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Perspective

Aqueous Micelles as Solvent, Ligand, and Reaction Promoter in Catalysis

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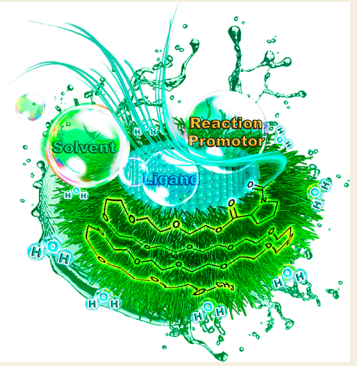
ABSTRACT: Water is considered to be the most sustainable and safest solvent. Micellar catalysis is a significant contributor to the chemistry in water. It promotes pathways involving water-sensitive intermediates and transient catalytic species under micelles' shielding effect while also replacing costly ligands and dipolar-aprotic solvents. However, there is a lack of critical information about micellar catalysis. This includes why it works better than traditional catalysis in organic solvents, why specific rules in micellar catalysis differ from those of conventional catalysis, and how the limitations of micellar catalysis can be addressed in the future. This Perspective aims to highlight the current gaps in our understanding of micellar catalysis and provide an analysis of designer surfactants' origin and essential components. This will also provide a fundamental understanding of micellar catalysis, including how aqueous micelles can simultaneously perform multiple functions such as solvent, ligand, and reaction promoter.



KEYWORDS: *Micellar catalysis, chemistry in water, ligand-free catalysis, nanoparticle, sustainability*

INTRODUCTION

In 1858, a Swiss botanist, Karl Wilhelm von Nägeli, coined the term "micelle" to describe aggregates formed by starch and cellulose in water.[1] Later, in 1913, McBain used the same term to refer to soap aggregation in aqueous solutions.[2] Hartley proposed that micelles have a spherical shape that consists of a hydrophilic exterior and a lipophilic interior.[3] In 1986, Bunton published a study on the effects of micelles on the rate of organic reaction using the pseudophase ion-exchange model.[4] Later on, Bunton, Romsted, and Yao coined the term micellar catalysis to describe the observed increase in the reaction rate in the presence of micelles.[5] The literature review by Cordes and Dunlap describes that the Twitchell process marks the beginning of micellar catalysis.[6] Twitchell first reported this reaction in 1898 as an industrial process for hydrolyzing fats/oils into fatty acids and glycerol with the aid of alkyl aryl sulfonic acid, also known as a Twitchell reagent.[7] From a mechanistic point of view, the Twitchell reagent acts as an emulsifier to catalyze the reaction. Observations indicated that increasing the temperature and amount of the Twitchell reagent accelerated the reaction rate. However, this process is no longer used to manufacture soaps due to certain drawbacks. Nonetheless, it represents a significant breakthrough in using micelles in organic reactions.[8]

Organic reactions can be challenging in water due to the poor solubility of organic substrates in an aqueous medium. To overcome this issue, Kobayashi,[9−12] Lipshutz,[13−18] Uozumi,[19,20] Leahy,[21,22] our group,[21−27] and other researchers[28−42] have developed various micellar technologies that use water as a reaction medium and are potentially sustainable. These technologies showcased that the micelles are necessary to solubilize organic substrates in water, and they are broadly classified as ionic and nonionic, depending upon the charge present in the hydrophilic region. Earlier studies on micellar catalysis involve anionic or cationic surfactants,[9−12] whereas recent methodologies mainly use nonionic surfactants for catalysis in water.[43,44] In 1994, Kobayashi and co-workers developed a method that used trifluoromethanesulfonic acid ytterbium(III) salt $Yb(OTf)_3$ to aid aldol and Mannich-type reactions in water.[45] Later, in 2000, the group used a Lewis-acid-type anionic surfactant $Sc(O_3SOC_{12}H_{25})_3$ as a catalyst and reaction promoter for the aldol reaction, which resulted in excellent yields.[46] In 2002, Kobayashi's group reported successful dehydration reactions in water using charged micelles of dodecyl benzenesulfonic acid (DBSA).[47] These included esterification, etherification, thioetherification, and dithiol-acetalization. In this report, the authors explained the mechanism of the esterification reaction between an acid and an alcohol in an aqueous micellar medium. The findings revealed that the micelles are small nanochambers formed by

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the self-aggregation of DBSA that charges the micelles with substrate molecules to enable dehydration reaction in water, avoiding the need for dehydrating agents. Later, the same group reported the first enantioselective Mannich-type reactions in water using ZnF_2 ligated with a chiral diamine ligand as a catalyst and cetyltrimethylammonium bromide (CTAB) surfactant.[48] The use of the cationic surfactant CTAB facilitated micellar or phase transfer catalysis. Thus, Kobayashi's seminal work opened the doorways for the successful implementation of micellar catalysis.

Nonionic surfactants have proven to be versatile for efficient micellar catalysis. The Lipshutz group has developed many such surfactants.[49] Before 2008, the field of micellar catalysis for organic synthesis was not well-known because of misconceptions that many reactions could not be achieved in water. However, Lipshutz's significant work, especially over the last two decades, proved that even water-sensitive chemistry can be achieved in aqueous micelles.[50,51] The group demonstrated that alkyl zinc and aryl magnesium species could be created and used in water with the help of the correct micelles designed by the group. Since then, the Lipshutz group has conducted research on various cross-couplings and valuable organic transformations, including Suzuki,[52−54] Heck,[55,56] Negishi,[57,58] Sonogashira[59−61] couplings, and aminations.[62−64] Lipshutz is widely regarded as a trailblazer in the domain of micellar catalysis owing to his significant contributions to the field.

The Lipshutz group first introduced the vitamin E-derived nonionic designer surfactant PTS in 2008 for olefin cross-metathesis in water at room temperature.[16] Later, in 2009, the same group introduced the designer surfactant PQS for ring-closing metathesis in water at room temperature.[65] The group has also extensively used PTS for Pd- and Ru-catalyzed reactions in water at room temperature.[13] For PTS and other nonionic surfactant structures, see Figure 1.

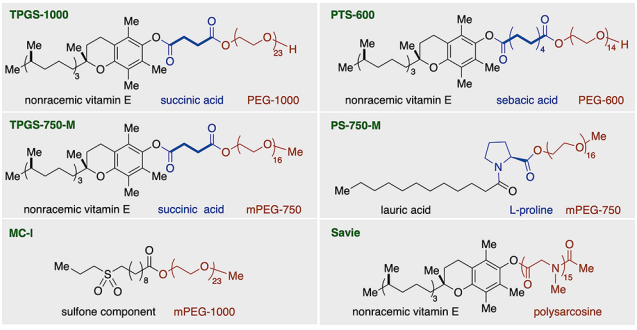

Figure 1. Representative nonionic amphiphiles.

In 2011, Lipshutz and co-workers designed a second-generation amphiphile, named TPGS-750-M. This new amphiphile was also based on vitamin E and has numerous advantages over PTS, including a higher reaction rate, better yield for Pd- and Ru-catalyzed cross-couplings, and a more straightforward synthesis.[66] Among many of the Lipshutz group's contributions in this area, the key reports are the asymmetric gold-catalyzed lactonization,[67] amidations,[68] organic solvent-free Suzuki−Miyaura coupling,[69] cross-couplings with iron (Fe)-based nanoparticles containing ppm palladium (Pd),[61,70] biocatalysis in TPGS-750-M,[71] and in situ generation of organometallic reagents.[51]

Recently, the same group reported another biodegradable surfactant, called Savie, derived from vitamin E and polysarcosine, which has been used for homogeneous, heterogeneous, and biocatalytic transformations, including a multistep chemoenzymatic sequence to conduct organic synthesis in water.[72] The traditional reagents, such as THF, Boc anhydride, and sodium hydride, were used in the synthesis of Savie. THF can be recycled, and sarcosine is a suitable degradable hydrophilic core.[73]

MICELLAR CATALYSIS: "ON WATER" OR "IN WATER" CHEMISTRY

In a recent review, Lipshutz, Gallou, and co-workers thoroughly discussed the topic of "on water" and "in water" chemistry.[15,74] Therefore, we will provide only a general overview of the subject with respect to micellar catalysis. In traditional organic reactions, both the organic solvent and water are involved, which are referred to as "with water" reactions. On the other hand, if water is used solely as a reaction medium and there is no solvation of the reaction components, they are known as "on water" reactions—this term was coined by Sharpless, who described the hydrophobic effect on reaction rate acceleration.[75] Prior to Sharpless, Breslow reported the reaction rate acceleration when water was utilized as a reaction medium in Diels−Alder cycloadditions.[76] If the reaction takes place in bulk water, involving the solvation of reaction components, it is considered an "in water" reaction.[77]

Regarding the classification of chemical reactions that occur in water or at the polar−nonpolar interface, the most convincing categorization was proposed by Butler and Coyle.[78] If the solubility of the substrates is greater than 0.01 mol/L and the transition state takes place in bulk water, it is considered to occur "in water." On the other hand, if the solubility of the substrates is less than 10^{-5} mol/L and the transition state preferentially occurs on the organic side of the interface, it is called "on water." For reactants with intermediate solubilities, both modes of reaction are likely to occur simultaneously. In "in water" reactions, the hydrophobic effect and cohesive energy density primarily lead to a tighter transition state and faster reactions. Based on these classifications, it is evident that aqueous micellar catalysis is not an "on water" phenomenon. Is it "in water" catalysis?

Depending on the nature of the reactants and the type of reaction, micellar catalysis occurs either in the hydrophobic interior or at the polar−nonpolar interface of the micelle. Micelles are formed after amphiphile molecules self-aggregate in water. Water also adds dynamism to micelles and plays a crucial role in micellar catalysis, regardless of the reaction site. Even though water is not directly involved in substrate solubilization and the transition state, its presence determines micellization that occurs in the bulk. Therefore, micellar catalysis can be considered an "in water" phenomenon.

EFFECTIVE LIGANDS FOR ORGANOMETALLIC MICELLAR CATALYSIS AND ORIGIN OF PS-750-M SURFACTANT

Ligands are essential in most metal-catalyzed reactions as they fine-tune the metal's electronic and steric properties, enabling control over reactivity and selectivity in the catalytic cycle.[43,79] The ligand also governs the physical properties of the organometallic catalyst, including its solubility.[80,81] The

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catalyst's solubility in the micellar medium is crucial for the reaction's success. An alternative way to achieve this is by using designer micelles, which can act as a ligand for the metal and a nanoflask for the reaction to occur in a hydrophobic environment. Another option is to design a ligand with improved solubility and binding affinity for micelles, reducing the need for excess ligands and metal. To ensure better binding between the micelle and catalyst, it is necessary to have a ligand that is lipophilic and a strong σ-donor. The right degree of lipophilicity makes the catalyst soluble in the micellar interior, whereas the optimal σ-donicity and sterics in the ligand provide stability and maximum catalytic activity. Following this rule, Lipshutz and co-workers developed the HandaPhos ligand for ppm Pd catalysis, enabling the Suzuki–Miyaura and Sonogashira couplings in aqueous micelles (Figure 2).[80] The same ligand was also effective for ppm Au

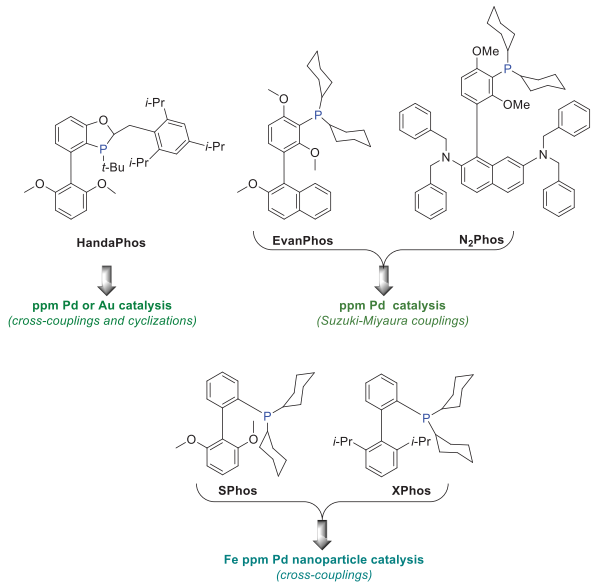

Figure 2. Key ligands effective for parts-per-million-level micellar Pd catalysis.

(gold) catalysis.[82] However, the ligand's synthetic methodology was tedious and resource-inefficient. To overcome this drawback, EvanPhos[83] and N_2Phos[84] ligands were also developed by Lipshutz and co-workers. EvanPhos also exhibited excellent performance in EtOAc which is an inexpensive and widely acceptable solvent. Another exciting technology developed by Lipshutz, Gallou, and Handa involves the processing of $FeCl_3$ containing ppm levels of Pd as an impurity to generate stable Fe ppm Pd nanoparticles that are highly effective in named cross-coupling reactions in water.[70] Buchwald's XPhos and SPhos ligands[85] worked well with the Fe ppm Pd chemistry due to their lipophilic and strong σ-donor nature. Later, tri-*tert*-butylphosphine ligand was found effective for ppm Pd micellar Heck reaction.[56] However, the reaction requires some levels of DMF. The authors did not completely justify the role of DFM. Nonetheless, reactions for highly polar substrates for sp^2–sp^3 couplings and other valuable transformations often required dipolar-aprotic solvents, which may have led to the design of PS-750-M[86] surfactant that acts as a reaction enabler and ligand. Other research groups[33,87−90] have also contributed significantly to "in water" palladium-catalyzed reactions, which are already well-covered by recent reviews by Lipshutz,[91] Gallou,[27] and Scarso.[92]

In 2017, we reported an amphiphile PS-750-M that structurally mimics dipolar-aprotic solvents, such as DMF, DMAc, and NMP. In the upcoming paragraphs, we will provide more information about this amphiphile.[86] Later, Lipshutz also reported MC-1, a surfactant to structurally mimic DMSO, which was effective for peptide synthesis in water at room temperature.[93] However, broader applications of MC-1 are missing from the literature compared to PS-750-M and TPGS-750-M. PS-750-M has been used for various organic transformations, with a broad range of polar substrates and reaction selectivity—we will describe some representative examples in this Perspective. Due to its unique structural features, such as the presence of 3° amide and carbonyl groups in the micellar interior or interface, PS-750-M has enabled ligand-free Pd catalysis, including the cross-coupling reaction of water-sensitive acid chlorides and the conversion of carboxylic acid derivatives to biaryl ketones.

In this Perspective, we will be discussing another vital aspect of PS-750-M. We will delve into how it stabilizes nano aggregates of Cu(I) and Cu(III) formed in the presence of light. Furthermore, this Perspective will provide a detailed analysis of some of the newer, ecofriendly methods our group has developed for synthesizing valuable organic compounds using micellar technology. Micelles behave as a solvent, ligand, and reaction promoter simultaneously in these methods.

