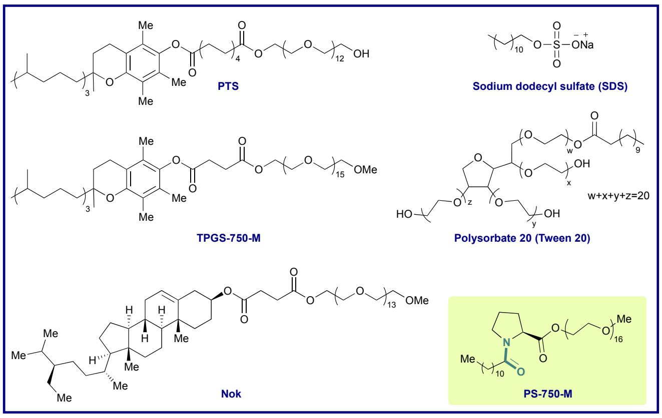
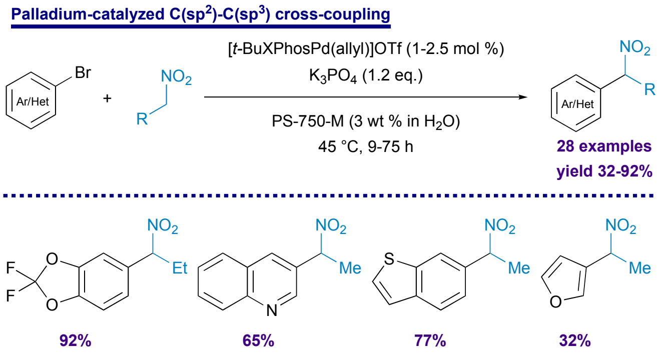


Figure 1. Examples of different state-of-the-art surfactants.

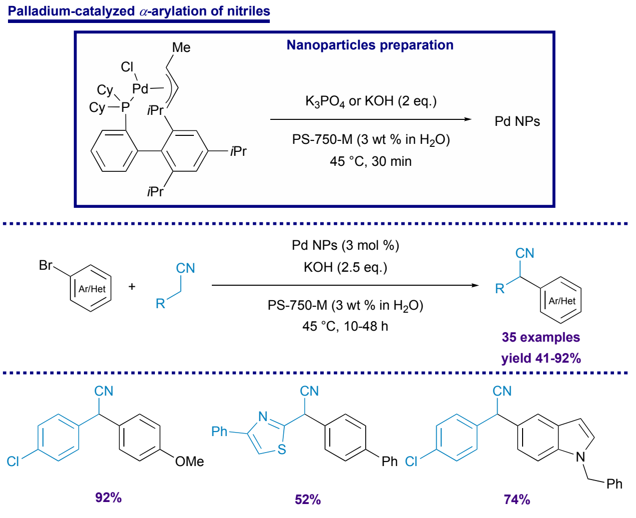
To the best of our knowledge, until 2017, the replacement of aforementioned toxic dipolar-aprotic solvents by mimicking their structure and polarity with the polarity of micellar inner core had never been explored besides our group.[17] These dipolar-aprotic solvents (DMF and NMP) are anticipated to be removed from the EU market by 2024;[18] thus, their greener alternatives are needed. Our journey on this topic started with the design of a proline-based nonracemic amphiphile, PS-750-M. It mimics the polarity of toxic dipolar-aprotic solvents. Besides, it promotes metal-micelle binding,[13,14] enables photoredox activity of Cu(II) for ppm level catalysis,[19] and provides shielding to water-sensitive reaction intermediates.[15,20] PS-750-M has a tertiary amide functional group connecting a polar mPEG chain with the non-polar hydrocarbon chain via a proline linker. Having an optimal balance between hydrophilic and lipophilic chains, the PS-750-M, upon dissolution in water (critical micellar concentration ca. 10^{-6} M), instantly forms micelles containing the tertiary amide group in the micellar core or occasionally at the polar-nonpolar interface, which assists in matching its activity with dipolar-aprotic solvents. Sigma-Aldrich commercially provides it to the chemistry community (catalog # 911178, 911151). Its synthesis is highly straightforward and only involves inexpensive starting materials, such as *L*-proline, lauric acid or lauroyl chloride, and mPEG-750-M. Our latest unpublished process includes two-step synthesis, i.e., (i) on-water amidation between *L*-proline and lauroyl chloride, (ii) esterification of the resulting intermediate with mPEG-750-M in toluene. Toluene recovered from the process is reusable. The synthetic protocol doesn't require any toxic organic solvents or tedious purification. The process is very operationally simple and scalable. Besides PS-750-M, other state-of-the-art surfactants have significantly contributed to the field of chemistry in water (Figure 1). The major surfactants include PTS, TPGS-750-M, Nok, Tween 20, SDS, etc.[3]



Scheme 1: First application of PS-750-M technology in transition-metal catalyzed sp^2-sp^3 cross-couplings.

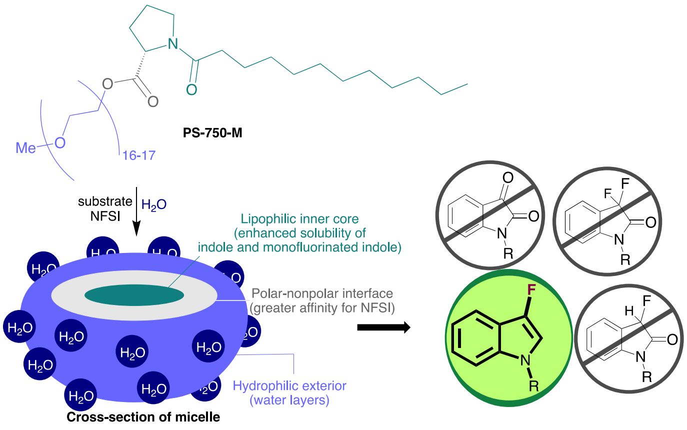
First Application of PS-750-M

After its development in 2017, the use of PS-750-M was showcased on palladium (Pd)-catalyzed sp^2-sp^3 couplings.[17] In general, such reactions traditionally required 1,4-dioxane or DMF solvents with high catalyst loading under harsh reaction conditions. Most of the time, Pd catalysts are preferred for these reactions due to better efficiency, scalability, and broader substrate scope. Although Pd catalysis has vast applications, the toxicity profile of Pd catalysts, the need for phosphine ligands and toxic dipolar-aprotic solvents in catalysis, and the dwindling availability of Pd are significant challenges in terms of sustainability. Besides, Pd strongly binds with product molecules, and its removal often is not simple. Traces of these active metals can still be detected after successive organic reactions. To tackle these issues, it is crucial to have highly active catalysts that work at a low loading level and have a better binding with the micelles. After catalysis, if the catalyst remains in the aqueous micellar layer, it can be reused, and the problem of carrying over the metal contents to the product can be solved. Besides, the reactions could be more efficient due to the higher concentration of catalysts and reactants in the micellar cores. With this approach, we employed micelles of PS-750-M to accomplish Pd-catalyzed couplings between bromoarenes and nitroalkanes (Scheme 1). Traditionally, these couplings were considered water-sensitive and required dry solvents. Employment of a low catalyst loading of Pd-catalyst containing electron-rich ligand allows the formation of C(sp^2)-C(sp^3) coupling products under mild conditions in moderate-to-excellent yields. This transformation also tolerated numerous heterocycles. The role of PS-750-M was accentuated by several recycling experiments. Colacot's π-allyl Pd species with *t*-BuXPhos ligand was the optimal catalyst.[21,22] The role of π-allyl Pd species was investigated with control experiments revealing that, most likely, the allyl group acts as a secondary ligand in the catalytic cycle. The limitation of this technology was that the reactions of aryl iodides were not as effective as aryl bromides or chlorides.



Scheme 2: Pd nanoparticles-catalyzed α-arylation of nitriles.

