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ARTICLE TYPE

## Recent Advances in Catalysis in Micellar Media

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The present review paper deals with the development of catalytic systems in water in the presence of micelles obtained by addition of surfactants, focusing on the effects of these simple, economic, green reaction media on important aspects like recyclability, activity, product and substrate selectivity. Contributions from 2005 to 2014 are surveyed with particular emphasis on emerging findings and directions of this field of catalysis. Surfactants enable formation of nanosized apolar aggregates in bulk water where the catalysts and reagents can be dissolved thanks to weak intermolecular interactions like hydrophobic effect and ion pairing operating in a more concentrated system compared to the bulk solvent. While in the past the use of surfactants was a straightforward approach to enable solubilization of reaction mixtures in water, nowadays specific interactions between substrates, catalysts and micelles are investigated by means of NMR and other techniques to better understand the molecular basis of this kind of supramolecular catalysis. Specifically designed surfactants to engineer micelles in order to complete efficiently with traditional catalysis in organic solvents are nowadays available.

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## 1. Introduction

### 1.1 Catalysis in water

Stringent environmental concerns are deeply changing the way chemical research evolves, in particular new advances in the chemical synthesis and catalysis areas are nowadays strongly tied to green chemistry. The latter is not merely a young sub-discipline of chemistry; it is the new standard all new researches in synthesis and catalysis have to comply with. This is mandatory to pass on these concepts to a new generations of scientists and to change the perception the public opinion have about our work and research. Among the twelve principles of green chemistry,<sup>1</sup> the proper solvent selection to minimize toxicity, energy demand, pollution and so on, is a key issue that has spurred a great effort in the development of alternative green solvents. In chemical reactions, solvents account for about 80% of the total mass handled<sup>2</sup> and in 70% of the cases they are incinerated to recover heat.<sup>3</sup> Therefore their substitution with more environmentally friendly ones can directly have a positive effect on both emissions and hazard issues.<sup>4</sup> However measuring the green character of a solvent is not trivial especially with respect to possible alternatives.<sup>5</sup> For example, as pointed out by Jessop, despite the large effort paid to studying ionic liquids because of their intriguing properties and advantages, the average current opinion does not consider them as real alternatives to the conscious employment of traditional solvents, or CO<sub>2</sub> and water to reduce the impact of synthetic chemistry on the environment.<sup>6</sup> In this respect possible strategies proposed are, among others, solvent-free conditions and mechanochemistry.<sup>7</sup>

Often, a solvent is requested to play several roles at the same time, e.g. to ensure contacts between substrates of different polarity, to control heat transfer, to favor the interaction that leads to the final transformation. In this scenario, among all possible liquids, water is certainly the one with the smallest impact on the environment. Water as solvent has been selected by Nature to carry out all kind of chemical transformations no matter whether substrates are soluble or insoluble. Of course, the comparison between *in flask* chemical synthesis and *in cell* synthesis is thought-provoking, but mimicking the strategies adopted by

Nature to perform chemical transformations in water will reach at least two goals: (i) more environmentally friendly chemistry and (ii) a better understanding of processes occurring in cells. Water as a solvent is extremely economic, non-toxic, non-flammable, it does not contribute to greenhouse emissions, it does not require synthesis, the energy necessary for its isolation in a pure form is low and its E factor value equals to zero,<sup>8</sup> which means it is not considered a waste in chemical transformations. Additional properties are a tuneable acidity, a large heat capacity and heat of evaporation which allows easy control of exothermic reactions, a high polarity, the coexistence of hydrogen bonds donor and acceptor that often make catalysis easier. In one word it is the green solvent *par excellence*. Despite these excellent properties, it is among the least used solvents simply because it is highly polar and its strong hydrogen bonds give rise to the hydrophobic effect, i.e. the property of water to segregate apolar species rather than provide single molecule solvation. This turns out in a low or negligible solubility low polarity functional groups endowed molecules. From the dawning of chemistry until the beginning of the 20<sup>th</sup> century when chemists were forced to use it as it was one of the few solvents available, water has found little use in industrial organic chemistry. A renovated interest arose in the early 80's with the Ruhrchemie-Rhône-Poulenc hydroformylation process to convert propene and 1-butene into the corresponding one carbon longer aldehydes using rhodium catalysts modified with sulfonate-containing phosphine ligands.<sup>9</sup> Ever since, the academic community has constantly pursued the search for new processes in water.<sup>10,11</sup> In particular C-C coupling catalytic reactions,<sup>12</sup> have disclosed important concepts like "in water" catalysis when the system is homogeneous to "on water" catalysis when the reaction is catalyzed by simple mixing the reactants with water under heterogeneous conditions.<sup>13</sup>

Historically, it has been known since 1980's that the hydrophobic effect can greatly accelerate reactions between poorly water soluble substrates. Breslow and coworkers<sup>14</sup> found that the Diels-Alder cycloaddition reaction in water as solvent was hundreds of times faster than in organic protic and aprotic solvents, an observation that excluded simple polarity or H-bonding effects on catalysis. This subject has been recently

reviewed<sup>15</sup> covering reactions with both water soluble substrates (in-water catalysis) and water insoluble substrates (on water catalysis).<sup>16</sup>

Concepts like the hydrophobic effect and the donor-acceptor hydrogen bonding ability of water have allowed to rationalize enhanced productivity as well as regio-, diastereo- and enantioselectivity in several catalytic reactions.<sup>10-13</sup> The above mentioned advantages are some of the motivations that prompt scientists to deeply explore the use of water as solvent. As far as catalysis is concerned, water as solvent provides the additional advantage of possible catalyst recycling when products are extracted with a water immiscible organic solvent leaving the catalyst dissolved in water.

However, the need for product extraction from aqueous phases poses some critical issues about the green character of catalysis in water, such as: (i) the volume of organic solvent used in the workup often exceeds the total volume of water used in the reaction by factors of up to 30-fold and this operation is of major concern for the overall green character of the system and (ii) the resulting water solution is essentially a water stream contaminated by organics that is subject to strict regulations and must be purified usually stripping under vacuum or adsorption of activated carbon.<sup>17</sup> From this point of view the green character of aqueous media in replacing organic solvents while using an organic solvent to extract products from water is questionable, but as long as water provides extra performance in terms of activity and selectivity, the concerns about the use of limited amounts of traditional solvents at the end of the reaction are at least mitigated and in the cases of successful recycling, reduced to a minimum.

Once again, Nature provides inspiration with enzymes as highly active water soluble catalysts operating within cells. In these systems weak intermolecular interactions, that are the toolbox of supramolecular chemistry, play a pivotal role i) in substrate as well as product selectivity, ii) in the extent of the catalytic phenomenon, iii) in the regulation of catalytic activity and iv) in biosynthetic pathways. The supramolecular viewpoint is helpful in rationalizing enzyme catalysis and this is testified by the emerging interest in supramolecular catalysis as the contact point between supramolecular chemistry and traditional homogeneous catalysis. Development of artificial enzyme models mimicking natural enzymes is a promising and active field that has been pursued by researchers for several decades.<sup>18</sup> Enzymes are macromolecular catalysts while traditional homogeneous catalysts are orders of magnitude smaller and can at most mimic the behavior of the enzyme active site without the extra properties induced by the surrounding protein. Therefore the simplest approach to mimic some of the features of enzymes consists in exploiting self-assembling units that generate highly-ordered structures capable of surrounding the catalyst. This ensures the formation of nanometric environments that, similarly to enzymes, can accommodate substrates, accelerate the reaction and impart peculiar selectivities on both sides of the reaction, i.e. reagents and products.<sup>19</sup>

The marriage between supramolecular chemistry and homogeneous catalysis led to the proposal of a number of

supramolecular artificial enzymes based on various unimolecular building blocks (like macrocycles, cyclodextrins, calixarenes, cyclophanes, crown ethers, cavitands, capsules, molecular cages and others), and self-assembled nanometer sized objects (metal-ligand or hydrogen bonded capsules, micelles, vesicles, nanoparticles, nanotubes and nanogels).<sup>20-22</sup> The ultimate goal of such systems consists in mimicking biosynthesis and catalysis even in total synthesis, emulating enzymatic cascade reactions.

## 1.2 Micelles: structure and properties

Surfactants (a short name for surface active agents) as amphiphilic molecules (Chart 1), in the presence of water and immiscible organic species tend to mediate between the two phases. If water is present in a large amount the hydrophobic effect drives the formation of spontaneous micellar aggregates in solution when the surfactant is present above a certain minimum concentration (c.m.c., critical micelle concentration). The nanoscale assemblies formed by aggregation of about 50-100 monomers are in thermodynamic equilibrium where monomers rapidly exchange among aggregates. For example, the typical lifetime of a surfactant micelle is in the order  $10^{-3}$ - $10^{-2}$  s.<sup>24</sup>

The use of surfactants under micellar conditions represents one of the simplest methods to achieve catalysis in water since surfactants are in most cases very economic thanks to their extensive everyday use in detergency. As recently pointed out by Sorrenti,<sup>25</sup> micellar environments are not just a soapy version of homogeneous catalysis, but micelles behave much more as nanoreactors characterized by unique features.

Most of the commercially available surfactants are derived from petroleum feedstock. In the recent years some classes of bio-surfactants have emerged where the amphiphilic molecule presents biological functionalities. They have been synthesized from natural resources through yeast, bacteria and plant transformation and they possess intrinsic biodegradability and biocompatibility. Examples are known based on glycolipids, lipopeptides, phospholipids, fatty acids, neutral lipids. In most cases they are anionic or neutral with the hydrophobic part of the molecule based on long-chain fatty acids, hydroxy fatty acids or  $\alpha$ -alkyl- $\beta$ -hydroxy fatty acids and the hydrophilic portion based on carbohydrates, amino acids, cyclic peptides, phosphates, carboxylic acids or alcohols.<sup>26</sup> Bio-surfactants, thanks to their self-assembling properties,<sup>27</sup> found interesting application directly in the environment,<sup>28</sup> or heavy metal or organic contaminant removal such as oil removal from contaminated soil or for bioremediation enhancement. Their extension as reaction media for chemical transformations is still an un-investigated topic, in some cases because they are biologically produced *in situ* where they are employed. The auspice is that in the near future their peculiar properties, in particular the presence of several enantiomerically pure bio-surfactants, will spur their employment for catalytic applications as alternative more environmentally friendly media.

Similarly to enzymes micelles are characterized by a hydrophobic core, shielded from the contact with water, and a hydrophilic surface where the hydrophilic groups remain exposed to water ensuring solubility. Water molecules surround the polar

external surface of the aggregate and their behavior and properties are rather different from water molecules in the bulk.<sup>29</sup> The type of aggregate formed is a function of several variables, (i) the molecular structure of the amphiphile, (ii) the proportion between hydrophilic and hydrophobic parts, (iii) the geometry of the molecule and (iv) the experimental conditions in which they are used such as temperature, pH and ionic strength.<sup>30</sup> The effect of concentration is extremely important since possible aggregates are initially typically spherical micelles, but as soon as the concentration increases also ellipsoidal micelles, rods, hexagonal liquid crystal phase (LC, hexagonal arrangement of long cylinders), lamellar LC phase and, eventually, reverse phases are possible. In the presence of large amounts of substrates, usually liquid to favor their intimate contact with water and surfactant, microemulsions are obtained and also under these conditions, enhancement of catalytic activity and selectivity has been observed.

### 1.3 Micellar effects

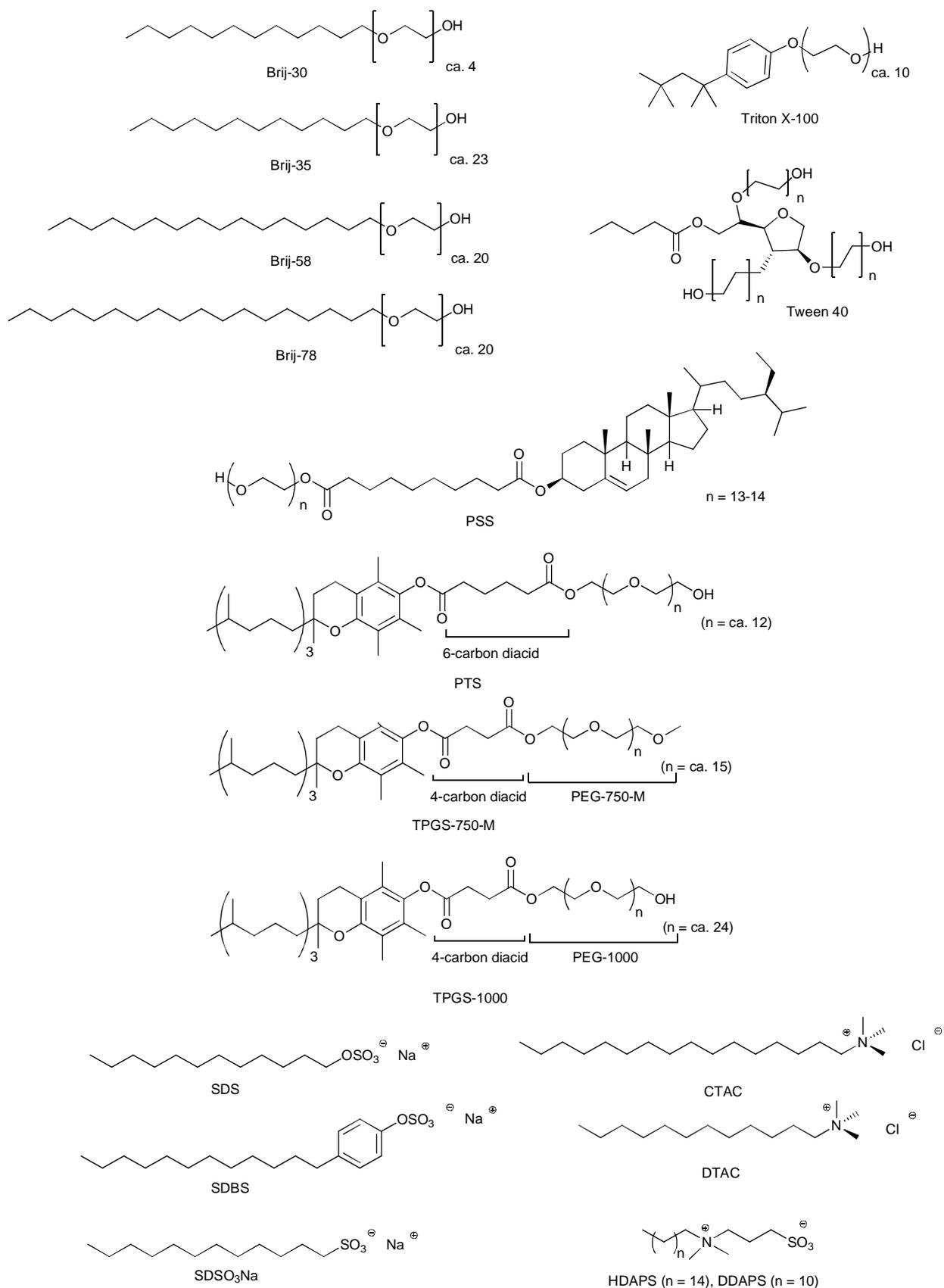
Early review papers on the subject of micellar catalysis date back to the late 1970's describing catalysis directly performed by the supramolecular aggregates.<sup>31</sup> Since that time this area has witnessed a growing interest demonstrated by the periodical update provided on some specific aspects of the topic.<sup>32</sup> The present contribution covers the field from 2005 until mid 2013 focusing the attention on the supramolecular features of this kind of catalysis, an aspect where further developments will likely appear in the future. Depending on the surfactant employed, micelles can be either charged or neutral with size and polar properties encompassing a wide range. Neutral surfactants are usually based on precisely defined apolar portions while the polar one is usually an oligomer of ethylene oxide. Therefore the latter class of surfactants usually do not have a precise chemical composition and a certain distribution of molecular weights is present.