DESIGN AND APPLICATIONS OF PS-750-M

Our group has developed a proline-based amphiphile (a molecule possessing both hydrophilic and hydrophobic properties) named PS-750-M that enables some key transformations in water. It is made from environmentally friendly precursors such as L-proline (a nonessential amino acid), lauric acid (a significant component of coconut oil), and polyethylene glycol monomethyl ether (abbreviated as mPEG). The amphiphile was designed to mimic DMF, DMAc, and NMP, toxic but highly useful solvents. The European Commission has adopted a regulation to restrict the solvent DMF.[94] Therefore, greener alternatives are highly desired. PS-750-M amphiphile, when dissolved in water at or above 10^{-6} M concentration, forms nanomicelles, enabling organic reactions in water in a greener fashion (Figure 3). It is commercially available at Sigma-Aldrich (catalog numbers 911178 and 911151).

Compared to TPGS-750-M, the published synthetic protocol for PS-750-M may not be considered sustainable.[86] It involved the use of dichloromethane and required purification of the intermediate of PS-750-M by column chromatography. Solving the specific problem by creating another problem is not a real solution to any problem, and it fits well with the first synthesis procedure of PS-750-M. Therefore, we have developed a simple and efficient two-step protocol that eliminates the need for column chromatography and uses only water and toluene solvents. The recovered solvents are reused for subsequent scale-up. First, L-proline and lauroyl chloride are reacted on water to create an amide bond. Second, the intermediate obtained from the first step is esterified. The esterification requires only 1.0 equiv of mPEG-750-M in toluene to produce the desired product in high yields. This second-generation synthetic process is sustainable, scalable, and straightforward.

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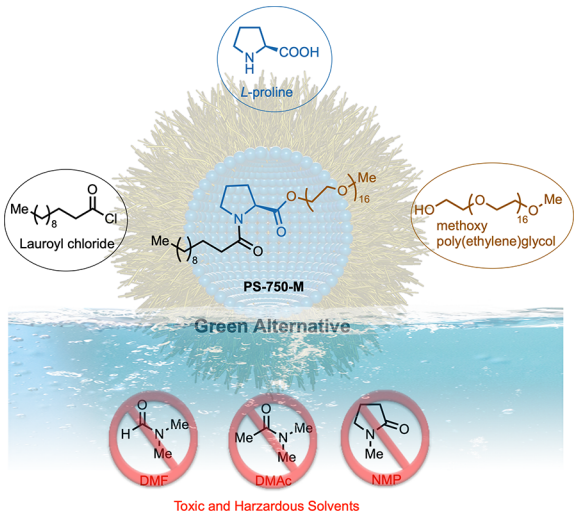


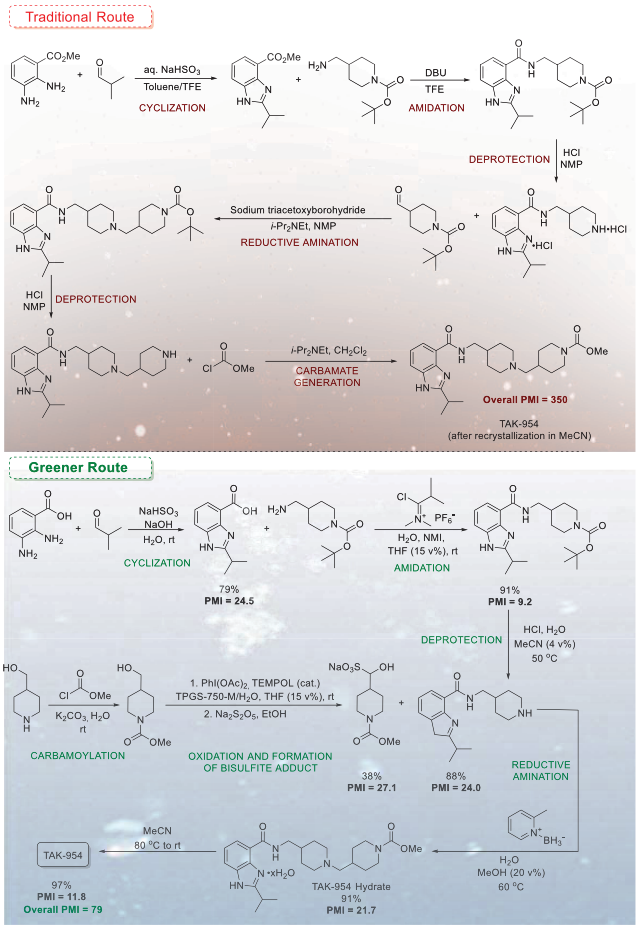
Figure 3. Structural components of PS-750-M—an amphiphile that structurally mimics DMF, DMAc, and NMP.

By using Colacot's π-allyl palladium catalyst with low loading,[95] we have successfully demonstrated the first application of PS-750-M to catalyze sp^2-sp^3 couplings of bromo(hetero)arenes and nitroalkanes under mild reaction conditions.[86] Later, this PS-750-M micellar technology enabled us to conduct various reactions more sustainably that typically require harsh reaction conditions, high catalyst loading, or unsafe solvents. Some examples include selective sulfonylation of perfluoroarenes,[96] fast amide couplings,[26,97] selective monofluorination of indoles and arenes,[98] selective Cbz cleavage,[99] Buchwald–Hartwig aminations under heterogeneous environment,[100] photocatalysis,[101] and transformation involving carbanion.[22,24] These reactions are conducted in water under mild conditions without any pernicious reaction medium. In this Perspective, we also elaborate on some of the representative reactions, including Bailey's synthetic method for TAK-954, Gallou's phenomenal broader work on micellar catalysis in industry, and practical aspects of micellar catalysis.[102]

Micelles as a Solvent

Micelles are excellent solvents that provide an appropriate environment to dissolve water-insoluble or nonpolar substances in water. A remarkable recent industrial example of using micelles and aqueous media to produce active pharmaceutical ingredient (API) TAK-954 was demonstrated by Bailey and co-workers at Takeda Pharmaceuticals (Scheme 1),[102] which led to the *ACS Peter J. Dunn for Green Chemistry and Engineering Impact in Industry Award* to the team.[103] The researchers developed a sustainable process to obtain a 5-HT4 receptor/TAK-954 (an API used for treating a postoperative gastrointestinal disorder) agonist in an aqueous medium. All of the critical transformations, including benzimidazole cyclization, amide bond formation, reductive aminations, and oxidation of alcohol, were performed in aqueous media. This resulted in a 94% reduction in the use of organic solvents and a 48% reduction in the level of water usage. Moreover, the overall yield was increased from 35% to 56%. Scheme 1 illustrates both the traditional and Bailey's synthetic methods for TAK-954. In Bailey's method, 2 wt % TPGS-750-M in water was used to overcome the limited solubility of specific reaction components in water.

Scheme 1. Traditional and Bailey's Synthetic Methods to Access TAK-954 Agonist



The pH modification also controlled the solubility of intermediates and the API in aqueous media throughout the process. This enabled reactions to occur in the solution phase and allowed product purification and separation by direct crystallization without using an organic solvent. The overall process mass intensity (PMI) was decreased from 350 to 79, reducing the number of components used to generate TAK-954 by 77% by transitioning from organic solvents to water as the reaction and isolation medium. During the multistep synthesis of TAK-954, bisulfite addition compound of aldehyde was used as a substrate for the reductive amination step in aqueous micellar media. Bisulfite addition compound as an aldehyde precursor was preferred over free aldehyde due to its stability and crystallinity, making purification easy.

The adduct formation involved aqueous TPGS-750-M, which serves as a surfactant solution. The advantage of using such a solution is that there is no need for an additional base to convert the bisulfite adduct to its free aldehyde form before the reductive amination reaction. The slow release of the aldehyde from the bisulfite adduct in micelles allows for selective reductive amination. The standard reaction conditions for reductive amination are 2 wt % TPGS-750-M, methanol as a cosolvent, α-picoline borane as a reducing agent, and 60 °C temperature. Methanol can be replaced by ethanol or isopropyl alcohol due to its hepatotoxicity.

Nevertheless, this protocol is compatible with (hetero)aryl and aliphatic aldehydes and substituted amines, as demonstrated by Lipshutz and co-workers.[104] Various drug precursors

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or drug molecules, including buclizine (antihistamine), piribedil (an anti-Parkinson agent), and cinacalcet (a calcium-sensing receptor agonist), can be prepared by using this methodology. Additionally, it has been shown that this technique can be used as part of one-pot reactions without isolating reaction intermediates.

Photoactive Aggregates Derived from Cu and Amphiphile—ppm-Level Cu(I) Catalysis in Water

[105] Cu(I) catalysis is used for various chemical reactions, including cross-couplings, cycloadditions, and cyclizations.[106−109] Cu catalysis at very low loading (ppm levels) has been rarely reported in the literature.[110] Thus, using a metal−micelle interaction approach, we developed catalytically highly active nano aggregates of Cu, SS-550-M amphiphile, and azide. These aggregates are photoactive, and when exposed to visible light, Cu(II) (Cu = copper) changes to Cu(I) and Cu(III), as shown by X-ray photoelectron spectroscopy. We used these highly-efficient aggregates possessing Cu(I) and Cu(III) for domino alkyne−azide cycloadditions. In this study, benzylic or alkyl halides reacted in situ with sodium azide to form the corresponding azide for the subsequent cycloaddition reaction. In this work, we used a micellar solution of SS-550-M, which is structurally similar to PS-750-M but has a different chain length from mPEG (n = 12). CuI was a precursor of Cu(II), most likely formed by oxidation caused by water (Figure 4). The initial reaction involved the formation of

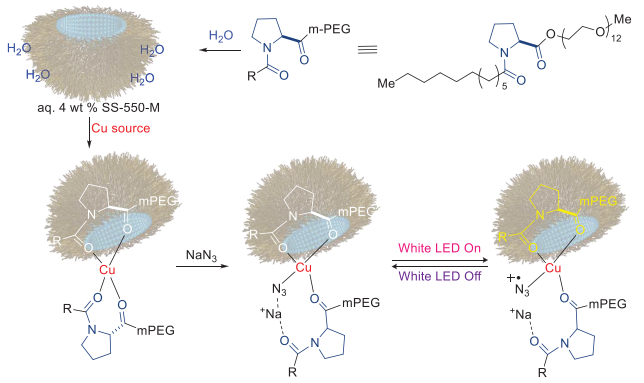
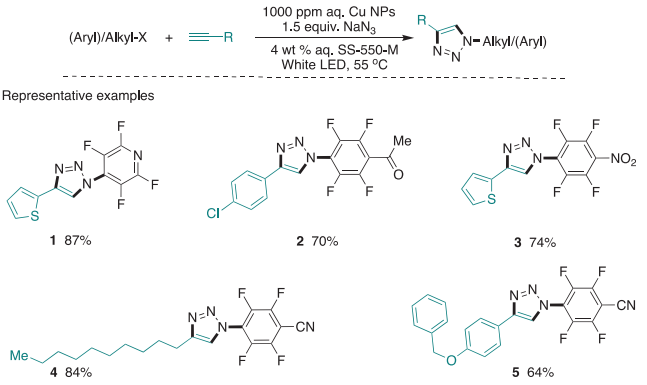


Figure 4. Metal−micelle interaction—micelle-stabilized Cu(I) for ppm-level catalysis.

CuN_3, which was then oxidized by water. The nucleophilic substitution of CuI by azide is more facile than the same reaction with CuBr and CuCl. Through density functional theory (DFT) and nuclear magnetic resonance (NMR) studies, we have proven that metal−amphiphile binding helps stabilize metal particles in water. Cu(I) was formed by the azide-to-Cu charge transfer process initiated upon light irradiation, enabling catalysis at the ppm level. Notably, these aggregates were stable in the aqueous micellar solution of SS-550-M for over a year. The aggregates containing Cu(II) ions were found to be between 100 and 120 nm in size when examined with high-resolution transmission electron microscopy (HRTEM). On the other hand, dynamic light scattering (DLS) studies revealed that dynamic micelles exist in a wide range of sizes, varying from 50 to 500 nm (average = 103 nm). Among these micelles, the larger aggregates represent Cu-containing micelles, while the smaller aggregates do not contain Cu.

The described approach allows the in-situ click reaction on a broader range of substrates, resulting in good-to-excellent yields. The representative examples **1**−**5** are depicted in Scheme 2. The reaction conditions tolerate functional groups,

Scheme 2. ppm-Level Cu(I) and Cu(III) Catalysis Enabled by Micelles of SS-550-M



such as chloro, bromo, carbonyl, nitro, and nitrile. It is worth noting that no aldol-type byproducts were observed in the substrate containing an active methyl group on carbonyls. Free amino groups and chelating pyridyl residues were also well-reacted without any detrimental effect on the catalytic activity. Overall, the method was simple, scalable, and safe. It did not require harsh conditions or reductants to generate in situ azides in water, which would otherwise be explosive in a thermal organic medium.

Stability and Reactivity of Water-Sensitive Intermediates in Aqueous Micelles

The aqueous micellar solution is a valuable solvent for reactions that involve unstable reaction intermediates, such as carbanions, carbenes, and acid chlorides.[21−24] The micelles act as solvents and protect the water-sensitive intermediate or reactant from water, enabling the desired catalysis. In this context, α-arylation of nitriles in water, catalyzed by ultrasmall Pd nanoparticles involving carbanions or ketenimines as reaction intermediates, was developed (Scheme 3).[22] The technology has been demonstrated with over 35 examples and one at a 50 g scale.

Current methods for the generation of ultrasmall Pd nanoparticles are expensive and inconvenient.[111] However, our strategy was to generate ultrasmall nanoparticles by using micelles in water. It was achieved by heating Colacot's[95] XPhosPd(crotyl)Cl at 45 °C in 3 wt % PS-750-M solution under mildly basic conditions (K_3PO_4 or KOH). These conditions led to the formation of ultrasmall nanoparticles, presumably via the fast elimination of elements of crotyl chloride.[28] These nanoparticles were uniformly distributed in the micelles, as indicated by scanning transmission electron microscopy−high-angle annular dark field imaging (STEM-HAADF).