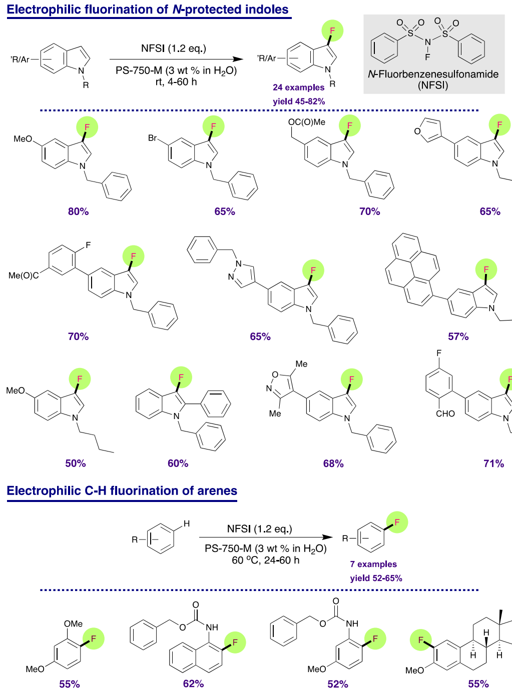
Following this work, we disclosed another C(sp^2)-C(sp^3) cross-coupling between bromoarenes and nitriles in micelles of PS-750-M (Scheme2).[23] Products were obtained in good-to-excellent yields under mild conditions using Pd nanoparticles (NPs) ligated with XPhos. These ultrasmall NPs (1.8 nm average size) were prepared in aq. PS-750-M and were stable and active for several weeks. PS-750-M was notably essential for stabilizing the NPs and likely the carbanion/ketimine intermediate during the reaction. The reaction was scalable upto 50 g, and the obtained nitriles could also be derivatized to the corresponding ketones using molecular oxygen in the same pot.



Scheme 3: Shielding and compartmentalization effect for selective monofluorination of indoles.

Shielding effect of PS-750-M allowing fluorination chemistry and stabilization of Cu(I) oxidation state

Dynamic aqueous micelles have the potential to shield water- and air-sensitive reaction intermediates from water and air, respectively.[12,13,15,16] Likewise, they can preserve the pseudo-stable oxidation state of the metal, such as ligand-free Cu(I) species in ultrasmall NPs form.[19] The optimal binding constant between such sensitive species and micelles (also known as metal-micelle binding) is responsible for such unanticipated stability. It results in reactivity that would otherwise require dry organic solvents or is not efficiently possible in organic media due to concentration and hydrophobic effect provided by the micelles.



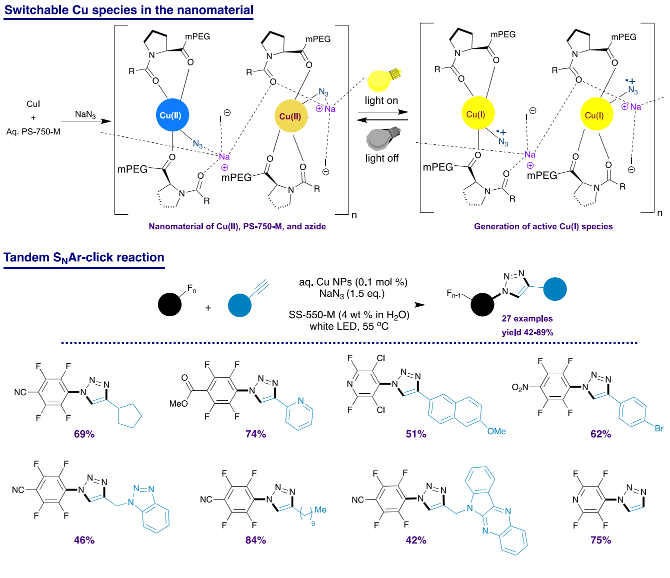
Scheme 4: Selective monofluorination of *N*-protected indoles and arenes.

Along the same lines, we have investigated the monofluorination of protected indoles enabled by the shielding effect of micelles of PS-750-M (Scheme 3).[16] The transformation provides facile access to industrially valuable monofluorinated indoles. The reaction pathway could follow both the radical and ionic paths. The presence of fluorine group at the 3-position of indoles induces more electrophilicity to that carbon leading to uncontrolled difluorination. The presence of water in the reaction medium may also cause fluorinated oxindole formation. However, the shielding of micelles protects the indole substrate. It also assists in controlling reactivity due to the high solubility of indoles in the micellar interior and optimal solubility of *N*-Fluorobenzenesulfonimide (NFSI) at the polar-nonpolar interface leading to compartmentalization of reactive species preventing the side reactions. Due to such compartmentalization, indoles can only react with the F-source during the exchange process, which is also responsible for controlled reactivity. The resulting monofluorinated product is relatively more soluble in the micelle than indole as a reactant, which slows down the exchange process. The slow exchange process caused by monofluorinated products prevents difluorination and other side reactions. Thus, the compartmentalization effect and low oxygen solubility in the micellar interior protect the radical intermediate that leads to the desired reaction pathway.

This methodology was tested for monofluorination of protected indoles and C-H fluorination of arenes (Scheme 4). It includes a total of 24 substrates possessing a variety of functional groups. The representative examples include *N*-benzyl and *N*-alkyl indoles possessing bromo, esters, aldehydes, ketones, and heterocycles. The reaction yields were moderate-to-excellent. This technology was not amenable to unprotected indoles.

C-H Fluorination of arenes was showcased on limited substrates. In the case of arene containing electron-donating group, the reaction was clean. However, the isolated yield was reduced due to unreacted starting material. Likewise, fluorination possibly selective to the ortho position of carbamate was observed. This may be due to the involvement of hydrogen bonding between NH of carbamate and NFSI for site-selective delivery of fluoronium ion or F-radical. Besides, fluorination was only observed on the arene rings when other reactive sp^3 carbons were present in the substrate. This methodology was showcased on a gram-scale reaction. Furthermore, the recycling of PS-750-M was performed three times, and the activity of the recycled aqueous solution of PS-750-M was evaluated on fluorination of 1,3,5-trimethoxybenzene. The reaction yields were 66-68% in each recycle.

Control experiments, which include radical trap with BHT and mass spectrometry study, support a radical pathway. Besides, control dynamic light scattering (DLS) experiments revealed the role of micelles of PS-750-M, i.e., site-specific solubility of the substrate and fluorine source.



Scheme 5: Oxidation state switchable nanomaterial for ppm level Cu(I) catalysis in water.

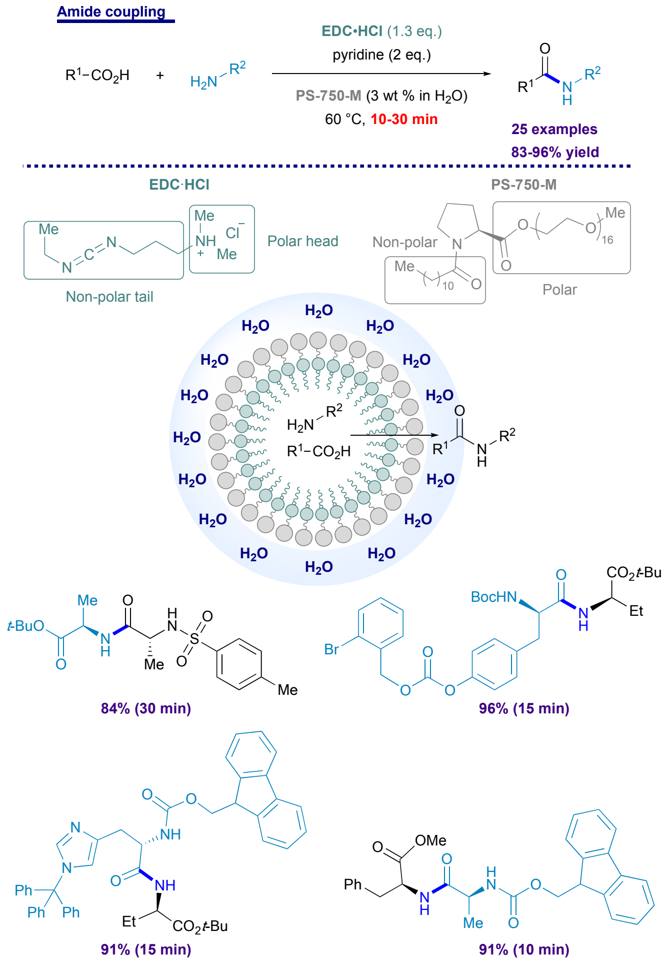
Another advantage of using aqueous micelles as a reaction medium is the employment of a low catalyst loading due to a higher concentration of catalyst inside or at the polar-nonpolar interface of micelles. Combining this concentration effect with the shielding effect, we explored the stability of ligand- or antioxidant-free Cu(I) species for one-pot azidation via S$_N$Ar and Cu(I)-catalyzed azide-alkyne cycloaddition reaction.[19] Generally, the +1-oxidation state of Cu is unstable in water and requires reductant or specific ligands or support to maintain that oxidation state. The addition of CuI and NaN$_3$ in the aqueous solution of PS-750-M, followed by visible light irradiation, generates nanomaterial containing PS-750-M, Cu, and azide (Scheme 5). This aqueous nanomaterial enables a switchable oxidation state of Cu. Upon light irradiation, the oxidation state of Cu(II) changes to Cu(I) via azide-to-metal single electron transfer. The +1-oxidation state of Cu predominantly catalyzed the desired transformation. In light's absence, the nanomaterial contains mononuclear Cu(II) species stabilized by surfactant. The surfactant PS-750-M was slightly modified by shortening the mPEG chain to achieve an optimal hydrophilicity-hydrophobicity under reaction conditions and increase the yield. The modified surfactant was named SS-550-M. Only 1000 ppm of Cu(II) was necessary to deliver triazole products in excellent yields under sustainable conditions. Light irradiation was found to be essential as a very low yield was obtained under dark conditions.

