32

Surfactant Assemblies as Nanoreactors for Organic Transformations

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32.1 Introduction

Performing chemistry in organic solvents will eventually become an embarrassing memory; a relic from a time when sustainability and mitigation of the environmental impact associated with organic synthesis was hardly a consideration. That's the future, at least if we have any say in the matter.

Growing environmental concerns over conventional methods used for organic synthesis have led to a boom in new green methodologies over the last few decades. Organic solvents, in particular, have garnered much of the attention as they constitute the bulk of waste generated by the chemical enterprise, and c. 80% within the pharmaceutical industry, according to the ACS Green Chemistry Institute [1]. Organic solvents themselves represent a considerable threat to both human and environmental health, many of them being toxic, carcinogenic, harmful to reproductive health, and/or flammable. Additionally, the solvent waste stream is problematic, as most is either burned (thereby releasing climate-altering greenhouse gases directly to the atmosphere) or buried where it can potentially breach containment and contaminate groundwater sources; i.e., an ecological catastrophe waiting to happen. If health and safety concerns are not enough to catalyze a switch to alternative solvent systems, perhaps the inevitable exhaustion of petroleum resources (estimated at 43 years from now) [2] will be the catalyst. Alternatively, an increasing number of regulations imposed by world governments will force the switch, e.g., the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) [3] regulation in the European Union, which seeks to mitigate health and environmental concerns related to bulk chemicals, including solvents. Whatever the driving force, it is imperative that the chemical industry adopt greener alternatives to conventional organic solvents.

Several such alternatives have materialized over the years and found niche applications to synthetic challenges, but ultimately the solution to the solvent problem will not come in the form of ionic liquids, fluorous media, or supercritical

Supramolecular Catalysis: New Directions and Developments, First Edition.
Edited by Piet W.N.M. van Leeuwen and Matthieu Raynal.

CO_2, but rather from Nature's chosen solvent: water. For billions of years, Nature has made use of water as the medium for the synthesis of staggeringly complex natural products. Water is nontoxic, nonflammable, nonvolatile, inexpensive, and omnipresent. If it is the obvious choice to replace harmful organic solvents, why hasn't it?

Historically, concerns over both solubility and the moisture sensitivity of reagents have led to apprehension toward, or flat-out refusal to consider, the use of water as a reaction medium for the majority of chemical transformations. This has led to the parochial convention that water should be avoided at all costs. However, just as biological systems make use of the lipophilic interior of phospholipid-derived vesicles to "dissolve" otherwise water-insoluble compounds, chemists can make use of self-assembling amphiphiles (e.g., surfactants) dissolved in water to provide a lipophilic microenvironment inside of which chemical transformations can take place. Additionally, water sensitivity presents a smaller obstacle to aqueous chemistry than previously thought, as illustrated by a number of reactions involving water-sensitive reagents (e.g., acyl chlorides [4], organolithium [5], and Grignard [6] reagents) that can be used smoothly *in water*. The key is the presence of a suitable lipophilic environment within the aqueous solution, such as surfactant-derived nanomicelles or suspended droplets of hexane, which provide a hydrophobic pocket to rapidly sequester reagent molecules before they have an opportunity to interact with the surrounding water.

Toward the goal of normalizing water as an alternative to conventional organic solvents, our group focuses on development and use of "designer" surfactants that enable chemistry in water under mild conditions. Our flagship surfactant, TPGS-750-M [7], is derived from biodegradable vitamin E (which serves as the lipophilic moiety) and hydrophilic poly(ethylene glycol) (PEG) monomethyl ether attached via a succinate linker. With this representative surfactant in hand, we have developed a growing portfolio of alternative surfactants that address particular synthetic needs (e.g., MC-1 for polar polypeptide synthesis in water) [8], as well as a library of synthetic methodologies using water as the global reaction medium. These technologies include Pd-catalyzed cross-couplings requiring only ppm levels of catalyst in Suzuki–Miyaura [9], Sonogashira [10], and amination reactions [11], ppm Au-catalyzed transformations (e.g., asymmetric lactonizations [12] and alkyne hydrations [13]), and reactions involving water-sensitive organozinc intermediates, generated in situ, that go on to participate in Negishi-like cross-couplings [14], to name just a few. However, this chapter is not intended as a comprehensive guide to chemistry in water; rather, our goal is to showcase the nanomicelles that have enabled those reactions and to highlight a series of synthetic transformations that can only be performed in the presence of aqueous surfactants.

32.2 Micellar Catalysis: Concepts

Surfactants are amphiphilic molecules, meaning that each is composed of both hydrophilic and lipophilic subsections. As such, when dissolved in water, they

self-assemble into entropically driven nanostructures (e.g., micelles or vesicles) with the hydrophilic heads directed outward toward the aqueous environment, and the lipophilic portions forming an inner core that excludes water. When appropriate surfactants are dissolved in water, the resulting nanoparticles (NPs) can be exploited to accommodate substrates and catalysts to perform numerous organic transformations. Because the total volume of the lipophilic core is very small compared to the total reaction volume, and because most substrates reside therein, while a typical reaction may have a 0.5 M concentration with respect to water, the concentration inside the micelles tends to be substantially greater. This high local concentration leads to increased interactions between reactants, thereby typically affording increased reaction rates at lower temperatures compared to less concentrated reactions in organic solvents.