As depicted in representative examples **6**−**13** in Scheme 3, these ultrasmall nanoparticles were highly active for the α-arylation of nitriles. The substrate scope was broad, and the functional group tolerance was excellent. Heteroaromatics, such as pyridyl (**6**), thiazole (**9**), indole (**11**), triazole (**12**), and protecting groups Cbz (**7**) and benzyl (**11**) have shown excellent tolerance. Notably, the chloro functionality did not participate in the reaction unless the temperature was raised to

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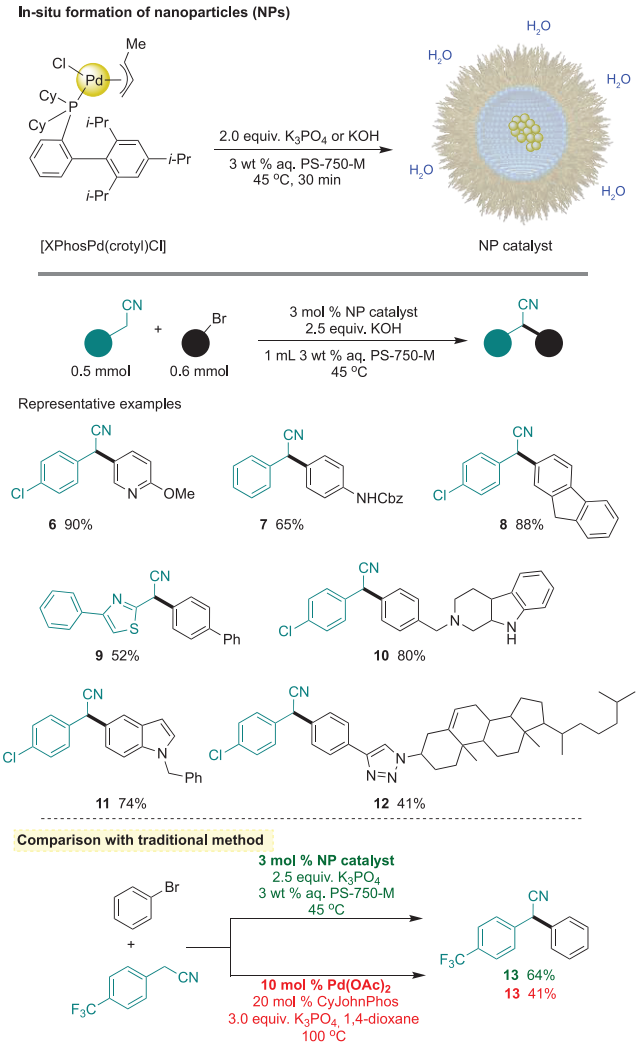
Scheme 3. A Sketch for Generation of Palladium Nanoparticles, Their Encapsulation by Micelle, and Applications in sp^2–sp^3 Couplings

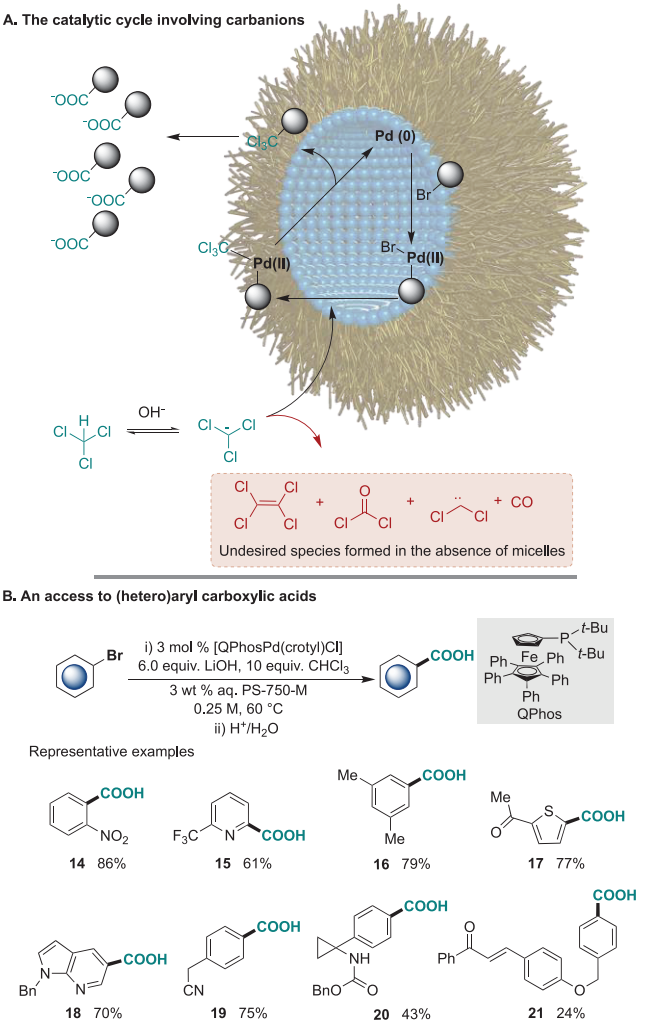


60 °C. As a result, this synthetic route can be a convenient handle for further functionalization.

These nanoparticles retained their catalytic activity, morphology, and composition for up to 4 weeks. Full mechanistic details were provided in the published report. This protocol enabled multiple complementary reactions in one pot such as α-arylation, Suzuki coupling, and Buchwald–Hartwig amination. The products obtained from α-arylation of nitriles, after one-pot oxidation using molecular oxygen, led to the formation of medicinally important biaryl ketones used to synthesize prodrug molecules (such as diphenoxylate).[112] The surfactant played three critical roles: first, stabilization of ultrasmall Pd nanoparticles via a fast reductive elimination process in nanoparticle precursor; second, prevention of reprotonation of carbanion/ketenimine intermediates by stabilizing them inside micellar hydrophobic cores; last, elimination of the need for hazardous organic solvents, typically dry 1,4-dioxane traditionally used for this reaction shown at the end of Scheme 3.

During the micelle-enabled catalytic carboxylation of (hetero)aryl halides, a carbanion intermediate was involved in the process.[24] This prevented the decomposition of trichloromethyl carbanions to carbon monoxide. Additionally, it facilitated the involvement of carbanion during the transmetalation and reductive elimination steps that occurred during the catalytic cycle. (Scheme 4 A). Through this method,

Scheme 4. Catalytic Formation of (Hetero)carboxylic Acids



a trichloromethyl carbanion was produced by lithium hydroxide base from chloroform. The micelles played a crucial role in stabilizing the carbanion to participate in the catalytic cycle, resulting in the formation of a benzotrichloride-type intermediate. This reaction intermediate was then promptly hydrolyzed to a water-soluble carboxylate anion, clearing the micelle for the next cycle.

Detailed mechanistic studies, such as kinetic studies in the presence of trichloromethyl carbanion or carbon monoxide, H/D exchange via trichloromethyl anion, and mass spectrometric analysis of reaction intermediates, supported the carbanion reaction pathway. The micelle of PS-750-M served better to stabilize carbanion compared with TPGS-750-M, TWEEN-20, Pluronic, and PTS-600. Reactions in neat chloroform, THF, and DMF only provided the desired product in traces, supporting the idea that the micellar medium has a significant role in the reaction. Colacot's [QPhosPd(crotyl)Cl] was the optimal catalyst for this transformation.[113]

This approach was utilized to obtain a variety of (hetero)aryl carboxylic acids in moderate-to-excellent yields, as shown in

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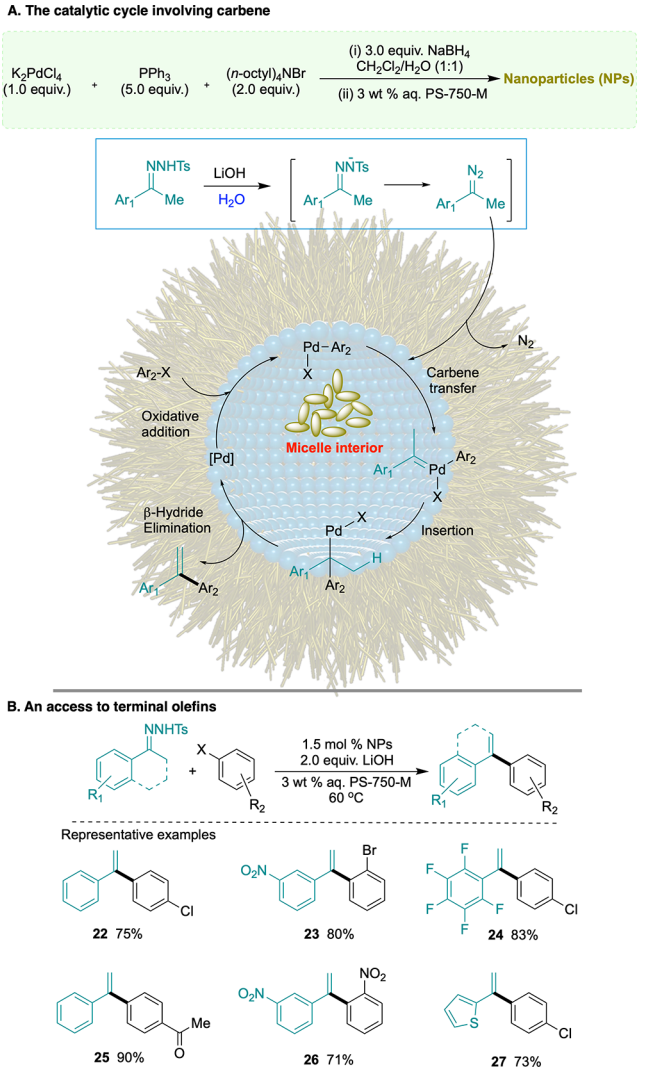
examples **14**–**21** in Scheme 4B. The yield was poor in some cases due to problems extracting the product from the aqueous layer. The scope of this approach was simultaneously proven on 40 substrates, revealing a wide functional and protecting group tolerance. The synthesis of isotopically enriched carboxylic acids using $^{18}OH_2$ and/or $^{13}CHCl_3$-labeled precursors was also accomplished using this technology, which is challenging with traditional methods.[114] The scalability of this process was shown on the carboxylation of 2-acetyl-5-bromothiophene (1 g) under optimum conditions to yield 63% product **17**. This method avoided harsh reductants and organometallic reagents for carboxylation, allowing for excellent compatibility between functional and protecting groups. In future studies, it may help expand the technology to late-stage functionalization for accessing complex molecules.

Carbene intermediates participate in reactions predominantly limited to hazardous organic solvents. However, our research has shown that it is possible to use micellar technology to create and stabilize carbenes in aqueous nanomicelles containing Pd nanoparticles.[23] This was achieved by Pd nanoparticles ligated with inexpensive triphenylphosphine and carbonyl groups of the PS-750-M amphiphile in water (Scheme 5A). We used various techniques, such as NMR, SEM, HRTEM, XPS, and TGA to investigate the nanocatalysts formed in water in detail. Both the catalyst and the micellar medium used in the process were recyclable. However, it is worth noting that dichloromethane was involved in the synthesis of the nanoparticles, which can be considered a drawback regarding sustainability.

We demonstrated the catalytic activity of this approach by converting *N*-tosyl hydrazone to terminal olefins in aqueous PS-750-M solution using an in-situ-formed carbene intermediate. The protocol used for catalysis was broadly applicable to diverse substrates, as shown in the representative examples **22**–**27** (Scheme 5B). Moreover, the functional groups, such as bromo, chloro, cyano, ester, ketone, pyridyl, thiophenyl, and trifluoromethyl, were well-tolerated. The reaction yields were good-to-excellent. This approach also achieved cyclic olefins, which are valuable synthons for biaryl compounds.

Scheme 5. Carbene in Micelle—An Access to Terminal Olefins



Micelles as Ligand

In cross-coupling chemistry, the efficiency of a nanocatalyst is dependent on the morphology of the nanoparticles as well as the oxidation potential of the metal in the catalyst. These factors dictate the selectivity and recyclability of the catalyst. In addition to controlling electronic parameters, the ligand controls the unwanted oxidation of the metal in the catalyst. The nature of the ligand or capping agent on the metal particles affects the process cost. Traditionally, Pd nanoparticle-catalyzed reactions used phosphine or nitrogen-based ligands.[115−117] However, the use of ligands can be avoided if the amphiphile PS-750-M has a greater tendency to bind to the metal through carbonyl groups. Nevertheless, carrying out ligand-free nanocatalysis can be challenging as nanoparticle agglomerates, which can lead to poor activity. By harnessing the metal−micelle cooperativity, coupling between water-sensitive acid chloride and boronic acid in water using phosphine ligand-free Pd nanoparticles was achieved.[21] The synthesis of these nanoparticles required PS-750-M, water, a carbonated base, and arylboronic acid (Scheme 6). No harsh reductants, such as MeMgBr, LAH, and $NaBH_4$, were needed to generate Pd(0) nanoparticles, making this the first report on such a mild synthetic protocol with precise control over the nanoparticle morphology and size. The average size of the nanoparticle was approximately 2.4 nm. Metal−micelle binding was probed with various spectroscopic methods, including ^{13}C NMR, SERS, and IR spectroscopic techniques.

These ligand-free Pd nanoparticles were highly efficient for the coupling of acid chlorides with (hetero)arylboronic acids, generating functionalized ketones (Scheme 6A). The technology's scope was evaluated on many substrates with excellent functional group tolerance, as shown in representative examples **28**–**30**. However, pyridyl-containing substrates were found to disturb the reaction due to the obstruction of metal−amphiphile binding, leading to the competitive formation of Pd−pyridine bonds. Acid chlorides are sensitive to water and can be readily hydrolyzed in water. To avoid this, the acid chloride was added last after other reaction components, so that the micelles were charged with the essential reaction components before adding the acid chloride. The more giant and charged micelles could easily accommodate and shield acid chloride for the desired coupling reaction. In addition to acid chloride couplings, the nanoparticles were also effective for traditional Suzuki−Miyaura

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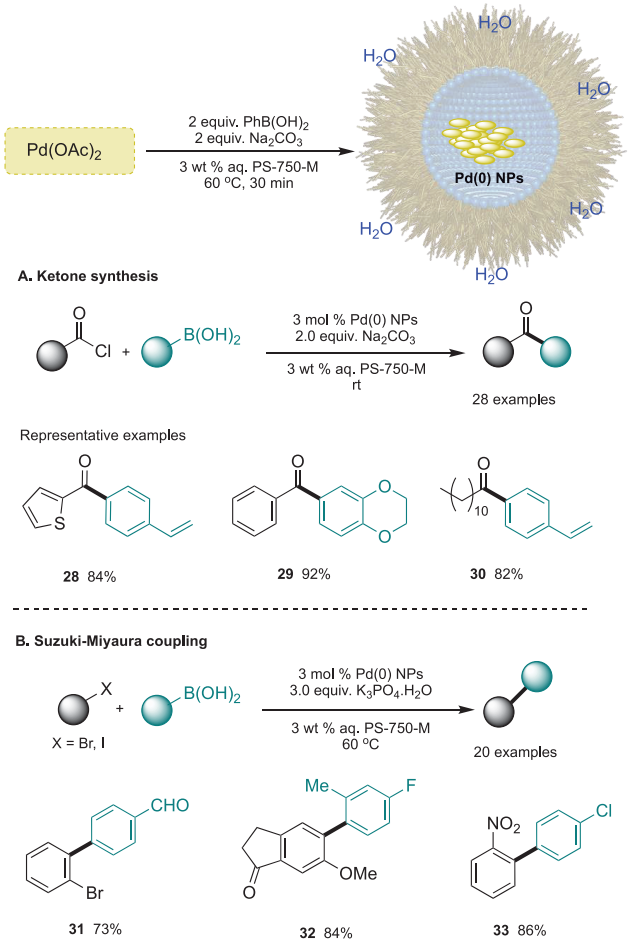
Scheme 6. Ligand-Free Pd Nanoparticles for Cross-Couplings