We also performed thorough investigation to understand the mechanistic insights, in particular, the nature of the catalyst. The catalyst characterization techniques include X-ray absorption spectroscopy (XAS), high-resolution transmission electron microscopy (HRTEM), nuclear magnetic resonance (NMR), ultraviolet-visible (UV-Vis), and infrared (IR) spectroscopies. The NMR spectroscopic data with the isotope labeling revealed that the tertiary amide group of PS-750-M binds with Cu. The role of light was investigated by determining the in-situ oxidation state of Cu by XAS analysis, which revealed the +1-oxidation state of Cu under light irradiation and higher oxidation states of Cu when light is turned off. The metal-micelle binding enabled this nanomaterial formation, while micelles' shielding effect provides some stability to the catalytically active species. The catalytic activity for domino azidation-cycloaddition reactions was showcased on various substrates. The representative examples are shown in Scheme 5.

Metal-free reactions: Amide couplings and sulfonylation chemistry

In this section, we only focus on classical metal-free reactions, which traditionally involved organic solvents as reaction medium for reaction work-up and purification processes. One can deduce with these demonstrations, i.e., completely organic solvent-free amide couplings[5,11] and column chromatography-free sulfonylation of polyfluoroarenes via S$_N$Ar,[24] that the micellar catalysis has much more benefits than just replacing traditional reaction media with it.

Amide bond formation is among the most valuable transformations in the industry.[25,26] From a sustainability viewpoint, it is one of the most noteworthy due to enormous waste generation. Although this reaction has been known for decades, it is still not sustainable enough from a green chemistry perspective. Even if the coupling partners (i.e., carboxylic acid and amine) are readily available from amino acids, the path to deliver the desired product generally requires the use of toxic solvents and activating reagents that can be toxic, explosive, or can create by-products challenging to remove.[27,28] Besides, solvents are required for product isolation and purification. Epimerization can also be observed when the coupling partner has an epimerizable chiral center, i.e., chiral *α*-carboxylic acid. To address these concerns, our group reported use of PS-750-M to achieve organic solvent- and epimerization-free amide couplings in water.[5] Using water-soluble EDC•HCl coupling reagent in aq. PS-750-M, the formation of mixed micelles enabled fast couplings due to the presence of coupling partners, base, and activating agent within the micelle (Scheme 6). The desired pathway operates at a faster rate under milder basic conditions, thus suppressing the unwanted epimerization pathway, leading to the enantiomerically pure product. Besides, the desired amide products were insoluble in the PS-750-M medium, and crashed out of the micelles. Upon simple filtration, products can be isolated in high purities.



Scheme 6: Mixed micelles of PS-750-M and EDC•HCl for fast and epimerization-free amide couplings.

Notably, the by-product of the coupling agent was soluble in water and remained in the aqueous layer. Thus, that water still needs cleaning before its disposal. Our group is now actively working to solve this critical issue. Nonetheless, only filtration of the reaction mixture was necessary to isolate the desired products in almost quantitative yield in less than 45 minutes. Traditionally, adding hydroxybenzotriazole (HOBt), which is explosive, was required to avoid epimerization of product.[29] However, using mixed micelles of EDC•HCl and PS-750-M, faster reaction rates can be accomplished while preventing epimerization. Most notably, our mixed-micelle technology is scalable, as showcased on several 10 grams scale examples. In our reports, we have mechanistically investigated the role and existence of mixed micelles by NMR spectroscopy and HRTEM analysis.[14] From a green chemistry perspective, this approach can be greener than existing technologies for amide couplings.

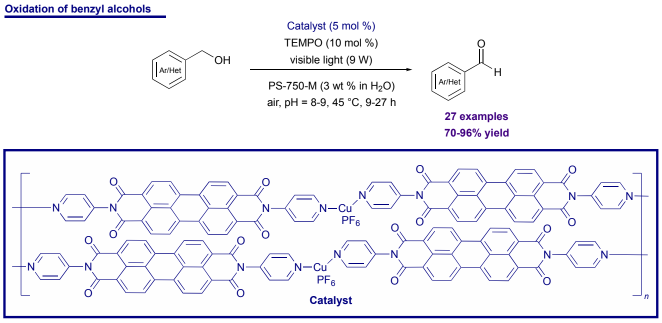
Application of PS-750-M for metal-free chemistry was not only restricted to amide couplings. Other reaction types have also been explored, such as S_NAr and photo-assisted oxyhalogenation of alkynes. S_NAr of polyfluoroarenes appears suitable for the micellar medium as the reaction could certainly occur inside the micelles. Lipshutz and coworkers disclosed the aromatic substitution of fluoro-, chloro-, or bromoarenes in TPGS-750-M using neutral nucleophiles, such as amines, alcohols, or thiols.[30] Later, our group reported the sulfonylation of polyfluoroarenes, employing challenging ionic nucleophiles and sodium sulfinates.[24] These transformations generally operate in dipolar-aprotic solvents at high temperatures. Nonetheless, this reaction was achieved at room temperature in water with PS-750-M and NaCl/acetone as additives. The medium could be recycled, and this process did not generate waste. The products were obtained in good-to-excellent yields.

Among the various applications, micelles of PS-750-M were also compatible with organophotocatalysis, whereas it could be expected to lower the reactivity due to the shielding effect of micelles. Similar to the previously mentioned applications of the shielding effect of micelles, *α,α'*-difunctionalized ketones were formed using visible light photocatalysis.[31] in the presence of eosin Y and *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) in the micellar medium of PS-750-M, the oxydihalogenation of alkynes could be achieved, generating the desired products in good-to-excellent yields. The Eosin Y photocatalyst could also be astutely recycled alongside the micellar medium without observing any erosion of the reactivity.

Another application of PS-750-M has been showcased on the functionalization of styrenes.[32] Preparation of α-functionalized ketones was performed by combining styrene, NBS, and a variety of nucleophiles in micelles of PS-750-M. The reaction could happen through the radical formation of α-haloketones that can be further functionalized in micelles with various nucleophiles, leading to the delivery of desired products in good yields.

