
Micellar Nanoreactors

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1 OVERVIEW

Homogeneous catalysis has nowadays reached extremely high levels of selectivity. Nevertheless, several efficient catalytic systems need to be reconsidered in light of emerging and increasingly stringent requirements represented by green chemistry principles. Since the solvent represents the major chemical constituent in the total mass of a reaction, it is compelling to consider the use of alternative solvents in homogeneous catalysis. Among all, water should be the solvent of choice; nevertheless, because of the difficult solubilization of organic species it is usually not considered when developing new catalytic systems. Nature operates in aqueous media and chemical transformations are carried out by enzymes being able to completely surround the substrates, thus favoring their solubilization and ensuring high activity and selectivity. Among several possible strategies to develop homogeneous catalysis in water, the use of surfactants that form micelles represents a straightforward method to circumvent solubilization issues and, at the same time, to ensure impressive examples of catalytic activities and selectivities due to the confinement effect of micelles and their anisotropic structure.

Micellar catalysis takes advantage of the wide availability of commercial, economic surfactants with different structural and physicochemical properties. Micelles can dissolve both apolar substrates and metal catalysts driven by the hydrophobic effect or ion pairing when considering charged surfactants. The confinement of the catalyst

in several cases enables simple catalyst recycling using an organic apolar solvent in limited amounts. Examples of application of micellar catalysis covers all kinds of chemical transformations also in the stereoselective form, in most cases with better performance compared to traditional organic solvents. Overall micellar media in catalysis are a solid alternative to traditional organic solvents and it is advisable that more and more people will consider this approach for their future studies.

2 INTRODUCTION

2.1 Catalysis in Water: Why it is so Important

Stringent environmental concerns are changing the society. The evolution of chemical synthesis and catalysis is at the forefront of innovation and because of this, such research areas are nowadays closely connected to green chemistry. The selection of the solvent, often an unavoidable component in a chemical reaction, is a crucial point because it can have a tremendous environmental impact. It is in fact known that solvent use worldwide amounts to about 30 million metric tons per year for different uses, it represents the largest portion of the total mass of a reaction (50–80% of the total mass of chemical handled),^{1,2} and in 70% of the cases solvents are simply incinerated to recover heat.³ The importance of the solvent is underlined in the fifth principle of green chemistry,^{4,5} but it affects several others. The solvent should be selected in order to minimize toxicity, energy demand, pollution, and so on. This is a key issue that has spurred a great effort towards the development of alternative solvents (see Solvent Systems for Sustainable Chemistry), sometimes called green, even though it is the use of the solvents that can be defined as green, not the solvent itself.

Among all possible liquids, water is certainly the one with the smallest impact on the environment. In fact, it is nontoxic, non-flammable, economic, and readily available and its *E* factor value equals zero,⁶ which means that it is not considered a waste in chemical transformations. Because of this, in the past there were several attempts to develop chemical transformations in water. A landmark example is represented by the Ruhrchemie–Rhône–Poulenc hydroformylation process carried out in water as solvent to convert propene and 1-butene into the corresponding one carbon longer aldehydes using rhodium catalysts modified with sulfonate-containing phosphine ligands.⁷ Apart from the latter example, the use of water in catalysis finds limited application because water is not a suitable solvent for most organic substrates and metal catalysts as well. On the contrary, in Nature all chemical transformations occur in water. The key difference is that in Nature chemical reactions take place within extremely advanced systems such as cells and are mediated by enzymes. The

latter operate through an in depth binding of the organic substrates, exposing the hydrophilic surface to bulk water, shielding somehow the hydrophobic substrate, exploiting successfully the hydrophobic effect. Conversely, traditional homogeneous catalysts are orders of magnitude smaller and cannot surround the substrate, thus being often incompatible with water because of mere solubility issues.

Therefore, the simplest approach to mimicking some of the features of enzymes consists in exploiting self-assembling units that generate highly ordered structures capable of surrounding the catalyst and dissolving the substrates.⁸ Development of artificial enzyme models mimicking natural enzymes is a promising and active field of catalysis that has been pursued by researchers for several decades.^{9–15} Among several possible supramolecular enzyme mimics based on various unimolecular building blocks,^{16–18} the use of micelles in water to cope with the low solubility of substrates and catalyst turned out to be one of the most effective and economic alternatives to traditional catalysis in organic solvents. In this critical review, selected contributions considering recent publications in the field are described with the aim of giving the reader a good survey of the great opportunities offered by micellar systems in homogeneous catalysis with the final aim of convincing scientists about the feasibility of catalysis in water in a simple and economic manner.

2.2 Structure and Properties of Micelles: Micellar Effects

Micelles are nanoscale assemblies formed by the spontaneous aggregation of about 50–100 monomers of surfactant molecules. The molecular structure of these amphiphilic monomers can be very different as reported in selected examples in Chart 1 with several combinations of hydrophilic and hydrophobic parts, charge, and size. These properties along with other experimental variables such as temperature, pH, ionic strength, and presence of organic solutes greatly influence the aggregation of micelles and in particular their solubilization properties toward other species.

The formation of the aggregate is spontaneous in water, it is driven by the hydrophobic effect, and it occurs at concentrations of surfactants above a minimum value called the critical micellar concentration (c.m.c.). Such aggregates can have different shapes and sizes and are in thermodynamic equilibrium where monomers rapidly exchange among aggregates. In analogy to enzymes, micelles are characterized by a hydrophilic surface where the hydrophilic head-groups are exposed to bulk water to ensure solubility and by a hydrophobic core created by the alkyl chains where organic species can be solubilized efficiently depending on their polarity, charge, and dimension. Apolar substrates exclusively hosted within micelles experience a local concentration within the supramolecular aggregates some orders of magnitudes higher than that

calculated considering the entire volume of the aqueous solution. This often turns out into higher catalytic activity and because of the non-isotropic properties of micelles, also in enhanced chemo-, regio-, and stereoselectivities. Similarly to substrates and thanks to ionic interactions with micelles of opposite charge, charged metal species can be concentrated and dissolved in micellar media that represent a sort of second coordination sphere¹⁹ of the metal center.

After the early seminal works dating back to the late 1970s,²⁰ micellar catalysis greatly improved over the years^{21–25} and today represents one of the simplest and most economic methods to combine easy metal catalyst dissolution in close contact with apolar substrates exploiting water and its unique features as the solvent, to achieve more sustainable catalytic systems. The above-mentioned advantages are further improved when recycling of the micellar medium by simple extraction is feasible. In such cases, an organic water-immiscible solvent is used and its chemical nature and amount contribute to the environmental impact of the entire process. Lipshutz and coworkers demonstrated that when recycling is possible, micellar catalysis is a very sustainable approach to homogeneous catalysis,²⁶ allowing drastic reductions of the *E* factor of processes compared to the use of organic solvents, in some cases to one tenth of the original value calculated in traditional media.

3 APPLICATION OF TRADITIONAL SURFACTANTS IN CATALYSIS

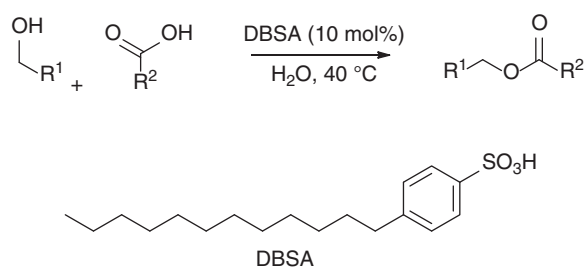
3.1 Examples of Yield Improvement Imparted by Micelles

3.1.1 Dehydration Reaction

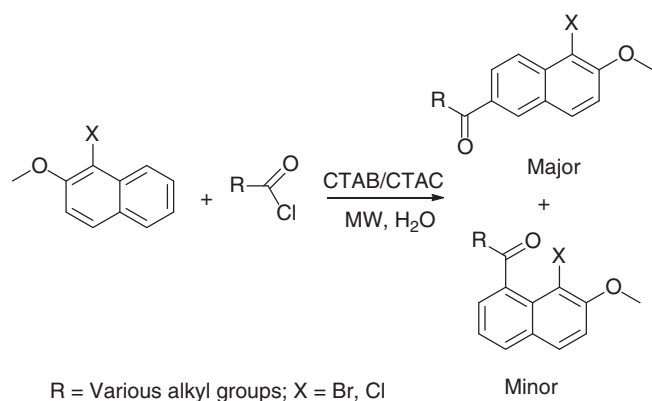
One of the most interesting applications of micellar catalysis that clearly describes the compartmentalization effect is the apparently impossible esterification reaction between apolar carboxylic acids and apolar alcohols carried out in water with the aid of an acid surfactant such as dodecylbenzenesulfonic acid (DBSA) in water. This seminal work by Kobayashi and coworkers²⁷ demonstrated that for substrates that are deeply hosted within the apolar core of the micelles it is possible to observe Brønsted acid catalyzed dehydration reactions even though the solvent employed is water. The hydrophobic effect pushes the substrates deep into the micelles where the reaction occurs and where the hydrophobic environment expels the produced water, leading to the formation of highly lipophilic esters in good yields under mild conditions (Scheme 1).