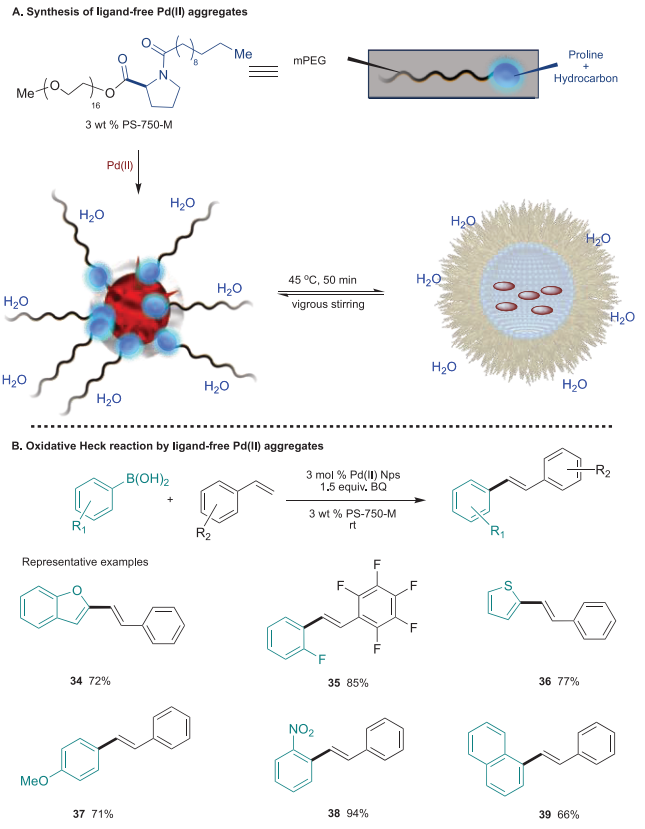
coupling, as shown in representative examples **31**−**33** (Scheme 6B).

We also synthesized aggregates composed of Pd(II) using a metal-micelle binding strategy (Scheme 7A). As shown in Scheme 7B (representative examples **34**−**39**), these aggregates were highly effective for oxidative Heck chemistry. It eliminated the need for traditional ligands.[118] We discovered that slow stirring leads to slow reaction rates, whereas fast stirring helps the larger Pd aggregates break down into ultrasmall active particles, and thus, leads to relatively fast reaction rates. The formation of large aggregates from ultrasmall nanoparticles is reversible, and thus, effective stirring >1000 rpm is essential for optimal catalytic activity.

The reaction occurs at the micellar interior/interface, as confirmed by a three-phase experiment where REM resin (acryloyl Wang's resin) bound styrene, phenylboronic acid, and Pd nanoparticles were taken in an aqueous PS-750-M solution. We observed no catalytic activity due to the poor penetration of REM-bound styrene inside the micelle. This study shows that the reaction occurs inside the micelles or at the interface and not outside of it.

In a separate report, we found that the micelles of PS-750-M played a key role in the spontaneous formation of Pd(0) nanoparticles from Pd_2dba_3.[119] The formation of these nanoparticles is even more rapid in the presence of molecular hydrogen. These nanoparticles were stabilized in water due to metal−amphiphile (ligand) binding. XPS analysis confirmed

Scheme 7. Aggregates of Pd(II) for Ligand-Free Oxidative Heck Reaction



the presence of Pd in a zero-oxidation state. The MALDI-TOF analysis of the nanoparticles revealed the presence of Pd-bound PS-750-M mass peaks at 1122 amu. However, the absence of a dba mass peak indicated that the carbonyl groups of the ester and amide functional moieties of surfactant molecules strongly bind to the Pd. The shielding effect of micelles on Pd nanoparticles facilitates the fast cross-coupling of moisture-sensitive triazine adducts of carboxylic acids to form biaryl ketones. The representative examples **40**−**47** are shown in Scheme 8.

Ligand-free Ni(0) is difficult to obtain in water without an electron-rich solid support. To stabilize Ni(0) in water and create bimetallic nanoparticles of Ni(0)Pd(0) (containing only 0.1 mol % Pd), we used metal−metal and metal−micelle binding approaches (Scheme 9A).[120] These nanoparticles were ideal for highly selective 1,4-reduction of Michael acceptors with other functional groups, such as nitro, Cbz, benzyl, chloro, and esters, while susceptible groups, such as sulfonate ester or silyl ether, remained intact. The representative examples **48**−**52** are shown in Scheme 9B. This technology was highly useful since no nitrile/ester hydrolysis has been observed in aqueous conditions.

Optical microscopy showed the formation of aggregates with an average diameter of 2.4 μm, consisting of bimetallic nanoparticles. The average diameter of 2.64 nm of nanoparticles Ni/Pd (Ni = nickel) was calculated from HRTEM analysis. While Ni(0) tends to activate the carbonyl group and form a Ni-bound substrate, oxidative addition of hydrogen takes place over Pd(0) particles, leading to selective 1,4-reduction of enones. Since the amount of Pd was less, multiple

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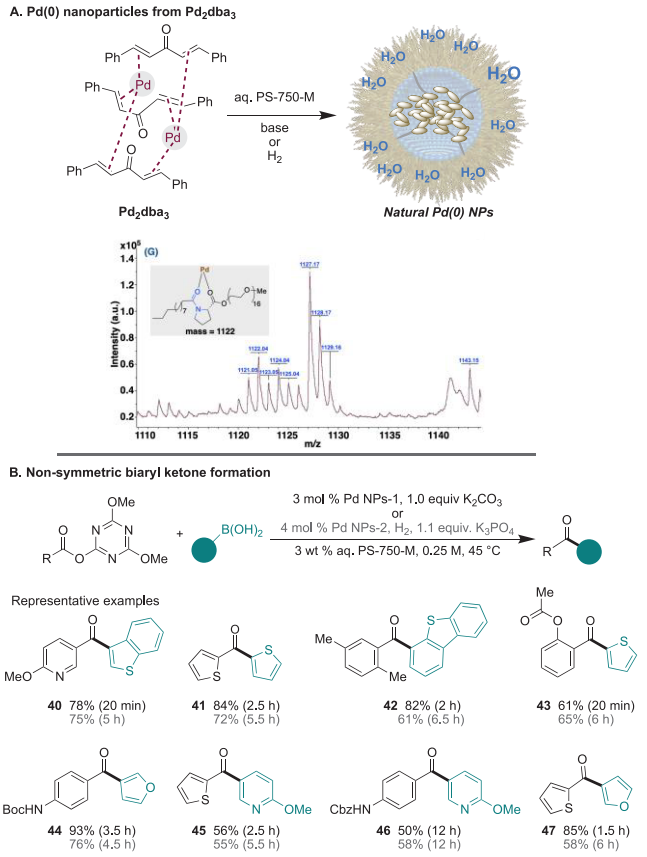
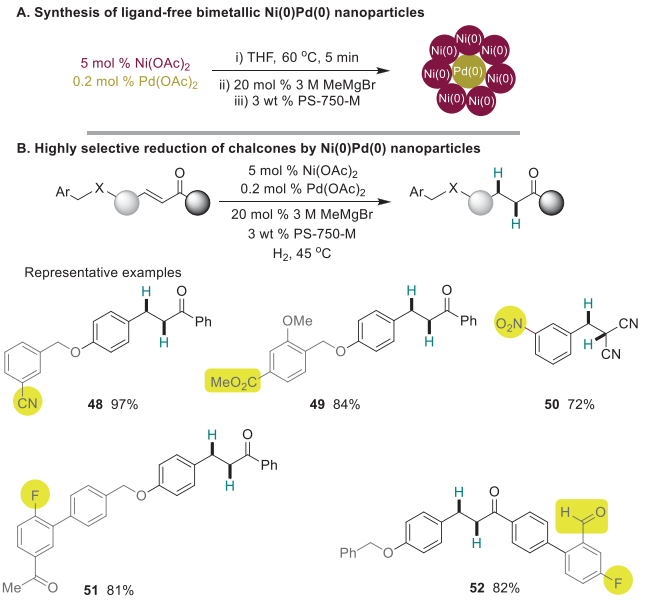
Scheme 8. Spontaneous Formation of Pd(0) from Pd_2dba_3 in Aqueous PS-750-M—The Catalytic Cross-Couplings of Carboxylic Acid Derivatives



Scheme 9. Ligand-Free Bimetallic Nanoparticles of Ni(0)Pd(0) for Highly Selective 1,4-Reduction of Enones



Ni(0) atoms were expected to surround the Pd atom in the particle.

Raman and surface-enhanced Raman scattering (SERS) spectroscopic techniques have shown evidence of metal–amphiphile binding. The shift of peaks 1624 and 1773 cm^{-1} of amide carbonyl vibrational mode and ester carbonyl vibrational mode of neat PS-750-M to 1611 and 1757 cm^{-1}, respectively, for nanoparticle-bound PS-750-M evidenced the ligation of metal nanoparticles with micelles.

Micelles as Reaction Promotors

Water has excellent potential as a solvent for both chemo- and biocatalysis.[44,121] Micelles can help promote this potential. Despite demonstrating the usefulness of chemo- and biocatalysts in one-pot processes, two significant challenges have recently been addressed.[44,71,122] First, enhancing the mass transfer of hydrophobic substrates to the micelle has improved the process efficiency. Second, combining chemo- and biocatalytic techniques has addressed incompatibilities between these catalytic systems. This approach enabled the subsequent sequence to use the product from the previous step without isolation, providing an opportunity to develop chemoenzymatic catalysis. The sequential addition of reagents and catalysts in a micellar medium was crucial to the reaction's success.

In a study by Lipshutz, Gallou, and co-workers, the authors described the compatibility of aqueous TPGS-750-M with alcohol dehydrogenase in the presence of an organometallic catalyst.[71] Pd-catalyzed Sonogashira and Heck and Rh-catalyzed Michael reactions were conducted in aqueous micelles of TPGS-750-M, and then enzymatic enantioselective reductions of ketones was achieved by adjusting the medium's pH using a buffer without isolating the reaction products. The challenge is to perform tandem chemoenzymatic micellar catalysis. The question is whether micelles can be designed to accommodate enzymes within their hydrophobic pockets and allow the substrates to move in and out of the micelles more quickly. At the same time, a heterogeneous organometallic catalyst should work on water or at the polar–nonpolar micellar interface to prevent possible enzyme poisoning. If successful, then this approach can help achieve multicomponent tandem chemoenzymatic transformations.

The authors achieved multiple transformations in a single process, as described in Scheme 10. These transformations included Sonogashira coupling followed by asymmetric reduction of the keto group, Heck coupling followed by similar keto reductions, and Au-catalyzed alkyne hydration followed by enzyme-catalyzed enantioselective reduction of keto to alcohol. The resulting products, **53**–**61**, serve as representative examples of these reactions. In the same report, the authors employed this strategy for the 1,4-addition to enones and asymmetric reduction.

Lipshutz and co-workers have also reported the asymmetric reduction of alkene using ene-reductases (EREDs) in 2 wt % TPGS-750-M in water.[123] In their study, they achieved a one-pot reduction through ERED, followed by amine formation using transaminase. In the same report, they also described three one-pot reactions that involved ERED reduction, Pd/C nitro reduction, and acylation reactions. The same group also documented lipase-catalyzed esterification in a micellar medium.[124] The authors used Palatase 20000 L for the reaction in the absence of a cofactor at 30 °C in an aqueous medium of 2 wt % TPGS-750-M. This technology enabled one-pot multistep reactions in water, such as Sonogashira cross-coupling, esterification catalyzed by an enzyme, and ADH reduction.

Notably, prior to Lipshutz, a similar approach was already adopted in organic solvents by Bäckvall and co-workers, where

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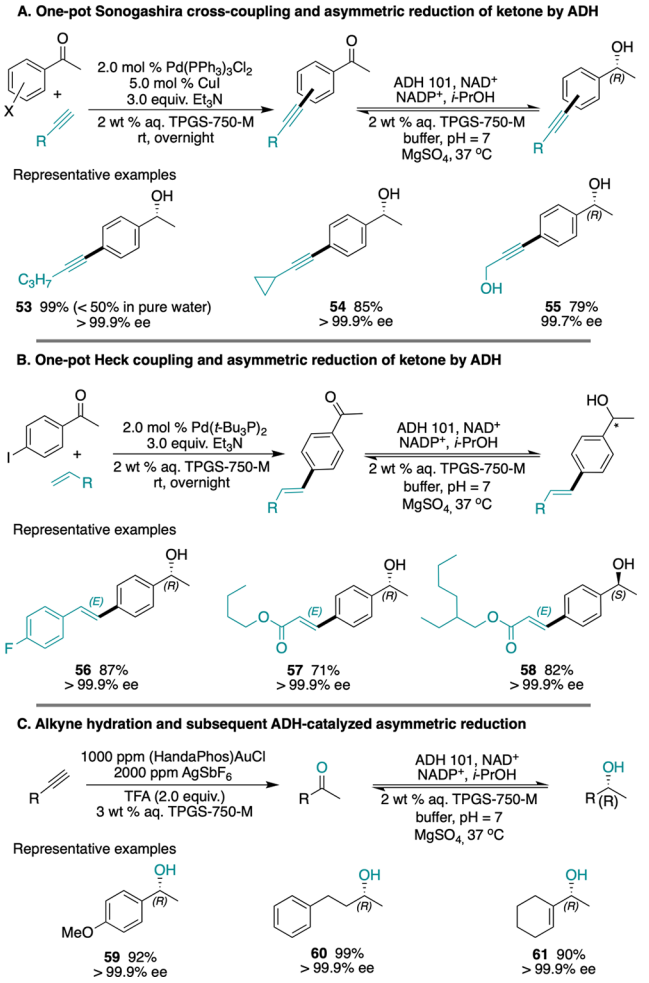
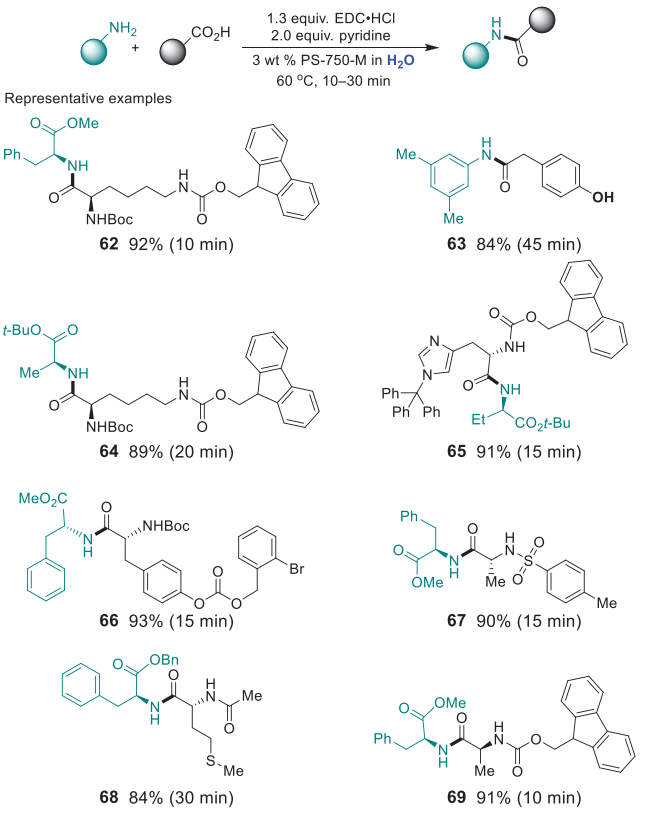
Scheme 10. One-Pot Chemoenzymatic Catalysis Enabled by Aqueous Micelles of TPGS-750-M



Scheme 11. Fast Amide Couplings Promoted by Micelles of PS-750-M—No Extraction and Column Chromatography Needed



the authors utilized a biphasic approach to separate enzymes from organometallic catalysts.[125] This led to successful chemoenzymatic catalysis, allowing for enantioselective acylation of amines via dynamic-kinetic resolution.