From a certain point of view micelles behave like enzymes, isolating species from the bulk solvent, playing several roles at a time like improving solubilization of organic reagents in water, favouring compartmentalization of reagents with enhancement of local concentration and reactivity, imparting unique chemo-regio- and stereoselectivities. A limitation of micellar catalysis is related to the amounts of substrates that can be loaded into the micelles, usually lower than in common organic solvents, although the higher selectivities often observed with micelles can partially compensate the disadvantage of working in diluted media. Since solubilization of the organic reagents occurs predominantly within micelles and not in the entire volume of the liquid phase, the local concentration may be higher even if the overall concentration of substrates typical for catalysis in the entire micellar medium is usually smaller than that possible in traditional organic solvents and usually falls in the range  $10^{-1}$ - $10^{-3}$  M. It is also worth to note that often the concentrations of surfactant used are much higher than the c.m.c. and micro-emulsion conditions are present. Under these conditions, the loading of substrates in the medium can be much higher than previously described.

Organic species added to micellar media are distributed between bulk water and micelles depending on their polarity, charge and dimension. Apolar substrates that are almost exclusively hosted within micelles experience a local concentration in the supramolecular aggregates some orders of magnitudes higher than that calculated considering the entire volume of solution. This is one of the main advantages of micelles, again a consequence of the hydrophobic effect. Moreover charged micelles tend to concentrate species of opposite charge on their surface. Therefore in cationic micelles the surface local pH is slightly more basic than in the bulk solution, and the opposite is observed for anionic micelles.<sup>33</sup>

Similarly, intrinsically water insoluble charged metal species can be concentrated and dissolved in micellar media thanks to ionic interactions with micelles of opposite charge. Like in metallo-enzymes non-covalent interactions in the second coordination sphere<sup>34</sup> play a significant role in determining activity and selectivity. Thus micellar catalysis represents one of the simplest methods to combine easy metal catalyst dissolution in close contact with apolar or charged secondary interactions thus providing suitable model complexes with a functional second coordination sphere.

The use of water as solvent opens the way to biphasic extraction of products and recycle of the catalyst. This is possible if the catalyst remains confined in the micellar aggregates during product removal. In the best cases, the product is insoluble and can be filtered off from the reaction mixture, but more often it is extracted with the aid of an organic water-immiscible solvent. A frequent problem is emulsion formation that limits the number of successful examples in the area. Moreover, the chemical nature of the extraction solvent and its amount contributes heavily to the environmental impact of the entire process. When product extraction is accomplished by adding directly in the flask a limited amount of a single organic solvent followed by removal of the organic phase, then the environmental impact of the process is greatly reduced. This was recently pointed out by Lipshutz and coworkers that underlined the extremely positive effect of the use of specific surfactants and water, with respect to traditional organic solvents, on the E factor of a broad series of transition-metal-catalyzed carbon-carbon and carbon-heteroatom bond formation reactions broadly employed both in industry and in the academia.<sup>35</sup>



**Chart 1.** Structures of commercially available surfactants.

These authors observed that the E factor drops dramatically, becoming in some cases much lower than one tenth of the original value in organic solvents, thus reaching values typical for bulk rather than fine chemicals. Moreover the possible recycling of the micellar medium containing the catalyst further reduces dependence on organic solvents. Since industrial fine chemical synthesis is more and more moving from old processes to new environmentally friendly processes, one of the driving forces for the future implementation of micellar catalysis in industry could certainly be the reduction of waste which is also an economic cost.

Recycling is subject to catalyst robustness as well as proper solvent choice for efficient phase separation. This point is more critical with neutral surfactants that generally have similar affinity for both water and organic solvents. Conversely, charged anionic or cationic surfactants can usually be exploited for extraction with apolar solvents like alkanes or diethyl ether as they remain in the aqueous phase.

Catalyst and surfactant interactions open a different scenario. In the best conditions it could be possible to simply extract efficiently the product leaving the catalyst and the surfactant in the micellar medium. This occurs when metal catalyst and surfactant are oppositely charged and the organic reagents and reaction products are rather apolar and easily removable from the micellar medium. In other cases product isolation is much more difficult because extraction with a solvent removes partially the surfactant and the catalyst from the aqueous phase. This often occurs when neutral surfactants, neutral metal complexes or organocatalysts are used. Nevertheless, even in these cases despite a less straightforward product isolation, the use of micellar media instead of organic solvents is justified when activity and selectivity are higher and overcome the drawbacks.

#### 1.4 Instrumental investigations on micellar systems

Several complementary techniques are available to investigate the kind of supramolecular aggregates formed by surfactants in water driven by hydrophobic effect. First of all, it is worth noting that properties like c.m.c., size, shape and distribution of micelles or other aggregates is heavily influenced by the presence in solution of the other reaction components like catalysts or substrates. Moreover, different aggregates are observed at different temperature. Therefore in catalytic studies care must be taken because the picture obtained about a certain surfactant solution at room temperature can be drastically different in the presence of other species and under different temperature and pressure. Hence, it is important to gain some hints on the micellar system under use, especially investigating the surfactant interaction with catalyst and substrates.

The first information needed in order to be sure to work under micellar conditions is the value of the c.m.c. of the surfactant employed. While for commercial ones, the value is known, for new surfactants synthesized for special applications this must be determined. Several methods are available, all based on the observation that the properties of the solution drastically change

crossing the c.m.c. value. The most common methods for the determination of the c.m.c. are based on surface tension measurements, UV-VIS or fluorescence analysis,<sup>36</sup> NMR spectroscopy,<sup>37</sup> conductometry and several others.

The average size of micellar aggregates can be easily determined by means of static and dynamic light scattering (DLS) analysis<sup>38</sup> that provide information concerning the hydrodynamic radius of the aggregates and the distribution of the different structures present in solution even if the measurement is an average of the contribution from the different kind of aggregates. Complementary to this, cryo-TEM analysis allow to achieve real pictures of the aggregates formed by the surfactant.<sup>39</sup>

Among other, even though less frequently employed, small angle scattering techniques based on neutron (SANS) or X ray (SAXS) scattering are used to investigate the nanometric dimension of micellar aggregates.<sup>40</sup> These techniques provide important information on the size, shape, distribution and transition among surfactant aggregates in solution and their interaction with other organic species and salts present in the medium.

As far as the interaction between catalyst, substrate and micellar aggregates is concerned, 1D and 2D NMR techniques are the most suitable to gain rapidly useful information. This topic has been recently reviewed and detailed information can be found.<sup>41</sup> Determination of diffusion coefficient of the micellar aggregate by means of pulsed field gradient diffusion NMR or DOSY<sup>42</sup> compared to the value of the free solute allow to ascertain if an interaction between the two is present, due to weak intermolecular forces, usually hydrophobic effect, ion pairing and H-bonding. NOESY or ROESY 2D NMR experiments can be used to find which portion of both the solute molecules and the surfactant interact with each other. If these are in close contact, cross-peaks are detected, whose intensity is function of the reciprocal distance.<sup>43</sup> An alternative approach, often providing reliable results, consists in monitoring the variation of the chemical shift of both surfactant and analyte for solution of increasing relative concentration.<sup>44-48</sup> To make sure that peak shift is caused by close contact between solute and surfactant, the determination of the peak separation between methylene units belonging to the apolar portion of the surfactant is followed. This separation changes with the amount of solute, clearly excluding other solvation effects and confirming the close contact between the most sensitive methylene unit and the solute. Often, changes in peak shape are also observed at high solute concentration.

## 2. Application of commercial surfactants in catalysis

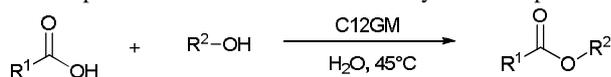
The present review is limited to the applications of surfactants in catalysis and does not cover either the use of polymeric self-assembling units like block co-polymers and hyperbranched polymers<sup>49</sup> because of their non-homogeneous molecular weight, or the use of dendrimers<sup>50</sup> because the latter do not form as a consequence of self-assembly in water induced by hydrophobic effect. This section includes mainly contributions concerning the use of large scale, commercially available

surfactants with just some mention on the use of bio-based surfactants. Surfactants are described on the basis of their applications in catalysis, either as a medium to disperse water insoluble transition and non-transition metals, organic catalysts, or directly as reaction promoters themselves. The material is divided according to the overall effect induced by micelles and the examples classified according to different reaction types in increasing order of complexity of the molecule produced.

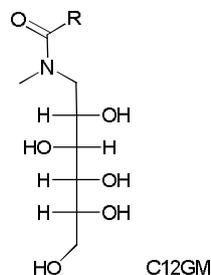
## 2.1.1 Yield improvement directly by micelles

### 2.1.1.1 Dehydration reaction

One of the most interesting applications of micellar catalysis consists in the apparent misleading esterification reaction between carboxylic acids and alcohols carried out in water with the aid of surfactants. This seminal work by Kobayashi and coworkers<sup>51</sup> opened the way to several other bi-component and multicomponent reactions that involve a dehydration step.

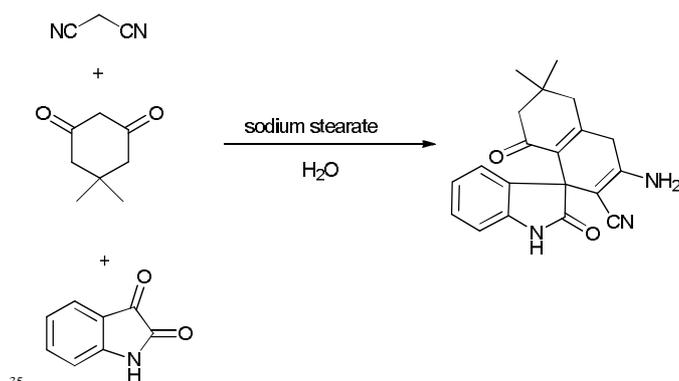


R<sup>1</sup> = aryl, alkyl  
R<sup>2</sup> = methyl, ethyl



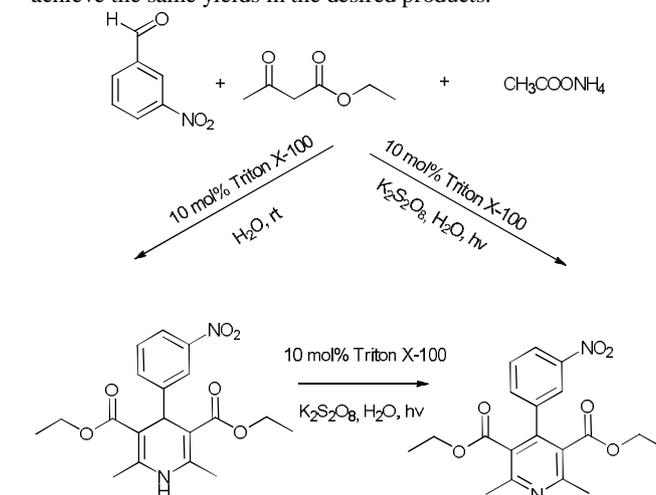
**Scheme 1.** Esterification of carboxylic acids with ethanol or methanol in water mediated by the bio-surfactant C12GM.

An important example of dehydration reaction conjugated with the development of bio-surfactant is the employment of catalytic amounts of a glucose-derived *N*-alkanoyl-*N*-methyl-1-glycylamine (C12GM) to promote the esterification in water at 45°C of a wide range of electron rich and electron poor aromatic acids as well as long alky chain aliphatic acids in the presence of methanol or ethanol (Scheme 1).<sup>52</sup> The surfactant can be obtained from glucose in three synthetic steps through reductive amination and amide formation with a methyl laurate ester. In particular, simple work-up of the reaction and recyclability of the bio-surfactant make this protocol a practical and economically attractive approach for further developments.



**Scheme 2.** Sodium stearate-catalyzed multicomponent reaction for the efficient synthesis of spirooxindoles in aqueous micellar media.

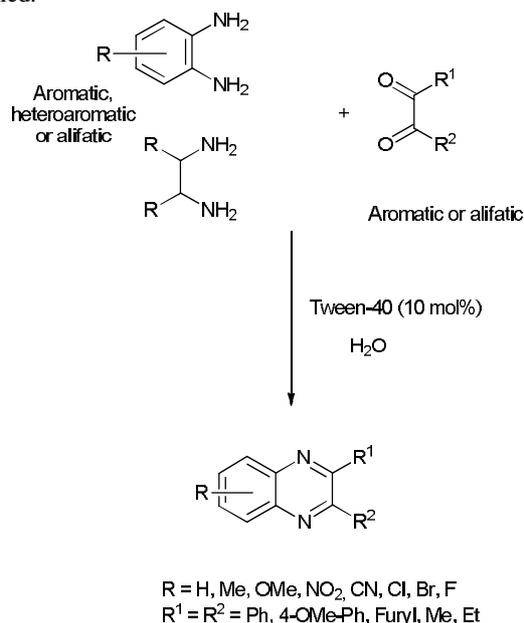
Micelles can be used to promote multicomponent reactions by taking advantage of the confinement effect as well as of the presence of certain functional groups on the surface of the aggregates. For example the use of weakly basic surfactants like sodium stearate proved to promote a simple and efficient method for the synthesis of spirooxindoles with fused chromenes, through the three-component one-pot reaction in aqueous micellar media (Scheme 2).<sup>53</sup> The surfactant self-assembles into micelles whose first effect is to form stable colloidal dispersion with water-insoluble substrates and thanks to the basic properties of the anionic surface it promotes the deprotonation of malononitrile, that reacts with isatin and further with a 1,3-dicarbonyl compound or 4-hydroxy-coumarin leading to the corresponding spirooxindoles derivatives in good yields (91-97%). These products find application as core structure in the synthesis of a number of pharmaceuticals and natural products. It is worth noting that neither the use of traditional surfactants like SDS or SDBS, nor the use of weak bases such as acetate, allowed to achieve the same yields in the desired products.



**Scheme 3.** Triton-X-100 catalyzed synthesis of 1,4-dihydropyridines and their aromatization to pyridines in water.

Another example of multicomponent reaction was proposed by Das and coworkers that reported the one step synthesis of 1,4-

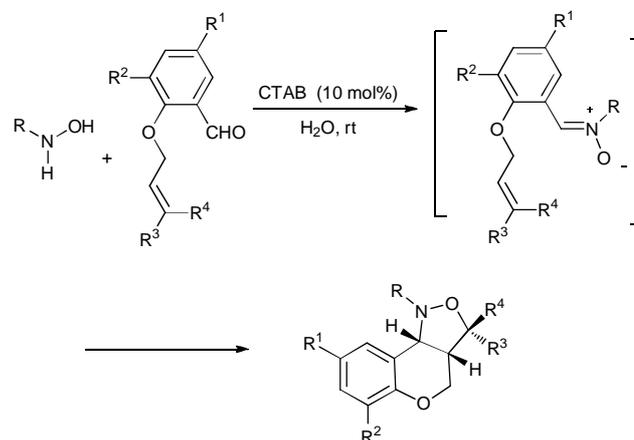
dihydropyridine derivatives directly from four component through Hantzsch reaction and consequent oxidation with monopersulphate to the corresponding pyridine derivative using the non-ionic surfactant Triton X-100 in water (Scheme 3).<sup>54</sup> It was observed that only this class of surfactants led to aggregates that ensured good catalytic activity, much better compared to charged cationic or anionic surfactants. The one pot protocol worked under very mild experimental conditions and offered excellent yields of the biologically relevant targeted molecules. More than twenty combinations of ammonium acetate with aromatic or aliphatic aldehydes and 1,3-bicarbonyl compounds were investigated providing the corresponding 1,4-dihydropyridine products within few hours with yields in all cases above 80% using only 10 mol% of surfactant that could be eventually recycled.



**Scheme 4.** Neutral surfactant promoted synthesis of quinoxalines in water.

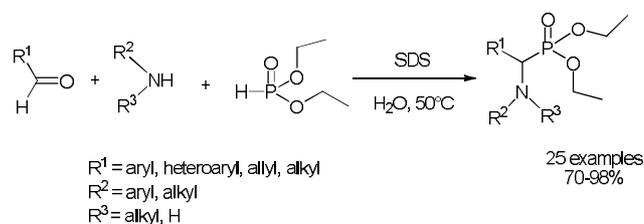
Another intriguing example of surfactant screening for the aqueous synthesis of organic molecules with potential medicinal application was reported by Chakraborti and co-workers that thoroughly investigated the synthesis of quinoxalines from 1,2-diamines and 1,2-dicarbonyl compounds testing about fifty different surfactants at room temperature (Scheme 4).<sup>55</sup> They found that among all, neutral surfactants and in particular Tween 40 led to the highest yield in the desired product while the catalytic potential followed the order: non-ionic surfactants > anionic surfactants > Brønsted acid surfactants > cationic surfactants. To comply with a green protocol simple recycling of the surfactant in the aqueous phase could be applied for five consecutive reactions. The use of the simple surfactant Tween 40 turned out to be more effective also compared to various Lewis/Brønsted acids combinations and the use of organic solvents showed lower yields compared to the micellar medium. The superiority of the micellar system is likely to be dependent on the high local concentration available within micelles for

highly apolar substrates in combination with the facile water expulsion typical of condensation reactions that are known to benefit from micellar conditions.