3.1.2 C–C bond Forming Reactions

The confinement effect typical of micellar catalysis allows developing traditional organic reactions in water



Scheme 1 Dodecylbenzenesulfonic acid catalyzed esterification of apolar acids and apolar alcohols in water



Scheme 2 Environmentally benign Friedel–Crafts acylation of 1-halo-2-methoxynaphthalenes and its related compounds under micellar conditions

such as the Friedel–Crafts acylation of aromatics, usually performed in organic solvents because of the presence of moisture-sensitive reagents. The reaction reported in Scheme 2²⁸ describes the positive effect imparted by the addition of cationic surfactants such as cetyl trimethylammonium bromide and chloride (CTAB or CTAC) to the reaction between acetyl chloride and 1-halo-2-methoxynaphthalenes, 2-methoxynaphthalene, anisole, 2-methoxypyridine, and 2-methoxypyrimidine derivatives, with high yields for the corresponding acylation products under mild experimental conditions with the aid of microwave irradiation. This approach allows avoiding annoying features such as prolonged reaction times, harsh reaction conditions (reflux temperature), metal triflates, mineral acids, and stoichiometric amount of metal halides that produce hazardous corrosive waste products.

Apart from the above, there are several examples of multicomponent reactions that make use of surfactants in water in order to develop sustainable syntheses of complex molecular structures. Detailed examples of these and other reactions in micellar media have been recently reviewed.²⁹

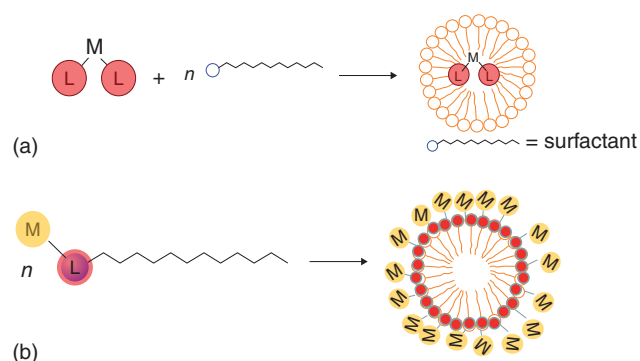


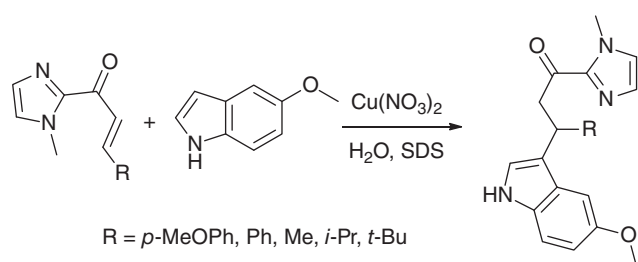
Figure 1 Approaches to metal catalysis in micellar media: (a) solubilization of metal catalysts on the surface or within micelles; (b) covalent metal–surfactant units forming metallomicelles

4 METAL-MEDIATED MICELLAR CATALYSIS: YIELD ENHANCEMENT

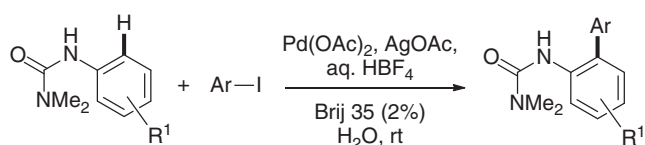
Micellar catalysis is completely compatible with metal catalysis. Two approaches are possible: (i) the employment of supramolecular aggregates to dissolve the catalyst thus maintaining the integrity of the original organic soluble catalyst and (ii) metallosurfactant molecules that self-assemble into micelles in solution (Figure 1). In the first case traditional metal catalysts developed for the organic media are reinterpreted in water without requiring tedious and time-consuming covalent ligand modifications but exploiting the solubilizing and confinement properties of micelles. In the second case, ligand modification is requested but is limited to the insertion of long hydrophobic ponytails into ligands leading to metal complexes that, thanks to the long alkyl chain, self-assemble in water forming micelles decorated on the surface with active metal centers. The latter approach has been demonstrated to be very efficient especially for asymmetric reactions as described later on.

4.1 C–C Bond-Forming Reactions

A simple example of the potentialities of micellar catalysis for traditional metal-mediated transformations is represented by the Friedel–Crafts alkylation of indoles. The reaction can be efficiently run in water with the aid of sodium dodecylsulfate (SDS) as inexpensive surfactant in the presence of simple Cu(II) salts as catalysts. It is remarkable that the presence of the anionic surfactants boosts the rate of the reaction up to 9.3×10^3 times compared to the same reaction in pure water (Scheme 3).³⁰ As typically observed in micellar systems, aryl derivatives that are more hydrophobic showed larger accelerations with respect to more hydrophilic substrates.



Scheme 3 Dramatic micellar rate enhancement of the Cu(II) catalyzed vinylogous Friedel–Crafts alkylation in water. (Adapted from Ref. 30 with permission from Royal Society of Chemistry)

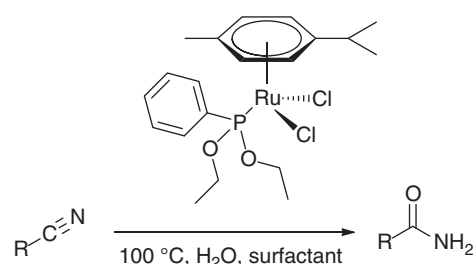


Scheme 4 Room temperature CH arylation of aryl urea derivatives mediated by Pd(II) in water with Brij 35. (Adapted from Ref. 31 with permission from Wiley)

Micellar catalysis often showed to greatly improve the experimental conditions requested for specific transformations, in most cases allowing milder experimental conditions. Another interesting example of the dramatic rate acceleration imparted by micellar media is the cross-coupling reactions of aryl halides with aromatic C–H bonds that is usually carried out with Pd catalysts at 100 °C or above. It is worth noting that in water in the presence of neutral surfactants such as Brij35, this reaction occurs at ambient temperature as described in Scheme 4³¹ where the mono-C–H activation of urea derivatives and their cross-coupling with aryl iodides was possible, leading to the corresponding biaryl derivatives in the 70–97% yield range.

4.2 C-Heteroatom Bond-Forming Reactions

Hydration reactions usually are performed in aqueous–organic solvent mixtures to cope with the poor solubility of organic substrates. The implementation of micellar catalysis for this class of reactions is highly desirable as described in the nitrile hydration leading to amide products. This kind of transformation usually requires harsh conditions and Lewis or Brønsted acid catalysis. Careful optimization of ligand, metal species, and experimental conditions allowed accomplishing an efficient nitrile hydration in water using poorly soluble [RuCl₂(η⁶-arene)(PR₃)] catalysts with the aid of neutral surfactants (Scheme 5).³² The optimized system led to the formation



Scheme 5 Micellar catalysis in the Ru(II) mediated nitrile hydration in water. (Adapted from Ref. 32 with permission from Royal Society of Chemistry)

of amides from nitriles with 40% to 95% yields for both aliphatic and aromatic amides at 100 °C.