The nature of the solute(s) also determines its (their) location within the micellar medium. While nonpolar compounds preferentially dissolve within the core of the micelles, hydrophilic molecules such as short alcohols or amines tend to concentrate at the surface of the aggregate [15, 16].

Our group has designed a number of efficient nonionic surfactants for organic transformations in water, each with enabling capabilities for various applications, the most versatile of which is TPGS-750-M [7]. The diameter of micellar aggregates made from TPGS-750-M was determined by cryo-TEM experiments and lies between 40 and 60 nm. This diameter does not coincide with the length of two amphiphiles placed end to end, which would lead to micelles with diameters between 15 and 20 nm, or three times smaller than what is observed. Density functional theory (DFT) calculations confirmed that the assembly is not a single micelle, but rather 30–40 individual, smaller (c. 10 nm) micelles forming compartmentalized NPs (Figure 32.1) [17]. DFT calculations also demonstrated that very little water is present in the core of the individual micelles, confirming the existence of hydrophobic inner cores, while a considerable amount of water is present in the PEG regions. In this model, the external interface with bulk water is stabilized by the variable amounts of vitamin E succinate impurity present in the surfactant [17]. This complex structural array facilitates transfer of chemical entities between micellar cores by involving shorter distances and less contact with water. This explains why some highly water-sensitive species, such as organozinc reagents, can be accommodated in such an aqueous environment. The average assembly size associated with TPGS-750-M is c. 46 nm at pH = 4.

A less expensive alternative to TPGS-750-M, "Nok," is constructed from plant-derived β-sitosterol rather than tocopherol and may offer similar or greater yields for transition-metal-catalyzed coupling reactions [18].

In some reactions involving polar substrates that may be distributed in large measure outside the micelles, achieving high conversion can be problematic. To address this issue, MC-1 [8], a surfactant inspired by the polar aprotic solvent dimethylsulfoxide (DMSO), was developed to facilitate peptide synthesis in water. By incorporating a sulfone along the lipophilic chain of the surfactant (Figure 32.1), polar substrates are accommodated inside the lipophilic core, thus leading to greater levels of conversion and ultimately, higher yields.

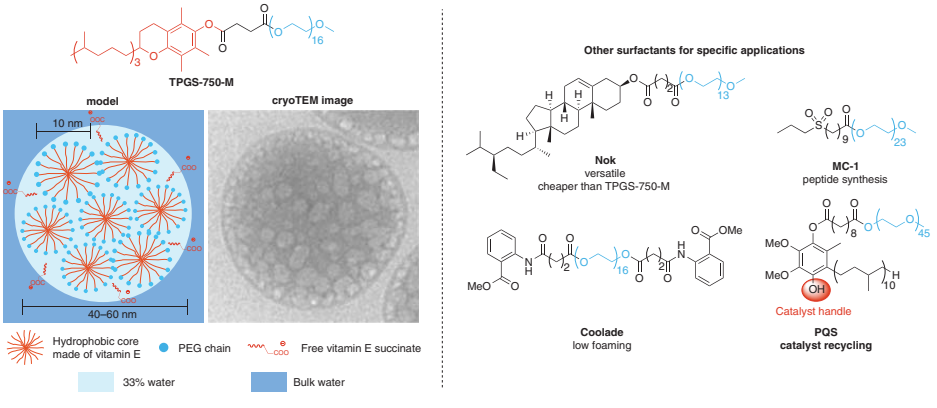


Figure 32.1 Designer surfactants and micelle-in-micelle assembly enabling organic transformations in water.

Surfactant design is often matched directly to the intended industrial application for which it is to be applied. In reactions that involve or generate gas, surfactant solutions have a propensity to foam, thereby limiting their utility especially at scale. Foaming of aqueous surfactant solutions is known to linearly decrease with decreasing length of the lipophilic moiety [19]. This led us to develop Coolade [20], a low-foaming designer surfactant constructed from a PEG chain in between two methyl anthranilate units. This design maintains the requisite hydrophilic–lipophilic balance to form micelles, but the short lipophilic chains limit foaming. Coolade is the surfactant of choice in reductions of *gem*-dibromocyclopropanes, nitro group and azide reductions, and in the preparation of Pd NPs.

Since these surfactants are engineered to remain in water during filtration or extraction of products, the aqueous layer can be reused multiple times upon addition of either fresh catalyst and/or starting materials. For the sake of recycling, a surfactant that can incorporate a catalyst covalently bound within its structure has also been developed. For example, polyethylene glycol ubiquinol succinate (PQS) [21], a platform made from the dietary supplement ubiquinol, has been used to attach proline [22] (for organocatalytic transformations), ruthenium carbenes (for olefin metathesis reactions), and an iridium catalyst (for photoredox applications) [23], within the lipophilic core of its nanomicelles.

Switching from organic solvents to aqueous surfactant solutions is not a simple media replacement. We discovered (and keep discovering) "new rules" along the way, specific to this type of technology [24]. Developing a good appreciation for these rules allows for better design elements for both surfactants and catalysts, leading to higher efficiencies for a given process.