**Scheme 5.** Dehydrative intramolecular nitron cyclization in confined aqueous media leading to *cis*-fused chromano[4,3-*c*]isoxazoles.

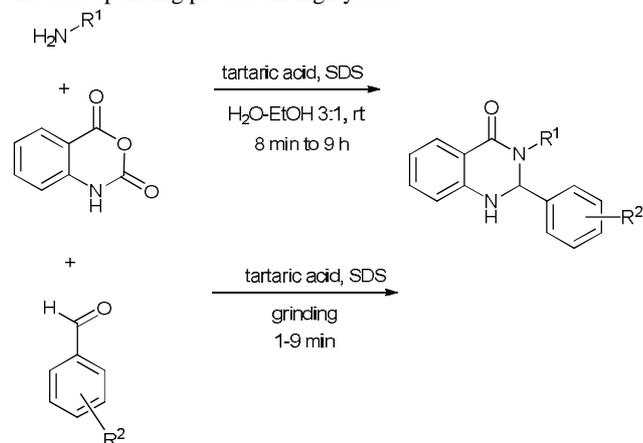
Another example in which the hydrophobic interior of micelles favors dehydration reactions with water as by-product was reported by Chatterjee and Bhattacharya in the environmentally friendly synthesis of chromano[4,3-*c*]isoxazoles via intramolecular 1,3-dipolar cycloaddition of *O*-allyl salicylaldehyde derivatives and hydroxylamine species by *in situ* formation of nitrones carried out in water with CTAB as surfactant (Scheme 5).<sup>56</sup> The cationic micelles favor the formation of the intermediate nitron by reaction of the salicylaldehyde and hydroxylamine with concomitant formation of water, followed by intramolecular 1,3-dipolar cycloaddition that leads to the final bicyclic product. The reaction operates well on a wide range of substrates observing that substituents in the aromatic ring of the *O*-allyl salicylaldehyde derivatives do not influence negatively the yield of chromano[4,3-*c*]isoxazoles. The latter could be easily isolated by cooling the reaction mixture at 5°C for several hours followed by filtration.



**Scheme 6.** Three component Kabacknik-Fields synthesis of  $\alpha$ -aminophosphonates catalyzed by SDS micelles.

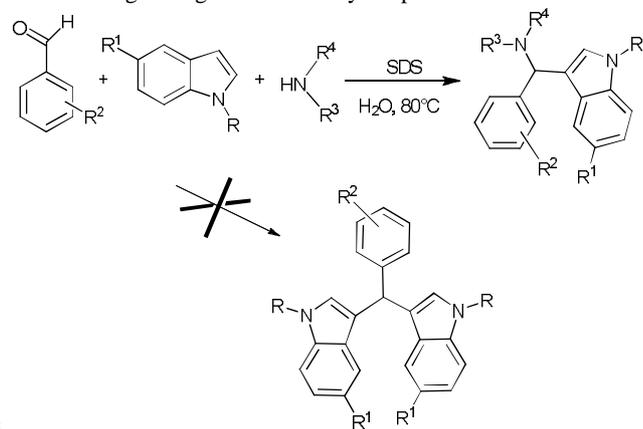
The reaction between amines, aldehydes and diethyl phosphite that provide  $\alpha$ -aminophosphonates can be efficiently promoted by SDS micelles in water (Scheme 6).<sup>57</sup> The reaction between two poorly reactive substrates like 4-methoxybenzaldehyde and 4-nitroaniline with diethyl phosphite at 50°C led to 86% yield of the corresponding  $\alpha$ -aminophosphonate, while in CTAB and Triton X-100 the reaction provided only 15 and 50% of the

desired product after 24h. Moreover under on water conditions, only 24% of product was obtained clearly underlying the positive effect of SDS in promoting the reaction. The protocol was applied to more than two dozens of combinations of substrates and even acid sensitive or polymerizable aldehydes smoothly led the corresponding product in high yields.



**Scheme 7.** Three component synthesis of 2,3-Dihydro/spiroquinazolin-4(1H)-ones catalyzed by tartaric acid in water with SDS.

Another example of multicomponent reaction was provided by Chauhan that investigated the synthesis of 2,3-dihydro/spiroquinazolin-4(1H)-ones in water form isoatoic anhydride, amines and carbonyl compounds using tartaric acid as catalyst in the presence of SDS in a 3:1 water/ethanol solvent mixture (Scheme 7).<sup>58</sup> The reaction run under mechanical stirring in this solvent mixture enabled the formation of the corresponding quinazolin-4(1H)-ones from aromatic aldehydes, cyclic ketones, aliphatic amines and even aqueous ammonia. The reaction medium could be recycled for four runs and the protocol was further improved in terms of reaction time excluding the presence of water thus working in solvent-free conditions under mechanical grinding still favored by the presence of SDS.

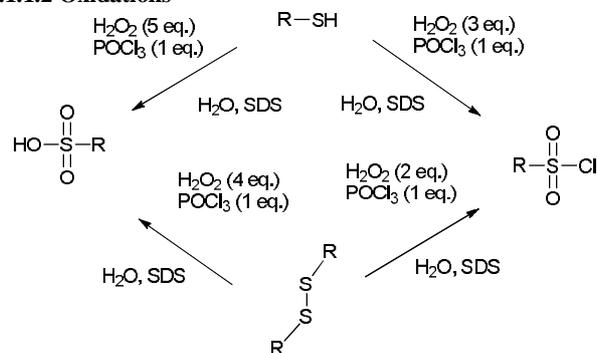


**Scheme 8.** Three-component Mannich-type direct synthesis of 3-amino alkylated indoles under SDS micellar conditions.

Kumar provided an interesting example of product selectivity induced by micelles in the one-pot synthesis of 3-amino alkylated indoles via a three-component Mannich-type reaction from

secondary amines, aldehydes and indoles.<sup>59</sup> While several other Brønsted and Lewis acids led almost exclusively to the formation of the *bis*-indole derivative, in the presence of water/SDS the reaction smoothly led to the formation of the desired 3-amino alkylated indoles in very good yields (Scheme 8). The hydrophobic core of the micelles favours initially iminium cation formation with water expulsion, followed by reaction of the cationic intermediate with indole. The method allowed easy preparation of 25 different products in 2-14h at 80°C with isolated yields in the range 78-94%.

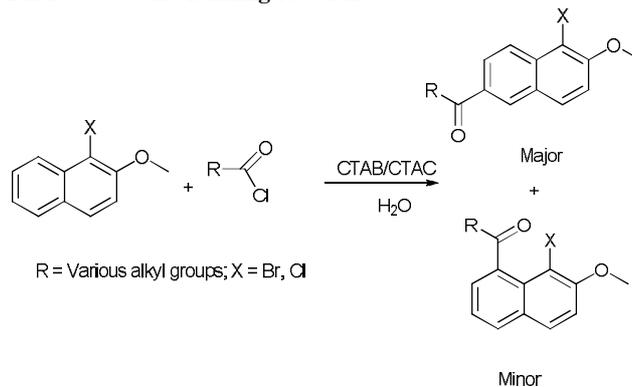
### 2.1.1.2 Oxidations



**Scheme 9.** Synthesis of sulfonyl chlorides and sulfonic acids from thiols or disulfides with hydrogen peroxide in water promoted by SDS.

SDS proved to promote in water at room temperature the reaction of sulfides or disulfides with hydrogen peroxide leading to the corresponding sulfonyl chlorides or sulfonic acids as a function of the amount of phosphoryl chloride present (Scheme 9).<sup>60</sup> The reaction was highly selective since the presence of other oxidizable functional groups on the reagents like alcohols, C=C double bonds, oxime and acetals was well tolerated. The reaction showed to be poorly sensitive to the electronic properties of the sulfur containing substrate. Anionic SDS as surfactant enabled fast reactions that were completed within 2h, while cationic CTAB or neutral triton X-100 turned out to significantly slow down the reaction rate.

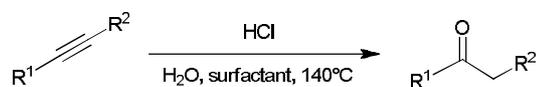
### 2.1.1.3 C-C bond forming reactions



**Scheme 10.** Friedel-Crafts acylation of 1-halo-2-methoxynaphthalenes in micellar media.

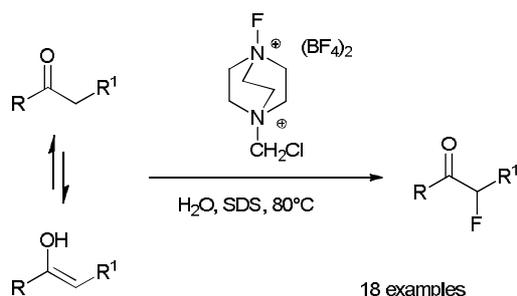
Even traditional organic reactions like the Friedel-Crafts acylation of aromatics can be easily run in water. The addition of cationic surfactants like CTAB or CTAC afforded good to excellent yields of acylation products between acetyl chloride and 1-halo-2-methoxynaphthalenes, 2-methoxynaphthalene, anisole, 2-methoxypyridine, and 2-methoxypyrimidine (Scheme 10)<sup>61</sup>. The reaction carried out under the same experimental conditions in traditional organic solvents gave better yields but the employment of microwave or ultrasound conditions made the reaction with cationic micelles even more competitive and efficient already at room temperature. With this approach the use of prolonged reaction times, harsh reaction conditions (reflux temperature), metal triflates, mineral acids, and stoichiometric amount of metal halides that give hazardous corrosive waste products could be avoided. Once again, carefully selected micellar media resulted compatible with moisture sensitive reagents.

#### 2.1.1.4 C-heteroatom bond forming reactions



**Scheme 11.** Acid-catalyzed hydration of alkynes in aqueous microemulsions.

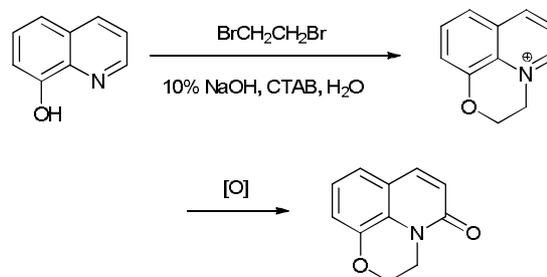
Alkyne hydration is a very well known reaction that usually requires the presence of transition metal catalysts to increase the electrophilicity of the alkyne. Recently Blum and coworkers demonstrated that it is possible to completely avoid the presence of metal species. Efficient hydration of terminal and internal aromatic alkynes as well as terminal alkenes was achieved in water exploiting simply Brønsted acid catalysis in the presence of surfactants at 140°C (Scheme 11).<sup>62</sup> Different classes of surfactants could be employed, with neutral and anionic tensides providing higher yields with respect to cationic surfactants. The reaction afforded exclusively the products corresponding to Markovnikov addition of water and the procedure could be efficiently scaled up to more than 100 mmoles. When run in deuterium oxide, the reaction applied to terminal alkynes led to the corresponding trideuteromethyl ketone derivatives.



**Scheme 12.** Selective  $\alpha$ -fluorination of ketones in water with SDS.

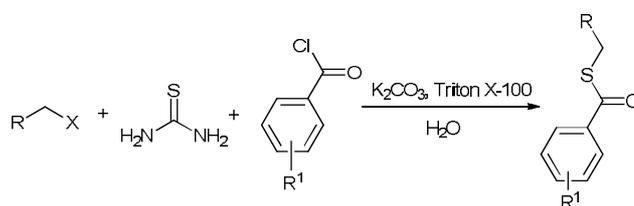
As reported by Stavber and coworkers, the direct fluorination

of ketones could be efficiently achieved combining Selectfluor F-TEDA tetrafluoroborate as reagent in micellar media (Scheme 12).<sup>63</sup> Key to success was the proper selection of surfactant. Only anionic SDS micelles allowed both solubilization of apolar substrates and sufficient enolization and consequent interaction with the cationic fluorinating agent Selectfluor. Cationic and neutral surfactants, or even on water conditions, were unsatisfactory. The amount of SDS turned out to be crucial to ensure sufficient tautomerization of the carbonyl substrate and a concentration lower than 200 mM was found to be sufficient to promote fluorination of cyclic, acyclic, aliphatic and methyl ketones.



**Scheme 13.** Synthesis of polycyclic fused 2-quinolones in aqueous micellar system.

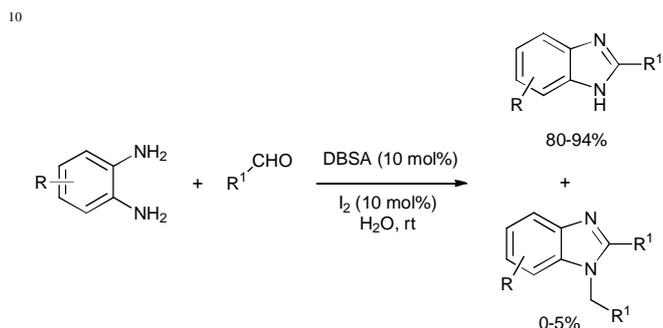
Another class of interesting potential drugs was efficiently obtained under micellar conditions with improved performance with respect to traditional homogeneous organic conditions. 2-Quinolones are known for their anticancer, antiviral, and antihypertensive properties and Mondal reported the synthesis of tri-, tetra-, and pentacyclic fused quinolones with excellent yields in a short reaction time using cetyltrimethylammonium bromide (CTAB) as a micellar catalyst in aqueous media, without the use of any organic solvent in the reaction (Scheme 13).<sup>64</sup> Anionic or neutral surfactants did not promote the reaction that operates well in cationic micelles under basic conditions with a possible mechanism that involves the nucleophilic attack of the 8-hydroxy-quinoline to the dibromo derivative followed by intramolecular attack of the quinoline ring nitrogen to form the quinolinium salt that further oxidized to the final product. Different derivatives of 8-hydroxyquinoline and 1, $\omega$ -dihaloalkanes/xylenes/methyl-quinoxalines as alkylating agents lead in all cases to yields above 90%.



**Scheme 14.** One-pot synthesis of thioesters from organic halides, thiourea and benzoyl chlorides in water with Triton X-100.

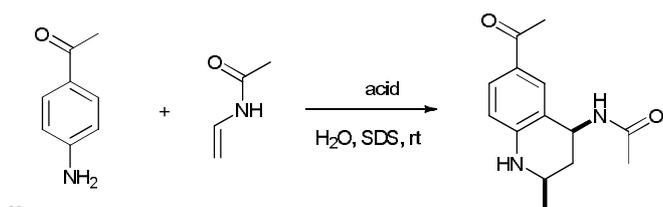
An example of the application of micellar catalysis to simplify the employment of noxious substrates was recently reported in the direct one-pot synthesis of thioesters from organic

halides, thiourea and benzoyl chlorides in water with Triton X-100 via stabilization of an intermediate S-alkylisothiuronium salt (Scheme 14).<sup>65</sup> It is worth noting that the micelles allowed sequestration of the benzoyl chloride thus avoiding its hydrolysis by water but rather favouring its reaction with thiourea. The protocol could be scaled up to 10 mmol of substrate and alternative electrophilic substrates like benzenesulfonyl chloride and benzoic anhydride could be successfully employed in place of benzoyl chloride.