5 METAL-MEDIATED MICELLAR CATALYSIS: PRODUCT SELECTIVITY

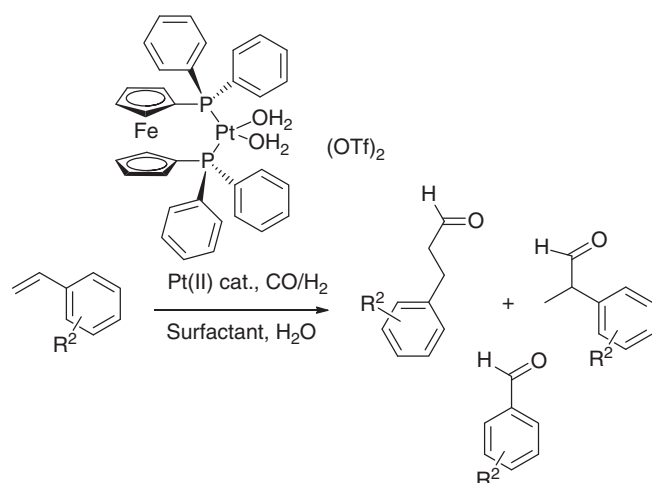
5.1 C–C Bond-Forming Reactions

The hydroformylation reaction is an extremely important industrial transformation for the preparation of elongated linear and branched aldehydes from alkenes. Several metal species promote the reaction with regioselectivities that are greatly influenced by the ligands coordinated to the metal center. Bis-cationic Pt(II) catalysts of the type [P₂Pt(H₂O)₂](OTf)₂ bearing large bite angle diphosphines were shown to promote the reaction in water in the presence of anionic surfactants such as SDS that favor catalyst solubilization in water through ion pairing (Scheme 6).³³ It is interesting to note that, apart from a substantial improvement of the catalytic performance of the reaction compared to the use of organic media, the use of anionic micellar media favored good linear/branched aldehyde selectivities (up to >99:1) that can rival the best traditional Rh(I) catalysts. Moreover, the micellar media also enabled an unusual reaction on styrene derivatives forming minor amounts of the corresponding benzaldehyde together with the expected elongated aldehydes. The good affinity of the cationic metal species with the anionic micelles enabled catalyst recycling for at least four times with only a modest decrease in activity and no effects on selectivity.

5.2 Stereoselective Catalytic Reactions

5.2.1 Hydrogenations

Catalyst recycling is especially important for asymmetric metal-catalyzed reactions in order to limit the loss of precious metal and ligands. Two examples of efficient recycling are reported in Scheme 7 for the asymmetric transfer

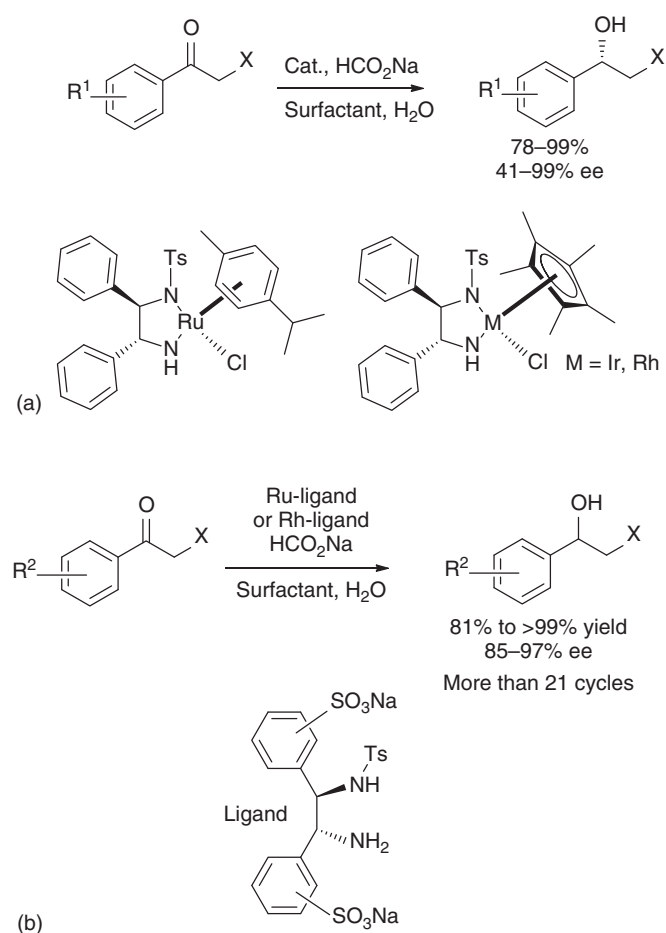


Scheme 6 Anionic micellar catalysis in the Pt(II) mediated hydroformylation of terminal alkenes in water. (Adapted from Ref. 33 with permission from Wiley)

hydrogenation of ketones to secondary alcohols mediated by different combinations of transition metal catalysts and surfactants. In particular, as described in Scheme 7a the catalyst (*R,R*)-TsDPEN-[Ru-Cl(cymene)] and the homologous Ir(I) and Rh(I) species proved to perform well when dissolved in water with sufficiently hydrophobic ketones in cationic CTAB micelles, leading to significant increases in activity with isolated yields up to 97% and enantioselectivity up to 99% ee.³⁴ The confinement of the catalyst within the micelles enabled efficient recycling for at least six times. Better results were obtained improving the interactions between catalyst and micelles with the use of Ru(II) and Rh(I) metal complexes bearing a sulfonated chiral ligand (Scheme 7b)³⁵ in water in the presence of cetylpyridinium bromide (CPB) as cationic surfactant. In this case, leaching of the metal was minimized and it was possible to recycle the catalyst for more than 20 times with almost unaltered enantioselectivity and yields.

5.2.2 Oxidations

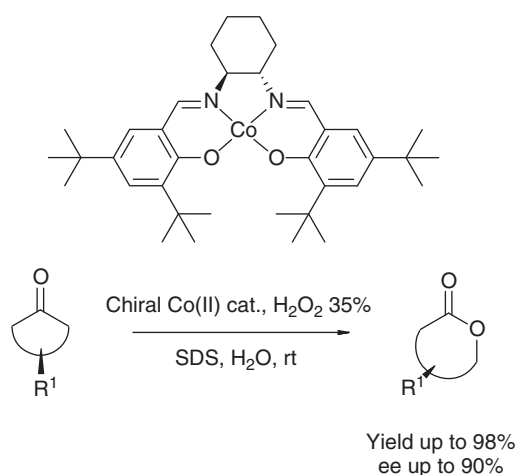
The use of water as solvent and micellar catalysis are examples of green chemistry approaches to chemical synthesis and catalysis. Following the same trend, reagents characterized by lower environmental impact should be preferred. This is the case of the selection of oxidants for oxidation reactions. Among others, molecular oxygen and hydrogen peroxide are the most interesting oxidants in terms of atom efficiency. Their use is preferable also because they provide water as the by-product. This makes these oxidants perfectly compatible with micellar catalysis in water. In the following, some examples of the synergistic effects observed by the use of hydrogen peroxide as oxidant



Scheme 7 Examples of asymmetric transfer hydrogenation reactions of ketones in micellar media: (a) neutral transition metal catalysts with cationic surfactant cetyl trimethylammonium bromide (CTAB) (Adapted from Wang *et al.*³⁴ with permission from American Chemical Society); (b) In situ formed anionic transition metal catalysts with different surfactants. (Adapted from Ref. 35 with permission from Royal Society of Chemistry)

and aqueous micellar media for metal-catalyzed asymmetric oxidation reactions are reported, observing in all cases enhancements of the stereoselectivity with respect to the same reactions run in traditional organic solvents.

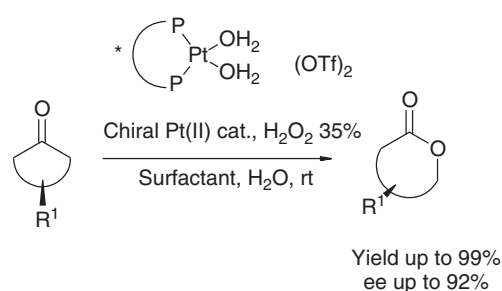
Micellar media in some cases were demonstrated to transform almost inactive metal complexes into active and stereoselective catalysts. This is the case of the Baeyer–Villiger oxidation with hydrogen peroxide of cyclic ketones with the Co(Salen) catalyst reported in Scheme 8.³⁶ The reaction on *meso*-cyclobutanones did not occur if carried out in organic solvents while the same metal complex led to significant asymmetric inductions if tested in water with the aid of anionic surfactants. Extension of the micellar catalytic system to the oxidation of chiral racemic cyclobutanones led to the formation of the corresponding five-membered ring lactones with diastereoselective ratios up to 84:1 and ee up to 90%.