32.3 Ligand Design

The world's declining supply of palladium has necessitated the development of highly effective palladium catalysts that function at low loadings, offer high functional group tolerance, reactivity and efficiency, and can be used under mild conditions. This is especially relevant to the pharmaceutical industry as targeted Active Pharmaceutical Ingredients (APIs) tend to increase in complexity while pressures to reduce drug prices mount. Added constraints arise from strict FDA guidelines requiring low levels of residual palladium ($\leq$10 ppm per dose) [25]. Typical conditions for Pd-catalyzed Suzuki–Miyaura cross-couplings (SMCs) involve the use of toxic organic solvents and rely on palladium loadings in the 1–5 mol % range. By increasing the lipophilicity of the ligand, however, catalyst residence time (i.e., its binding constant) within the micelle increases. Hence, given the high (usually $\geq$2 M) local concentration of substrates, lower levels of catalyst are required for these same C—C bond-forming transformations. With this new rule having been uncovered, EvanPhos, a *meta*-biaryl phosphine-containing platform constructed in only two steps, was developed as a highly active catalyst for SMCs [26]. By utilizing $Pd(OAc)_2$ and pre-activation of the derived ligated palladium(II) complex, the resulting

$(EvanPhos)_2Pd$ catalyst was effective at loadings in the ppm (0.1–0.5 mol%) range, an order of magnitude lower than traditional organic methods (Figure 32.2). Although designed for micellar systems, the catalyst system is also amenable to a typical use in the greener organic solvent EtOAc, affording coupled products in excellent yields.

Among the many advantages of this new catalytic system is the modular nature of the ligand. Its facile synthesis allows for derivatization of the skeletal structure, enabling development of new variants based on the need for more active species while maintaining the same benefits. The limited activity of $(EvanPhos)_2Pd$ toward aryl chlorides prompted the design of N_2Phos, a biaryl phosphine ligand that, likewise, enables ppm level SMCs in water [27].

DFT calculations illustrate that the greater steric congestion associated with N_2Phos induces increased steric crowding around the palladium center. This steric effect helps to destabilize the 2 : 1 ligand-Pd(0) complex derived from N_2Phos and $Pd(OAc)_2$, thereby favoring formation of the far more active 1 : 1 ligand-Pd(0) species. This new system is amenable to a wide array of aryl/heteroaryl halides and employs lower palladium loadings compared to EvanPhos. Most notably, highly functionalized aryl chlorides afford products at loadings of palladium in the 0.25 mol % range (Figure 32.2).

Palladacycles, which are characterized as among the most powerful precatalysts due to their ability to form highly active monoligated Pd(0) species, have been investigated as a means of achieving even lower palladium loadings [28–31]. To increase the efficacy of palladacycles in micellar systems, modifications were made to increase solubilization by increasing their affinity for the lipophilic core of the micelles, thereby greatly reducing the amount of Pd and ligand needed to facilitate cross-coupling reactions in water. Novel-substituted palladacycles have been prepared incorporating HandaPhos as ligand, wherein the palladacycle contains lipophilic *tert*-butyl, CF_3, or isopropyl residues. The di-isopropyl-substituted HandaPhos palladacycle proved to be the most effective when applied to Suzuki–Miyaura couplings needing only 300 ppm loadings of palladium for aryl bromides (Figure 32.3) [32]. Some coupling reactions could be performed at levels of palladium down to 25–100 ppm, showcasing the efficacy of this new precatalyst system. Reaction partners containing electron-donating and/or -withdrawing groups, in addition to heterocycles, were well-tolerated, as were less reactive aryl chlorides when loadings of 500 ppm palladium were employed.

It was found that the most effective palladacycle precatalyst contained isopropyl residues on both the aryl ring and on the nitrogen within the biaryl array. When paired with readily available and inexpensive EvanPhos and triflate as counterion, this new precatalyst shows increased efficacy toward highly valued reactions such as Heck and Sonogashira couplings at loadings of palladium in the 500–1500 ppm range [33]. Ligand development along these lines has proven to impart considerable catalytic activity to the resulting palladium complexes. This approach, which takes advantage of the simple notion of "like dissolves like" associated with micellar catalysis, opens new possibilities for sustainable processes applicable to syntheses of complex agrochemicals (e.g., Arylex, Rinskor) [34], APIs (e.g., sonidegib) [4], and other fine chemicals.

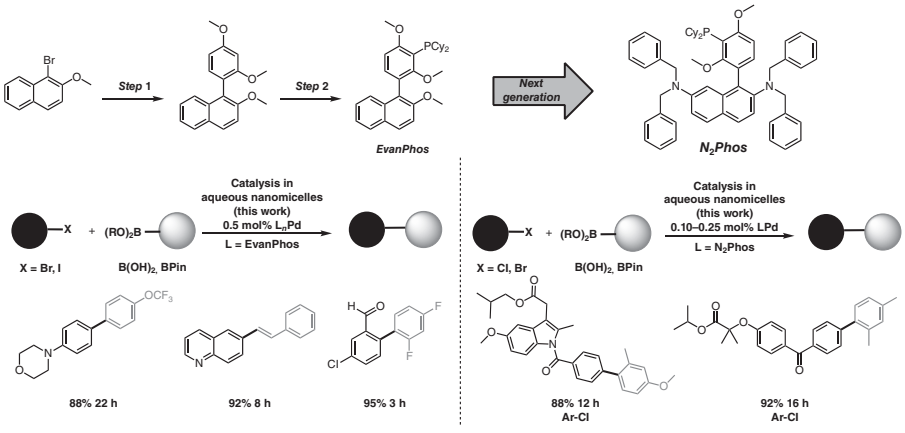


Figure 32.2 Ligand design and application to Suzuki–Miyaura cross couplings.