The micelles also act as reaction promoters in fast amide couplings. Our research group has reported that micelles can facilitate fast amide coupling in water.[26,97] The process was achieved through mixed micelles of EDC•HCl and PS-750-M, without requiring HOBt to prevent product epimerization. The PS-750-M has a proline linker with a 3° amide group that helps to maintain optimal polarity inside the micelles, making fast amide couplings possible. Under the reaction conditions, the product precipitates, which can be isolated through filtration without the use of organic solvents. The representative examples **62**–**69** are shown in Scheme 11. It is worth noting that in aqueous basic conditions, Fmoc cleavage did not take place. The reaction was selective to only amine nucleophiles, and the hydroxy group in the coupling partner remained unreactive. However, this technology has a downside: it requires a pyridine base. This base is necessary for product precipitation and to retain the amphiphilic nature of EDC•HCl.

Theoretical models corroborated that micelles or surfactants are great reaction promoters, allow the solubility of hydrophobic substrates, and increase their concentration in the micelles. Molecular dynamics (MD) simulations coupled with Umbrella Sampling or the CosmoMK analysis have provided more insights into the anisotropic environment of the micelle.[126] MD simulations are used to explore the partition between aqueous and micellar environments. The free energy profile estimates the solute's proximity to the micelles. These simulation techniques were generally used to study the lipid bilayer partition. Recently, these techniques have been applied to micellar catalysis.[127,128] MD simulations on the Suzuki–Miyaura reaction between phenylboronic acid and methyl-4-bromo phenylacetate in the presence of Kolliphor-EL surfactant supported that molecular species involved in the reaction are concentrated in the micelles acting like nanoreactors.[127] Due to the high concentration of substrates in the confined environment of micelles, they act as phenomenal reaction promoters.

The scope of computational chemistry has been extended to calculate the local environment of the micelles by Kozlowski and our group.[105] Instead of considering a whole micellar structure, a fragment of micelle was optimized with its components present around. Specifically, the local environment of photochemically active Cu-containing nanomicelles was estimated by the DFT method, where the spin-restricted wave function was obtained by using the hybrid B3LYP/def-T2VP level of theory, which clearly revealed the binding between Cu and PS-750-M surfactant through carbonyl groups, which was in agreement with XAS analysis. Such binding was crucial for single-electron transfer to promote catalysis.

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Practical Aspects of Micellar Catalysis

Regarding micellar catalysis, there are some crucial factors to consider for achieving repeatability and practicality.[129] These include the preparation of surfactant solution, the order of addition, the temperature limit, the stirring rate, the particle size of solid reagents, careful selection of solvent (if product extraction is required), and the particle size of the empty micelle.

The preparation of a surfactant solution is easy. Generally, a 2−3 wt % aqueous solution is optimal for micellar catalysis. For consistency, deionized water should be used in the preparation of the surfactant solution. Most surfactants are instantaneously soluble in water and do not require overnight stirring. However, TPGS-750-M is not instantaneously soluble in water and requires several hours of stirring to obtain a clear aqueous solution. Surfactants containing an optimal mPEG chain length are always clear and transparent in their solution form. If the solution is turbid, it indicates the presence of a free hydrophobic fragment of the surfactant that is suspended in the form of an impurity. Such aqueous solutions generally give inferior activity. To avoid foaming while preparing an aqueous surfactant solution, add the surfactant to the container first, followed by a slow addition of water before stirring the mixture. Shaking the container should be avoided.

When catalytic reactions are performed in micellar media, it is essential to pay close attention to the order of addition. If possible, adding the base last is recommended. Portionwise addition of the water-sensitive reagent may be performed for better results. Also, portionwise addition is recommended when dealing with pyridyl (MIDA) boronoate esters, as the release of pyridyl boronic acid is faster than the desired catalytic reaction, which can otherwise lead to significant hydrodeborylation.[69] When a very low amount of catalyst is used, i.e., 500−1000 ppm, it should be added first. The catalyst can be added in solution form with a minimal cosolvent to ensure its uniform distribution in micelles. After the catalyst was added, the mixture should be stirred at room temperature for approximately 5 min before adding other reaction components. This will allow the catalyst to distribute evenly in the micelles.

Micellar technology can achieve transformations at ambient temperatures that otherwise require elevated temperatures in organic solvents. Based on our internal unpublished data, micellar catalysis has an upper-temperature limit of 65 °C. At higher temperatures, reactants are exchanged between different micelles more frequently, allowing less time for reactants to interact with the catalyst inside the micelles, especially when catalysis is designed to have more lipophilicity to stay within the micelle. In situations where elevated temperature is necessary, a higher weight percent of surfactant is desirable; otherwise, it may deteriorate micellization. Caution must be taken when heating the mixture to temperatures beyond 80 °C. At higher temperatures, impurities tend to form more easily. It is important not to overheat the mixture in anticipation of a higher reaction rate. Overheating must be avoided if the reaction proceeds smoothly under room temperature or mild heating. In addition, uniform and effective stirring is required from the beginning until product extraction or filtration.

Efficiency in micellar catalysis can be affected by the physical nature of reactants. If the reactants are highly crystalline, they may have difficulty getting into the micelle, which can lead to poor catalytic efficiency. To avoid this issue, the crystalline material can be ground into a powder, or 5−10% cosolvent (THF, toluene, or acetone) can be added.[67,130,131] Adding a cosolvent can increase reactant solubility and expand the micelles. However, it is important to note that cosolvent should only be used if the reaction does not proceed smoothly without it. It is preferable to use an appropriate amphiphile to address solubility issues. Additionally, using a cosolvent can solubilize the desired product, which may have otherwise crystallized in the reaction mixture and just required isolation by a simple filtration.

During a reaction, mild heating can cause the evaporation of volatile components (if used), leading to a poor reaction yield. To prevent this, it is recommended to use pentane or ether as a cosolvent. These volatile cosolvents form a layer of vapors above the reaction mixture, increasing the pressure and preventing the vaporization of the volatile reaction partners. If the volatile compound has a boiling point above acetone's boiling point, then acetone is preferred as a cosolvent. It is important to note that the cosolvent should have a boiling point of at least 5 °C higher than the volatile reactant.

To track the progress of the reaction, a sample must be taken out while stirring the reaction mixture. The sample is then diluted with water and EtOAc to break the micelles and allow the product and starting material to dissolve in the organic solvent for accurate analysis. After the reaction is complete, if the product appears as a solid, it can be filtered using a frit and washed with water to remove any remaining surfactant. Based on the solubility of the product in the surfactant or the type and amount of cosolvent used, the product crystallizes in the surfactant solution or otherwise requires extraction with an appropriate organic solvent. If the product is not crystallized, EtOAc equal to the amount of surfactant solution should be added. The mixture should be stirred for a few minutes before being centrifuged. The organic layer is then separated, which extracts the product in the organic phase. If the residual product is still in the surfactant solution, it must be diluted with water and extracted again using a minimum amount of organic solvent (EtOAc or *i*-PrOAc or MTBE preferred).

When working with a magnetic stir bar in micellar catalysis, it is common for a solid product to form a ball and stick to it. In such cases, using a small amount of cosolvent (acetone) can help resolve this issue. It is important to avoid using a high catalyst loading as it can lead to the formation of more impurities. Extraction of the product with dichloromethane should also be avoided since it dissolves designer surfactants (TPGS-750-M, PS-750-M, Nok, Savie, etc.) in the organic layer. If the product is not soluble in ethyl acetate, then simply filtering it out can be effective. Additionally, before using the surfactant, it is best to degas it while gently heating the aqueous solution. This process yields better results for Pd catalysis.

BROADER IMPLEMENTATION OF MICELLAR CATALYSIS

Gallou, an industrial leader in micellar catalysis from Novartis Pharmaceuticals, was the first to implement and telescope micellar catalysis and biocatalysis in the micellar medium in API synthesis.[132,133] The authors have made significant contributions to the field of micellar catalysis, including both fundamental and applied work. Gallou's seminal work demonstrated that implementing micellar catalysis reduces the PMI, increases the overall yield, and thus lowers the cost of

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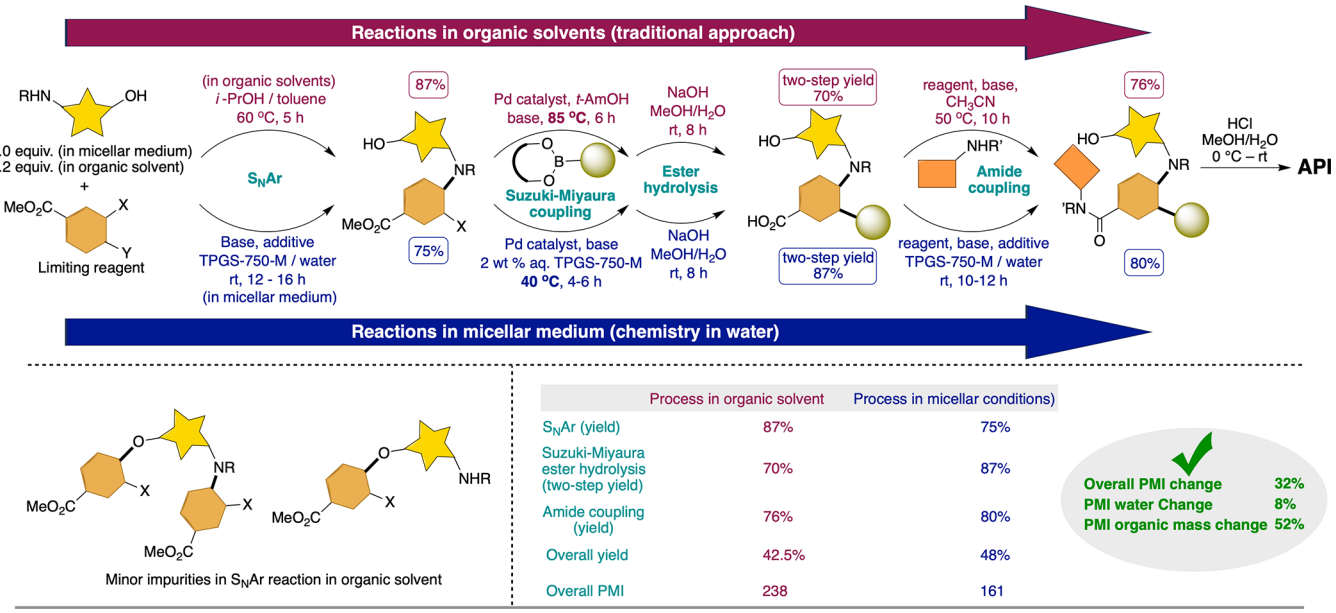
Scheme 12. First Implementation of Micellar Catalysis in Active Pharmaceutical Ingredient (API) Synthesis



API synthesis. The author's team has also developed strategies to address the wastewater generated from TPGS-750-M.[134]

Gallou and co-workers carried out a multistep synthesis of an API at a multikilogram scale using aqueous micellar technology, as described in Scheme 12.[132] The synthetic strategy began with a nucleophilic aromatic substitution reaction, followed by a Suzuki–Miyaura coupling, ester hydrolysis, and amide coupling, ultimately leading to the final API after treating the prefinal compound with HCl. It is worth noting that due to intellectual property matters, the structure of the API and the reaction intermediates were not disclosed.

To begin the process, the S_NAr reaction formed a C–N bond between the trisubstituted heteroaromatic ester and the nucleophilic amine bearing an unprotected hydroxy group. Only a 1:1 stoichiometry of coupling partners was used to ensure selectivity and avoid waste-generating protecting group chemistry. The transformation was primarily selective, leaving the hydroxy group unreacted. Next, the resulting product underwent Suzuki–Miyaura couplings with the boronic ester to obtain the desired biaryl adduct containing the methyl ester group. The ester was hydrolyzed in situ to obtain the free carboxylic acid, which was further subjected to amide coupling in the next step.

To determine the advantages of chemistry in water, a detailed comparative study between synthesis in water versus organic solvents was conducted by the authors. The S_NAr reaction was carried out in *i*-PrOH/toluene organic solvent, which resulted in an 87% yield of the desired product. The reaction required a temperature of 60 °C. However, some minor *O*-arylated byproducts were also formed in this reaction, which had to be removed by recrystallization. On the other hand, the same reaction in aqueous micelles of TPGS-750-M provided the desired product with a 75% isolated yield and required a much lower temperature, i.e., room temperature. Additionally, the reaction in the micellar medium required only a 1:1 stoichiometry of the nucleophile and electrophile, while the *i*-PrOH/toluene conditions demanded a 1:1.2 stoichiometry. This indicates the improved atom economy with the chemistry in water. After rigorous optimization, the overall yield in the micellar medium was further improved to the lower 90s.