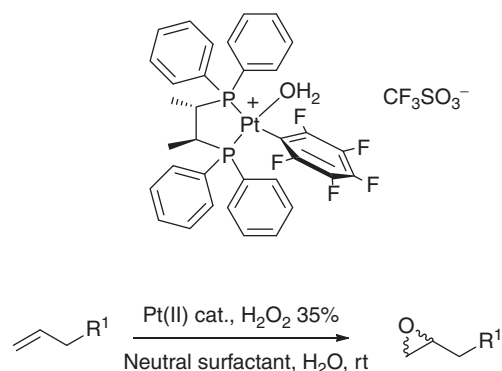
Scheme 8 Anionic micellar media promoted Co(salen) mediated enantioselective Baeyer–Villiger oxidation of cyclic ketones with hydrogen peroxide. (Adapted from Ref. 36 with permission from Royal Society of Chemistry)

The same asymmetric oxidation reaction of cyclic ketones was also optimized with chiral Pt(II)-diphosphine catalysts (Scheme 9).³⁷ After a careful optimization of all reaction players, namely, catalyst, surfactant, substrate, it was possible to obtain very good results in terms of yield of the corresponding lactones and degree of asymmetric induction. In particular, the application of the optimized catalytic system to the more reactive *meso*-cyclobutanones allowed the formation of the lactones in high yields and ee up to 56%, while extension to *meso*-cyclohexanones resulted in a general decrease in yields but an increase of stereoselectivities with ee up to 92%. It is worth noting that in most cases, especially for more hydrophobic substrates, a marked increase of stereocontrol of the reaction was observed in micellar media compared to organic media and this positive effect could be attributed to the more ordered environment present within the micelles where substrates are dissolved that leads to tighter supramolecular control on the stereoselective reaction.

Recycling of oxidation catalysts is usually more difficult compared to hydrogenation catalyst because of more harsh experimental conditions that sometimes lead to catalyst inactivation. An example of the positive effect provided by micelles was observed in the asymmetric epoxidation reaction of terminal alkenes mediated by chiral Pt(II) complex $\{[(S,S)\text{Chiraphos}]\text{Pt}(\text{C}_6\text{F}_5)(\text{H}_2\text{O})\} (\text{OTf})$ using hydrogen peroxide as the terminal oxidant as depicted in Scheme 10.³⁸ In this case neutral surfactants turned out to be the proper choice to ensure sufficient catalyst solubilization and good product formation with enhanced stereoselectivity for the epoxide products. This is the case of, e.g., the oxidation of 4-methyl-pentene that provided the corresponding epoxide with only 58% ee in DCE while



Scheme 9 Chiral Pt(II) catalyst mediated asymmetric Baeyer–Villiger oxidation of cyclic ketones to the corresponding lactones in micellar media. (Adapted from Ref. 37 with permission from Wiley)

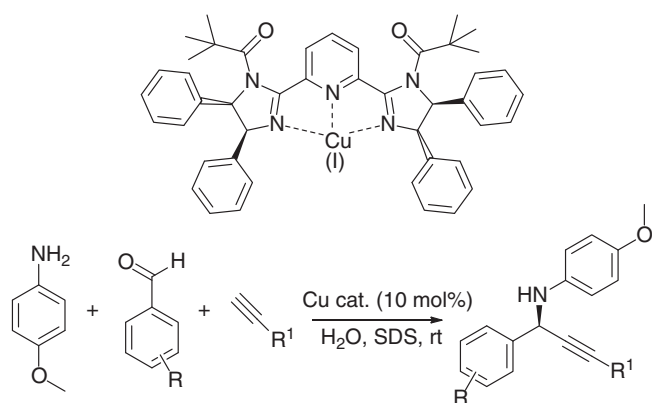


Scheme 10 Neutral micellar media promoted asymmetric epoxidation of terminal alkenes catalyzed by chiral Pt(II) species. (Adapted from Ref. 38 with permission from Wiley)

under micellar conditions with water/Triton-X100 the stereoselectivity increased up to 82% ee. It is also worth noting that recycling of the system was possible for up to three consecutive runs with constant conversion and enantioselectivity.

5.2.3 C–C Bond-Forming Reactions

Micellar catalysis is especially valuable for hydrophobic substrates. Even multicomponent reactions that involve more than two reagents take advantage from the compartmentalization effect favored by the presence of surfactants in water. An example of this is the stereoselective three-component condensation reaction between anilines, aldehydes, and alkynes using a cationic hydrophobic bis(imidazoline)-Cu(I) catalyst. The anionic micelles provided the proper environment to promote the intimate contact between the catalyst and the three different substrates. Simple dissolution of the metal catalyst was achieved in water with SDS as surfactant, observing the formation of the corresponding propargylamines



Scheme 11 Stereoselective aniline aldehyde alkyne synthesis of chiral propargylamines mediated by Cu(I) catalyst in anionic micelles. (Adapted from Ref. 39 with permission from Wiley)

under mild conditions with excellent yields and high enantioselectivities (Scheme 11).³⁹

6 SUBSTRATE SELECTIVITY

Enzymes are examples of product- and substrate-selective^{40–43} homogeneous catalysts. The ability of enzymes to select preferentially one substrate from a mixture of similar molecules comes from the recognition events that precede the catalytic event. This property is generally not present in traditional metal-based catalysts because the interaction with the substrate occurs on reduced contact surfaces thus leading to much poorer substrate selection, which indeed remains a challenging task.

All selection rules pertain to the toolbox of supramolecular recognition, with size and shape matching driven by steric interactions and attractive contact between substrate and active site through weak intermolecular forces such as *in primis* the hydrophobic effect and hydrogen bonding, cation– π , π – π , as well as other weaker attractive intermolecular forces. Micellar aggregates share with enzymes the presence of apolar internal spaces exerting a certain degree of control on the recognition of homologous substrates, thus leading to examples of catalysis endowed with substrate selectivity properties.

The work of Kobayashi on the direct esterification of lipophilic carboxylic acids with lipophilic alcohols in DBSA micelles turned out to be the first example of a micellar system able to display substrate selectivity. In fact, when a 1:1 mixture of lauric acid and acetic acid in water was esterified in the presence of DBSA, the longer ester was produced in 81% yield, and the shorter in only 4% yield.²⁷

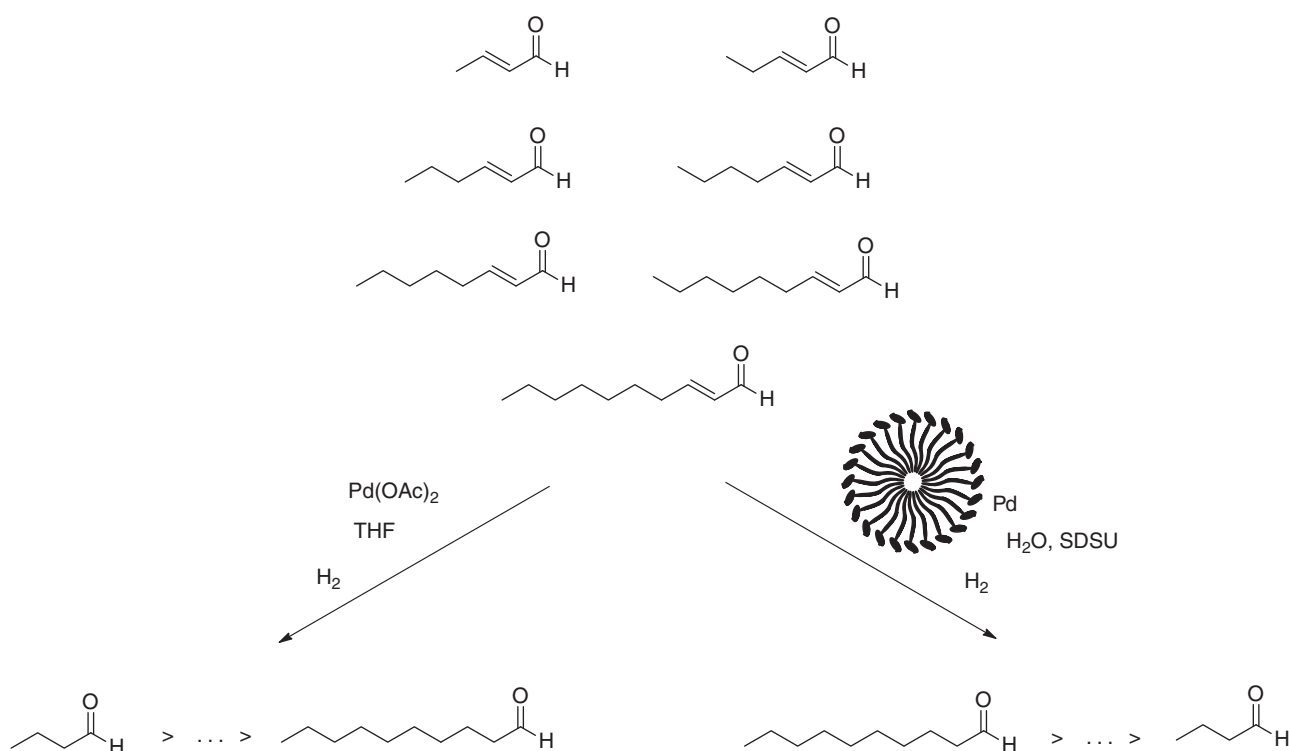
The recognition properties for more hydrophobic substrates with respect to more hydrophilic ones can be combined with more common catalytic systems in order to

develop efficient substrate-selective chemical transformations. An interesting example of the possible supramolecular features conjugating metal nanoparticle catalysis and surfactants was reported by Scarso and coworkers using *in situ* generated Pd nanoparticles with an average size of 4.6 nm and a narrow size distribution, stabilized by sodium dodecyl sulfonate (SDSU) in water (Scheme 12).⁴⁴