Employment of PS-750-M in completely heterogeneous photocatalysis

For this case study, we developed a heterogeneous photocatalyst containing nanochannels through which micelles containing reactant molecules can travel and undergo catalytic events. This way, compatibility between micellar media and visible light heterogeneous photocatalysis has been established to oxidize benzylic alcohols into aldehydes (Scheme 7).[33] The creation of a heterogeneous polymeric Cu(I) based on a perylene diimide (PDI) unit allows the oxidation of alcohol through the Cu(I)-Cu(II) cycle in the presence of co-catalytic TEMPO under air and visible light. As this polymer was insoluble in organic solvents, recyclability has been demonstrated for this transformation, delivering aldehydes in mostly good-to-excellent yields. A broad substrate scope, excellent selectivity, and no over-oxidation of resulting aldehydes supported the effectiveness of this approach. Control experiments and time dependent density functional theory (DFT) calculations further revealed that the catalysis involves charge transfer states. The catalyst was thoroughly characterized by electron microscopic analysis.

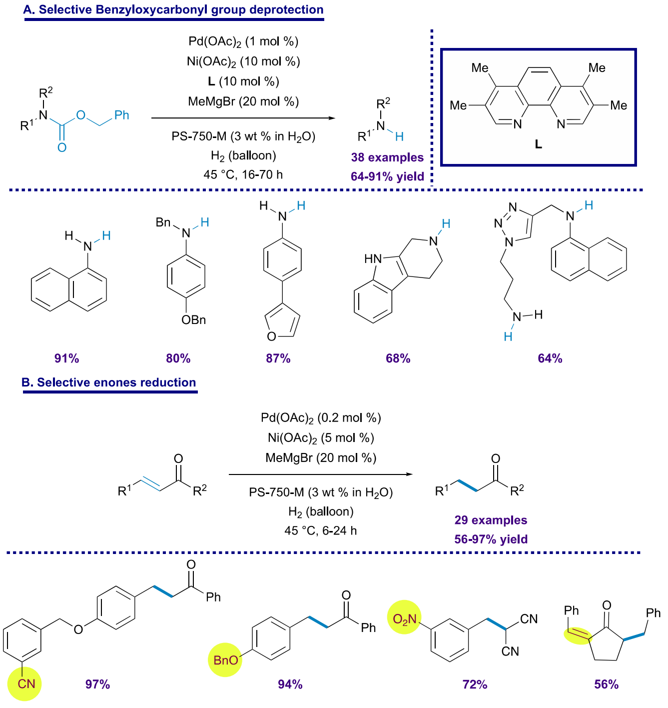


Scheme 7: Micellar photocatalysis mediated by heterogenous catalyst.

Bimetallic nanoparticles for selective reductions

Among applications other than cross-couplings,[12,13,15] bimetallic NPs have also been applied for selective hydrogenation, relying on the greater solubility of hydrogen gas inside the micelles and metal-metal as well as metal-micelle interactions for catalytic selectivity. Along these lines, we astutely utilized bimetallic NPs to selectively remove benzyloxycarbonyl (Cbz) protecting groups in the presence of other functional groups sensitive to hydrogenolysis or hydrogenation (Scheme 8A).[34] Ni(0)Pd(0) bimetallic NPs ligated to a phenanthroline ligand were generated from Pd(II) and Ni(II) source using MeMgBr as reductant. The combination of a minimal amount of Pd with an inexpensive Ni source allows the generation of highly selective and reactive NPs with an average diameter of 1 nm. The zero oxidation state of Ni and Pd was confirmed by X-ray photoelectron spectroscopy (XPS) analysis, with some Ni(II) traces due to air exposure. The oxidation state of Ni was notably crucial as no selectivity was observed when Ni(II) was employed. Using these Ni(0)Pd(0) NPs, only Cbz groups could be cleaved in the presence of other benzyl moieties under hydrogen pressure. Products were isolated in high yields using either fresh or aged nanocatalysts.

Following this work, we also explored other selective reductions using bimetallic NPs. The synergetic combination of Pd, Ni, and micelles of PS-750-M also enabled the selective reduction of enones (Scheme 8B).[14] The NPs were prepared as previously reported but no ligands were required this time, and a very low amount of Pd (0.2 mol %) was sufficient to achieve the 1,4-reduction of enones in high yields. This reaction tolerates numerous functional groups that otherwise can be reduced under hydrogen pressure, such as benzyl, esters, or aldehydes. The reduction was also selective for enenitrile, enamide, and α-ketoamide substrates. Unfortunately, due to the instability of the Ni(0) catalyst under air, the NPs could not be completely recycled. The presence of Ni(0) and Pd(0) NPs was also confirmed by XPS and HRTEM analysis. To get more insights into the potential selective mechanism, we hypothesized the activation of the carbonyl group by Ni(0), while Pd(0) was responsible for dihydrogen activation.

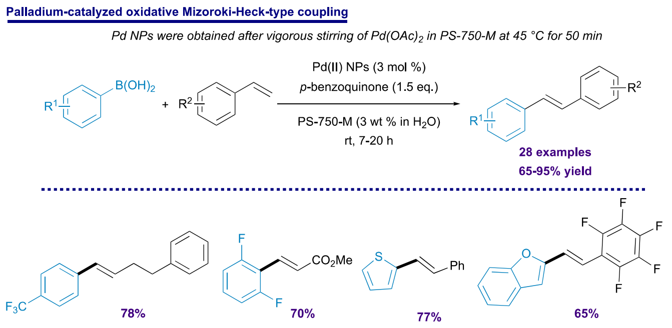


Scheme 8: Selective Ni(0)Pd(0) bimetallic catalysis in water.

Phosphine ligand-free Pd catalysis

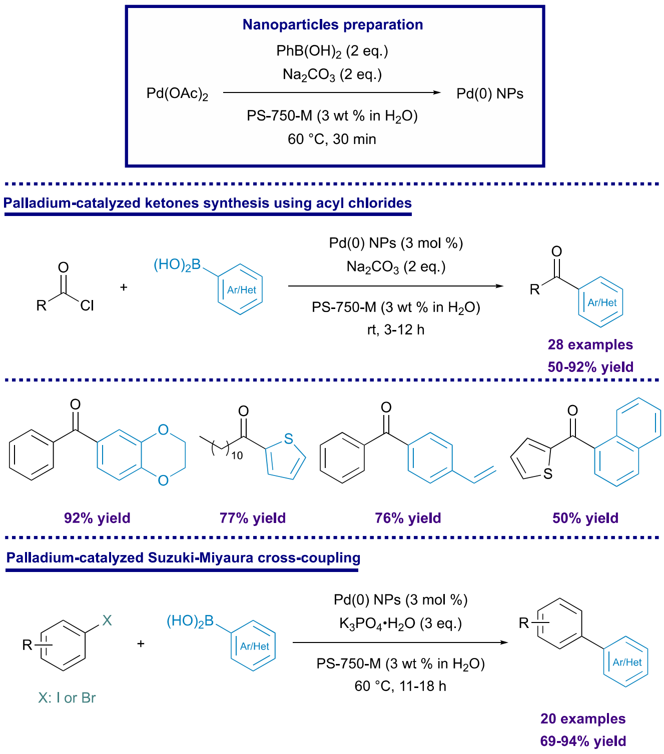
Transition metals are nowadays heavily used for a panel of organic reactions. Pd-catalyzed cross-couplings are heavily used in industry due to their operational simplicity and broad scope. In recent years, cross-couplings with earth-abundant metals provided an alternative to Pd.[35] These efforts must be warmly appreciated. Occasionally, in the more comprehensive range, earth-abundant metal catalyst involves expensive ligands, and in fact, such ligands may require Pd in their synthesis. Thus, such efforts may not lead to sustainable catalysis. Metals are easier to recycle than ligands; therefore, we recently focused on ligand-free Pd catalysis.[12-15] Technically, in such processes, our amphiphile PS-750-M acts as a ligand and a monomer of micelles, replacing both the traditional ligands and reaction media.

With this approach, our group explored cross-couplings, including Mizoroki-Heck-type reaction using ligand-free Pd NPs in micelles of PS-750-M (Scheme 9).[12] These oxidative couplings between styrenes and boronic acids could occur in mild conditions delivering the expected products in excellent yields. The scalability of this transformation was also highlighted on a 100-gram scale reaction. We also focused on understanding the behavior of these NPs in micelles of PS-750-M. This amphiphile remarkably stabilizes the Pd(II) NPs (average size of 2-3 nm) and avoids the usual employment of phosphine ligands. The binding between Pd and carbonyls of the proline unit of PS-750-M was proven by spectroscopic analysis, including high-resolution mass spectrometry (HRMS). Stirring above 1000 rpm of these NPs was also very important to avoid aggregation of the catalyst and deactivation, as it was shown that the reactivity was decreased at a low stirring rate.