The Suzuki–Miyaura couplings of the *N*-arylated heterocyclic compound with the boronate ester proceeded smoothly under aqueous micellar conditions with an improved reaction stoichiometry (1:1.2) and lower Pd catalyst loading at a temperature of 40 °C. This crude product was then hydrolyzed in situ to obtain carboxylic acid. In contrast, the same reaction in organic solvent (*t*-AmOH) required a temperature of 85 °C and a higher catalyst loading. In this case, the two-step Suzuki coupling and ester hydrolysis yield was only 70%, which was significantly lower than that of the reaction in water. Due to the presence of the unprotected hydroxy group in the molecule, the next amide-bond-forming reaction was the most challenging under organic solvent conditions. As a result, significant amounts of ester byproduct were formed, leading to a reduced yield compared to that of the reaction in aqueous micelles (76% versus 80%). Besides, additional solvents were consumed in product purification under organic solvent conditions. It is worth noting that the overall yield of this API was significantly higher under micellar conditions (48%) compared to that under traditional organic solvent conditions (42.5%). The PMI that measures the environmental performance was also much reduced to 161 under micellar conditions. Prior to the development of more efficient processes that use significantly less palladium, this research was conducted. This has implications not just for reducing initial costs, but also for downstream expenses like the removal of any remaining palladium. The findings were published in 2016, and we are currently in 2024 with significant advancements made in micellar technology since then.

CONCLUSION AND OUTLOOK

Micellar catalysis offers many opportunities and also some challenges.[135] In general, this alternative approach to synthesis has played an important role in reducing the consumption of organic solvents in numerous valuable transformations. Some of the critical highlights of micellar catalysis include ligand-free

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and parts-per-million-level organometallic catalysis, in situ formation of valuable organometallic reagents and their subsequent utilization in cross-coupling reactions, extra stabilization of water-sensitive species by the shielding effect of micelle, one-pot sequence reactions based on no intermediates' isolation, often product isolation by simple filtration, and chemo- and biocatalysis in one pot. The outstanding work on the mechanistic understanding of micellar catalysis by Blum and co-workers has the potential to address some of the unanswered questions and open new pathways to micellar chemistry for its broader adoption.[136,137]

Despite these advances, many questions still need to be addressed to establish the foundation of this new regime. These questions mainly focus on the fundamental understanding of the interaction between the catalyst, micelle, substrate, and substrate−micelle−catalyst. Although NMR, mass spectrometry, and FLIM techniques are used to address some of these questions, many related questions remain unanswered, especially under conditions matching actual reaction conditions. This understanding is crucial in designing new reactivities and selecting appropriate surfactant solutions for the desired reaction. Rigorous experimental and theoretical investigations are required in this direction to address these challenges.

To advance the sustainability features of micellar catalysis, the micelle design should allow for the synthesis of amphiphiles in or on water or direct isolation from renewable natural resources without using organic solvents. While telescoping the potential of micellar technologies, one can reasonably find that strategies for properly disposing or recycling the leftover water from micellar catalysis are still missing. Our group is actively searching for new techniques to clean up water waste without consuming too much energy. Membrane filtration can be employed in this regard.

The carbon footprint of surfactants is not zero, as emphasized by Fleck, Roschangar, and Haydl.[138] Therefore, new surfactants with much lower carbon footprints are needed. These surfactants should be designed to be environmentally friendly, biodegradable (but resource-efficient), made from natural or semisynthetic materials, and affordable. These surfactants should also promote the evolution of green chemistry.

Similar to the other state-of-the-art surfactants, the surfactant PS-750-M, developed by the author's lab, has a lot of potential due to its proline moiety. It is a chiral and tunable surfactant. The carbon α to the ester linkage in PS-750-M can be further substituted to enhance or fine-tune the chirality in the surfactant. The author's lab has disclosed that proline carbonyls bind with Pd or Cu, causing the formation of active catalytic species.[105,118] These interactions cause metal-micelle binding, leading to the desired selective catalysis. The author's lab has also developed PS-750-M-like surfactants with pronounced chirality, which will be employed in asymmetric catalysis, and findings will be disclosed in due course. Despite the versatility of PS-750-M, there is still no information available regarding the biodegradation of PS-750-M. Additionally, no literature is available on wastewater treatment of an aqueous layer containing PS-750-M or its fragments.

The field of organic chemistry is increasingly embracing sustainable practices. Micellar catalysis, in particular, is gaining popularity for enabling a variety of reactions in water. However, it is imperative to address the issues that have been overlooked in micellar catalysis and develop strategies for the effective use of water, which is essential for future generations.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. Credit: **Jagdeep Kaur Virdi** resources, validation, writing-original draft, writing-review & editing; **Ashish Dusunge** resources, validation, writing-original draft, writing-review & editing; **Sachin Handa** conceptualization, formal analysis, investigation, project administration, supervision, validation, writing-review & editing.

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ABBREVIATIONS

API, Active Pharmaceutical Ingredient; **Cbz-Cl**, Benzyl chloroformate; **CTAB**, Cetyltrimethylammonium bromide; **dba**, Dibenzylideneacetone; **DFT**, Density functional theory; **DMAc**, Dimethylacetamide; **DMF**, Dimethylformamide; **DMSO**, Dimethyl sulfoxide; **EDC**, 1-Ethyl-3-(3-(dimethylamino)propyl)carbodiimide; **EtOAc**, Ethyl acetate; **$FeCl_3$**, Ferric chloride; **FLIM**, Fluorescence lifetime imaging microscopy; **HAADF**, High-angle annular dark field; **HCl**, Hydrochloride; **HOBt**, Hydroxybenzotriazole; **HRTEM**, High-resolution transmission electron microscopy; **5-HT4**, 5-Hydroxytryptamine receptor 4; **IR**, Infrared; **KOH**, Potassium hydroxide; **K_3PO_4**, Potassium phosphate; **LAH**, Lithium aluminum hydride; **MALDI-TOF**, Matrix-assisted laser desorption time-of-flight; **MD**, Molecular dynamics; **mPEG**, Polyethylene glycol monomethyl ether; **NMP**, *N*-Methyl pyrrolidone; **PMI**, Process mass intensity; **ppm**, parts per million; **PQS**, Polyethylene glycol UniQuinol succinate; **PTS**, Polyoxyethanyl-α-tocopheryl sebacate; **rpm**, rotations per minute; **SEM**, Scanning electron microscopy; **SERS**, Surface-enhanced Raman spectroscopy; **STEM**, Scanning transmission

electron microscopy; **TGA**, Thermogravimetric analysis; **THF**, Tetrahydrofuran; **TPGS-750-M**, Tocopherol methoxypolyethylene glycol succinate; **XPS**, X-ray photoelectron spectroscopy

REFERENCES

(1) Nägeli, C. Die Stärkekörner: Morphologische, Physiologische, Chemisch-Physicalische Und Systematisch-Botanische Monographie. *Schulthess* **1858**, *2*, 321−356.
(2) McBain, J. W.; Martin, H. E. XCII.—Studies of the Constitution of Soap Solutions: The Alkalinity and Degree of Hydrolysis of Soap Solutions. *J. Chem. Soc. Trans.* **1914**, *105*, 957−977.
(3) Hartley, G. S. Organised Structure in Soap Solutions. *Nature* **1949**, *163*, 767−768.
(4) Biresaw, G.; Bunton, C. A. Nucleophilic Reactions in Functional and Nonfunctional Micelles. *Validity of the Pseudophase Ion-Exchange Model. J. Org. Chem.* **1986**, *51*, 2771−2777.
(5) Romsted, L. S.; Bunton, C. A.; Yao, J. Micellar Catalysis, a Useful Misnomer. *Curr. Opin. Colloid Interface Sci.* **1997**, *2*, 622−628.
(6) Cordes, E. H.; Dunlap, R. B. Kinetics of Organic Reactions in Micellar Systems. *Acc. Chem. Res.* **1969**, *2*, 329−337.
(7) Twitchell, E. Process of Decomposing Fats or Oils into Fatty Acids and Glycerine. US 601603A, 1898.
(8) Langmuir, A. C. The Twitchell Process and the Glycerine Trade. *Ind. Eng. Chem.* **1917**, *9*, 195−196.
(9) Kobayashi, S.; Nagayama, S.; Busujima, T. Lewis Acid Catalysts Stable in Water. *Correlation between Catalytic Activity in Water and Hydrolysis Constants and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands. J. Am. Chem. Soc.* **1998**, *120*, 8287−8288.
(10) Kitanosono, T.; Zhu, L.; Liu, C.; Xu, P.; Kobayashi, S. An Insoluble Copper (II) Acetylacetonate-Chiral Bipyridine Complex That Catalyzes Asymmetric Silyl Conjugate Addition in Water. *J. Am. Chem. Soc.* **2015**, *137*, 15422−15425.
(11) Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. Catalytic Organic Reactions in Water toward Sustainable Society. *Chem. Rev.* **2018**, *118*, 679−746.
(12) Kitanosono, T.; Kobayashi, S. Reactions in Water Involving the "On-Water" Mechanism. *Chem.—Eur. J.* **2020**, *26*, 9408−9429.
(13) Lipshutz, B. H.; Isley, N. A.; Fennewald, J. C.; Slack, E. D. On the Way Towards Greener Transition-Metal-Catalyzed Processes as Quantified by E Factors. *Angew. Chem., Int. Ed.* **2013**, *52*, 10952−10958.
(14) Lipshutz, B. H.; Ghorai, S.; Aguinaldo, G. T. Ring-Closing Metathesis at Room Temperature within Nanometer Micelles Using Water as the Only Solvent. *Adv. Synth. Catal.* **2008**, *350*, 953−956.
(15) Cortes-Clerget, M.; Yu, J.; Kincaid, J. R. A.; Walde, P.; Gallou, F.; Lipshutz, B. H. Water as the Reaction Medium in Organic Chemistry: From Our Worst Enemy to Our Best Friend. *Chem. Sci.* **2021**, *12*, 4237−4266.
(16) Lipshutz, B. H.; Aguinaldo, G. T.; Ghorai, S.; Voigtritter, K. Olefin Cross-Metathesis Reactions at Room Temperature Using the Nonionic Amphiphile "PTS": Just Add Water. *Org. Lett.* **2008**, *10*, 1325−1328.
(17) Lipshutz, B. H.; Isley, N. A.; Moser, R.; Ghorai, S.; Leuser, H.; Taft, B. R. *Rhodium-Catalyzed Asymmetric 1, 4-Additions, in Water at Room Temperature, with In-Flask Catalyst Recycling. Adv. Synth. Catal.* **2012**, *354*, 3175−3179.
(18) Handa, S.; Slack, E. D.; Lipshutz, B. H. *Nanonickel-Catalyzed Suzuki-Miyaura Cross-Couplings in Water. Angew. Chem. Int. Ed.* **2015**, *54*, 11994−11998.
(19) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. Asymmetric Suzuki-Miyaura Coupling in Water with a Chiral Palladium Catalyst Supported on an Amphiphilic Resin. *Angew. Chem., Int. Ed.* **2009**, *48*, 2708−2710.
(20) Yamada, Y. M. A.; Sarkar, S. M.; Uozumi, Y. Amphiphilic Self-Assembled Polymeric Copper Catalyst to Parts per Million Levels: Click Chemistry. *J. Am. Chem. Soc.* **2012**, *134*, 9285−9290.
(21) Ansari, T. N.; Sharma, S.; Hazra, S.; Jasinski, J. B.; Wilson, A. J.; Hicks, F.; Leahy, D. K.; Handa, S. Shielding Effect of Nanomicelles: Stable and Catalytically Active Oxidizable Pd (0) Nanoparticle Catalyst Compatible for Cross-Couplings of Water-Sensitive Acid Chlorides in Water. *JACS Au* **2021**, *1*, 1506−1513.
(22) Bihani, M.; Ansari, T. N.; Finck, L.; Bora, P. P.; Jasinski, J. B.; Pavuluri, B.; Leahy, D. K.; Handa, S. Scalable α-Arylation of Nitriles in Aqueous Micelles Using Ultrasmall Pd Nanoparticles: Surprising Formation of Carbanions in Water. *ACS Catal.* **2020**, *10*, 6816−6821.
(23) Duong, U. T.; Gade, A. B.; Plummer, S.; Gallou, F.; Handa, S. Reactivity of Carbenes in Aqueous Nanomicelles Containing Palladium Nanoparticles. *ACS Catal.* **2019**, *9*, 10963−10970.
(24) Ansari, T. N.; Sharma, S.; Hazra, S.; Hicks, F.; Leahy, D. K.; Handa, S. Trichloromethyl Carbanion in Aqueous Micelles: Mechanistic Insights and Access to Carboxylic Acids from (Hetero) Aryl Halides. *ACS Catal.* **2022**, *12*, 15686−15695.
(25) Hedouin, G.; Ogulu, D.; Kaur, G.; Handa, S. Aqueous Micellar Technology: An Alternative beyond Organic Solvents. *Chem. Commun.* **2023**, *59*, 2842−2853.
(26) Sharma, S.; Buchbinder, N. W.; Braje, W. M.; Handa, S. Fast Amide Couplings in Water: Extraction, Column Chromatography, and Crystallization Not Required. *Org. Lett.* **2020**, *22*, 5737−5740.
(27) Ansari, T. N.; Gallou, F.; Handa, S. Palladium-Catalyzed Micellar Cross-Couplings: An Outlook. *Coord. Chem. Rev.* **2023**, *488*, 215158.
(28) Petersen, H.; Ballmann, M.; Krause, N.; Weberskirch, R. Gold (I) NHC Catalysts Immobilized to Amphiphilic Block Copolymers: A Versatile Approach to Micellar Gold Catalysis in Water. *ChemCatChem.* **2022**, *14*, No. e202200727.
(29) Lempke, L.; Sak, H.; Kubicki, M.; Krause, N. Gold-Catalyzed Cycloisomerization of Trifluoromethylated Allenols: Sustainability and Mechanistic Studies. *Org. Chem. Front.* **2016**, *3*, 1514−1519.
(30) Ceriani, C.; Ghiglietti, E.; Sassi, M.; Mattiello, S.; Beverina, L. Taming Troublesome Suzuki-Miyaura Reactions in Water Solution of Surfactants by the Use of Lecithin: A Step beyond the Micellar Model. *Org. Process Res. Dev.* **2020**, *24*, 2604−2610.
(31) Ceriani, C.; Pallini, F.; Mezzomo, L.; Sassi, M.; Mattiello, S.; Beverina, L. Micellar Catalysis beyond the Hydrophobic Effect: Efficient Palladium Catalyzed Suzuki-Miyaura Coupling of Water and Organic Solvent Insoluble Pigments with Food Grade Surfactants. *J. Organomet. Chem.* **2022**, *962*, 122267.
(32) Bhonde, V. R.; O'Neill, B. T.; Buchwald, S. L. An Improved System for the Aqueous Lipshutz-Negishi Cross-Coupling of Alkyl Halides with Aryl Electrophiles. *Angew. Chem., Int. Ed.* **2016**, *55*, 1849−1853.
(33) Patel, N. D.; Rivalti, D.; Buono, F. G.; Chatterjee, A.; Qu, B.; Braith, S.; Desrosiers, J.-N.; Rodriguez, S.; Sieber, J. D.; Haddad, N.; Fandrick, K. R.; Lee, H.; Yee, K. N.; Busacca, C. A.; Senanayake, C. S. Effective BI-DIME Ligand for Suzuki-Miyaura Cross-Coupling Reactions in Water with 500 Ppm Palladium Loading and Triton X. *Asian J. Org. Chem.* **2017**, *6*, 1285−1291.
(34) Hunter, J. H.; Prendergast, L.; Valente, L. F.; Madin, A.; Pairaudeau, G.; Waring, M. J. High Fidelity Suzuki-Miyaura Coupling for the Synthesis of DNA Encoded Libraries Enabled by Micelle Forming Surfactants. *Bioconjugate Chem.* **2020**, *31*, 149−155.
(35) Graham, J. S.; Stanway-Gordon, H. A.; Waring, M. J. Micelle-Mediated Sonogashira Coupling for DNA-Encoded Library Synthesis. *Chem.—Eur. J.* **2023**, *29*, No. e202300603.
(36) Stanway-Gordon, H. A.; Odger, J. A.; Waring, M. J. Development of a Micellar-Promoted Heck Reaction for the Synthesis of DNA-Encoded Libraries. *Bioconjugate Chem.* **2023**, *34*, 756−763.
(37) Graham, J. S.; Hunter, J. H.; Waring, M. J. Micellar Buchwald-Hartwig Coupling of Aryl and Heteroarylamines for the Synthesis of DNA-Encoded Libraries. *J. Org. Chem.* **2021**, *86*, 17257−17264.
(38) Vaidya, G. N.; Choudhary, R. H.; Nagpure, M.; Lokhande, S. K.; Rana, P.; Kumar, D. 'In-Water', Nickel-Catalyzed Mild Preparation of Allylic Amines Employing Alcohols: Application to 'All-Water'Synthesis of Pharmaceuticals. *Green Chem.* **2022**, *24*, 3977−3984.