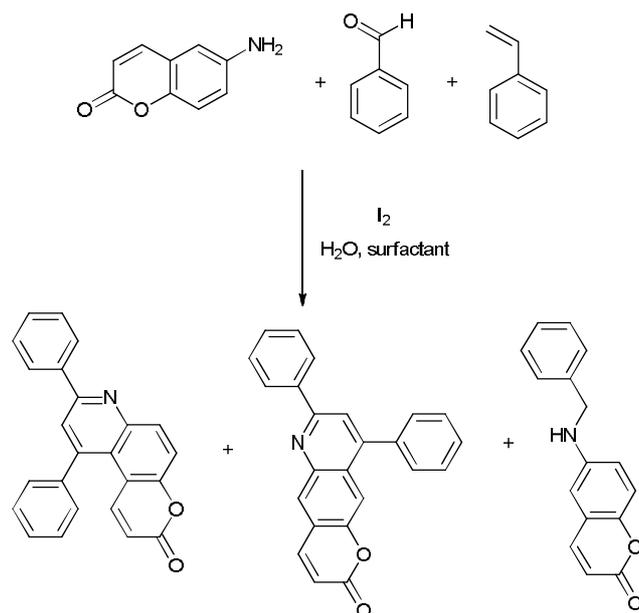
**Scheme 15.** Dodecylbenzenesulfonic acid and iodine catalyzed synthesis of 2-substituted benzimidazoles in water.

15 Exploiting the properties of acid surfactants to promote condensation and dehydration reactions allowed to develop an efficient synthetic method for the facile synthesis of 2-substituted benzimidazoles, based on the catalytic effect of dodecylbenzenesulfonic acid with iodine on the reaction between  
20 *o*-diaminoarenes and a variety of aldehydes (Scheme 15).<sup>66</sup> The reaction is characterized by operational simplicity, excellent yields, high chemoselectivity allowing the synthesis of thirty derivative all in good yields.



**Scheme 16.** Synthesis of tetrahydroquinolines in water with SDS.

30 The use of micellar media is particularly useful for the synthesis of pharmacologically relevant molecules like in the case of 4-amidyl-2-methyl-1,2,3,4-tetrahydroquinolines (Scheme 16).<sup>67</sup> This class of molecules was directly produced diastereospecifically in high yields through a domino type ABB' imino Diels–Alder reaction in acidified water in the presence of  
35 sodium dodecyl sulfate observing direct evidence of the influence of the concentration of the surfactant on the yield of the reaction, with better results when above the critical micellar concentration. The catalysis was the result of the combination of the compartmentalization effects imparted by the surfactant together  
40 with low pH provided by acid addition.

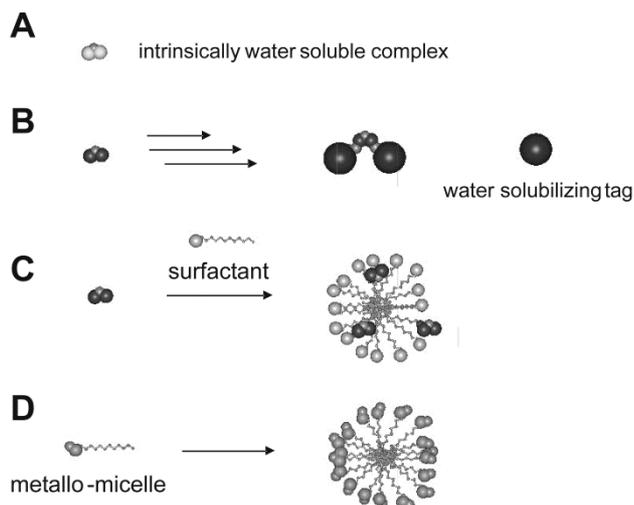


**Scheme 17.** Synthesis of pyridocoumarins with iodine in aqueous  
45 micellar media.

Another example of multicomponent reaction involving Diels Alder cycloadditions was reported involving 6-aminocoumarin, aromatic aldehydes and an excess of styrene in water with SDS and iodine (Scheme 17).<sup>68</sup> The reaction initially formed the formal Povarov adducts subsequently aromatized under auto-tandem iodine catalysis. The unusual linear fusion of the pyridine ring to the existing benzenoid ring of the coumarin followed by iodine oxidation led under neutral conditions to prepare a small  
55 library of pyrano[3.2-f]quinolin-3-ones and pyrano[2.3-g]quinolin-2-ones in good to acceptable yields under neutral conditions.

### 60 2.1.2 Yield improvement in metal catalyzed reactions

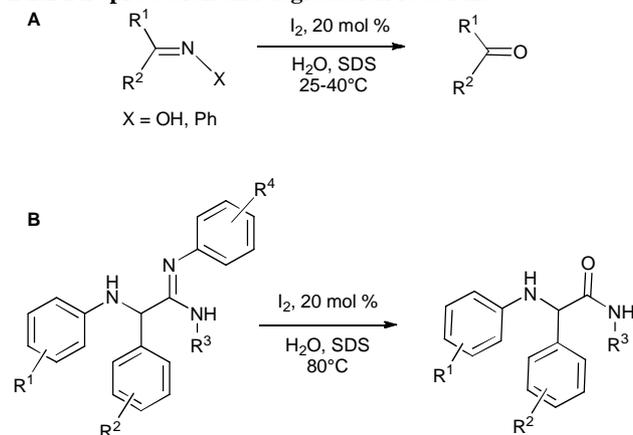
With respect to solubility in water, metal catalysts can be classified into four general types (Figure 1): a) intrinsically soluble catalysts; b) catalysts developed for organic media and covalently modified with water soluble pony tails<sup>69</sup> that often turn  
65 out in tedious and time consuming synthetic steps and that in some cases alter profoundly the electronic and steric properties of the catalysts; c) the employment of supramolecular aggregates to dissolve the catalyst thus maintaining the integrity of the original organic soluble catalyst and d) metallo-surfactant molecules that  
70 self-assembles into micelles in solution.



**Figure 1.** Approaches to metal catalysis in water: A) intrinsically water soluble catalyst; B) covalent modification of ligands with water solubilizing tags; C) solubilization of catalysts in micelles or in hosts by means of supramolecular hydrophobic effect. D) covalent metal-surfactant adduct forming metallo-micelles.

Even though the third approach reported in Figure 1C is the simplest one and provides the best advantages in terms of greening up existing processes developed to run in organic solvents, the first two approaches (Figure 1A and B) based on water-soluble catalysts can also benefit from the presence of micelles in aqueous media. In fact interactions between apolar substrates dissolved within micelles and water-soluble charged catalysts are possible employing surfactants with complementary charge with respect to the catalyst, thus favoring the interaction between the two reaction partners in the Stern layer of the micelles (Figure 1C). The approach reported in Figure 1D has been introduced some time ago<sup>32f</sup> but, even if a complex synthetic effort is requested, it provides excellent micellar catalysts especially for asymmetric reactions, as described below.

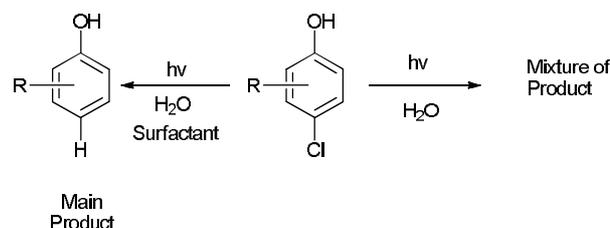
### 2.1.2.1 Deprotection and degradation reactions



**Scheme 18.** A) Deprotection of oximes and imines under neutral conditions in water with  $\text{I}_2$  in the presence of surfactants; B) Hydrolysis of phenylacetimidamide with  $\text{I}_2$  and SDS in water leading to the corresponding phenylacetamide.

Deprotection of oximes and imines to the corresponding carbonyl compounds is not a trivial reaction as it often requires the employment of Lewis acids, harsh experimental conditions and in some cases toxic reagents. Konwar and coworkers disclosed a simple deprotection method for both classes of compounds based on the use of molecular iodine as catalyst with SDS in water under neutral conditions at 25–40 °C (Scheme 18A).<sup>70</sup> The reaction benefits from the micellar environment to solubilize both the reagent and 20 mol %  $\text{I}_2$  while in the absence of surfactant the reaction is sluggish. SDS favors the attack of iodine to the C=N bond possibly leading to an iodonium ion. The latter species is stabilized by the negative micellar surface and is subsequently hydrolyzed forming the final free carbonyl compound.

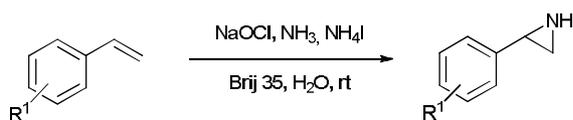
This reaction has been recently applied successfully for the transformation of 2-arylamino-2-phenylacetimidamide, obtained via Ugi three-component reaction, into the corresponding 2-amino-2-phenylacetamide derivatives as interesting scaffold for medicinal chemistry (Scheme 18B).<sup>71</sup> Conversely, alkaline hydrolysis of the multicomponent reaction afforded the *N*-substituted  $\alpha$ -amino acid.



**Scheme 19.** Surfactant effect on the photo-degradation of 4-chlorophenols in water.

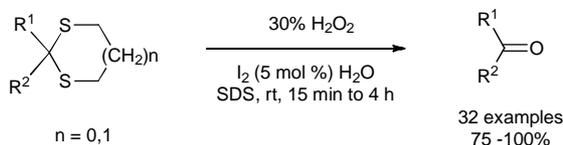
Photochemical reactions are often sensitive to media properties as observed by Fagnoni and coworkers in the investigation of the product distribution in the photochemical degradation of chloro-phenol derivatives often employed as anti-microbial agents but characterized by strong environmental concern. These authors observed that while in pure water a complex mixture of de-chlorinated products are formed comprising quinones and hydroquinones, in the presence of micelles the main reaction was the photo-reduction to the corresponding phenol with chlorine loss, regardless of the chemical properties of the surfactant employed (Scheme 19).<sup>72</sup> Since the toxicity of phenols are even higher than that of the corresponding chlorinated phenols, the presence in the environment of surfactants together with chlorophenols complicates their natural abatement by solar irradiation.

### 2.1.2.2 Oxidations



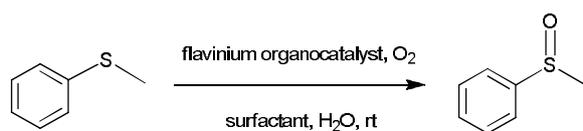
**Scheme 20.** Aziridine synthesis from alkenes with hypochlorite, ammonia and iodide in water mediated by neutral ethoxylated fatty alcohols surfactants.

5 Aziridines are largely employed as useful chemical intermediates and pharmaceuticals. Their synthesis is not trivial and often requires the employment of complex nitrogen-containing sources, which lead to *N*-substituted aziridines that  
 10 require a subsequent deprotection step. Micellar catalysis enabled the direct incorporation of ammonia into olefins simply using non-ionic surfactants, such as ethoxylated fatty alcohols or sorbitan esters, with molecular iodine as catalyst in the presence of bleach (Scheme 20).<sup>73</sup> The reaction was much more efficient  
 15 compared to the use of organic water soluble co-solvents, as it required a few hours at room temperature. The reaction efficiently converted a wide range of ring-substituted styrenes, including substrates containing electron-donating or -withdrawing groups. Conversely, aziridine yields were much  
 20 lower for aliphatic olefins with various substitution patterns because of intrinsic lower activity.  $\alpha$ -Methylstyrene gave a higher aziridine yield (92%) than styrene itself, while  $\beta$ -methylstyrene provided a lower yield (56%). The use of mild experimental conditions, the high atom efficiency and the employment of  
 25 inexpensive reagents made the process extremely environmentally benign.



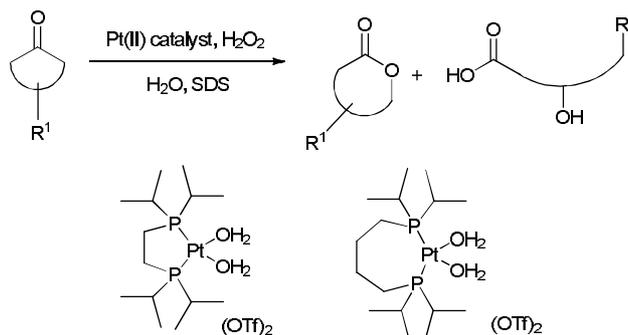
**Scheme 21.** 1,3-dithianes deprotection with hydrogen peroxide catalyzed by molecular iodine in water with SDS.

35 Traditional cleavage of *S,S*-dithioacetals as protecting groups for carbonyl compounds usually employs hazardous or polluting heavy metal salts. An alternative protocol that uses catalytic amounts of molecular iodine with hydrogen peroxide as oxidant for *S* in water with SDS as surfactant was reported recently (Scheme 21).<sup>74</sup> The reaction worked well both on thioacetals and thioketals on a 1-5 mmol scale with high chemoselectivity avoiding over-oxidation of the released carbonyl compound and  
 40 tolerating the presence of other protecting groups like benzyl, BOC, carbamate and silyl ethers. The mild experimental conditions were applied successfully to more than thirty sulfur protected carbonyl compounds. Efficient recovery of acid labile carbonyl compounds like cinnamaldehyde and furan-2-aldehyde  
 45 and even non-activated substrates was possible within 4h at room temperature. Cationic CTAB and neutral Triton X-100 gave less satisfying results both in terms of conversion and reaction time.



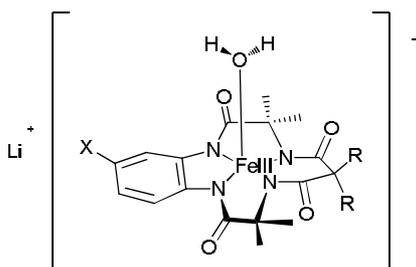
**Scheme 22.** Organocatalytic sulfoxidation in micellar systems containing amphiphilic flavinium salts using hydrogen peroxide as a terminal oxidant.

The polar or apolar nature of an organocatalyst dictates its  
 55 affinity for the micellar environment or the aqueous phase and this influences the outcome of the reaction. A clear example of this was reported by Cibulka and coworkers investigating the sulfoxidation reaction of thioanisole mediated by amphiphilic flavinium  
 salt [10-dodecyl-5-ethyl-3,7,8-trimethylisoalloxazinium perchlorate that interacts strongly with micellar aggregates with respect to its hydrophilic homologue 5-ethyl-3,7,8,10-tetramethylisoalloxazinium perchlorate that is  
 60 soluble in pure water (Scheme 22).<sup>75</sup> The reaction rates were strongly dependent on the type of micellar matrix and on the pH value with the highest acceleration found for the amphiphilic flavinium salt in SDS micelles at pH 4.4 (TOF =  $3 \cdot 10^3 \text{ h}^{-1}$ ) while the micellar aggregate did not favor the reaction with the water  
 65 soluble homologue, this effect being especially pronounced in cationic micelles, for which the non-catalyzed reaction was markedly suppressed. The micellar environment enhanced the rate of the reaction with the ratio  $v_{\text{cat}}/v_0$  of the catalyzed and non-catalyzed reaction rates as high as 40 times in cetyl  
 70 trimethylammonium nitrate (CTANO<sub>3</sub>), while in homogeneous solution its value did not exceed 7. For all micellar systems investigated, the sulfoxidation rate ( $v_{\text{obs}}$ ) observed in the presence of flavinium salt was higher compared to the reaction in  
 75 homogeneous solution; the factor of acceleration ranging from approximately 1.5 in non-ionic micelles to 3 in anionic micelles.



**Scheme 23.** Synergic combination between a water soluble Pt(II) catalyst and SDS to promote the Baeyer-Villiger oxidation of cyclic ketones with H<sub>2</sub>O<sub>2</sub>.

The use of micellar conditions in water can be an efficient strategy to enhance the catalytic activity of intrinsically water soluble catalysts. The role of the surfactant in this case is to facilitate substrate solubilization and its close contact with the catalyst. This is the case of the Baeyer Villiger oxidation of cyclic ketones with hydrogen peroxide mediated by intrinsically water soluble *bis*-cationic Pt(II) complexes bearing small alkyl-diphosphines (Scheme 23)<sup>76</sup> for which the use of SDS in water led to enhanced catalytic activity compared to that with organic solvents. Mild experimental conditions, such as moderate temperature and low catalyst loading ( $\leq 2$  mol %), enabled moderate to good yields. For more acid-sensitive substrates, higher productivity was paralleled by formation of the corresponding  $\omega$ -hydroxy acids because of Brønsted acid catalyzed hydrolysis of the uncurrent intermediate lactones.