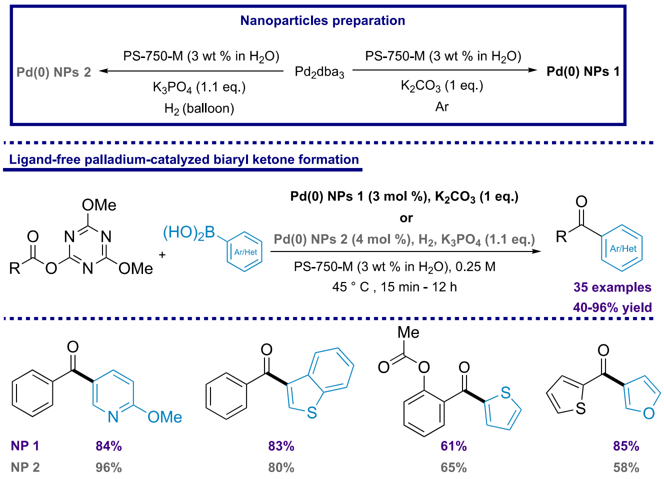
Scheme 9: Ligand-free ultrasmall Pd(0) nanoparticles for Mizoroki-Heck-type couplings.

Following this work on the stabilization of Pd NPs in micelles of PS-750-M, we have explored a cross-coupling reaction employing phosphine ligand-free Pd(0) NPs (Scheme 10).[13] Micelles of PS-750-M were expected to stabilize the Pd(0) NPs, obtained after the reduction of $Pd(OAc)_2$ with a boronic acid in micelles of PS-750-M. Otherwise, these Pd NPs are prone to oxidation. Characterization of these NPs by HRTEM, energy-dispersive X-ray spectroscopy (EDS), and XPS demonstrated the formation of Pd(0) NPs with an average size of 2 nm. The interaction of the Pd NPs with PS-750-M was also confirmed by ^{13}C-NMR, infrared, and surface-enhanced Raman scattering (SERS) studies. We tested their reactivity on cross-couplings of acid chlorides. Using these Pd(0) NPs in PS-750-M, acyl chlorides were reacted with boronic acids to form ketones in excellent yields under mild conditions. Acyl chlorides bearing alkyl, aryl, and heteroaryl moieties were well tolerated. In addition to the protective effect of micelles on acid chloride, boronic acids were expected to lower the pH of the medium to avoid the degradation of acyl chlorides. Thus, adding boronic acid prior to the acid chloride was the key to successfully implementing this approach. Moreover, the efficiency of these NPs was also highlighted for the Suzuki-Miyaura cross-coupling of aryl halides. This transformation could be achieved without using any phosphine ligand, delivering biaryl products in excellent yields.



Scheme 10. Ligand-free Pd(0) nanoparticles for Suzuki-Miyaura couplings.

Furthermore, we recently developed a highly efficient method for ligand-free cross-coupling of water-sensitive triazine adducts of carboxylic acid with boronic acids to generate biaryl ketones (Scheme 11).[15] This method uses water- and air-sensitive Pd_2dba_3 to in-situ form phosphine ligand-free Pd(0) NPs. A simple stirring of Pd_2dba_3 in the presence of a mild base in aqueous PS-750-M results in formation of Pd(0) NPs stabilized by PS-750-M—we named these NPs “natural nanoparticles.” If the same reaction components are stirred under a hydrogen atmosphere, it causes de-ligation of dba via reduction, resulting in the formation of new NPs, again stabilized by PS-750-M—we named these NPs “synthetic nanoparticles.” The catalytic activity of both natural and synthetic NPs demonstrated that the former had better reactivity than the latter. The formation of catalytically highly active Pd(0) NPs results from metal-micelle binding. IR, ^{1}H NMR, and matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) confirm the generation of Pd(0) NPs and their binding with amphiphilic PS-750-M. HRTEM and high-angle annular dark-field scanning transmission electron microscopy (STEM-HAADF) demonstrate an average diameter of 3.8 nm and 6.4 nm for the natural and synthetic NPs, respectively. The NPs were scalable, highly active, and stable for upto a week. In particular, this catalytic transformation involves a water-sensitive triazine adduct of carboxylic acid. The shielding effect of micelles provides sufficient stability to these adducts for participating in cross-couplings before decomposing. In general, the reactions were fast and the natural and synthetic NPs were employed on a broad range of substrates, as showcased in Scheme 11.

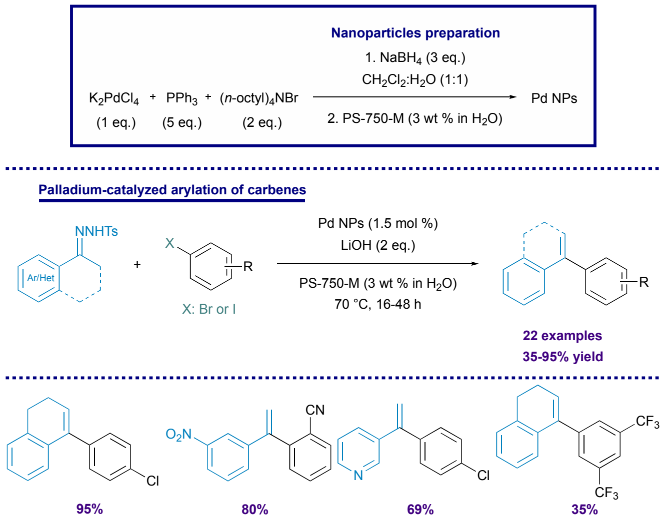


Scheme 11: Synthetic versus natural ligand-free nanoparticles for cross-couplings of water-sensitive carboxylic acid derivatives in aqueous micelles.

Reactivity of carbenes and carbanions in micelles

Carbenes are highly valuable reaction intermediate used in C-C bond-forming reactions. To understand their reactivity and stability in aqueous micelles, we developed Pd NPs ligated with triphenylphosphine. The reactivity of carbenes and Pd NPs in micelles of PS-750-M was investigated for cross-coupling to access terminal olefins (Scheme 12).[20] Pd NPs were prepared from K_2PdCl_4 precursor combined with triphenylphosphine and tetraoctylammonium bromide using $NaBH_4$ as reductant, followed by capping the resulting NPs with aqueous PS-750-M. HRTEM and XPS analysis evidenced the presence of minor Pd(II) on the surface of the material, and significant Pd(0) inside the organic material. The reduction of surface Pd(II) to Pd(0) was assumed to occur during the reaction and was tracked by ^{31}P-NMR experiments. DLS control experiment revealed the micelles' importance for stabilizing the NPs as the average diameter of the micelles increased from 200 nm to 520 nm upon the addition of the NPs. This shows the possible accommodation of these NPs inside micelles of PS-750-M. In particular, the NPs were applied in the cross-coupling of *N*-tosyl hydrazones with iodo- or bromoarenes. Only 1.5 mol % catalyst was used in the reactions to access olefins in excellent yields. This transformation is remarkable as this is the first example of Pd-carbene in micellar media, accentuating the shielding effect of these micelles. The reaction was scalable, and the catalyst could be recycled without a decrease in reactivity after three cycles.