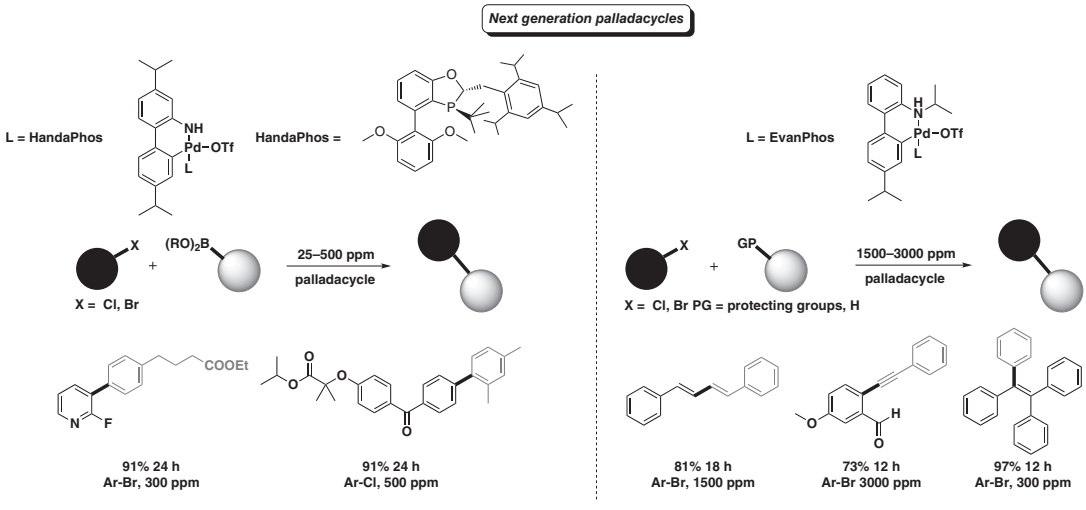


Figure 32.3 Next-generation palladacycles for cross couplings.

32.4 The "Nano-to-Nano" Effect

The use of transition metal-containing NPs has emerged as an alternative method for catalysis that relies on only ppm level quantities of catalyst. However, two important complications may arise when considering use of such NPs in aqueous surfactant solutions: (i) deactivation of the catalyst due to aggregation (which reduces the catalytic surface area) and (ii) transporting the substrate from the lipophilic core of the micelle to the aqueous phase containing the metal NPs. Fortunately, both complications are obviated when PEG-containing surfactants such as TPGS-750-M and Nok are used due to the "nano-to-nano" effect. This refers to the tendency of polyether PEG chains to act as stabilizing ligands on metal NPs, thus preventing aggregation [35, 36]. Moreover, the observation that PEG associates with the NPs means that the nanomicelles containing lipophilic substrates agglomerate around the catalyst NPs (hence "nano-to-nano"), effectively acting as an internal delivery system (Figure 32.4a–c). The unexpectedly high rates of reaction, mild reaction temperatures, and need for only ppm levels of metal catalyst to achieve the desired conversions are, therefore, attributed to the increased proximity of the substrates to the catalyst.

In 2015, a new platform was disclosed for delivering metal catalysts to aqueous nanomicelles: Fe/ppm Pd NPs [9]. These NPs are formed by the reduction of $FeCl_3$ containing ppm amounts of palladium, with MeMgCl. This process resulted in a solid, spherical nanomaterial that contained mostly metal salts and THF in which the NPs are made. Attempts to use this material as a catalyst for Mizoroki–Heck reactions [37] *in organic solvents* did not lead to any conversion. However, when dissolved in a 2 wt % aqueous solution of TPGS-750-M, the NPs acted as a highly effective catalyst. Cryo-TEM images of the nanomaterial before and after dissolution in aqueous surfactant demonstrated a remarkable change in shape and size (from micron-sized spheres to 50 nm rods; Figure 32.4). This effect, referred to as "water sculpting," is thought to be the result of salts being pulled out from the originally fashioned NPs and into the surrounding water, leaving the Pd-containing active catalyst behind. The images also demonstrate the nano-to-nano effect in action as the Fe/ppm Pd nanorods can be seen exclusively aggregated around the surfactant-derived nanomicelles.

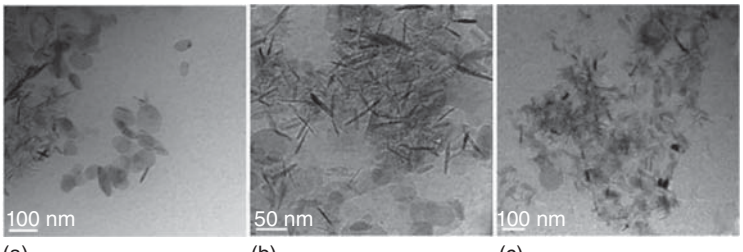


Figure 32.4 Cryo-TEM images; three different views (a–c) of TPGS-750-M-derived nanomicelles aggregated around Fe/ppm Pd nanorods.