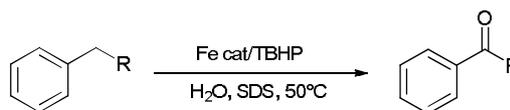


**Scheme 24.** Structure of the Fe(III)-TAML- catalyst.

Another example of combination of the positive effect imparted by micelles in keeping in close contact substrate and catalyst is provided by the application of Fe(III) complexes of tetra-amidato macrocyclic ligands (TAMLs) in the hydrogen peroxide or *t*-butyl hydroperoxide oxidation and decolorization of Orange II and Sudan III dyes (Scheme 24).<sup>77</sup> Overall, due to the negative charge of the metal complex, cationic micelles turned out to be the most effective and the system has been exploited also in the deactivation of bacterial spores. The surfactant was less effective under pH conditions where the axial aqua ligand of the catalysts was deprotonated thus increasing the overall negative charge of the metal species that become more hydrophilic and interacts less with the micelles. Analogously, more hydrophobic substrates showed enhanced activity being in closer contact with the metal catalyst on micelles.

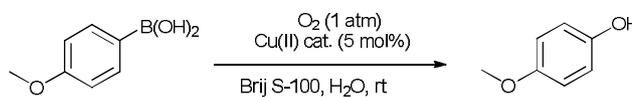
Liu and coworkers applied micellar catalysis to the development of an efficient artificial mimic of glutathione peroxidase enzyme that is active in the catalytic decomposition of hydroperoxides by glutathione thanks to the presence in the active site of a selenocysteine residue thus playing an important role in protecting cells from oxidative stress. A simple enzyme mimic was developed employing the typical surfactant aggregation behavior of cationic surfactants like CTAB in combination with the dissolution of benzeneseleninic acid as catalytically unit through hydrophobic and electrostatic interactions.<sup>78</sup> The micellar catalytic system displayed substrate specificity for both 3-carboxy-4-nitrobenzenethiol and cumene hydroperoxide, and enabled 500-fold rate acceleration with respect to PhSeO<sub>2</sub>H alone. The combination of the apolar core of the artificial enzyme and the positive charges present on the

surface played a pivotal role for binding substrates and accelerating the enzyme-like reaction. The authors exploited a similar self-assembly strategy based on hydrophobic effect also for the construction of other glutathione peroxidase mimics based on the use of block co-polymers,<sup>79</sup> pseudo-block copolymers<sup>80</sup> or surfactants endowed with terminal alkene moieties as polymerizable units achieving simple approaches for tailoring the properties and the catalytic activities of these enzyme mimics.<sup>81</sup>



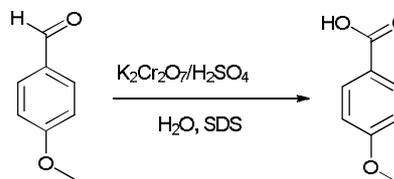
**Scheme 25.** Iron-surfactant nanocomposite-catalyzed benzylic oxidation in water.

Oxidation of benzylic substrates into the corresponding carbonyl compounds is a highly desirable reaction that often makes use of toxic transition metal catalysts. Novák and coworkers proposed the use of *t*-butyl hydroperoxide as terminal oxidant in the presence of simple Fe(III) species such as FeCl<sub>3</sub> or Fe<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> as environmentally friendly metal catalyst in the presence of anionic surfactant SDS to promote efficient substrate dissolution and consequent reaction (Scheme 25).<sup>82</sup> With this protocol more than two dozen of substituted aromatic substrates bearing benzyl moiety and sufficiently electron rich were smoothly converted into the corresponding carbonyl compounds with high rate acceleration.



**Scheme 26.** Synthesis of phenols from aryl boronic acids mediated by Cu(II) micellar media.

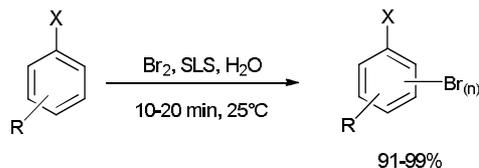
The synthesis of phenols from the corresponding boronic acid through Cu(II) oxidation with molecular oxygen in water proved to benefit greatly from the presence of amphiphilic surfactants like Brij S-100 without requiring the presence of bases and ancillary ligands (Scheme 26).<sup>83</sup> In particular the reaction proceeded under mild experimental conditions and well tolerated the presence of several other functional groups on the boronic acids (e.g. alkoxy, acetyl, cyano, halogen atoms) leading to the corresponding phenols in 50-95% isolated yield.



**Scheme 27.** Cr(VI) oxidation of *p*-anisaldehyde to *p*-anisic under micellar catalysis at room temperature in water.

As a confirmation of the intimate contact between positively charged cationic metal catalysts and anionic surfactants providing

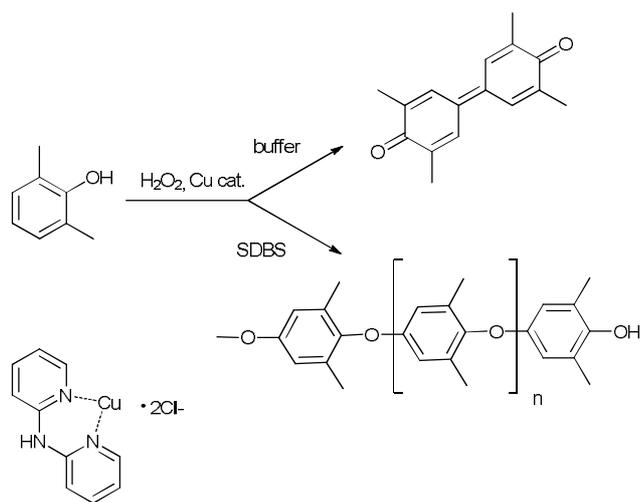
anionic micelles the oxidation of *p*-anisaldehyde by chromic acid was reported to produce *p*-anisic acid in presence of micellar catalysts in aqueous media at room temperature (Scheme 27)<sup>84</sup> with an almost three-fold acceleration compared to the uncatalyzed path, whereas *N*-cetylpyridinium chloride (CPC) cationic surfactant and triton-X-100 (TX-100) neutral surfactant inhibited the reaction.



X = OH, NH<sub>2</sub>, NHCOMe, NHCOPh, CHO, COOH  
R = H, OH, NO<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>

**Scheme 28.** Aqueous bromination method for the synthesis of industrially-important intermediates catalyzed by micellar solution of SDS.

Since bromination of electron rich aromatic compounds occurs via formation of the positively charged bromonium ion, it is easy to explain why the same reaction in water in the presence of SDS as anionic surfactant is favored. The authors observed rapid disappearance of bromine at room temperature under the above described experimental conditions for the rapid synthesis of a wide range of mono, di and tri brominated phenols, naphthols and anilines obtained in excellent yields (91–99%) and purity (>99%) (Scheme 28).<sup>85</sup> The generation of CaBr<sub>2</sub> (an industrially significant product) instead of HBr waste and the recovery of the surfactant in the form of calcium dodecyl sulphate are both the green features of the system.

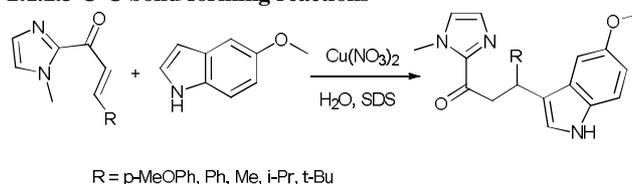


**Scheme 29.** Metal complexes catalyzed oxidative coupling of 2,6-dimethylphenol in micellar media.

An example of oxidative coupling reaction was reported by Meng and coworkers where different micellar media led to different relative amounts of dimeric 3,3',5,5'-tetramethyl-4,4'-diphenoquinone (DPQ) or polymeric poly(2,6-dimethyl-1,4-

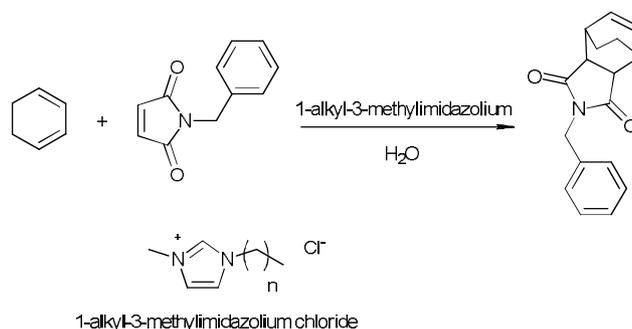
phenylene ether) (PPO) in the hydrogen peroxide oxidation of 2,6-dimethylphenol (DMP) with catalyzed by Cu(II) complexes bearing *N* ligands 2,2'-dipyridylamine and *N,N'*-bis(2-pyridinecarbonyl) ethylenediamine (Scheme 29).<sup>86</sup> In particular with cationic surfactant CTAB or gemini *bis*-cationic surfactants the reaction was up to three times faster than in buffer solution. Conversely, with Triton X-100 and SDBS, a small effect on the reaction rate compared with the buffer solution was observed. DPQ was easily generated in aqueous solution, while PPO was remarkably promoted in micellar media, especially with SDBS, and could be easily separated from the solution while maintaining the Cu(II) catalyst in the micellar medium.

### 2.1.2.3 C-C bond forming reactions



**Scheme 30.** Dramatic micellar rate enhancement of the Cu(II) catalyzed vinylogous Friedel–Crafts alkylation in water.

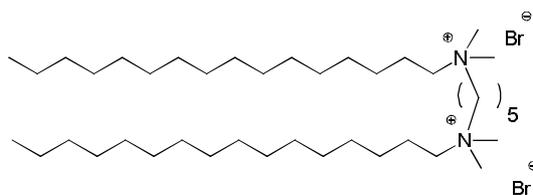
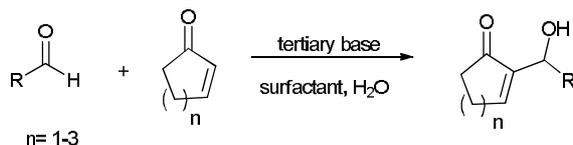
Synergic combination of metal catalyst and micellar aggregates showed to boost the Friedel–Crafts alkylation of indoles in water (Scheme 30).<sup>87</sup> The presence of sodium dodecyl sulfate (SDS) as surfactant led to a substantial increase of the rate of the reaction catalyzed by Cu(II) observing an increase of up to  $9.3 \cdot 10^3$  fold rate acceleration was found in the presence of 8 mM SDS compared to the reaction catalyzed by Cu(II) alone. The acceleration observed was found to be also dependent on the R groups on the enone moiety. Aryl derivatives that are more hydrophobic showed an about five times larger acceleration with respect to the substrate bearing a small methyl group. Overall, the possibility to perform this reaction in water with very short reaction times and in good yields makes this an attractive procedure for catalytic Friedel–Crafts alkylation reactions.



**Scheme 31.** Diels–Alder reaction in micellar media derived by water–ionic liquid systems.

As recently disclosed, amphiphilic ionic liquids bearing long alkyl chains and polar head-groups like 1-alkyl-3-methylimidazolium ionic liquids ([C<sub>*n*</sub>mim]Cl, *n* = 8–14) lead to micelle formation in water. Such nanometric reactors turned out

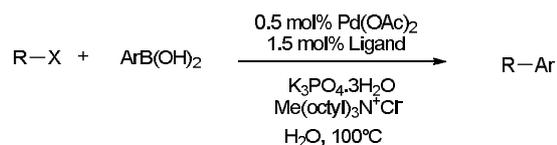
to catalyze the Diels–Alder reaction between 1,3-cyclohexadiene and maleimide derivatives showing up to 4.1 accelerations with respect to the same reaction in pure water (Scheme 31).<sup>88</sup> Moreover, the maximum reaction rate occurred above the CMC of the respective amphiphilic ionic liquid, with values larger than those observed with traditional surfactants such as CTAB and SDS. Combining the amphiphilic ionic liquids with a Lewis acid like  $\text{InCl}_3$  led to the formation of surface active chloroindate ionic liquids that were responsible for a further rate enhancement.



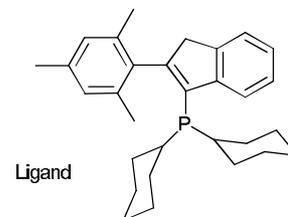
**Scheme 32.** Micellar approach to Morita-Bayliss-Hillman reaction.

The Morita-Bayliss-Hillman (MBH) is the reaction in which a tertiary amine as catalyst interacts with an unsaturated carbonyl compound leading to a zwitterionic ammonium-enolate intermediate that attacks electrophilic molecules such as aldehydes leading to  $\alpha$ -substituted unsaturated carbonyl compounds. The reaction was greatly accelerated by cationic surfactants that positively stabilize the enolate intermediate. In particular, it was observed that the classical cationic surfactant CTAB and the *bis*-cationic analogue pentanediyl-1,5-bis(dimethylcetylammmoniumbromide) at or above c.m.c. dramatically increased both reaction rates and yields of the reaction. The micellar aggregate was crucial to impart substrate solubilization and enolate stabilization, while traditional cationic phase transfer agents like tetraethyl ammonium or tetrabutyl ammonium halides turned out to be inefficient (Scheme 32).<sup>89</sup>

Micellar catalysis found application also on the synthesis of hydrophobically modified polysaccharides that are attracting more and more interest because they possess other important properties such as biocompatibility and biodegradability. Chemical modification of dextran, a neutral bacterial polysaccharide consisting of  $\alpha$ -1,6 linked glucose units, was possible employing terminal epoxides bearing  $\text{C}_8$  to  $\text{C}_{18}$  alkyl chains in water under basic conditions employing dodecyltrimethylammonium bromide (DTAB) as surfactant.<sup>90</sup> This led to a good product formation within 96 h, while anionic SDS or neutral surfactants turned out to be much less effective. It is likely that the cationic micelles ensure close contact between hydrophobic epoxides, dextran and the hydroxyl anion that tends to concentrate on the surface of the cationic micelles promoting the reaction.

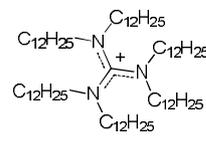
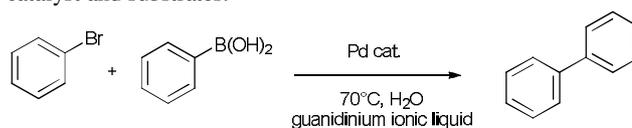


R = Aryl, heteroaryl



**Scheme 33.** Suzuki-Miyaura cross-coupling reaction of aryl and heteroaryl chlorides in micellar media.

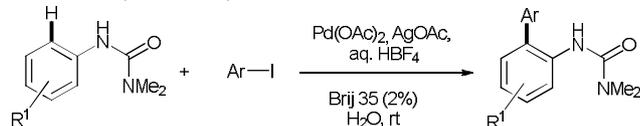
The Suzuki-Miyaura cross-coupling reaction is a well established catalytic reaction for the preparation of biaryl derivatives and it has been deeply investigated also in water as solvent. Despite the impressive progress, a number of challenges remain unresolved, for example the coupling of the readily available and low-cost aryl chlorides and heteroaryl chlorides remains difficult to achieve. Recently, Yu and Liu proposed a catalytic protocol to address these problems, consisting in the use of methyl-trioctyl-ammonium chloride as an additive for the reaction between aryl chlorides and arylboronic acids at 100°C mediated by ultra-low loading of  $\text{Pd}(\text{OAc})_2$ /(2-mesitylindenyl)dicyclohexylphosphine as catalyst (Scheme 33).<sup>91</sup> The positive effect played by tetraalkylammonium species in cross-coupling reactions is known. The same is likely to apply to this catalytic system where the role played by the ammonium additive was not elucidated, even though some kind of aggregation was possible with the overall effect to favor the intimate contact between catalyst and substrates.