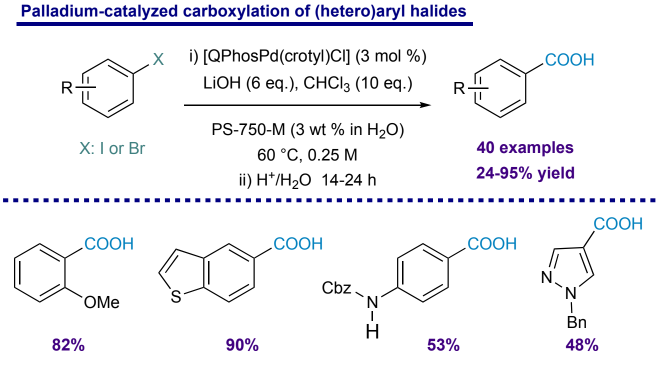
The shielding effect provided by micelles to unstable reaction intermediates allowed stabilization of trichloromethyl carbanion in-situ generated from chloroform using LiOH as a base. In general, under basic aqueous conditions, trichloromethyl carbanion decomposes into carbon monoxide, while under anhydrous conditions in organic solvents, it gets converted to dichlorocarbene, which further polymerizes. Very recently, we thoroughly investigated the stability of in-situ generated trichloromethyl carbanion in aqueous micellar medium and its application in Pd-catalyzed cross-couplings to access highly valuable (hetero)aryl carboxylic acids.[36] The technology involves Pd ligated with QPhos as a catalyst, LiOH base, (hetero)aryl bromide as an electrophile, trichloromethyl carbanion nucleophile, and micelles of PS-750-M. The involvement of trichloromethyl carbanion in transmetallation, followed by reductive elimination, was probed by control experiments. The aqueous micelles significantly contributed to the stabilization of trichloromethyl carbanion, which participates in the primary catalytic cycle. In addition, detailed mechanistic studies support the involvement of trichloromethyl carbanion in the pathway. In particular, these experiments include:



Scheme 12: Pd-catalyzed arylation of carbenes in micelles of PS-750-M.

- Kinetic reaction profile in the presence of trichloromethyl carbanion or carbon monoxide.
- H/D exchange in chloroform mediated by trichloromethyl anion.
- Mass spectrometric analysis of reaction intermediates.

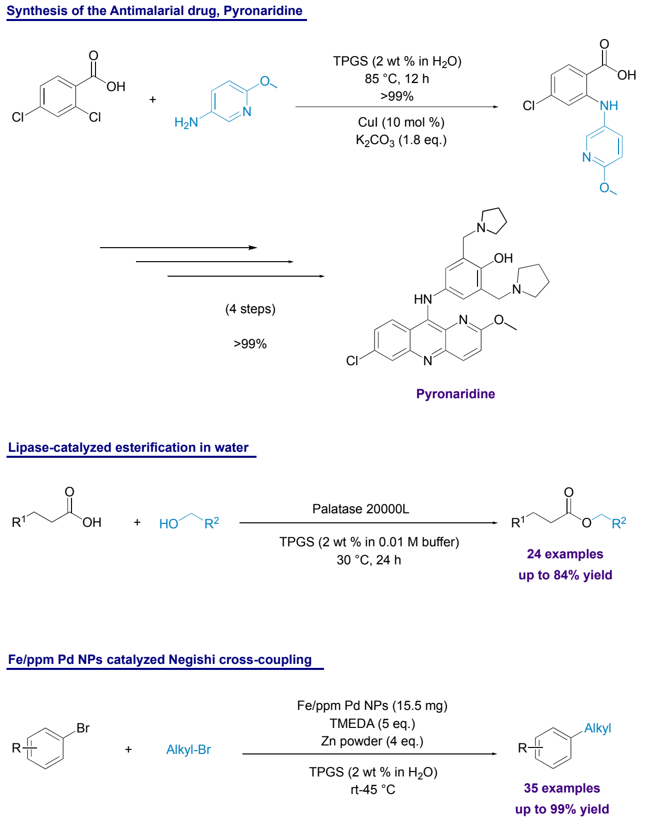
In collaboration with Takeda, this technology was employed on 40 substrates with high functional and protecting group tolerance, as showcased in Scheme 13.



Scheme 13: Carbanion-mediated catalytic carboxylic acid formation in water.

Transformations in Lipshutz medium, TPGS-750-M

Over the last decade, Lipshutz's group, a pioneering group in the field, have developed a variety of novel micellar methodologies to allow for effective chemical transformations in water.[3,10,27,37-39] We have highlighted a few of the most exciting and recent contributions in Scheme 14. Using amphiphilic TPGS-750-M in water, the group has reported a plethora of cross-coupling reactions and synthesis of target therapeutic compounds under mild and environmentally benign conditions. Pyronaridine, an antimalarial drug, was synthesized by the group under micellar conditions with high yield. Most notably, the calculated E factor showed a 5-fold reduction in waste compared to the circumstances described in the existing literature.[39]



Scheme 14: Most recent significant chemical transformations in TPGS-750-M.

The same group has also revealed an enzyme-catalyzed esterification reaction using micelles of TPGS-750-M. In good-to-moderate yields, the esterification of carboxylic acids and primary alcohols is reported to be accomplished by utilizing lipase from *Rhizomucor miehei*, Palatase 20000L.[40] The enzyme catalyzes the reaction using diverse range of alcohols. The micelles prevent the hydrolysis side reaction. In addition, the Lipshutz group has applied TPGS-750-M to one-pot chemo and biocatalysis.[41] The surfactant did not interfere with the performance of the enzyme. Another interesting chemistry crafted by the Lipshutz group is the Negishi coupling in water catalyzed by Fe/ppm Pd NPs.[42] The authors have showcased transfer of the substrate to the NP catalyst via the water to micelles. TEM investigation of the NP revealed that when exposed to the aqueous surfactant, the NP form changed from tiny, sphere-like particles to large nanorods. Scanning transmission electron microscopy (STEM) studies further showed the active NP in aqueous micelles, with the ligand and Pd, essentially dissolving in water and the iron remaining in the nanorod. The nano-to-nano effect and the micelles that surround the NPs were shown by cryo-TEM and DLS. However, the analytical conditions were different from those used in the actual reaction, which still left many unanswered questions. Most appreciably, Blum and co-workers studied a similar system under reaction conditions that revealed the better mechanism.[43] Nonetheless, using aryl and alkyl bromides as coupling partners, the activity of the NPs was evaluated with high to excellent yields, and the NPs were recyclable.

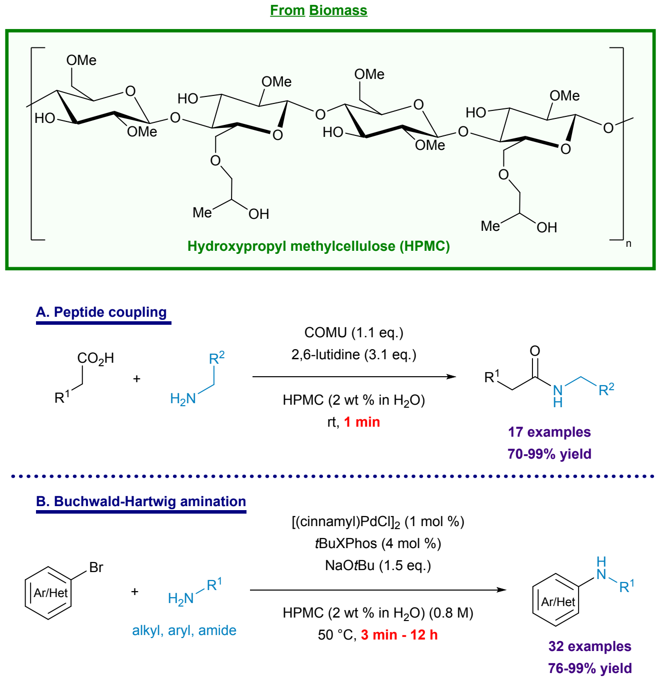
Furthermore, the surfactant TPGS-750-M has also been applied industrially for diverse synthetic transformations. Novartis Pharma recently employed TPGS-750-M in the C(sp^2)-C(sp^3) cross-electrophilic coupling by harnessing the synergistic effect from bimetallic nickel and copper catalysts.[44] The micelles were essential for the effective transformation as reactions in sole organic solvent resulted in reduced yields. Likewise, AbbVie has reported the synthesis of dihydroquinolinones using aq. TPGS-750-M.[45] The authors have reported the one-pot rhodium-catalyzed 1,4-addition of 2-aminoboronic acids to different α,β-unsaturated esters in good-to-excellent yields.