The benefits of the "nano-to-nano" effect have been applied to numerous reaction types using different transition metal-containing NPs. The first of these was for Lindlar-like reductions of alkynes to *Z*-olefins using Pd NPs [38]. Several have been developed for Fe/ppm Pd NPs, including Suzuki–Miyaura [9] and Sonogashira cross-couplings [39]. NPs containing other transition metals have also been developed, including Fe/ppm Ni NPs which have demonstrated greater efficiency in the reduction of nitroarenes to their corresponding anilines compared to those using Fe/ppm Pd NPs [40], and Fe/ppm Cu NPs which effect highly efficient azide-alkyne click reactions [41]. In addition to the benefits regarding reaction rate, temperature, and low levels of catalyst loading, an important benefit of these NPs is recyclability. While heterogeneous catalysts containing lipophilic ligands (*vide supra*) may be partially or fully removed upon extraction of products, NP catalysts remain bound to the exterior of nanomicelles and can be reused in subsequent batches without the need for new catalyst. Another important consideration in pharmaceutical applications are the low levels of residual metals found in the final product. In all cases using Fe/ppm Pd/Cu/Ni NPs, residual metals have been shown to be well below the FDA-approved limits.

32.5 Reservoir Effect

Biocatalysis has emerged as a versatile and sustainable approach to generating chemo-, regio-, and stereoselective products with high levels of efficiency. The recent Nobel Prize for directed evolution highlights the potential of this methodology in the realm of organic synthesis and method development [42]. As powerful as this new tool is, most biolytic transformations, with the exception of some classes of lipases, require a buffered aqueous medium due to organic solvents' propensity to denature proteins, thereby diminishing their activity, or halting it entirely [43]. While greener alternatives have been developed to assuage this obstacle (e.g., eutectic solvents and ionic liquids), sterically demanding and larger lipophilic substrates often exhibit poor conversion in these media due to their poor solubility [44–47]. In an effort to expand the utility of biocatalysis, without the need for an additional organic solvent (e.g., DMSO), the compatibility of enzymatic systems under micellar conditions was investigated [48].

The well-studied oxidoreductase (i.e., alcohol dehydrogenase [ADH]) was investigated on a number of aryl ketones (Figure 32.5). All reactions were performed in a phosphate buffer at pH = 7 both with and without 2 wt % TPGS-750-M/H_2O. Enzymatic super activity was observed in the surfactant solutions as the lipophilicity of the substrates increased, implying a synergistic effect. In the case of the larger more lipophilic 2-ethylhexyl acrylate (Figure 32.5), the reduction reached 82% conversion after 24 hours, while slope discontinuity at 25% was observed after one hour in just buffered media, indicating enzyme saturation.

The rationale for this phenomenon is that under typical conditions, entrance into the enzyme active site is eventually hindered by the accumulation of water-insoluble substrates and products, thus leading to incomplete conversion in the buffered aqueous medium. In the presence of micelle-containing media, however, the

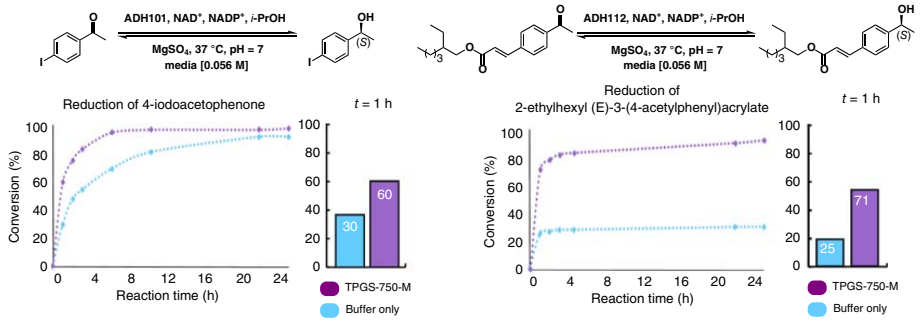


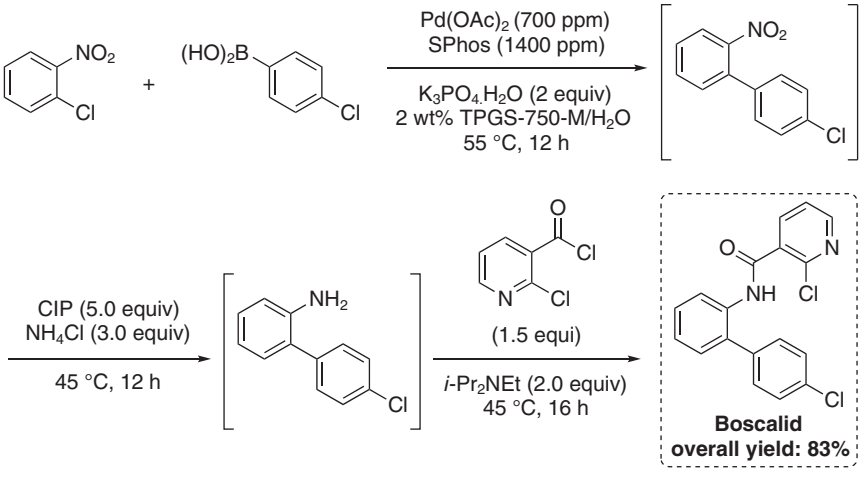
Figure 32.5 Positive effect of TPGS-750-M on enzymatic activity, exemplified by reduction of aryl ketones by ADH112.