**Scheme 34.** Suzuki coupling reaction in water mediated by guanidinium ionic micellar aggregates.

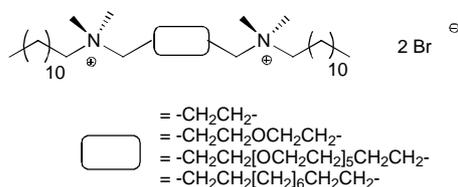
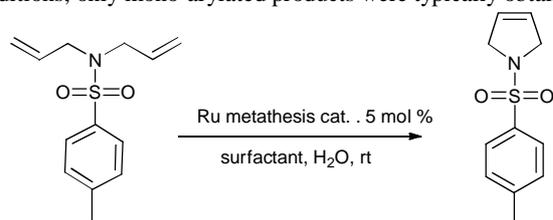
Li and coworkers disclosed the positive effect played by the addition of guanidinium ionic liquids endowed with six lipophilic alkyl chains in the Suzuki coupling between aryl bromides and chlorides in water at 70°C using ligand-free Pd catalysts (Scheme 34).<sup>92</sup> The ionic liquid formed micelles as confirmed by TEM analysis. The supramolecular aggregates played the fundamental role to stabilize the formation of elemental Pd nanoparticles of 5.1 nm average size that efficiently promoted the coupling reaction. The efficiency of the coupling was found to be dependent on the length of the lipophilic portion of the guanidinium additive. In fact the reaction between 4-

bromoanisole and phenylboronic acid led to slightly more than 30% product using the hexaethyl-guanidinium bromide as additive, while almost complete conversion was observed with the hexa-dodecyl-guanidinium bromide analogue. With aryl bromides as coupling partners, catalyst loading as low as 1% mol was possible leading to 95% yield of the corresponding biphenyl product, while with aryl chlorides the amount of catalyst required was 2% under slightly higher reaction temperatures. The efficient stabilization of the Pd nanoparticles provided by the amphiphilic guanidinium species in solution favored the recycling of the Pd containing aqueous phase for up to five runs without significant loss of catalytic activity.



**Scheme 35.** Pd(II) catalyzed CH arylation in the *ortho* position of aryl urea derivatives in water with Brij 35.

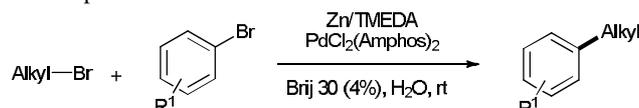
Another interesting example of the dramatic rate acceleration imparted by micellar media was reported by Lipshutz concerning the palladium-catalyzed cross-coupling reactions of aryl halides with aromatic C-H bonds. This coupling reaction is usually carried out under forcing conditions like temperature above 100°C necessary to overcoming the low reactivity of aryl C-H bonds. The same reaction carried out in water with neutral surfactants could be performed under much milder experimental conditions at ambient temperature. In particular, the room temperature mono-C-H activation of urea derivatives and their cross-coupling with aryl iodides in water was possible using Pd(OAc)<sub>2</sub>, AgOAc, HBF<sub>4</sub> with neutral surfactants, with Brij35 as the best one (Scheme 35)<sup>93</sup> The reaction proved to have a very broad scope, yielding the corresponding biaryl derivatives bearing a variety of functional groups in the 70–97% yield range at room temperature. It is worth noting that under these mild conditions, only mono-arylated products were typically obtained.



**Scheme 36.** Ring-closing metathesis in aqueous micellar medium with Ru catalysts mediated by gemini *bis*-cationic surfactants in water.

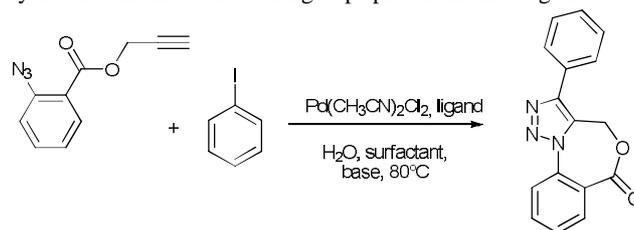
In some cases the use of variants to traditional surfactants leads to improved catalytic efficiency as in the case of gemini

*bis*-cationic tensides with respect to the corresponding monocationic compounds in the ring closing reaction of *N,N*-diallyl tosylamine in water catalyzed by commercially available first generation Grubbs, Hoveyda–Grubbs and Zhan catalyst (Scheme 36).<sup>94</sup> These surfactants, formed by two amphiphilic units linked with a molecular spacer, showed to enhance the catalytic activity of the catalyst even though in depth NMR investigation demonstrated that the substrate was completely solubilized in the reaction medium while the ruthenium catalysts and the products were not.



**Scheme 37.** Organozinc Palladium-catalyzed cross-couplings between alkyl and aryl bromides in Brij 30 micellar media.

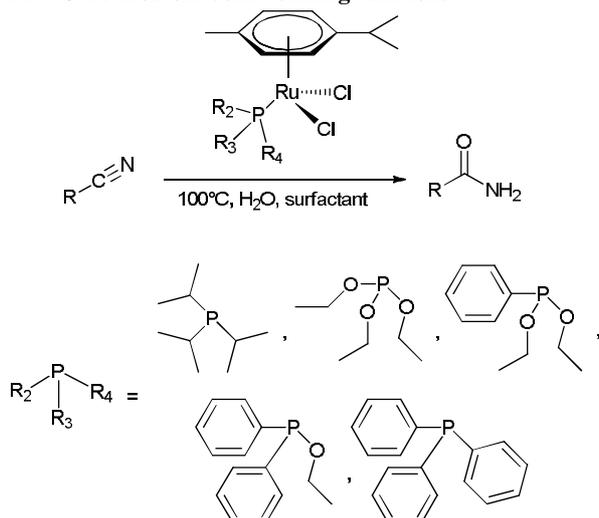
Several other coupling reactions were investigated under micellar conditions. An unusual one, the direct cross-coupling between alkyl and aryl bromides was achieved in water at room temperature employing Brij 30 as surfactant (Scheme 37).<sup>95</sup> Careful optimization of each component of the catalytic system was required leading to a precise combination of the type of zinc derivative, amine ligand, surfactant, and palladium catalyst. This protocol enabled efficient coupling between alkyl and aryl bromides leading to the corresponding alkyl arenes through the formation of organozinc reagents. The latter, even being intrinsically intolerant of water, survived in the presence of micellar aggregates. Even secondary alkyl bromides were reactive leading to the corresponding branched products indicating that metal-mediated isomerization of the alkyl bromide did not occur, at variance with what often observed in this class of coupling reactions. Moreover, the reaction is tolerant to ester, cyano and chloride functional groups present in the reagents.



**Scheme 38.** Efficient synthesis of triazole containing benzoxazepines and benzodiazepines mediated by Pd(II) in micellar media.

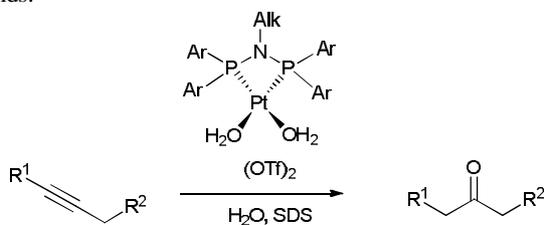
An interesting example of conjugation of a C-C bond forming reaction like the Sonogashira coupling with a dipolar cycloaddition was reported recently. The reaction between prop-2-ynyl 2-azidobenzoates and aryl iodides with Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> and ethanedial, 1,2-bis(2-methyl-2-phenylhydrazone) under micellar conditions led to subsequent direct intramolecular azide-alkyne cyclization without requiring the presence of copper catalysts, directly forming triazole fused benzoxazepines or benzodiazepines in high yields (Scheme 38).<sup>96</sup>

## 2.1.2.4 C-heteroatom bond forming reactions



**Scheme 39.** Ru(II) catalyzed nitrile hydration to the corresponding amides mediated by neutral micellar media.

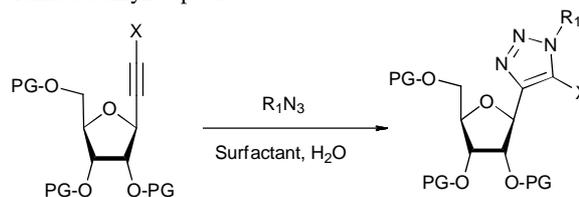
Substitution of organic solvents with water is desirable, but it becomes especially suited for those chemical transformations in which water is one of the reagents. This is the case of the nitrile hydration which is an atom economic transformation that usually requires harsh conditions and Lewis or Brønsted acid catalysis. Micellar systems have the great advantage to allow sufficient catalyst solubilization in water to enable fast catalyst and ligand screening. This is the case of the efficient nitrile hydration to the corresponding amide derivatives carried out in water using poorly soluble  $[\text{RuCl}_2(\eta^6\text{-arene})(\text{PR}_3)_2]$  catalysts with the aid of surfactants (Scheme 39).<sup>97</sup> In particular neutral surfactant Triton-X114 in combination with the Ru(II) complex bearing diphenylethoxy-phosphine led to efficient nitrile hydration with 40 to 95% yields for the corresponding aliphatic and aromatic amides at 100°C with 5% mol catalyst loading. The results observed are comparable to those observed employing intrinsically water soluble Ru<sup>II</sup> catalysts bearing hydrophilic ligands.



**Scheme 40.** Pt(II) diphosphinamine catalyzed alkyne hydration in water mediated by anionic surfactant SDS.

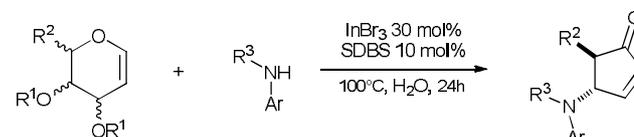
A further example of hydration reaction with improved environmental acceptability is the addition of water to alkynes mediated by highly active monomeric *bis*-cationic Pt(II) catalysts bearing small bite angle diphosphinamine (*N,N*-bis(diarylphosphino)amine) 'PNP' in micellar media (Scheme 40)<sup>98</sup> Even with these *bis*-cationic catalysts the best solubilizing surfactant was SDS as confirmed by <sup>1</sup>H and <sup>31</sup>P NMR as well as DOSY NMR experiments. The use of the surfactant ensured good

catalyst dissolution and good contact of the latter with the substrate. This led to higher catalytic activity displayed in the micellar medium, while the reaction carried out in water/organic solvent mixtures like acetone-water, dioxane-water or biphasic  $\text{CHCl}_3/\text{water}$  1:1 was sluggish. Hydration products could be isolated by means of extraction with an apolar solvent and the catalyst, that remained confined in the aqueous phase as counter-cation for the anionic micelles, could be recycled up to four times without loss of catalytic activity. For all the alkynes investigated, the Pt(II) mediated reaction led to the formation of the carbonyl compounds corresponding to Markovnikov water addition. A careful catalyst speciation in solution showed that the specific role played by the micellar aqueous medium was to favour the formation of catalytically active Pt(II) species bearing  $\sigma$  vinyl residues while in water/organic media the reaction stops at the  $\pi$  coordinated alkyne species.



**Scheme 41.** Huisgen cycloaddition reaction of C-alkynyl ribosides under micellar catalysis for the synthesis of Ribavirin Analogues.

An example of how important is the choice of the surfactant on the diastereoselectivity of a reaction is witnessed by the synthesis of Ribavirin derivatives containing ribosyl-1,2,4-triazole moieties (Scheme 41)<sup>99</sup> that is a molecule that exhibits a broad-spectrum of antiviral activity. The Huisgen 1,3-dipolar cycloaddition between the azide and the alkyne led to ratios between 1,4- and 1,5-regioisomers that was influenced by the nature of the surfactant employed. In particular for terminal alkynes the reaction carried out in cationic dodecyltrimethylammonium chloride (DTAC) or in octylglucosylhydrazide (OGH) led to >80% formation of the cycloaddition products with a ratio between 1,4 and 1,5 regioisomers of 83:17 and 87:13, respectively for the two surfactants. Differently, for disubstituted alkynes the best surfactant turned out to be the anionic SDS with 79% yield with 27/73 ratio between the 1,2,3-triazole-5-carboxylate and 1,2,3-triazole-4-carboxylate (Scheme 41).

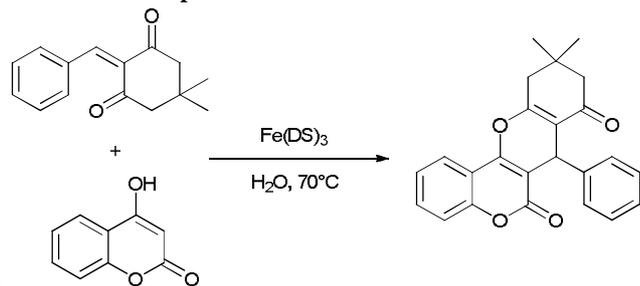


**Scheme 42.** Synthesis of 4-aminocyclopentenones from glycals in water mediated by Lewis acid in the presence of anionic surfactant.

The combination of  $\text{InBr}_3$  with sodium dodecylbenzene sulfonate showed to greatly favor the reaction between glycals and secondary anilines leading to the efficient synthesis of 4-aminocyclopentenones known to be important building blocks for

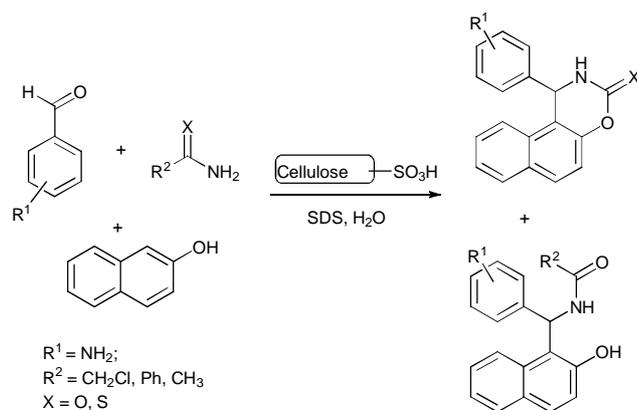
the development of aminocyclopentitols with potential antiviral and anticancer activities, such as Aristeromycin and Mannostatin A (Scheme 42).<sup>100</sup> The reactions proceeded via a  $4\pi$  conrotatory electrocyclization that provides two stereocenters and one new carbon–nitrogen bond in a one-pot reaction. In all cases the corresponding 4-aminocyclopentenones was obtained in good yields with excellent diastereoselectivities.

### 2.1.2.5 Multicomponent reactions



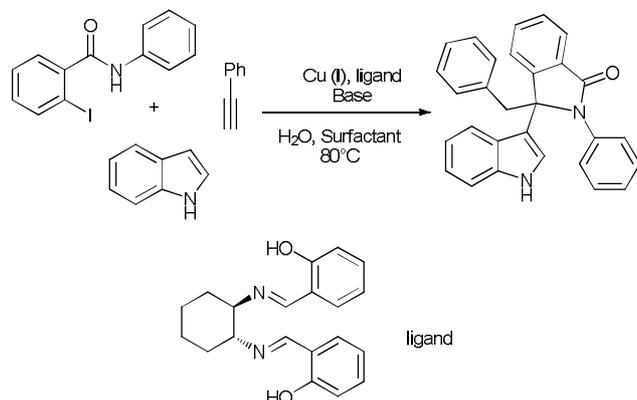
**Scheme 43.**  $\text{Fe}(\text{DS})_3$ , an efficient Lewis acid-surfactant-combined catalyst (LASC) for the one pot synthesis of chromeno[4,3-b]chromene derivatives.

Very few methods have been reported for the synthesis of chromeno[4,3-b]chromene derivatives because they require high reaction temperature and prolonged reaction time leading often to unsatisfactory yields. Employing the ‘Lewis acid-surfactant-combined catalyst (LASC)’ a three-component protocol for the synthesis of chromeno[4,3-b]chromene derivatives by assembling 4-hydroxycoumarin, aldehyde, and 1,3-diketo compound was reported using  $\text{Fe}(\text{dodecyl sulfate})_3$  ( $\text{Fe}(\text{DS})_3$ ) in aqueous media (Scheme 43).<sup>101</sup> This enabled the preparation of a library of chromeno[4,3-b]chromene derivatives combining 1,3-diketo compounds, 4-hydroxycoumarin with various aromatic aldehydes bearing electron-donating as well as electron-withdrawing functionalities. The reaction was efficient regardless of the electronic nature of the aromatic aldehyde leading to the desired compounds with high purity. This efficient multicomponent hetero-annulation protocol involves the initial Knoevenagel condensation followed by Michael addition and final intramolecular cyclization. The LASC converts the initially floating reaction mass into a homogeneous mixture, which on stirring becomes a turbid emulsion of colloidal aggregates whose size and shape was confirmed by optical microscopy and DLS.



**Scheme 44.** Micelle promoted and cellulose sulphate catalyzed synthesis of 1,2-dihydro-1-aryl-3H-naphth[1,2-e][1,3]oxazin-3-one and amidoalkyl naphthol derivatives in water through three component reaction.