Cellulose-based hydrophilic polymer to enhance reactivity

From the discussion above, it can be gauzed that aqueous micelles are more than an alternate reaction medium. Other than compartmentalization, concentration, shielding effect, and their employment in ligand-free catalysis, such dynamic nanoarchitectures have more potential that needs more exploration. Thus, the new knowledge of chemistry in water enabled by other additives could assist in learning. Other researchers and our group have explored other readily available greener additives.[46-49] Along these lines, hydroxypropyl methylcellulose (HPMC) appears as an attractive reaction additive to enable chemistry in water. It is a semisynthetic polymer obtained from cellulose that comes from biomass.[48,49] Our recent works revealed the significant effect of HPMC on reaction rates. The formation of hydrophobic pockets of HPMC in water allows for considerable enhancement of the reactivity by concentrating all the reagents in a confined space.[49] Thus, it works similarly but not in the same fashion as micelles. These hydrophobic pockets are far less dynamic than those characteristics of micelles, and often require organic solvents for product extraction. Recently, we studied the rapid formation of Cu(I) NPs from CuI in aq. HPMC that enabled fast and solvent-free one-pot azidation-azide-alkyne cycloaddition reaction providing triazole products in excellent yields.[50] More importantly, the products crashed out of the aqueous system and were isolated by simple filtration. All products were pure and did not require further purification by crystallization or column chromatography.

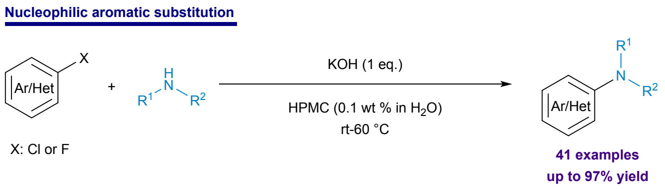
The most exciting benefit of using HPMC technology is the ultrafast reaction rates for amide couplings and C-C bond-forming reactions, i.e., reactions could be achieved in only a few minutes. A low loading of HPMC (0.1-2 wt %) in water is sufficient to enable good reactivity.

The first use of this additive has been showcased and patented by AbbVie[47] on various organic reactions, but with a limited scope. A few years later, our collaborative work with AbbVie displayed the remarkable effect of HPMC, enabling Buchwald-Hartwig aminations and amide coupling reactions which also complete in a few minutes with overall excellent yields (Scheme 15).[49]



Scheme 15: Representation of Hydroxypropyl methylcellulose (HPMC) and application for A. Peptide coupling and B. Buchwald-Hartwig amination.

The most attractive transformation in aqueous HPMC was amide coupling, achieved within a minute, using COMU as coupling reagent and 2 wt % of HPMC in water.[49] The effectiveness of this additive was also proved on Buchwald-Hartwig cross-coupling. Amination was accomplished using stabilized Pd NPs in a very high concentration of HPMC (up to 2.5 M), delivering secondary amines in high yields and generally 5 to 60 minutes.



Scheme 16: Nucleophilic aromatic substitution in water using HPMC as additive.

The usefulness of this additive was also demonstrated in the aromatic nucleophilic substitution of aryl halides (Scheme 16).[52] With this approach, an amination of (hetero)aryl fluorides or chlorides enables the formation of a broad scope of secondary and tertiary amines, using only 0.1 wt % of HPMC in water. The reaction was also extended to the employment of thiols and alcohols as nucleophiles after slightly optimizing the standard conditions. The recyclability of the aqueous solvent was also demonstrated without any loss of reactivity. The reports on this additive are very recent, but the potential to enhance reaction rate is very promising, and further applications are anticipated to be released in the coming years.

Conclusion

While demand for more sustainable processes increases, developing new additives to enable organic chemistry in aqueous media could partially bring a unique solution to replace petroleum-based solvents. Previously inconceivable reactions in water can now be attained in micellar media, thanks to the shielding effect of micelles. In addition to the protective effect, micelles can coordinate and stabilize transition metals, substituting the role of ligands. Future work using more abundant metals like copper, nickel, cobalt, and iron, will further increase popularity of micellar catalysis. At the moment, asymmetric reactions using chiral micelles are still underdeveloped,[53] and micelles of PS-750-M, which are chiral, have only been used for achiral reactions. Thus, the application of PS-750-M or the development of the second generation of this additive for asymmetric synthesis could be anticipated in the following years to ensure more environmentally friendly cross-coupling reactions. So far, only a few commercially available and general micellar systems have been elaborated in synthetic applications. The development of more diverse and innovative additives with novel functionalities and applications is requested to deliver new reactivities. Nonetheless, to approach a higher bar of green chemistry, the route towards new surfactants must follow the specifications of sustainable chemistry, which implies only a few synthetic steps with the non-toxic reagents, and from preferably natural components. The problem of water cleaning and the biodegradability of surfactants is another area that needs more attention.[54] The authors welcome any fair criticism and suggestions from the chemistry community.

Author Contributions

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

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

S.H. is grateful to the US National Science Foundation for financial support (CHE-2044778).

Notes and references

1 https://www.tiktok.com/@philipgjessop. Last accessed: January 5, 2023.

2 T. N. Ansari, F. Gallou, S. Handa, *Organometallic Chemistry in Industry,* Wiley-VCH, 2020, Ch8, 203–238.

3 B. H. Lipshutz, S. Ghorai, M. Cortes-Clerget, *Chem. Eur. J.,* 2018, **24**, 6672–6695.

4 T. Kitanosomo, K. Masuda, P. Xu, S. Kobayashi, *Chem. Rev.*, 2018, **118**, 679-746

5 S. Sharma, N. W. Buchbinder, W.M. Braje, S. Handa, *Org. Lett.,* 2020, **22**, 5737.

6 Y. Tamboli, J. T. Kilbile, A. Y. Merwade, *Org. Process. Res. Dev.*, **2023**, ASAP, https://doi.org/10.1021/acs.oprd.2c00299

7 G. Kaur, K. Kaur, S. Handa, *Curr. Opin. Green Sustain. Chem*. 2022, **38**, 100690.

8 P. A. Holman, D. R. Shonnard, J. H. Holles, *Ind. Eng. Chem. Res., 2009,* **48**, 14.

9 B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston, R. C. Gadwood, *J. Org. Chem.*, 2011, **76**, 4379-4391.

10 B. H. Lipshutz, S. Ghorai, M. Cortes-Clerget, *Chem. Eur. J.*, 2018, **24**, 6672–6695.

11 S. Sharma, G. Kaur, S. Handa, *Org. Process Res. Dev.,* 2021, **25**, 1960–1965.

12 T. N. Ansari, J. B. Jasinski, D. K. Leahy, S. Handa, *JACS Au,* 2021, **1**, 308–315.

13 T. N. Ansari, S. Sharma, S. Hazra, J. B. Jasinski, A. J. Wilson, F. Hicks, D. K. Leahy, S. Handa, *JACS Au,* 2021, **1**, 1506–1513.

14 D. Ogulu, P. P. Bora, M. Bihani, S. Sharma, T. N. Ansari, A. J. Wilson, J. B. Jasinski, F. Gallou, S. Handa, *ACS Appl. Mater. Interfaces*, 2022, **14**, 6754–6761.

15 G. Kaur, J. B Jasinski, F. Gallou, S. Handa, *ACS Appl. Mater. Interfaces,* 2022, **14**, 50947–50955.

16 P. P. Bora, M. Bihani, S. Plummer, F. Gallou, S. Handa, *ChemSusChem*, 2019, **12**, 3037–3042.

17 J. Brals, J. D. Smith, F. Ibrahim, F. Gallou, S. Handa, *ACS Catal.*, 2017, **7**, 7245-7250.

18 EU Commission Regulation. Last accessed: January 6, 2023.

19 S. Sharma, S. Parmar, F. Ibrahim, A. H. Clark, M. Nachtegaal, J. B. Jasinski, F. Gallou, P. M. Kozlowski, S. Handa, *Adv. Funct. Mater.*, 2022, **32**, 2204459.