https://doi.org/10.1021/jacsau.3c00605
JACS Au 2024, 4, 301−317

(39) Lorenzetto, T.; Fabris, F.; Scarso, A. Recent Metallosurfactants for Sustainable Catalysis in Water. *Curr. Opin. Colloid Interface Sci.* **2023**, *64*, 101689.
(40) Trentin, F.; Chapman, A. M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G.; Wass, D. F. Platinum (II) Diphosphinamine Complexes for the Efficient Hydration of Alkynes in Micellar Media. *Adv. Synth. Catal.* **2012**, *354*, 1095−1104.
(41) Yetra, S. R.; Rogge, T.; Warratz, S.; Struwe, J.; Peng, W.; Vana, P.; Ackermann, L. Micellar Catalysis for Ruthenium(II)-Catalyzed C-H Arylation: Weak-Coordination-Enabled C-H Activation in H2O. *Angew. Chem., Int. Ed.* **2019**, *58*, 7490−7494.
(42) Mattiello, S.; Ghiglietti, E.; Zucchi, A.; Beverina, L. Selectivity in Micellar Catalysed Reactions. *Role of Interfacial Dipole, Compartmentalisation, and Specific Interactions with the Surfactants. Curr. Opin. Colloid Interface Sci.* **2023**, *64*, 101681.
(43) Firsan, S. J.; Sivakumar, V.; Colacot, T. J. Emerging Trends in Cross-Coupling: Twelve-Electron-Based L1Pd (0) Catalysts, Their Mechanism of Action, and Selected Applications. *Chem. Rev.* **2022**, *122*, 16983−17027.
(44) Gröger, H.; Gallou, F.; Lipshutz, B. H. Where Chemocatalysis Meets Biocatalysis: In Water. *Chem. Rev.* **2023**, *123*, 5262−5296.
(45) Kobayashi, S.; Hachiya, I. Lanthanide Triflates as Water-Tolerant Lewis Acids. *Activation of Commercial Formaldehyde Solution and Use in the Aldol Reaction of Silyl Enol Ethers with Aldehydes in Aqueous Media. J. Org. Chem.* **1994**, *59*, 3590−3596.
(46) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. Organic Synthesis Inside Particles in Water: Lewis Acid-Surfactant-Combined Catalysts for Organic Reactions in Water Using Colloidal Dispersions as Reaction Media. *J. Am. Chem. Soc.* **2000**, *122*, 7202−7207.
(47) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. Dehydration Reactions in Water. *Brønsted Acid-Surfactant-Combined Catalyst for Ester, Ether, Thioether, and Dithioacetal Formation in Water. J. Am. Chem. Soc.* **2002**, *124*, 11971−11978.
(48) Hamada, T.; Manabe, K.; Kobayashi, S. Enantio- and Diastereoselective, Stereospecific Mannich-Type Reactions in Water. *J. Am. Chem. Soc.* **2004**, *126*, 7768−7769.
(49) Lipshutz, B. H. Illuminating a Path for Organic Synthesis Towards Sustainability. *No One Said It Would Be Easy. . .. Synlett* **2021**, *32*, 1588−1605.
(50) Duplais, C.; Krasovskiy, A.; Lipshutz, B. H. Organozinc Chemistry Enabled by Micellar Catalysis. *Palladium-Catalyzed Cross-Couplings between Alkyl and Aryl Bromides in Water at Room Temperature. Organometallics* **2011**, *30*, 6090−6097.
(51) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. Zn-Mediated, Pd-Catalyzed Cross-Couplings in Water at Room Temperature Without Prior Formation of Organozinc Reagents. *J. Am. Chem. Soc.* **2009**, *131*, 15592−15593.
(52) Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. Room-Temperature Suzuki- Miyaura Couplings in Water Facilitated by Nonionic Amphiphiles. *Org. Lett.* **2008**, *10*, 1333−1336.
(53) Nishikata, T.; Lipshutz, B. H. Allylic Ethers as Educts for Suzuki- Miyaura Couplings in Water at Room Temperature. *J. Am. Chem. Soc.* **2009**, *131*, 12103−12105.
(54) Takale, B. S.; Thakore, R. R.; Irvine, N. M.; Schuitman, A. D.; Li, X.; Lipshutz, B. H. Sustainable and Cost-Effective Suzuki-Miyaura Couplings toward the Key Biaryl Subunits of Arylex and Rinskor Active. *Org. Lett.* **2020**, *22*, 4823−4827.
(55) Lipshutz, B. H.; Taft, B. R. Heck Couplings at Room Temperature in Nanometer Aqueous Micelles. *Org. Lett.* **2008**, *10*, 1329−1332.
(56) Pang, H.; Hu, Y.; Yu, J.; Gallou, F.; Lipshutz, B. H. Water-Sculpting of a Heterogeneous Nanoparticle Precatalyst for Mizoroki-Heck Couplings under Aqueous Micellar Catalysis Conditions. *J. Am. Chem. Soc.* **2021**, *143*, 3373−3382.
(57) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. Stereoselective Negishi-like Couplings between Alkenyl and Alkyl Halides in Water at Room Temperature. *Org. Lett.* **2010**, *12*, 4742−4744.
(58) Hu, Y.; Wong, M. J.; Lipshutz, B. H. Ppm Pd-Containing Nanoparticles as Catalysts for Negishi Couplings ... in Water. *Angew. Chem. Int. Ed.* **2022**, *61*, No. e202209784.
(59) Lipshutz, B. H.; Chung, D. W.; Rich, B. Sonogashira Couplings of Aryl Bromides: Room Temperature, Water Only, No Copper. *Org. Lett.* **2008**, *10*, 3793−3796.
(60) Handa, S.; Smith, J. D.; Zhang, Y.; Takale, B. S.; Gallou, F.; Lipshutz, B. H. Sustainable HandaPhos-Ppm Palladium Technology for Copper-Free Sonogashira Couplings in Water under Mild Conditions. *Org. Lett.* **2018**, *20*, 542−545.
(61) Handa, S.; Jin, B.; Bora, P. P.; Wang, Y.; Zhang, X.; Gallou, F.; Reilly, J.; Lipshutz, B. H. Sonogashira Couplings Catalyzed by Fe Nanoparticles Containing Ppm Levels of Reusable Pd, under Mild Aqueous Micellar Conditions. *ACS Catal.* **2019**, *9*, 2423−2431.
(62) Lipshutz, B. H.; Chung, D. W.; Rich, B. Aminations of Aryl Bromides in Water at Room Temperature. *Adv. Synth. Catal.* **2009**, *351*, 1717−1721.
(63) Nishikata, T.; Lipshutz, B. H. Aminations of Allylic Phenyl Ethers via Micellar Catalysis at Room Temperature in Water. *Chem. Commun.* **2009**, *42*, 6472−6474.
(64) Thakore, R. R.; Takale, B. S.; Casotti, G.; Gao, E. S.; Jin, H. S.; Lipshutz, B. H. Chemoselective Reductive Aminations in Aqueous Nanoreactors Using Parts per Million Level Pd/C Catalysis. *Org. Lett.* **2020**, *22*, 6324−6329.
(65) Lipshutz, B. H.; Ghorai, S. PQS: A New Platform for Micellar Catalysis. *RCM Reactions in Water, with Catalyst Recycling. Org. Lett.* **2009**, *11*, 705−708.
(66) Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A.; Gaston, R. D.; Gadwood, R. C. *TPGS-750-M: A Second-Generation Amphiphile for Metal-Catalyzed Cross-Couplings in Water at Room Temperature. J. Org. Chem.* **2011**, *76*, 4379−4391.
(67) Handa, S.; Lippincott, D. J.; Aue, D. H.; Lipshutz, B. H. Asymmetric Gold-catalyzed Lactonizations in Water at Room Temperature. *Angew. Chem., Int. Ed.* **2014**, *53*, 10658−10662.
(68) Gabriel, C. M.; Keener, M.; Gallou, F.; Lipshutz, B. H. Amide and Peptide Bond Formation in Water at Room Temperature. *Org. Lett.* **2015**, *17*, 3968−3971.
(69) Isley, N. A.; Gallou, F.; Lipshutz, B. H. Transforming Suzuki-Miyaura Cross-Couplings of MIDA Boronates into a Green Technology: No Organic Solvents. *J. Am. Chem. Soc.* **2013**, *135*, 17707−17710.
(70) Handa, S.; Wang, Y.; Gallou, F.; Lipshutz, B. H. Sustainable Fe-Ppm Pd Nanoparticle Catalysis of Suzuki-Miyaura Cross-Couplings in Water. *Science* **2015**, *349*, 1087−1091.
(71) Cortes-Clerget, M.; Akporji, N.; Zhou, J.; Gao, F.; Guo, P.; Parmentier, M.; Gallou, F.; Berthon, J.-Y.; Lipshutz, B. H. Bridging the Gap between Transition Metal- and Bio-Catalysis via Aqueous Micellar Catalysis. *Nat. Commun.* **2019**, *10*, 2169.
(72) Kincaid, J. R. A.; Wong, M. J.; Akporji, N.; Gallou, F.; Fialho, D. M.; Lipshutz, B. H. Introducing Savie: A Biodegradable Surfactant Enabling Chemo-and Biocatalysis and Related Reactions in Recyclable Water. *J. Am. Chem. Soc.* **2023**, *145*, 4266−4278.
(73) Zhou, P.; Shen, T.; Chen, W.; Sun, J.; Ling, J. Biodegradable Polysarcosine with Inserted Alanine Residues: Synthesis and Enzymolysis. *Biomacromolecules* **2022**, *23*, 1757−1764.
(74) Lipshutz, B. H.; Ghorai, S.; Cortes-Clerget, M. The Hydrophobic Effect Applied to Organic Synthesis: Recent Synthetic Chemistry "in Water. *Chem.—Eur. J.* **2018**, *24*, 6672−6695.
(75) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. "On Water": Unique Reactivity of Organic Compounds in Aqueous Suspension. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275−3279.
(76) Rideout, D. C.; Breslow, R. Hydrophobic Acceleration of Diels-Alder Reactions. *J. Am. Chem. Soc.* **1980**, *102*, 7816−7817.
(77) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. Water in Organocatalytic Processes: Debunking the Myths. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798−3800.