The effect of the surfactant was observed for concentrations above 80 mM, conditions where the surfactant is not completely dissolved in water causing the formation of an aqueous colloid-like solution where Pd nanoparticles turned out to be extremely stable and catalytically active for hydrogenation reactions. In particular, the catalytic system was applied to the competitive hydrogenation reaction of a series of seven α,β -unsaturated aliphatic aldehydes from C₄ to C₁₀, all fed at the same time, observing that the shorter substrates C₄ and C₅ were characterized by a very low conversion rate, while a gradual increase in reactivity was observed with longer and more hydrophobic substrates causing the complete conversion of C₁₀ within 40 min. Notably, between the most and the least active substrates, a ratio of more than 330 was observed. It is also worth noting that the same reaction when carried out in organic solvents such as methanol or THF led to an inverse substrate selectivity, with the shorter substrates converted faster than the longer ones. This result is very impressive if we consider that the selection is mainly due to the hydrophobic effect that causes the partition of the substrates between the bulk water and the apolar support provided by the surfactant that stabilizes the Pd-NPs.

7 DESIGNER SURFACTANTS

In recent years, the development of micellar catalysis was spurred by a new approach introduced by Lipschutz and coworkers consisting in the development of the so-called “designer surfactants” as new amphiphilic molecules easily prepared preferentially from biorenewable feedstocks (see Sustainable Surfactants Based on Amino Acids).^{45,46} These surfactants were designed specifically for catalytic applications such as the case of polyoxyethanyl- α -tocopheryl sebacate (PTS, Chart 1) and polyoxyethanyl- α -tocopheryl succinate (TPGS), which are non-ionic surfactants composed of racemic vitamin E as apolar portion, a bicarboxylic acid as spacer, and PEG units as the hydrophilic portion. The proportion between lipophilic and hydrophilic portions has been tailored in order to allow a broader array of chemical reactions in water. These surfactants demonstrated to favor the dispersion in water of high loadings of organic substrates and metal complexes, enabling the development of several extremely efficient catalytic systems characterized by mild experimental conditions, high product yield, easy isolation of the products and, in some cases, possible catalyst recycling. Some examples are described in the following.



Scheme 12 Opposite substrate selectivity observed in the competitive Pd catalyzed hydrogenation of α,β -unsaturated aldehydes conducted in organic solvent or in aqueous micellar medium. (Adapted from Ref. 44 with permission from Wiley)

7.1 Mild Cross-Coupling Reactions with Designer Surfactants

The peculiar application of these new surfactants covers several aspects of palladium-catalyzed cross-coupling reactions specifically carried out under mild conditions in water. In the following, examples of Heck and Suzuki–Miyaura as typical cross-coupling reactions are described.

7.1.1 Heck

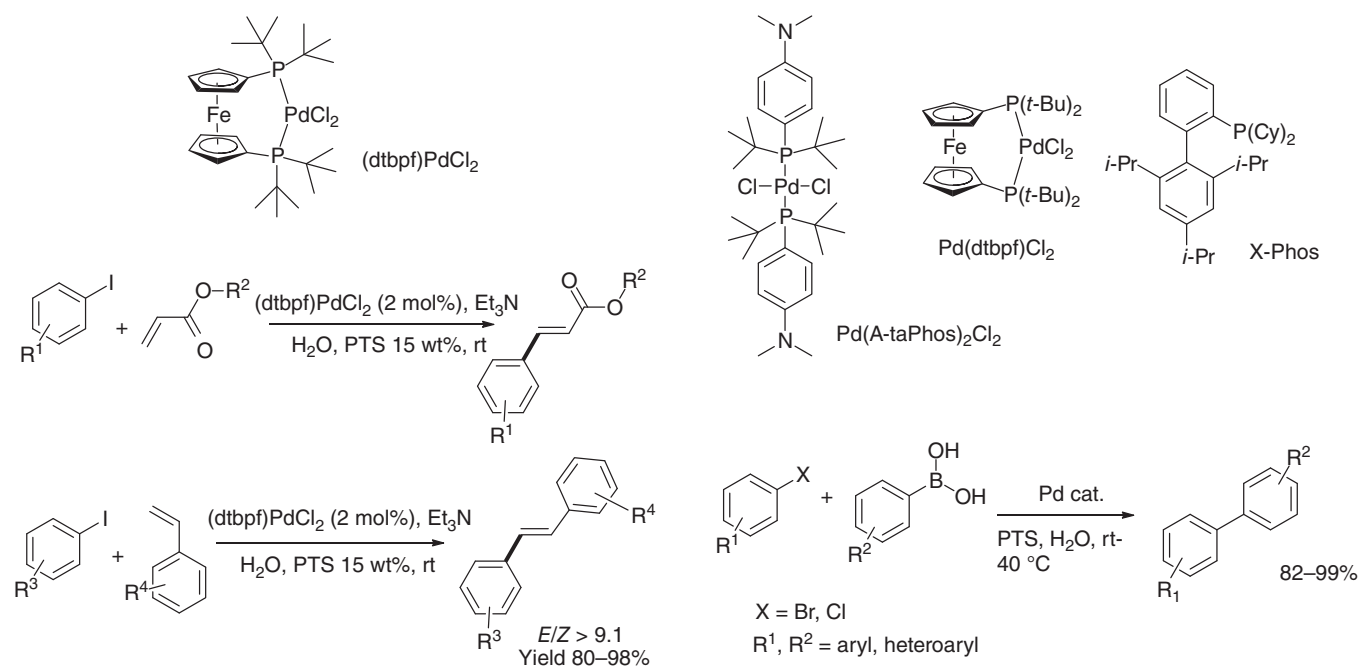
Heck coupling is generally promoted by Pd species and is known to take advantage of the presence of cationic tetralkyl ammonium additives in order to prevent catalyst inactivation. As disclosed by Lipshutz, the same purpose can be achieved using the neutral surfactant PTS that efficiently promotes the Heck coupling between aryl iodides and acrylate esters or styrene derivatives in water at room temperature with reaction times up to 24 h (Scheme 13).⁴⁷ The same protocol was successfully extended to intrinsically less reactive aryl bromides simply raising the reaction temperature to 50 °C or, alternatively, working at room temperature but forcing a more close contact between species by the addition of 3 M NaCl to the reaction system containing 5% w/w of PTS with the final effect of increasing

the ionic strength of the solution and modifying the aggregation of the surfactant.⁴⁸

7.1.2 Suzuki

Also in the Suzuki–Miyaura Pd-catalyzed couplings between several heteroaromatic bromides and chlorides together with boronic acids, the use of PTS as surfactant in water showed to efficiently promote the reaction. The use of optimized Pd species as reported in Scheme 14⁴⁹ was necessary and in all cases 2% PTS as surfactant was necessary since the same reactions carried out just in water did not provide good results. The potentialities of PTS micelles for this kind of couplings is clearly demonstrated considering the reaction between the electronically deactivated 2,6-dimethyl-chlorobenzene and 3-thiophenylboronic acid that in organic solvents is traditionally performed at 100 °C with several equivalents of inorganic salt as base leading to only 77% yield, while the same reaction could be carried out at a much lower temperature (38 °C) with PTS in water, this time leading to 90% isolated yield of the corresponding coupling product.