20 U. T. Duong, A. B. Gade, S. Plummer, F. Gallou, S. Handa, *ACS Catal.*, 2019, **9**, 10963–10970.

21 A. J. DeAngelis, P. G. Gildner, R. Chow, T. J. Colacot, *J. Org. Chem.*, 2015, **80**, 6794-6813.

22 S. J. Firsan, V. Sivakumar, T. J. Colacot, *Chem. Rev.*, 2022, **122**, 16983-17027.

23 M. Bihani, T. N. Ansari, L. Finck, P. P. Bora, J. B. Jasinski, B. Pavuluri, D. K. Leahy, S. Handa, *ACS Catal*., 2020, **10**, 6816-6821.

24 J. D. Smith, T. N. Ansari, M. P. Andersson, D. Yadagiri, F. Ibrahim, S. Liang, G. B. Hammond, F. Gallou, S. Handa, *Green Chem.,* 2018, **20**, 1784–1790.

25 R. M. de Figueiredo, J.-S. Suppo, J.-M. Campagne, *Chem. Rev.*, 2016, **116**, 12029–12122.

26 A. El-Faham, F. Albericio, *Chem. Rev.*, 2011, **111**, 6557–6602.

27 C. M. Gabriel, M. Keener, F. Gallou, B. H. Lipshutz, *Org. Lett.*, 2015, **17**, 3968–3971.

28 K. D. Wehrstedt, P. A. Wandrey, D. J. Heitkamp, *Hazard. Mater.,* 2005, **126**, 1–7

29 F. Albericio, A. El-Faham, *Org. Process Res. Dev.,* 2018, **22**, 760–772.

30 N. A. Isley, R. T. H. Linstadt, S. M. Kelly, F. Gallou, B. H. Lipshutz, *Org. Lett.,* 2015, **17**, 4734–4737.

31 L. Finck, J. Brals, B. Pavuluri, F. Gallou, S. Handa, *J. Org. Chem.*, 2018, **83**, 7366–7372.

32 U. T. Duong, T. N. Ansari, S. Parmar, S. Sharma, P. M. Kozlowski, J. B. Jasinski, S. Plummer, F. Gallou, S. Handa, *ACS Sustain. Chem. Eng.*, 2021, **9**, 2854–2860

33 S. Hazra, G. Kaur, S. Handa, *ACS Sustain. Chem. Eng.*, 2021, **9**, 5513–5518.

34 M. Bihani, P. P. Bora, M. Nachtegaal, J. B. Jasinski, S. Plummer, F. Gallou, S. Handa, *ACS Catal.,* 2019, **9**, 7520–7526.

35 B. Su, Z. Z. C. Cao, Z. J. Shi, *Acc. Chem. Res.,* 2015, **48**, 886–896.

36 T. N. Ansari, S. Sharma, S. Hazra, F. Hicks, D. K. Leahy, S. Handa, *ACS Catal*., 2022, **12**, 15686–15695.

37 B. H. Lipshutz, T. B. Petersen, A. R. Abela, *Org. Lett.*, 2008, **10**, 1333-1336.

38 P. Klumphu, B. H. Lipshutz, *J. Org. Chem.*, 2014, **79**, 888–900

39 J. R. A. Kincaid, R. D. Kavthe, J. C. Caravez, B. S. Takale, R. R. Thakore, B. H. Lipshutz, *Org. Lett.,* 2022, **24**, 3342–3346.

40 V. Singhania, M. Cortes-Clerget, J. Dussart-Gautheret, B. Akkachairin, J. Yu, N. Akporji, F. Gallou, B. H Lipshutz, *Chem. Sci*., 2022, **13**, 1440–1445.

41 N. Akporji, V. Singhania, J. Dussart-Gautheret, F. Gallou, B. H. Lipshutz, *Chem. Commun.*, 2021, **57**, 11847-11850.

42 Y. Hu, M. J. Wong, B. H. Lipshutz, *Angew. Chem. Int. Ed.*, 2022, **61**, e202209784

43 H. Peacock, S. A. Blum, *J. Am. Chem. Soc.*, 2022, **144**, 3285–3296.

44 N. Ye, B. Wu, K. Zhao, X. Ge, Y. Zheng, X. Shen, L. Shi, M. Cortes-Clerget, M. L. Regnier, M. Parmentier, F. Gallou, *Chem. Commun.*, 2021, **57**, 7629-7632.

45 A. M. Linsenmeier, W. M. Braje, *Tetrahedron*, 2015, **71**, 6913-6919.

46 J. Xiao, Z. Lu, Y. Li, *ind. Eng. Chem. Res.*, 2015, **3**, 790-797.

47 H. Zhang, Y. Yang, W. Dai, D. Zhang, S. Lu, Y. Ji, *Catal. Sci. Technol.*, 2012, **2**, 1319–1323.

48 N. Borlinghaus, V. Wittmann, W. M. Braje, *Curr. Opin. Green Sustain. Chem.*, 2022, **33**, 100571.

49 D. Petkova, N. Borlinghaus, S. Sharma, J. Kaschel, T. Lindner, J. Klee, A. Jolit, V. Haller, S. Heitz, K. Britze, J. Dietrich, W. M. Braje, S. Handa, *ACS Sustain. Chem. Eng.*, 2020, **8**, 12612–12617.

50 S. Sharma, W. Braje, J. Jasinski, S. Handa, *ChemSusChem*, 2022, e202201826. https://doi.org/10.1002/cssc.202201826

51 W. Braje, K. Britze, J. D. Dietrich, A. Jolit, J. Kaschel, J. Klee, T. Lindner, WO2017129796, 2017.

52 N. Borlinghaus, T. N. Ansari, L. H. von Garrel, D. Ogulu, S. Handa, V. Wittmann, W. M. Braje, *Green Chem.*, 2021, **23**, 3955–3962.

53 T. Lorenzetto, D. Frigatti, F. Fabris, A. Scarso, *Adv. Synth. Catal.*, 2022, **364**, 1776-1797.

54 C. Krell, R. Schreiber, L. Hueber, L. Sciascera, X. Zheng, A. Clarke, R. Haenggi, M. Parmentier, H. Baguia,S. Rodde, F. Gallou, *Org. Process Res. Dev.* 2021, **25,** 900–915.

Biographical Information

Gaspard Hedouin received his Ph.D. in 2021 from the University of Strasbourg, working on the design of novel chiral diphosphine ligands for asymmetric catalysis, under the supervision of Dr. Joanna Wencel-Delord and Pr. Françoise Colobert. He is currently a postdoctoral associate researcher at the University of Louisville, developing new catalysts for sustainable chemistry, under the guidance of Dr. Sachin Handa.

Deborah Ogulu is a fourth year graduate student at University of Louisville. She received her B.Sc. from Brescia University, Owensboro, Ky in 2017 and joined Dr. Sachin Handa's research group in 2019 where she received her M.Sc. from University of Louisville, Ky in 2021. Her recent research interests are focused on novel catalytic systems to enable green and sustainable chemistry in water.

Gaganpreet Kaur received a B.S. degree in 2013 and an M.S. degree in Organic Chemistry in 2015 from Mata Gujri College, Fatehgarh Sahib, Punjab, India. Later, she worked in pharmaceutical industry. In January 2020, she began her Ph.D. studies under the supervision of Prof. Sachin Handa at the University of Louisville, Kentucky. He research interest is sustainable organometallic catalysis.

Sachin Handa was raised in Patti, a small town of Punjab (India), where he completed his undergraduate studies. He received a Ph.D. degree under the guidance of Prof. LeGrande Slaughter in the USA, where his research focus was the development of nonracemic acyclicdiaminocarbenes. Subsequently upon completing postdoctoral training under Prof. Bruce H. Lipshutz at UC Santa Barbara, he started his independent career as an assistant professor at the University of Louisville in August 2016. In July 2021, he was promoted to associate professor with tenure. His research laboratory focuses on the development of sustainable catalysts and reaction pathways. He is a recipient of the 2018 Ralph E. Powe Junior Faculty Enhancement Award by ORAU, the 2018 Peter J. Dunn Award for Green Chemistry and Engineering Impact in Industry by the American Chemical Society, and the NSF CAREER Award in 2021.