micelles function as a "solvent" for the substrates and products, compartmentalizing them and acting as a reservoir. The dynamic nature of micellar environments allows for a slow release of organic molecules into the aqueous phase where the enzyme is present so that the biocatalytic transformation can occur. Thus, micelles in the buffer help to control both substrate and product concentrations in the aqueous medium, providing a measured supply that does not overcrowd and, in turn, lead to enzymatic inhibition, allowing for higher rates of conversion. Other enzyme classes are currently being investigated and a similar outcome has been observed, indicating that the effect may be general, thereby opening the door to new transformations that can be performed biocatalytically.

32.6 Access to Opportunities for Telescoping Sequences

Synthetic sequences to APIs regularly involve several steps; therefore, having the ability to telescope several of them, i.e., perform multiple synthetic steps in a single pot, can substantially reduce solvent waste both by limiting the total volume of reaction solvents as well as eliminating multiple purification processes. On the multi-kilogram scale, this translates into considerable cost savings, both monetarily and environmentally. Unfortunately, it is rare that chemists who employ traditional synthetic methods in organic solvents have the luxury of telescoping reactions since these sequences typically require steps that occur in different solvent media. Fortunately, the nondiscriminatory nature of aqueous nanomicelles provides an alternative that not only makes tandem sequences possible, but also affords an opportunity to telescope reactions under mild conditions using only water as the global reaction medium.

Several demonstrations of tandem sequences have already been described, including the industrially relevant one-pot, three-step sequence leading to the fungicide boscalid (Scheme 32.1) [4]. This multistep process not only improved upon prior



Scheme 32.1 Synthetic path toward boscalid.

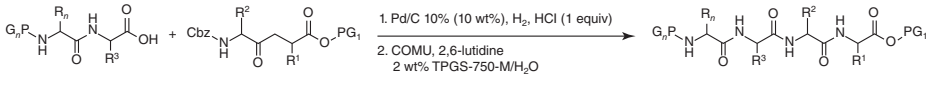
methods en route to this target by reducing catalyst loading and temperature (as a result of the high local concentration within the micelles, as discussed previously) but also required only 9.0 ml of water containing very little surfactant for the three steps performed on a 5 mmol scale.

Another example of a one-pot, multistep sequence in an aqueous surfactant medium is the tandem deprotection/coupling of Cbz-protected oligopeptides (Scheme 32.2) [49]. Amide bond formation is one of the most heavily utilized transformations in the chemical enterprise, including the synthesis of oligo- and polypeptides. However, common methods for their syntheses typically involve copious quantities of environmentally egregious organic solvents (e.g., DMF, DMSO) and coupling reagents which often lead to E Factors upward of 250–1000. The tandem procedure now available avoids this by replacing organic solvents with an aqueous surfactant solution and replacing harmful coupling reagents such as HOBt and piperidine with the comparatively mild (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) and 2,6-lutidine. Moreover, both the deprotection and coupling steps are combined into a sequential, 1-pot procedure. Using this method, E Factors as low as 10 have been obtained. The decapeptide Cbz-D-Phe-Pro-Val-Orn(Boc)-Leu-D-Phe-Pro-Val-Orn(Boc)-Leu-OMe (the linear precursor of the antibiotic gramicidin S) was synthesized via both an [8 + 2] and a [5 + 5] convergent strategy, leading to 82% and 72% yields, respectively. Shorter peptides such as Cbz-Phe-Leu-OEt were obtained in nearly quantitative yields.

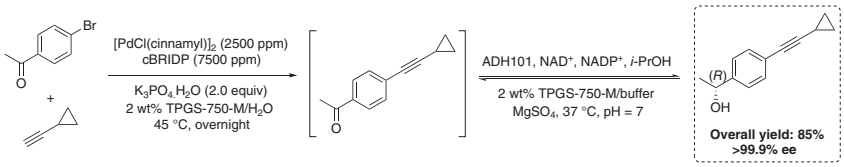
An especially interesting prospect enabled by micellar catalysis involves tandem chemo-/bio-catalytic sequences. Because enzymes are oftentimes restricted to an aqueous environment, telescoping bio-catalyzed reactions with traditional chemo-catalyzed transformations in organic solvents is possible but requires removal of the organic medium and replacement by an aqueous buffer solution. This exchange is avoided by use of an aqueous surfactant reaction medium for effecting both bio- *and* chemo-catalysis. For instance, several telescoped sequences have been developed for the enzyme ADH such as a tandem ppm Pd, Cu-free Sonogashira cross-coupling followed by ADH-catalyzed asymmetric ketone reduction (Scheme 32.3), and the ppm Au-catalyzed alkyne hydration followed by ketone reduction by ADH (Scheme 32.4) [48].