Organoboronic acids in synthesis are extremely versatile since these reagents can be coupled with several electrophiles including alkyl, aryl, alkenyl, and alkynyl groups. Conversely, examples of applications with allylic partners



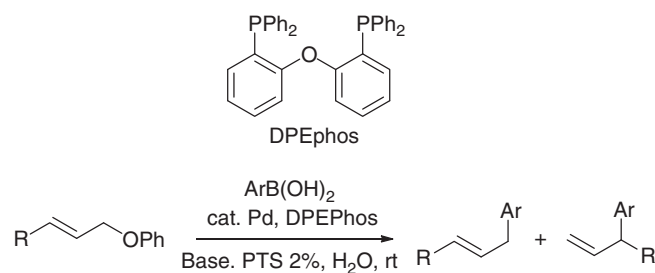
Scheme 13 PTS micelles mediated Heck couplings catalyzed by Pd species in water at room temperature. (Adapted from Ref. 47 with permission from American Chemical Society)

Scheme 14 PTS micelles mediated Suzuki–Miyaura cross-couplings catalyzed by Pd species in water. (Adapted from Ref. 49 with permission from American Chemical Society)

bearing acetates, carbonates, halides, and pseudohalides as leaving groups are rare. An exception was developed by Lipshutz and coworkers exploiting the unique features of PTS as surfactant in water medium. The reaction is based on the use of Pd(II) precursors with DPEPhos as bidentate phosphine ligand that efficiently promotes the formation of linear *trans*-alkene products under micellar conditions by reaction of aryl boronic acids and cinnamyl phenyl ether as described in Scheme 15.⁵⁰ The reaction can be carried out with a large combination of boronic acids, even with traditionally less reactive *ortho*-substituted boronic acids combined with a wide range of cinnamyl ethers bearing dibenzylamine-, aminoacid-, and malonate ester-substituents. In all these cases very good yields in the corresponding products were observed in few hours at room temperature.

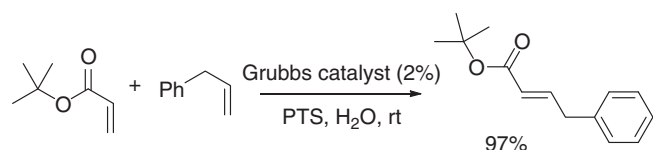
7.2 Olefin Metathesis

Metathesis reactions are extremely important transformations involving terminal alkene moieties usually performed employing Ru catalysts in organic media as well as in water as solvent, in several cases with water soluble complexes.^{51,52} The use of micellar media allows the use of traditional complexes known for organic media directly dissolved and operative in water. In fact, typical metathesis catalysts such as Grubbs 2 have been showed to be active

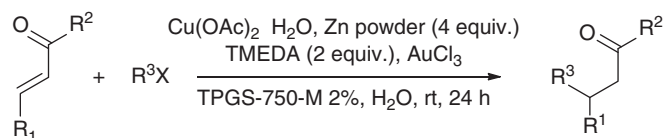


Scheme 15 PTS micelles mediated Suzuki–Miyaura couplings on allylic ethers catalyzed by Pd(II) in water at room temperature. (Adapted from Ref. 50 with permission from American Chemical Society)

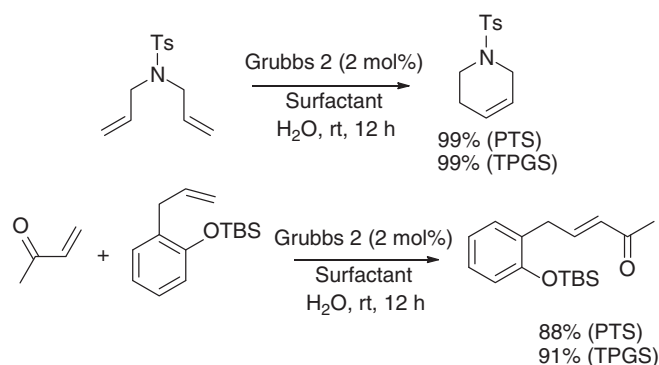
in the reaction between allylbenzene and *tert*-butyl acrylate in the presence of PTS as surfactant in water, leading to the formation of the desired product in good yield at room temperature (Scheme 16).⁵³ The reaction works very well with a wide combination of substrates, showing good compatibility with the presence of other functional groups and leading to the desired products in all cases with *E/Z* ratios comparable to those typically observed in organic media. The same protocol was applied to lipophilic substrates bearing terminal diene functional groups providing the corresponding cyclic 5-, 6-, and 7-membered ring products in high yields.⁵⁴



Scheme 16 PTS micelles mediated olefin cross-metathesis catalyzed by Grubbs catalyst in water at room temperature. (Adapted from Ref. 53 with permission from American Chemical Society)



Scheme 18 TPGS-750-M mediated Michael conjugate addition to enones catalyzed by Cu(II) species in water at room temperature. (Adapted from Ref. 56 with permission from American Chemical Society)



Scheme 17 PTS and TPGS micelles mediated metathesis reactions in water. (Adapted from Ref. 55 with permission from American Chemical Society)

Alternatively, this class of reactions can be efficiently performed with TPGS-750-M as surfactant in water observing comparable or better results (Scheme 17)⁵⁵ for a broad combinations of substrates both for intramolecular ring-closing metathesis and for bimolecular metathesis reactions. Moreover, the catalytic system showed to be sensitive to the pH of the system and the reaction repeated in the presence of KHSO_4 enabled the coupling between allylbenzene derivatives and the unusual substrate methyl vinyl ketone observing a substantial improvement in yield from 74% to 91%.

7.3 Other C–C Cross-Couplings

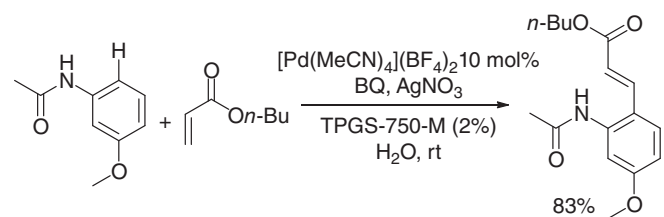
The new surfactant TPGS-750-M turned out to be extremely efficient also for other coupling reactions such as the Michael conjugate addition to enones catalyzed by organocopper derivatives that usually require carefully dry conditions to ensure good product yields. As described above, for the esterification reaction in water,²⁷ micellar catalysis offers “dry” conditions within micelles even though the surrounding solvent is water. The reaction disclosed by Lipshutz is based on the use of Cu(II), Au(III), and Zn(0) together with a bidentate nitrogen-containing ligand as catalytic system (Scheme 18).⁵⁶ The reaction occurs initially forming organozinc species subsequently

transmetalated to Cu and finally transferred to the enone, providing the corresponding β -substituted carbonyl compounds. With this procedure, it was possible to conjugate several alkyl bromides and iodides bearing functional groups to cyclic and acyclic enones. Moreover, thanks to the affinity of the catalytic system for the micellar aggregates, it was possible to recycle directly the micellar phase for 3–4 runs in the original flask, removing the products by means of simple extraction with hexane.

Among coupling reactions, transformations such as the *ortho*-directed C–H activation of anilides (Fujiwara–Moritani reaction) is gaining interest in the scientific community because of its high synthetic potentialities. As a further demonstration of the possible extension of coupling reactions from organic solvents to water, Lipshutz and coworkers optimized the shift of the Fujiwara–Moritani reaction in water using TPGS-750-M as preferred surfactant. As described in Scheme 19,⁵⁷ the reaction was optimized using $[\text{Pd}(\text{MeCN})_4](\text{BF}_4)_2$ as the metal precursor that activates anilide derivatives toward acrylate substrates. It is worth noting that no addition of external acid was required that is otherwise present in the traditional practice of the reactions. The reaction was applied to a broad combination of functionalized anilide derivatives in combination with acrylates of different length affording the corresponding products regioselectively in 70–96% yields.

7.4 Other C–Heteroatom Cross-Couplings

The synthesis of amine derivatives is extremely important and in recent years examples of metal-mediated C–N



Scheme 19 PTS mediated Fujiwara–Moritani reaction catalyzed by Pd(II) species in water at room temperature. (Adapted from Ref. 57 with permission from American Chemical Society)

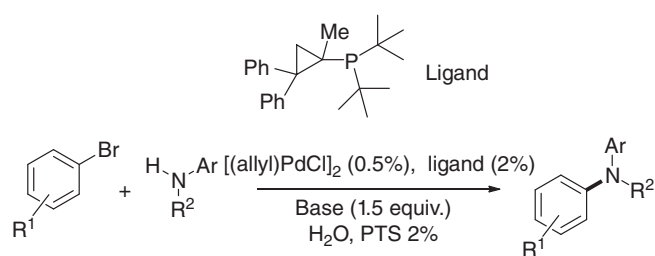
bond-forming reactions were developed, attracting the attention of the scientific community. Two examples of the direct extension of these reactions in water with surfactants are reported here.

One example is the efficient direct diaryl and triaryl aniline synthesis starting from simple anilines and aryl bromides.⁵⁸ The reaction reported in Scheme 20 is based on the use of Pd precursors and specific phosphine ligands that were carefully optimized in order to maximize product formation. The use of micellar conditions enabled a drastic decrease in catalyst loading, which is an important result from an economic point of view. The reaction proved to be very sensitive to the base used. After optimization of the system with this catalytic protocol, it was possible to prepare about 20 aniline derivatives with yields in the range 72% to >99%.