In some cases Brønsted acid surfactants are not sufficient to catalyze specific multicomponent reactions. A green alternative consists in the use of derivative of natural polymers like cellulose properly modified with sulfuric moieties in order to obtain water soluble acid that in combination with traditional surfactants enable facile synthesis of complicated target molecules. This is the case of the synthesis of 1,2-dihydro-1-aryl-3H-naphth[1,2-e][1,3]oxazin-3-one and amidoalkyl naphthol derivatives using cellulose sulfuric acid as a solid catalyst and SDS as a surfactant in water by combination of 2-naphthol/1-naphthol, aromatic/heteroaromatic aldehyde and urea/thiourea/amide substrates (Scheme 44).<sup>102</sup> The cellulose catalyst can be easily recovered and recycled for up to four times with only minimal loss of catalytic activity and a series of 28 different products were prepared in all cases with yields above 80%. Among others, only SDS as anionic surfactant ensured good substrate solubilization together with interaction with the acid catalyst that is requested for the reaction.



**Scheme 45.** Efficient synthesis of 3-benzyl-3-(indol-3-yl)-2-phenyl-2,3-dihydroisoindolinone derivatives in aqueous micellar system.

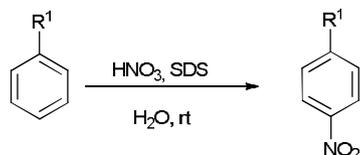
An interesting example of a three-component Cu(I) mediated palladium-free domino Sonogashira-cyclization of *o*-bromo or *o*-iodo-*N*-phenylbenzamides with phenylacetylene followed by

regioselective addition of indole, all in one-pot, is reported in Scheme 45.<sup>103</sup> A series of surfactants was tested for the reaction observing the best results with neutral tensides, in particular using polyoxyethanyl- $\alpha$ -tocopheryl sebacate (PTS, see Chart 1) and triethylamine as base at 80°C. The yield in the corresponding product was 76%. An important role was also played by the ligand employed to activate the Cu(I) metal center, with 2,20-(1*E*,10*E*)-(1*R*,2*R*)-cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene)*bis*(methan-1-yl-1-ylidene)diphenol as the best one, even though no asymmetric induction in the product was observed in a series of ten derivatives prepared with the above method.

## 2.2 Product selectivity

### 2.2.1 Regioselectivity improvement

#### 2.2.1.1 Oxidation reactions



**Scheme 46.** Regioselective nitration of aromatic compounds with nitric acid in an aqueous SDS micellar medium.

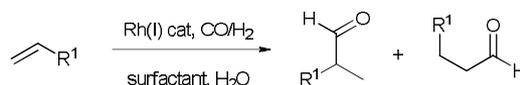
An example of application of economic but efficient micellar catalysis to traditional organic chemistry transformation was reported by Ismail and coworkers that reinvestigated the nitration of aromatic compounds with nitric acid. They found that in the presence of anionic SDS micelles (50 mM), the reaction of nitric acid 1M with phenol as substrate proceeds smoothly at room temperature within 30 minutes leading exclusively to the *p*-nitrophenol isomer (Scheme 46).<sup>104</sup> The regioselective reaction can be easily extended to other aromatic electron rich substrates like aniline that do not need -NH<sub>2</sub> protection as well as electron poor aromatic substrates such as the nitro, carboxylic acid, keto and other derivatives all leading to the corresponding nitro compounds in good to excellent yields with high regioselectivity imparted by the electronic properties of the substrate. SDS micelles are known to undergo hydrolysis in acidic media and it is likely that in the presence of HNO<sub>3</sub> 1-dodecanol is initially formed liberating HSO<sub>4</sub><sup>-</sup> that provides the acidic medium to promote the formation of the nitronium ion whose existence was confirmed by means of Raman spectroscopy. Side effects typical of nitration reaction such as poly-nitration, tedious work-up, and problems associated with use of organic solvents are all solved issues with this micellar method. The anionic micelles dissolve the substrate and promote its close contact with the cationic nitronium reagent formed *in situ*.

#### 2.2.1.2 C-C bond forming reactions

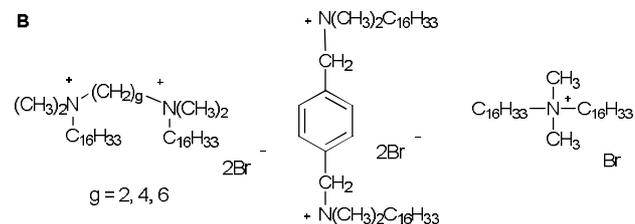
The combination of water-soluble Rh/TPPTS complexes [TPPTS = P(C<sub>6</sub>H<sub>4</sub>-*m*-SO<sub>3</sub>Na)<sub>3</sub>] with micellar medium has been applied also to the hydrogenation of the completely water-insoluble heavy polybutadiene (PB). In particular it was found that micelles formed by the cationic surfactant

dodecyltrimethylammonium chloride (DTAC) turned out to favor hydrogenation of PB possessing a high 1,4-units content (98.0 wt% vs. 2.0 wt% 1,2-units), while mixed micelles created by DTAC with either non-ionic or anionic surfactants allowed efficient hydrogenation of PB starting material consisting of 61.0 wt% of 1,2-units and 39.0 wt% of 1,4-units, in both cases under relatively mild conditions.<sup>105</sup> Overall, contact between the extremely lipophilic substrate and the poly-anionic Rh(I) catalyst was assured by the presence of cationic surfactants. Moreover, high catalytic activity was observed under neutral conditions, while acidic or basic conditions strongly deactivated the catalytic system. Similar catalytic system showed to efficiently hydrogenate also polybutadiene-1,4-*block*-poly(ethylene oxide).<sup>106</sup>

**A**



**B**

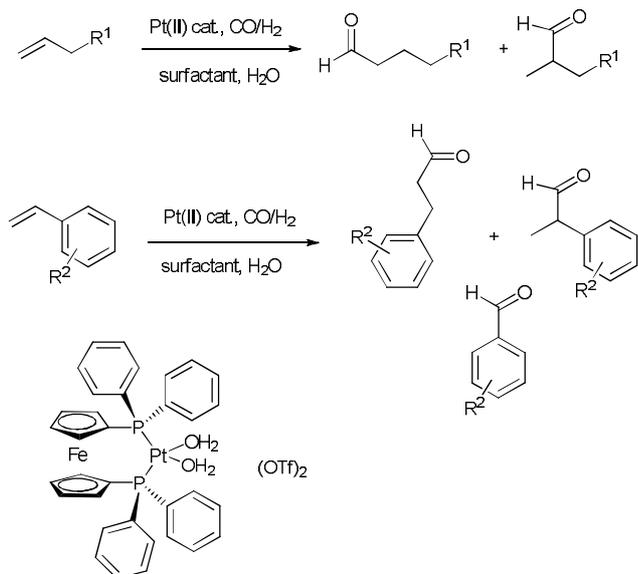


**Scheme 47.** A) Rh(I) catalyzed hydroformylation of 1-octene in neutral alkyloxyethylene micellar media. B) Cationic gemini surfactants employed to improve Rh(I) hydroformylation of 1-dodecene in water.

Since, as described in the introduction, Ruhrchemie-Rhône-Poulenc hydroformylation works well for short alkenes characterized by sufficient water solubility, the hydroformylation of higher olefins has been addressed employing surfactants to cope with the water solubility of the catalyst and the insolubility of the substrate. Rhodium-TPPTS hydroformylation of 1-octene and other higher olefins was found to benefit of the presence in solution of non-ionic alkyloxyethylene type amphiphiles Lutensol® ON 70 or Lutensol® ON 80 that were used at concentration as low as 1 wt.% (Scheme 47A).<sup>107</sup> In this medium, highly efficient hydroformylation was achieved and performing the reaction in a single-phase micro-emulsion was found unnecessary as high reaction rates could be achieved in biphasic systems.

Alternatively, the hydroformylation of 1-dodecene catalyzed by RhCl(CO)(TPPTS)<sub>2</sub>-TPPTS [TPPTS = tris(sodium-*m*-sulfonatophenyl) phosphine] was investigated in water in the presence of cationic gemini surfactants with a flexible (G(Eth)), G(But) and G(Hex)) or rigid spacer (G(Xyl)) group. (Scheme 47B).<sup>108</sup> It was found that the reaction occurred with higher turnover frequency (TOF) and higher regioselectivity towards the linear aldehyde with respect to that obtained with the conventional monomeric surfactant CTAB. This was attributed to the propensity of cationic gemini surfactants to form more

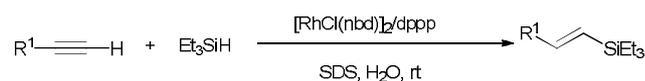
compact and spherocylindrical micelle in the solution thanks also to their lower c.m.c.



**Scheme 48.** Bis-cationic Pt(II) catalyzed hydroformylation of terminal alkenes in water mediated by anionic surfactants.

Hydroformylation of alkenes is a typical reaction where product selectivity is very important in view of the possible uses of linear aldehydes. Anionic micelles based on the use of SDS surfactant showed to improve both the catalytic performance and the regioselectivity of the hydroformylation reaction of alkenes mediated by bis-cationic Pt(II) catalyst of the type  $[P_2Pt(H_2O)_2](OTf)_2$  bearing large bite angle diphosphines (Scheme 48).<sup>109</sup> The system shows catalytic activity comparable, and in some cases better, than traditional Pt-Sn systems, with good l/b selectivities that can rival with the best Rh(I) catalysts. The use of surfactants is essential to ensure dissolution of the catalyst and substrate in water with catalysts being positioned on the anionic surface of the micelles. A variety of terminal and internal alkenes can be efficiently converted into the corresponding aldehydes obtained with linear to branched ratios up to > 99:1. In particular the more apolar the substrate the higher the product formation observed, in agreement with the catalyst positioning as counter-cation on the anionic micelles that host the substrates. It is worth noting that the micellar system enabled also an unusual reaction pathway when styrene was tested. In this case quantitative conversion occurred with formation of three products, the linear and branched aldehydes together with the corresponding benzaldehyde in a 82:9:9 ratio. The catalyst could be separated by extraction of the organic products with hexane and recycled for at least four times employing 1% mol catalyst loading with only a modest decrease in activity and no effect on selectivity.

### 2.2.1.3 C-heteroatom bond forming reactions

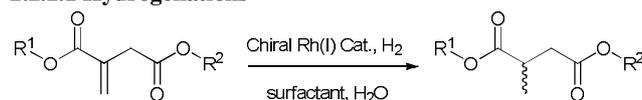


**Scheme 49.** Hydrosilylation of alkynes with a cationic Rhodium species formed in an anionic micellar system.

Micellar catalysis is compatible with the formation of new Si-C bonds. A combination of  $[RhCl(nbd)]_2$  and *bis*-(diphenylphosphino)propane (dppp) enabled the (*E*)-selective hydrosilylation of terminal alkynes in the presence of sodium dodecyl sulfate (SDS) in water (Scheme 49).<sup>110</sup> The anionic micelles well solubilize the cationic Rh(I) species obtained by dissociation of the Rh-Cl bond. The selectivity of the reaction can be simply switched from (*E*)- alkenylsilanes to the corresponding (*Z*)-alkenylsilanes by addition of sodium iodide

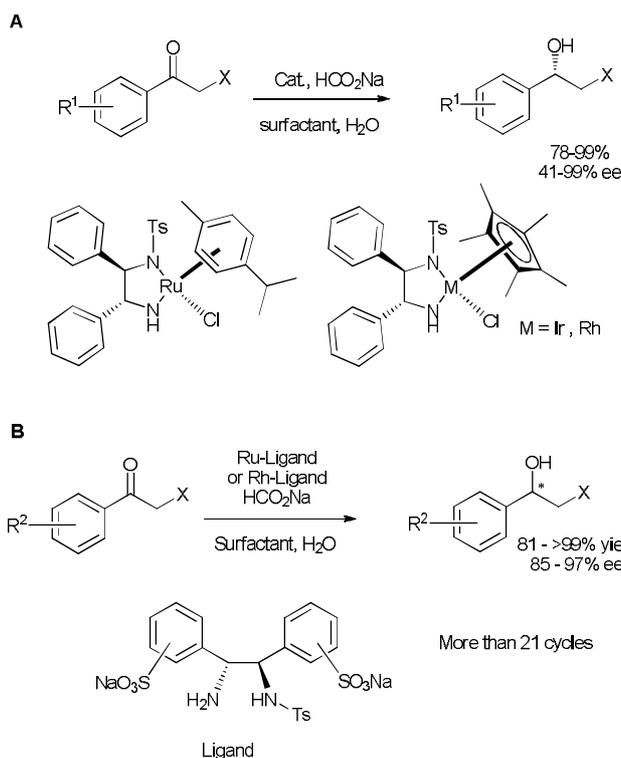
## 2.2.2 Enantioselectivity improvement

### 2.2.2.1 Hydrogenations

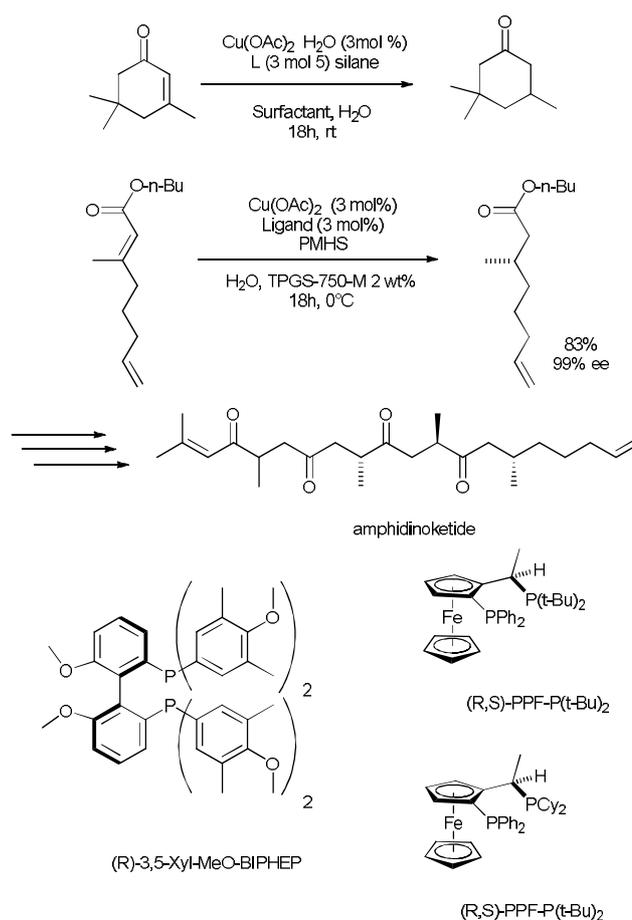


**Scheme 50.** Rhodium catalyzed hydrogenation reactions in aqueous micellar systems as green solvents.

As observed in most of the catalytic system described in the present review, careful optimization of the combination of surfactant, substrate and experimental conditions is pivotal to ensure effective catalytic transformations. This is the case of the enantioselective hydrogenation of important benchmark substrates like itaconic acid and dimethyl itaconate whose asymmetric hydrogenation with chiral Rh(I) catalysts was transferred from traditional methanol to aqueous micellar solutions of SDS and Triton X-100 (Scheme 50).<sup>111</sup> In the best cases the selectivity was the same as in methanol even though with lower rates due to intrinsically lower hydrogen solubility in water but with high turn-over-numbers (up to 1000) without evident deactivation of the catalyst. The micellar medium enabled catalyst recycle by means of filtration step with proper membranes.



**Scheme 51.** A) Asymmetric ketone transfer hydrogenation in water with CTAB. B) Highly recyclable asymmetric ketone transfer hydrogenation in water with CPB.



**Scheme 52.** Asymmetric Cu(II)-hydride catalyzed 1,4-reductions of  $\alpha\beta$ -unsaturated carbonyl compounds in water at room temperature in the presence of neutral designer surfactants.