Both reaction types gave rise to good overall yields and excellent enantioselectivities, while the enzyme was unaffected by residual metal catalysts and salts leftover from each of these prior transformations, a phenomenon further exemplified by the three-step, one-pot sequence shown in Scheme 32.5. This process generates relatively large quantities of metal and salt impurities, and yet the enzymatic reduction proceeds unimpeded, presumbly a result of the nanomicelles present that accomodate the ligated metals. Tandem processes using different enzymes such as ene-reductase and lipase, as well as sequences where the biocatalytic step precedes the chemo-catalytic step, are currently under study.

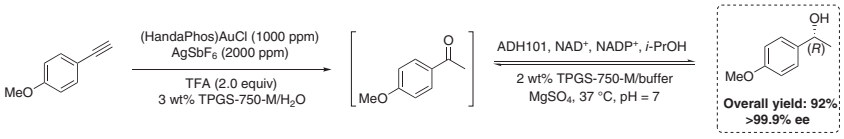
With the recent advances in aqueous micellar catalysis, there is no longer any question over whether telescoping reactions is possible, and the focus is shifting now toward how best to design these sequences to minimize waste and maximize efficiency.



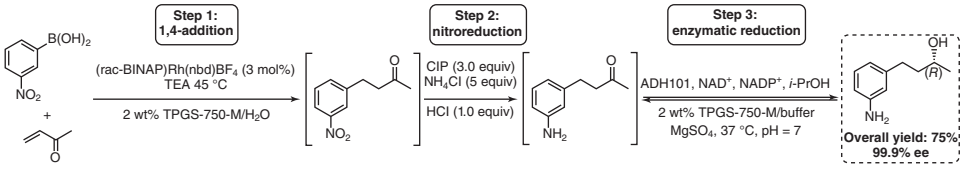
Scheme 32.2 Tandem peptide deprotection/coupling.



Scheme 32.3 ppm Pd, Cu-free Sonogashira coupling, then ADH.



Scheme 32.4 ppm Au-catalyzed alkyne hydration, then ADH.



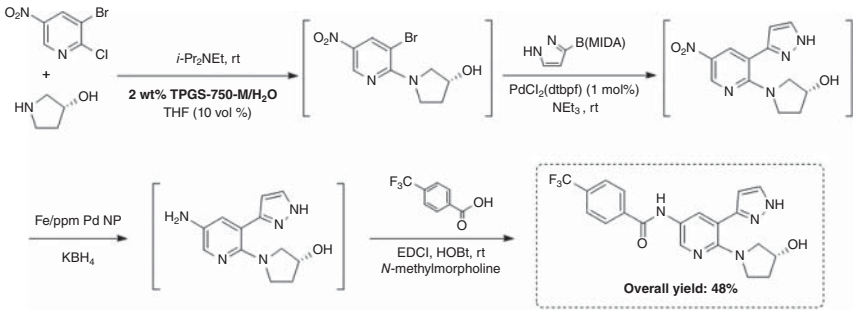
Scheme 32.5 Three-step, 1-pot sequence involving both chemo- and biocatalysis.

32.7 Industrial Applications

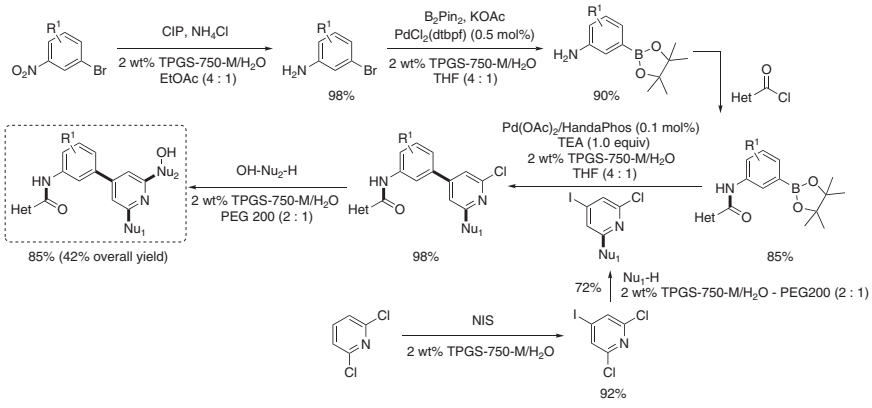
While recent discoveries regarding micellar catalysis and the "new rules" that govern it are exciting from an academic standpoint, the greatest real-world impact is observed when reactions are increased to an industrial scale. As discussed, chemistry in water offers obvious economic and productivity benefits such as lower cost associated with waste management, higher reaction rates, selectivities, and yields, and importantly, improved safety compared to organic solvents. Also noteworthy is that micellar catalysis improves greatly on the environmental impact of industrial syntheses. One key metric used to evaluate the greenness of chemical processes is process mass intensity (PMI), which is calculated as the mass of materials used divided by the mass of the final product, with lower PMIs indicating greener processes.

An example of an industrial application of micellar catalysis comes from Novartis, which developed several multistep, one-pot syntheses in water. The example illustrated in Scheme 32.6 involves a four-step, one-pot process featuring a selective S_NAr, a Suzuki–Miyaura cross-coupling, a nitro group reduction using ppm Pd-containing NPs, and lastly, amide bond formation [50]. All steps were performed in a single pot without isolation of intermediates using only an aqueous solution of TPGS-750-M and a small amount of cosolvent. The final product was accessed with 48% overall yield (vs. 43% in organic solvents), and the overall PMI was estimated at 161 (vs. 238).