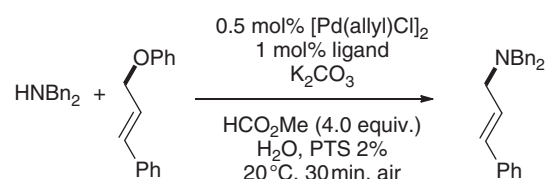
The second example of amine synthesis that greatly benefits from the use of micellar media is the direct allylic amination of allyl ethers. The reaction was developed with the use of PTS with a Pd(II) precursor. As reported in Scheme 21,⁵⁹ the reaction between cinnamyl-phenyl ether and dibenzylamine with methyl formate as activating group led to the formation of the linear product in very high yield at room temperature. Analogously, the reaction was extended to a large combination of allyl ethers and nucleophilic secondary amines observing the formation of the corresponding products with generally high yields and selectivities.

7.5 Cyclization Reactions

Homogeneous catalysis with Au species is nowadays a well-established method that offers unique reactivities. The Soft Lewis acid character of Au(I) species and to some extent of Au(III) species makes this class of catalysts compatible with water and with micellar media. An example of this is the intramolecular cyclization of various α -hydroxy- and α -aminoallenes leading to cyclic products. Lipshutz and Krause showed that neutral surfactants PTS and TPGS promote the reaction under mild experimental conditions within 10–80 min at room temperature



Scheme 20 PTS mediated amination of aryl bromides catalyzed by Pd(II) in water at room temperature



Scheme 21 PTS mediated amination of allylic phenyl ethers catalyzed by Pd(II) in water at room temperature. (Adapted from Ref. 59 with permission from Royal Society of Chemistry)

in air (Scheme 22).⁶⁰ Even more importantly, the micellar medium containing the noble metal catalyst was efficiently recycled by means of simple product extraction with hexane thus leading to four complete runs with unaltered yield for the cyclized products and limited metal leaching.

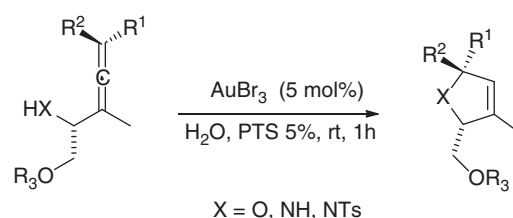
7.6 Stereoselective Cyclizations with Designer Surfactants

The use of designer surfactants has been recently applied also to stereoselective transformations such as in the asymmetric gold-catalyzed intramolecular cyclizations of β -allenic acids. The reaction is mediated efficiently by chiral Au(I) cationic complexes endowed with an atropoisomeric diphosphine ligand together with a chiral phosphate anion.

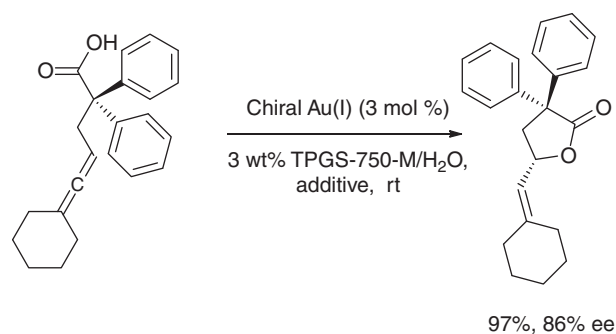
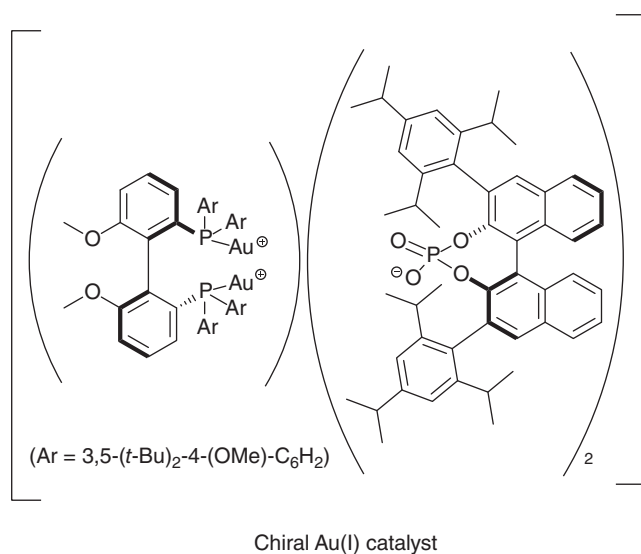
The aqueous micellar medium obtained with TPGS-750-M in water showed to ensure intimate contact between the species leading efficiently to the formation of the β -allenic acids to give enantioenriched lactones in high yields and good to excellent ee's in water at room temperature (Scheme 23).⁶¹ Both catalyst and surfactant were recyclable with this system providing a clear-cut example of how micellar media can favor both activity, selectivity, and recyclability of metal-catalyzed reactions.

8 METALLOSURFACTANT CONJUGATES

The development of cationic metal species endowed with aliphatic ponytails represents a synthetically more demanding approach to micellar catalysis that is worthy of being



Scheme 22 PTS mediated intramolecular cyclization of various α -hydroxy- and α -aminoallenes catalyzed by AuBr₃ at room temperature in water. (Adapted from Ref. 60 with permission from Wiley)

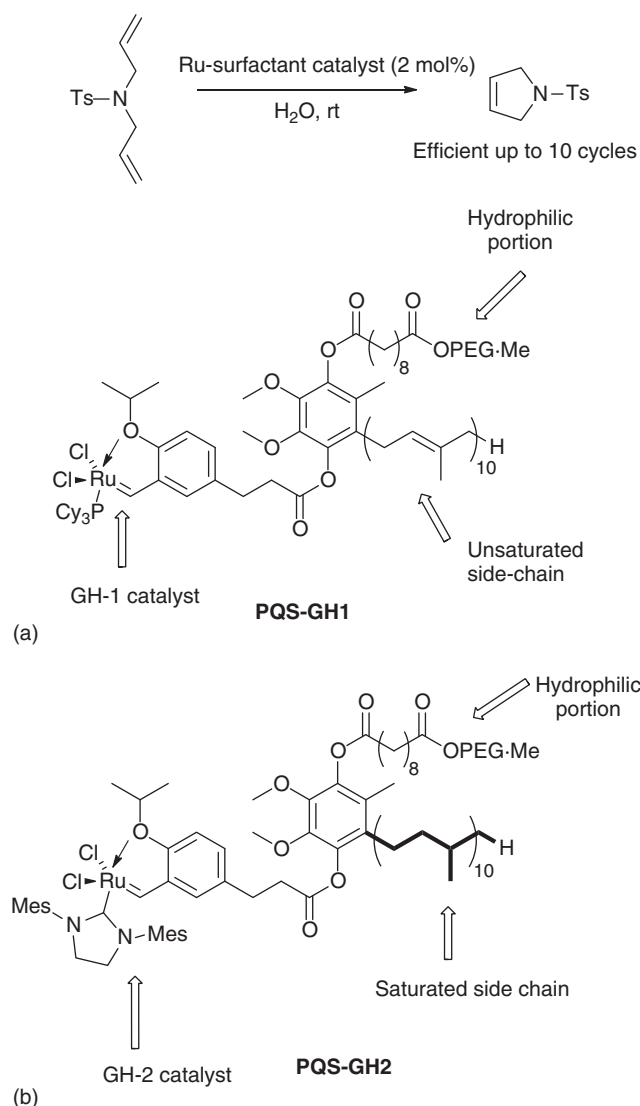


Scheme 23 Neutral TPGS-750-M micellar promoted stereoselective intramolecular lactonization catalyzed by chiral Au(I) complexes. (Adapted from Ref. 61 with permission from Wiley)

used for special purposes. In particular, this strategy can be applied for efficient catalyst recycling through extraction with organic solvents and reuse of the aqueous phase. This is particularly advantageous when precious metal species are employed or, more importantly, in the case of asymmetric catalytic reactions with chiral metallosurfactants.

8.1 Metathesis Reactions

Grubbs Hoveyda 1 Ru(II) is a well-known catalyst for ring-closing metathesis and it was covalently connected to the PQS surfactant unit to take advantage of both compartmentalization effects and easy catalyst recycling for the reaction of dienic substrates in pure water at room temperature, leading to the corresponding five, six, and seven-membered ring products in 79–96% yield. (Scheme 24a).⁶² The metal-containing surfactant formed micelles of about 40 nm average size ensuring an extremely robust catalytic method and, more importantly, the metal–surfactant system could be recycled 10 times simply using diethyl ether



Scheme 24 Examples of designer metallosurfactant conjugates bearing PQS units and Ru(II) ring closing metathesis derivatives. (Adapted from Ref. 62 with permission from American Chemical Society)

as a solvent to extract the products leaving the metallosurfactant in water unaltered.