https://doi.org/10.1021/jacsau.3c00605
JACS Au 2024, 4, 301−317

(78) Butler, R. N.; Coyne, A. G. Organic Synthesis Reactions On-Water at the Organic-Liquid Water Interface. *Org. Biomol. Chem.* **2016**, *14*, 9945−9960.
(79) Tolman, C. A. Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis. *Chem. Rev.* **1977**, *77*, 313−348.
(80) Handa, S.; Andersson, M. P.; Gallou, F.; Reilly, J.; Lipshutz, B. H. HandaPhos: A General Ligand Enabling Sustainable Ppm Levels of Palladium-catalyzed Cross-couplings in Water at Room Temperature. *Angew. Chem., Int. Ed.* **2016**, *55*, 4914−4918.
(81) Herrmann, W. A.; Kohlpaintner, C. W. *Water-soluble Ligands, Metal Complexes, and Catalysts: Synergism of Homogeneous and Heterogeneous Catalysis. Angew. Chem. Int. Ed.* **1993**, *32*, 1524−1544.
(82) Klumphu, P.; Desfeux, C.; Zhang, Y.; Handa, S.; Gallou, F.; Lipshutz, B. H. Micellar Catalysis-Enabled Sustainable Ppm Au-Catalyzed Reactions in Water at Room Temperature. *Chem. Sci.* **2017**, *8*, 6354−6358.
(83) Landstrom, E. B.; Handa, S.; Aue, D. H.; Gallou, F.; Lipshutz, B. H. *EvanPhos: A Ligand for Ppm Level Pd-Catalyzed Suzuki-Miyaura Couplings in Either Organic Solvent or Water. Green Chem.* **2018**, *20*, 3436−3443.
(84) Akporji, N.; Thakore, R. R.; Cortes-Clerget, M.; Andersen, J.; Landstrom, E.; Aue, D. H.; Gallou, F.; Lipshutz, B. H. N 2 Phos-an Easily Made, Highly Effective Ligand Designed for Ppm Level Pd-Catalyzed Suzuki-Miyaura Cross Couplings in Water. *Chem. Sci.* **2020**, *11*, 5205−5212.
(85) Surry, D. S.; Buchwald, S. L. Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361.
(86) Brals, J.; Smith, J. D.; Ibrahim, F.; Gallou, F.; Handa, S. Micelle-Enabled Palladium Catalysis for Convenient Sp2-Sp3 Coupling of Nitroalkanes with Aryl Bromides in Water Under Mild Conditions. *ACS Catal.* **2017**, *7*, 7245−7250.
(87) Littke, A. F.; Fu, G. C. *Palladium-catalyzed Coupling Reactions of Aryl Chlorides. Angew. Chem. Int. Ed.* **2002**, *41*, 4176−4211.
(88) Christoffel, F.; Ward, T. R. *Palladium-Catalyzed Heck Cross-Coupling Reactions in Water: A Comprehensive Review. Catal. Letters* **2018**, *148*, 489−511.
(89) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-catalyzed Cross-coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085.
(90) Zhang, L.; Hu, W.; Li, H.; Shi, J.; Yuan, B. TXPhos: A Highly Stable and Efficient Ligand Designed for Ppm Level Pd-Catalyzed Suzuki-Miyaura Coupling in Water. *Green Chem.* **2023**, *25*, 6635−6641.
(91) Lipshutz, B. H. On the Sustainability of Palladium in Organic Synthesis: A Perspective. *Johnson Matthey Technol. Rev.* **2023**, *67*, 278.
(92) La Sorella, G.; Strukul, G.; Scarso, A. Recent Advances in Catalysis in Micellar Media. *Green Chem.* **2015**, *17*, 644−683.
(93) Cortes-Clerget, M.; Spink, S. E.; Gallagher, G. P.; Chaisemartin, L.; Filaire, E.; Berthon, J.-Y.; Lipshutz, B. H. MC-1. A "Designer" Surfactant Engineered for Peptide Synthesis in Water at Room Temperature. *Green Chem.* **2019**, *21*, 2610−2614.
(94) EU Commission Regulation. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2021.415.01.0016.01.ENG&toc=OJ%3AL%3A2021%3A415%3ATOC&_cldee=cm9uYW4ubWFnZWVAaHNlbmkuZ292LnVr&recipientid=lead-d457c97bf4c9eb11812b0050569 52b31-63fdc33244cf498c923ac35b03be86cd&esid=16469f50-104d-ec11-8132-005056b9310e Last accessed: November 30, 2023.
(95) DeAngelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. Generating Active "L-Pd(0)" via Neutral or Cationic π-Allylpalladium Complexes Featuring Biaryl/Bipyrazolylphosphines: Synthetic, Mechanistic, and Structure-Activity Studies in Challenging Cross-Coupling Reactions. *J. Org. Chem.* **2015**, *80*, 6794−6813.
(96) Smith, J. D.; Ansari, T. N.; Andersson, M. P.; Yadagiri, D.; Ibrahim, F.; Liang, S.; Hammond, G. B.; Gallou, F.; Handa, S. Micelle-Enabled Clean and Selective Sulfonylation of Polyfluoroarenes in Water under Mild Conditions. *Green Chem.* **2018**, *20*, 1784−1790.
(97) Sharma, S.; Kaur, G.; Handa, S. Insights into Fast Amide Couplings in Aqueous Nanomicelles. *Org. Process Res. Dev.* **2021**, *25*, 1960−1965.
(98) Bora, P. P.; Bihani, M.; Plummer, S.; Gallou, F.; Handa, S. Shielding Effect of Micelle for Highly Effective and Selective Monofluorination of Indoles in Water. *ChemSusChem* **2019**, *12*, 3037−3042.
(99) Bihani, M.; Bora, P. P.; Nachtegaal, M.; Jasinski, J. B.; Plummer, S.; Gallou, F.; Handa, S. Microballs Containing Ni(0)Pd(0) Nanoparticles for Highly Selective Micellar Catalysis in Water. *ACS Catal.* **2019**, *9*, 7520−7526.
(100) Ansari, T. N.; Taussat, A.; Clark, A. H.; Nachtegaal, M.; Plummer, S.; Gallou, F.; Handa, S. Insights on Bimetallic Micellar Nanocatalysis for Buchwald-Hartwig Aminations. *ACS Catal.* **2019**, *9*, 10389−10397.
(101) Finck, L.; Brals, J.; Pavuluri, B.; Gallou, F.; Handa, S. Micelle-Enabled Photoassisted Selective Oxyhalogenation of Alkynes in Water under Mild Conditions. *J. Org. Chem.* **2018**, *83*, 7366−7372.
(102) Bailey, J. D.; Helbling, E.; Mankar, A.; Stirling, M.; Hicks, F.; Leahy, D. K. Beyond Organic Solvents: Synthesis of a 5-HT 4 Receptor Agonist in Water. *Green Chem.* **2021**, *23*, 788−795.
(103) Wang, L. Daniel Bailey wins Peter J. Dunn Award. *Chem. Eng. News.* **2020**, *98*, 37 Last accessed: October 5, 2023.
(104) Li, X.; Iyer, K. S.; Thakore, R. R.; Leahy, D. K.; Bailey, J. D.; Lipshutz, B. H. Bisulfite Addition Compounds as Substrates for Reductive Aminations in Water. *Org. Lett.* **2021**, *23*, 7205−7208.
(105) Sharma, S.; Parmar, S.; Ibrahim, F.; Clark, A. H.; Nachtegaal, M.; Jasinski, J. B.; Gallou, F.; Kozlowski, P. M.; Handa, S. Sustainable and Bench-Stable Photoactive Aqueous Nanoaggregates of Cu(II) for Ppm Level Cu(I) Catalysis in Water (Adv Funct. Mater. 36/2022). *Adv. Funct. Mater.* **2022**, *32*, 2270202.
(106) Agrahari, A. K.; Bose, P.; Jaiswal, M. K.; Rajkhowa, S.; Singh, A. S.; Hotha, S.; Mishra, N.; Tiwari, V. K. *Cu(I)-Catalyzed Click Chemistry in Glycoscience and Their Diverse Applications. Chem. Rev.* **2021**, *121*, 7638−7956.
(107) Ma, D.; Cai, Q. Copper/Amino Acid Catalyzed Cross-Couplings of Aryl and Vinyl Halides with Nucleophiles. *Acc. Chem. Res.* **2008**, *41*, 1450−1460.
(108) Beletskaya, I. P.; Cheprakov, A. V. Copper in Cross-Coupling Reactions: The Post-Ullmann Chemistry. *Coord. Chem. Rev.* **2004**, *248*, 2337−2364.
(109) Clark, A. J. Copper Catalyzed Atom Transfer Radical Cyclization Reactions. *Eur. J. Org. Chem.* **2016**, *2016*, 2231−2243.
(110) Larsson, P.; Correa, A.; Carril, M.; Norrby, P.; Bolm, C. Copper-catalyzed Cross-couplings with Part-per-million Catalyst Loadings. *Angew. Chem., Int. Ed.* **2009**, *121*, 5801−5803.
(111) Favier, I.; Pla, D.; Gómez, M. Palladium Nanoparticles in Polyols: Synthesis, Catalytic Couplings, and Hydrogenations. *Chem. Rev.* **2020**, *120*, 1146−1183.
(112) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902−7917.
(113) Johansson Seechurn, C. C. C.; Parisel, S. L.; Colacot, T. J. Air-Stable Pd(R-Allyl)LCl (L= Q-Phos, P(t-Bu)3, Etc.) Systems for C-C/N Couplings: Insight into the Structure-Activity Relationship and Catalyst Activation Pathway. *J. Org. Chem.* **2011**, *76*, 7918−7932.
(114) Jiang, X.; Zhang, J.; Ma, S. Iron Catalysis for Room-Temperature Aerobic Oxidation of Alcohols to Carboxylic Acids. *J. Am. Chem. Soc.* **2016**, *138*, 8344−8347.
(115) MacQueen, P. M.; Holley, R.; Ghorai, S.; Colacot, T. J. Convenient One-Pot Synthesis of L2Pd (0) Complexes for Cross-Coupling Catalysis. *Organometallics* **2023**, *42*, 2644−2650.
(116) Trzeciak, A. M.; Augustyniak, A. W. The Role of Palladium Nanoparticles in Catalytic C-C Cross-Coupling Reactions. *Coord. Chem. Rev.* **2019**, *384*, 1−20.

https://doi.org/10.1021/jacsau.3c00605
JACS Au 2024, 4, 301−317

(117) Lipshutz, B. H.; Caravez, J. C.; Iyer, K. S. Nanoparticle-Catalyzed Green Synthetic Chemistry. . .Water. *Curr. Opin. Green Sustain. Chem.* **2022**, *38*, 100686.
(118) Ansari, T. N.; Jasinski, J. B.; Leahy, D. K.; Handa, S. Metal-Micelle Cooperativity: Phosphine Ligand-Free Ultrasmall Palladium (II) Nanoparticles for Oxidative Mizoroki-Heck-Type Couplings in Water at Room Temperature. *JACS Au* **2021**, *1*, 308−315.
(119) Kaur, G.; Jasinski, J. B.; Gallou, F.; Handa, S. Metal-Micelle Interaction Leading to Spontaneous Formation of Ligand-Free Palladium (0) Nanoparticles: Highly Efficient Catalysis Enabling Biaryl Ketone Formation from Carboxylic Acid Derivatives. *ACS Appl. Mater. Interfaces* **2022**, *14*, 50947−50955.
(120) Ogulu, D.; Bora, P. P.; Bihani, M.; Sharma, S.; Ansari, T. N.; Wilson, A. J.; Jasinski, J. B.; Gallou, F.; Handa, S. Phosphine Ligand-Free Bimetallic Ni (0) Pd (0) Nanoparticles as a Catalyst for Facile, General, Sustainable, and Highly Selective 1, 4-Reductions in Aqueous Micelles. *ACS Appl. Mater. Interfaces* **2022**, *14*, 6754−6761.
(121) Gallou, F.; Gröger, H.; Lipshutz, B. H. Status Check: Biocatalysis; It's Use with and without Chemocatalysis. How Does the Fine Chemicals Industry View This Area? *Green Chem.* **2023**, *25*, 6092−6107.
(122) Rudroff, F.; Mihovilovic, M. D.; Gröger, H.; Snajdrova, R.; Iding, H.; Bornscheuer, U. T. Opportunities and Challenges for Combining Chemo-and Biocatalysis. *Nat. Catal.* **2018**, *1*, 12−22.
(123) Akporji, N.; Singhania, V.; Dussart-Gautheret, J.; Gallou, F.; Lipshutz, B. H. *Nanomicelle-Enhanced, Asymmetric ERED-Catalyzed Reductions of Activated Olefins. Applications to 1-Pot Chemo-and Bio-Catalysis Sequences in Water. Chem. Commun.* **2021**, *57*, 11847−11850.
(124) Singhania, V.; Cortes-Clerget, M.; Dussart-Gautheret, J.; Akkachairin, B.; Yu, J.; Akporji, N.; Gallou, F.; Lipshutz, B. H. *Lipase-Catalyzed Esterification in Water Enabled by Nanomicelles. Applications to 1-Pot Multi-Step Sequences. Chem. Sci.* **2022**, *13*, 1440−1445.
(125) Engström, K.; Johnston, E. V.; Verho, O.; Gustafson, K. P. J.; Shakeri, M.; Tai, C.; Bäckvall, J. Co-immobilization of an Enzyme and a Metal into the Compartments of Mesoporous Silica for Cooperative Tandem Catalysis: An Artificial Metalloenzyme. *Angew. Chem., Int. Ed.* **2013**, *52*, 14006−14010.
(126) Saranjam, L.; Fuguet, E.; Nedyalkova, M.; Simeonov, V.; Mas, F.; Madurga, S. Prediction of Partition Coefficients in SDS Micelles by DFT Calculations. *Symmetry* **2021**, *13*, 1750.
(127) Ranaudo, A.; Greco, C.; Moro, G.; Zucchi, A.; Mattiello, S.; Beverina, L.; Cosentino, U. Partition of the Reactive Species of the Suzuki-Miyaura Reaction between Aqueous and Micellar Environments. *J. Phys. Chem. B* **2022**, *126*, 9408−9416.
(128) Andersson, M. P.; Gallou, F.; Klumphu, P.; Takale, B. S.; Lipshutz, B. H. Structure of Nanoparticles Derived from Designer Surfactant TPGS-750-M in Water, As Used in Organic Synthesis. *Chem.—Eur. J.* **2018**, *24*, 6778−6786.
(129) Ansari, T. N.; Gallou, F.; Handa, S. Cross-Couplings in Water - A Better Way to Assemble New Bonds. *In Organometallic Chemistry in Industry;* **2020**, 203−238.
(130) Lippincott, D. J.; Landstrom, E.; Cortes-Clerget, M.; Lipshutz, B. H.; Buescher, K.; Schreiber, R.; Durano, C.; Parmentier, M.; Ye, N.; Wu, B.; Shi, M.; Yang, H.; Andersson, M.; Gallou, F. Surfactant Technology: With New Rules, Designing New Sequences Is Required! Org. *Process Res. Dev.* **2020**, *24*, 841−849.
(131) Gabriel, C. M.; Lee, N. R.; Bigorne, F.; Klumphu, P.; Parmentier, M.; Gallou, F.; Lipshutz, B. H. Effects of Co-Solvents on Reactions Run under Micellar Catalysis Conditions. *Org. Lett.* **2017**, *19*, 194−197.
(132) Gallou, F.; Isley, N. A.; Ganic, A.; Onken, U.; Parmentier, M. Surfactant Technology Applied toward an Active Pharmaceutical Ingredient: More than a Simple Green Chemistry Advance. *Green Chem.* **2016**, *18*, 14−19.
(133) Parmentier, M.; Wagner, M.; Wickendick, R.; Baenziger, M.; Langlois, A.; Gallou, F. A General Kilogram Scale Protocol for Suzuki-Miyaura Cross-Coupling in Water with TPGS-750-M Surfactant. *Org. Process Res. Dev.* **2020**, *24*, 1536−1542.
(134) Krell, C.; Schreiber, R.; Hueber, L.; Sciascera, L.; Zheng, X.; Clarke, A.; Haenggi, R.; Parmentier, M.; Baguia, H.; Rodde, S.; Gallou, F. Strategies to Tackle the Waste Water from α-Tocopherol-Derived Surfactant Chemistry. *Org. Process Res. Dev.* **2021**, *25*, 900−915.
(135) Hauk, P.; Wencel-Delord, J.; Ackermann, L.; Walde, P.; Gallou, F. Organic Synthesis in Aqueous Multiphase Systems — Challenges and Opportunities Ahead of Us. *Curr. Opin. Colloid Interface Sci.* **2021**, *56*, 101506.
(136) Peacock, H.; Blum, S. A. Surfactant Micellar and Vesicle Microenvironments and Structures under Synthetic Organic Conditions. *J. Am. Chem. Soc.* **2023**, *145*, 7648−7658.
(137) Peacock, H.; Blum, S. A. *Single-Micelle and Single-Zinc-Particle Imaging Provides Insights into the Physical Processes Underpinning Organozinc Reactions in Water. J. Am. Chem. Soc.* **2022**, *144*, 3285−3296.
(138) Fleck, N.; Roschangar, F.; Haydl, A. M. API Syntheses in Aqueous Media: Assessing the Environmental Footprint En Route from Academic Discovery to Industrial Applications as "Green Opportunity" for Process Chemistry. *Org. Process Res. Dev.* **2023**, *27*, 822−830.

https://doi.org/10.1021/jacsau.3c00605
JACS Au 2024, 4, 301−317