Lippincott et al. demonstrated a Suzuki–Miyaura cross-coupling reaction under micellar catalysis conditions between a dichloropyridine and a bromoaniline [51].



Scheme 32.6 Industrial example of a 4-step, 1-pot synthesis toward an API.

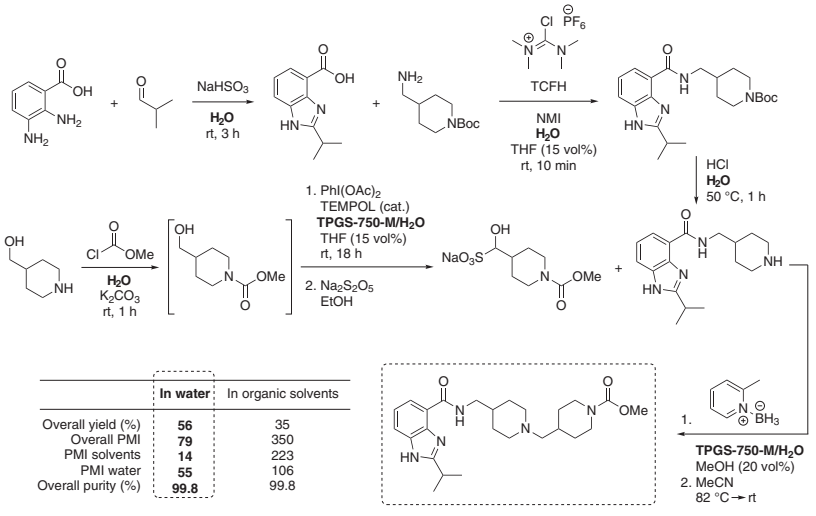


Scheme 32.7 Multistep synthesis enabled by micellar catalysis in water.

A higher selectivity (vs. oversubstitution) was observed when the initially used toluene was replaced by a 2 wt% aqueous solution of TPGS-750-M. Owing to the high lipophilicity of the newly introduced ligand HandaPhos, catalyst loadings as low as 1000 ppm (0.1 mol %) were sufficient to afford the desired product in >95% yield. Optimization of the reaction scheme by judiciously adjusting the polarity of each starting material led to a convergent five-step synthesis involving nitro reduction, borylation, iodination, Suzuki–Miyaura coupling, and finally, an S_NAr reaction, all in the same aqueous solvent system, with an overall yield of 42% (Scheme 32.7).

Recently, Bailey at Takeda Pharmaceuticals received the 2020 Peter J. Dunn Award for the synthesis of a 5-HT_4 receptor agonist, made predominantly in water, where use of TPGS-750-M was crucial for several key steps [52]. The initial route as developed involved five different organic solvents and led to a 35% overall yield with a production mass intensity (PMI) of 350. The new route afforded the product in 56% yield and featured a PMI as low as 79 with identical purity (Scheme 32.8). Operating in water also allowed adjustment of the workup pH, thus facilitating precipitation of the desired intermediates/product.

These selected examples are illustrative of the opportunities that micellar technology offers to the industrial arena, as well as the benefits to be realized using this approach to synthesis. Use of micellar catalysis makes sense, not only from an



	In water	In organic solvents
Overall yield (%)	**56**	35
Overall PMI	**79**	350
PMI solvents	**14**	223
PMI water	**55**	106
Overall purity (%)	**99.8**	99.8

Scheme 32.8 Takeda's synthesis of a 5-HT4 receptor agonist in water.

environmental point of view but also from an economic perspective. Generating less waste, using a single medium over multiple steps, lowering catalyst loadings, and accessing greater yields under milder conditions are all facilitated by surfactant technology.

32.8 Conclusions

Not long ago, performing a multitude of organic reactions in water was unthinkable; but with advancements associated with newly engineered "designer" surfactants, Nature's solvent has proven itself to be a powerful alternative to environmentally egregious organic solvents. The nanoreactors generated upon dissolution of very small amounts of surfactant in water lead to concentrated solutions of water-insoluble substrates and catalysts within their lipophilic cores, thereby enabling lower reaction temperatures and catalyst loadings compared to those required using organic solvents. This technology has been applied to industrial targets and is readily amenable to multi-step, one-pot reactions affording lower PMI outcomes and hence, a significant reduction in associated waste generation. The nanoreactors' role as substrate/product reservoirs has enabled biocatalysis involving lipophilic substrates in water by minimizing enzymatic inhibition, thus allowing for access to greater levels of conversions and thus greater yields compared to those seen in conventional aqueous buffers. Using aqueous surfactant solutions as a common medium for both bio- and chemo-catalysis enables tandem processes, saving costly workup between steps. The affinity between metal NPs and the MPEG moiety of surfactants gives rise to the nano-to-nano effect, delivering substrate-filled nanomicelles directly to nanoparticle catalysts. None of these features exist in conventional organic solvents and are only possible because of the unique properties of

nanomicelles and aqueous media. There is no longer any question whether water is a suitable "solvent" for organic reactions; while counter-intuitive, it is the *preferred* medium for organic synthesis of the future.

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