The same approach was extended to Grubbs Hoveyda 2 catalysts conjugated to variants of the PQS tenside bearing a completely saturated alkyl chain (Scheme 24b)⁶³ observing closing metathesis between acrylates and other alkenes and efficient RCM of heterocyclics and carbocyclics from five- to seven-membered rings, in all cases with efficient catalyst recycling.

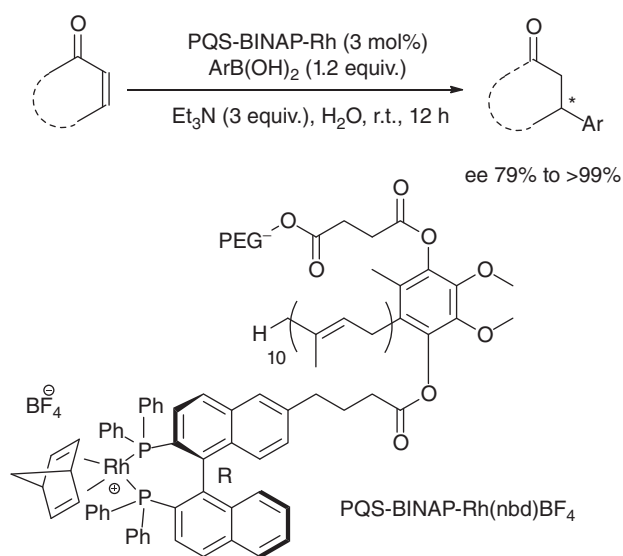
8.2 Chiral Metallosurfactants

Even though the creation of chiral surfactants is not complicated, the use of chiral micelles is very limited.^{64–67}

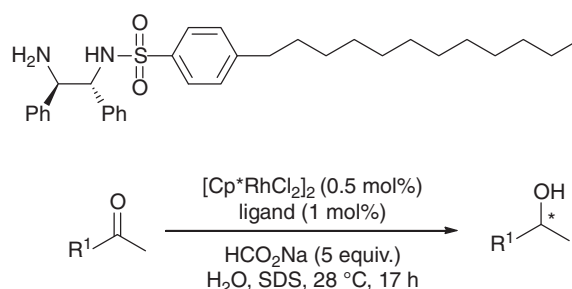
The major difficulty encountered in observing high asymmetric inductions is mainly due to the large average distance between the chiral environment provided by the micelles and the true achiral catalyst where the reaction takes place. Alternatively, the use of chiral metallosurfactants allows obtaining chiral micelles that promote chemical transformations efficiently and with high stereoselectivity. Examples of this approach are reported here.

One example of the potentialities of metallosurfactants with the aim of obtaining high catalytic performance together with efficient catalyst recycling is represented by the amphiphilic metal complex reported in Scheme 25⁶⁸ based on an organic scaffold connected to a BINAP-Rh(I) species. This metallosurfactant proved to efficiently promote the 1,4-conjugate addition of aryl boronic acids to unsaturated cyclic and acyclic ketones in water at room temperature with high stereoselectivities, comparable to those observed in organic media but with the great advantage of simple product extraction with diethyl ether and recycling of the aqueous phase for up to four cycles.

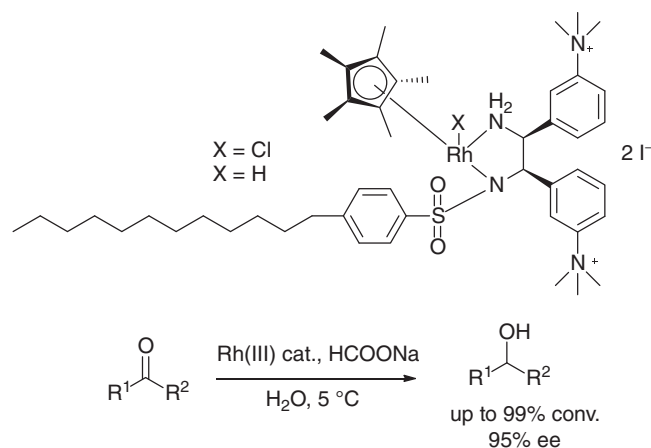
Hydrogenation reactions are among the most general and utilized asymmetric transformations. In particular, hydrogenation of carbonyl compounds leads to the synthesis of highly valuable chiral secondary alcohols. Adolfsson and coworkers proposed the preparation of chiral metallosurfactant species composed of a chiral lipophilic mono-sulfonated diamine ligand coordinated to a Rh(II) metal center to be used in water together with SDS as co-surfactant (Scheme 26),⁶⁹ leading to the formation of micelles of about 33 nm size. These micelles efficiently promoted the enantioselective transfer hydrogenation of



Scheme 25 Chiral Rh(I) metallosurfactant catalyzed asymmetric 1,4-addition in water at room temperature. (Adapted from Ref. 68 with permission from Wiley)



Scheme 26 SDS mediated asymmetric transfer hydrogenation of alkyl and aryl ketones catalyzed by chiral Rh(III) metallosurfactant conjugates in water. (Adapted from Ref. 69 with permission from Royal Society of Chemistry)



Scheme 27 Chiral Rh(III) metallosurfactant mediated asymmetric transfer hydrogenation of aliphatic ketones. (Adapted from Ref. 70 with permission from American Chemical Society)

ketones with formate in solution, in particular aryl alkyl ketones turned out to be excellent substrates obtaining the corresponding alcohols with excellent conversion and enantioselectivity.

An alternative to the previous system is based on similar metallosurfactant species endowed with positive ammonium charges on the hydrophilic portion of the ligand (Scheme 27).⁷⁰ This chiral metallosurfactant self-assembles in water and was employed for the efficient asymmetric transfer hydrogenation of aliphatic ketones forming secondary aliphatic alcohols that are more difficult to obtain with high yields and stereoselectivities. The asymmetric reaction showed high dependence on the length of the aliphatic ketone. In particular, better selectivities were observed with longer substrates (2-hexanol 76% ee and 2-tridecanol 94% ee) with down to 100:1 substrate:metal ratio. The good level of stereoselectivity was consequence of the positive effect obtained combining the catalytic metal

center and the hydrophobic microenvironment present in the core of the metallo-micelle.

9 SUMMARY AND FUTURE PERSPECTIVES

As clearly described in the series of illustrative examples reported above, the use of micellar environments in catalysis is not just a soapy version of homogeneous catalysis.⁷¹ Micelles behave much more as nanoreactors characterized by unique features with all the extra advantages intrinsic in the use of water as solvent. Micellar catalysis has been demonstrated to be suitable to almost all classes of chemical transformations, in particular for a wide range of reactions promoted by metal complexes or organometallic species, also with impressive examples in asymmetric catalysis.

The great advantage of using catalysts already developed for use in organic media without the need of ligand modifications to make the catalyst compatible with water, together with the self-assembling nature of surfactants, is the key factor for the success of micellar catalysis with metal species. The surfactant is not just a spectator as usually the solvent is believed to be, rather it directs the overall system. A critical balance between catalyst, substrate, and surfactant properties must be analyzed in detail in order to ensure high yield, selectivity, and recyclability. It can be predicted that, thanks to their generally low cost, surfactants will soon find some applications in large-scale synthetic methods suitable for industrial applications.

10 ACKNOWLEDGMENTS

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11 ABBREVIATIONS AND ACRONYMS

BINAP = (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl); Chiraphos = bis(diphenylphosphino)butane; CM = closing metathesis; c.m.c. = micellar concentration; CPB = cetylpyridinium bromide; CTAB = cetyltrimethylammonium bromide; CTAC = cetyltrimethylammonium chloride; DBSA = dodecylbenzenesulfonic acid; DCE = 1,2-dichloroethane; DPEPhos = bis[(2-diphenylphosphino)phenyl] ether; NPs = nanoparticles; Salen = salicylaldehyde and ethylenediamine based ligands; PEG = polyethylene glycol; PQS = polyoxyethanylethanol ubiquinol succinate; PTS = polyoxyethanyl- α -tocopheryl sebacate; RCM = ring closing metathesis; SDBS = sodium dodecylbenzenesulfonic acid; SDS = sodium dodecyl sulfate; SDSU = sodium dodecyl sulfonate; TPGS = polyoxyethanyl- α -tocopheryl succinate.

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