Asymmetric transfer hydrogenation is an important method for the preparation of chiral alcohols. The Noyori-Ikariya catalyst, (*R,R*)-TsDPEN-[Ru-Cl(cymene)] proved to perform well when dissolved in water with sufficiently hydrophobic ketones in cationic CTAB micelles. Formate used as reducing agent tends to locate as a counter-anion on the surface of the micellar aggregate and this enhances the catalytic activity of the reaction. The reaction worked well also with similar Ir(I) and Rh(I) catalysts (Scheme 51A) and it was successfully applied to a wide range of ketones, in particular bromomethyl aromatic ketones observing significant increase in activity with isolated yields up to 97%, and enantioselectivity up to 99% ee for 2-bromoaryl alcohols as precursors to  $\beta$ -adrenergic receptor agonists.<sup>112</sup> The confinement of the catalyst within the micelles enabled efficient recycle for at least six times.

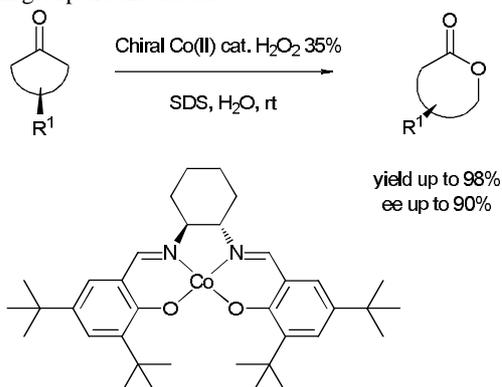
The same authors focused their attention on the recyclability of the system and very recently reported an improved Ru(II) and Rh(I) catalyst bearing a sulfonated chiral ligand (Scheme 51B)<sup>113</sup> that in water in the presence of cetylpyridinium bromide (CPB) as cationic surfactant and formate as reducing agent enabled to recycle the catalyst for more than 20 times maintaining both enantioselectivity and yield of the enantioenriched alcohol product almost unaltered.

An example of the importance of proper combination of chiral catalyst, substrate and surfactant to ensure good level of asymmetric induction was provided by Lipshutz in the hydrogenation of unsaturated prochiral carbonyl compounds with polymethylhydrosiloxane (PMHS) as an environmentally friendly reducing agent using Cu(II) catalysts in the presence of chiral diphosphine ligands (Scheme 52)<sup>114</sup> It was found that isophorone led to the corresponding saturated ketone using TPGS-750-M as surfactant and (*R*)-3,5-xyl-MeO-BIPHEP as chiral ligand, while for other acyclic  $\beta,\beta$ -disubstituted Michael acceptors ferrocenyl based ligands led to more active and enantioselective hydrosilylations. Proof of the robustness of the method was provided by the use the micellar asymmetric catalytic system in the synthesis of an intermediate involved in the preparation of the natural product amphidinoketide I that was obtained in 83% yield and >99% ee (Scheme 52).

#### 2.2.2.2 Oxidations

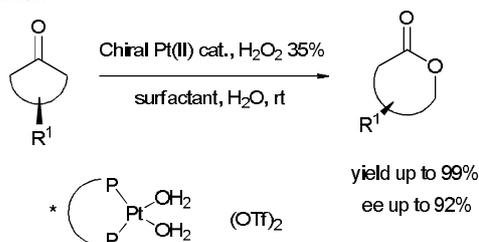
Oxidation reactions are important chemical transformations where the choice of the oxidant species is crucial for the environmental impact of the reaction. Molecular oxygen and hydrogen peroxide are the most interesting oxidants in terms of

atom efficiency; moreover the latter oxidant form just water as a by-product. As a consequence, asymmetric oxidations with hydrogen peroxide are obviously predisposed to be carried out in water rather than in organic media. In the following several examples of successfully asymmetric oxidation reactions from our research group are discussed.



**Scheme 53.** Co(salen) catalyzed enantioselective Baeyer-Villiger oxidation of cyclic ketones with hydrogen peroxide in micellar media.

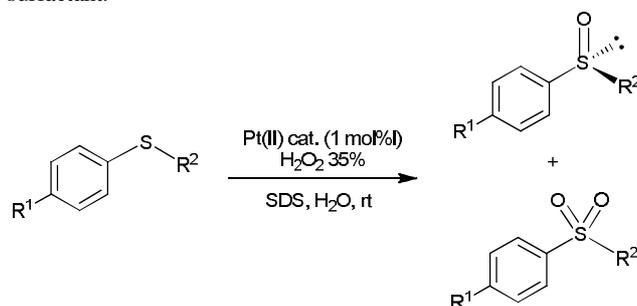
In some cases micellar media resulted crucial to transform an inactive and non-stereoselective complex in organic media into an active and stereoselective catalyst in water in the presence of the proper surfactant. This is the case of the Baeyer-Villiger oxidation of cyclic ketones with the Co(Salen) catalyst reported in Scheme 53<sup>115</sup> that was completely inactive towards meso-cyclobutanones when employed in several organic solvents. The same complex turned out to induce significant asymmetric induction when employed in water, with best results with SDS as surfactant. Even better results were observed in the oxidation of chiral racemic cyclobutanones that allowed to obtain the corresponding five membered ring lactones with ee up to 90% and dr up to 84:1. In the latter cases, careful surfactant optimization was necessary since, as observed in other oxidation reactions, every combination of substrate and catalyst behave in a different way when using different surfactants and this needs optimization.



**Scheme 54.** Chiral Pt(II) catalyst mediated asymmetric Baeyer-Villiger oxidation of cyclic ketones to the corresponding lactones in micellar media.

The asymmetric Baeyer-Villiger oxidation of cyclic ketones with hydrogen peroxide mediated by chiral Pt(II)-diphosphine catalysts were extensively investigated in water in the presence of surfactants (Scheme 54).<sup>116</sup> The reaction turned out to be extremely sensitive on the combination of substrate, catalyst and

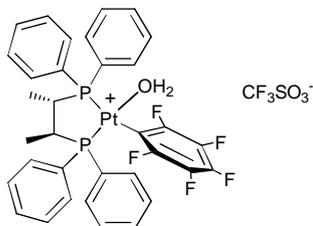
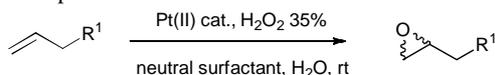
surfactant employed and only careful optimization of all three parameters enabled good results in terms of asymmetric induction and yield of lactone. To support this, it was found that the oxidation of meso-cyclobutanones in micellar media allowed the reaction to proceed in high yields and the enantiomeric excess (ee up to 56%) with respect to organic media. Extension to meso-cyclohexanones resulted in a general decrease in yields but an enhancement of enantioselectivity (ee up to 92%) among the best reported in the literature and second only to enzymatic catalysis. The enhancement in stereocontrol observed from organic media to micellar media, especially for more hydrophobic substrates, could be interpreted in terms of tighter supramolecular control imparted by the palisade created by the alkyl chains of the surfactant.



**Scheme 55.** Asymmetric sulfoxidation mediated by chiral Pt(II) catalysts in anionic micellar media.

As a further confirmation that micellar media often provides more stereoselective oxidation reactions with respect to organic media, also the asymmetric sulfoxidation of aryl alkyl thioethers with hydrogen peroxide mediated by the chiral platinum diphosphine complex  $[(R)\text{-BINAP}]\text{Pt}(\mu\text{-OH})_2(\text{BF}_4)_2$  showed to be beneficial for the employment of surfactants in water (Scheme 55).<sup>117</sup> Because of the bis-cationic nature of the catalyst, anionic surfactants and SDS in particular, allowed its complete solubilization. With respect to dichloromethane as organic solvent, the use of water/SDS enabled comparable yield of sulfoxide, better chemoselectivity between sulfoxide and sulfone (SO:SO<sub>2</sub> 80:1 in CH<sub>2</sub>Cl<sub>2</sub> and SO:SO<sub>2</sub> >200:1 in water/SDS) and better enantioselectivity (16% ee in dichloromethane and 40% ee in water/SDS) for the oxidation of thioanisole. The stereoselective oxidation showed to be more influenced by electronic properties of the substrates rather than by the steric hindrance of the substituents of the thioether. In fact the highest enantioselectivity was observed with more electron-poor aryl alkyl thioethers bearing electron-withdrawing moieties. It is worth noting that the Pt(II) catalyst can coordinate the enantioenriched sulfoxide causing its slow racemization which is more evident for more electron-poor sulfoxides. The micellar medium showed to limit this parasite reaction with respect to organic media thus avoiding

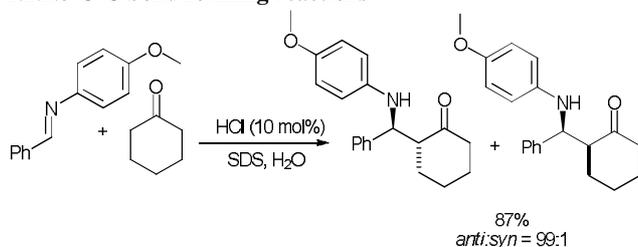
erosion of the enantioselectivity created in the asymmetric oxidation step.



**Scheme 56.** Asymmetric epoxidation of terminal alkenes mediated by chiral Pt(II) catalysts in neutral micellar media.

If the asymmetric oxidation reaction operates on apolar substrates like alkenes and provides sufficiently apolar products like epoxides, it is possible to recycle the chiral precious metal catalyst employed by simple extraction of the reaction products with *n*-hexane. An example of this is provided by the asymmetric epoxidation of terminal alkenes by the 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 (Scheme 56).<sup>118</sup> The use of neutral surfactants was crucial to ensure sufficient catalyst solubilization as demonstrated by 2D-NOESY experiments where clear cross-peaks between the aromatic moieties of the complex and the terminal *tert*-butyl group of the surfactant were observed, indicating that the catalyst is located deeply in the apolar core of the micelles that behave as nanoreactors. This micellar medium allowed comparable conversions with respect to organic media for instance in the epoxidation of 4-methyl-pentene, but with marked increase in enantioselectivity from 58% ee in DCE to 82% ee with water/Triton-X100. Recycling of the system was possible observing practically constant conversion and enantioselectivity over three consecutive runs in the oxidation of 4-methyl-1-pentene.

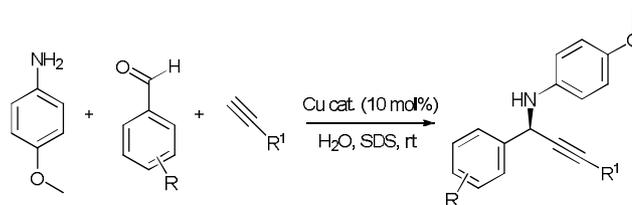
### 2.2.2.3 C-C bond forming reactions



**Scheme 57.** HCl-catalyzed stereoselective Mannich reaction in water promoted by SDS.

The Mannich reaction is known to be efficiently catalyzed by Brønsted acids while the diastereoselective ratio between *syn* and *anti* product isomers is heavily influenced by the reaction medium. It was found that efficient and highly *anti* selective Mannich reaction was promoted and directed by anionic SDS micelles in water (Scheme 57).<sup>119</sup> For instance, the reaction

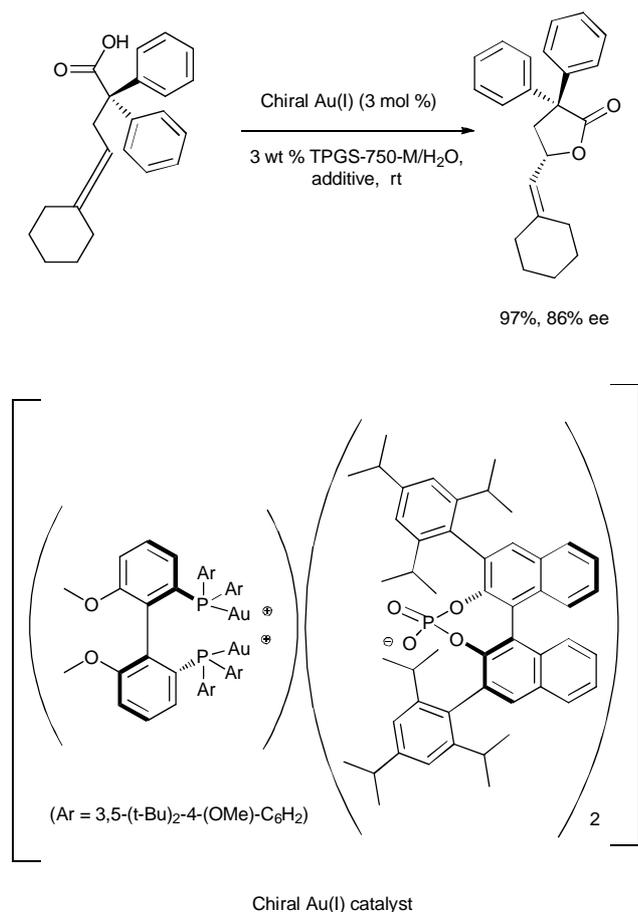
between benzaldehyde, 4-methoxyaniline and cyclohexanone led to only 30% yield with 70:30 *anti/syn* selectivity when run with HCl in methanol:water 9:1, while in water with SDS the product was obtained in 84% yield and 96:4 *anti/syn* ratio. Similarly favored *anti* products were observed with a wide combination of aryl imines as well as aromatic aldehydes and anilines.



**Scheme 58.** Stereoselective three-component aniline aldehyde alkyne synthesis of chiral propargylamines mediated by Cu(I) catalyst in water with SDS.

Exploiting the positive effect of compartmentalization in the condensation between aldehydes and anilines, Nakamura and collaborators recently disclosed the three components asymmetric aldehyde-aniline-alkyne condensation using a *bis*(imidazole)-Cu(I) catalysts having a hydrophobic substituent and sodium dodecyl sulfate as a surfactant (Scheme 58).<sup>120</sup> The corresponding propargylamines were obtained with excellent yields and high enantioselectivities for a broad range of aldehydes and alkynes.

### 2.2.2.4 C-heteroatom bond forming reactions



**Scheme 59.** Asymmetric Gold-catalyzed intramolecular lactonization in water mediated by TPGS-750-M.

5 The apolar nano-environment present in TPGS-750-M micelles showed to ensure intimate contact between the chiral Au(I) cation bearing an atropisomeric diphosphine and the chiral phosphate anion thus greatly favouring the asymmetric gold-catalyzed intramolecular cyclizations of  $\beta$ -allenic acids to give  
 10 enantioenriched lactones in water at room temperature (Scheme 59).<sup>121</sup> This combination turned out to be highly effective in achieving especially challenging asymmetric intramolecular hydrocarboxylation of allenes in high yields and good to excellent ee's. The aqueous micellar reaction medium favoured  
 15 both catalyst and surfactant recycling providing a clear cut example of how micellar media can favour activity, selectivity and recyclability of metal catalyzed reactions.

### 20 2.3 Substrate selectivity

Natural enzyme catalysts are characterized for being both product as well as substrate selective.<sup>122-125</sup> The ability of enzymes to select preferentially one substrate from a mixture of similar molecules comes from the recognition event preceding  
 25 the catalytic event (the lock and key concept) that strongly depends on the interplay of functional groups in the vicinity of the active site as the result of the complexity of the polypeptide chain. With molecular metal catalysts this environment is replaced by simple solvation and the interaction with the

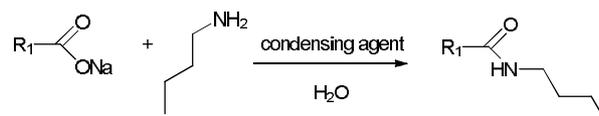
30 substrate cannot be aided by external factors, thus leading to very poor substrate selection that remains a challenging task.

The selection rules all pertain to the toolbox of supramolecular recognition, with size and shape matching because of steric interactions and attractive contact between  
 35 substrate and active site through weak intermolecular forces such as *in primis* hydrophobic effect and then hydrogen bonding, cation- $\pi$ ,  $\pi$ - $\pi$ , as well as other weaker attractive intermolecular forces. Micellar aggregates share with enzymes the presence of polarly anisotropic internal spaces that can control to some extent  
 40 the recognition event in a series of competitive substrates, thus leading to examples of micellar catalysis endowed with substrate selectivity properties.

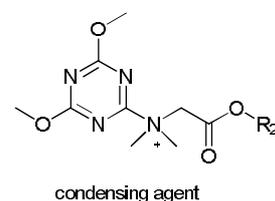
### 2.3.1 C-heteroatom bond forming reactions

45 The work of Kobayashi on the direct esterification of lipophilic carboxylic acids with lipophilic alcohols in DBSA micelles turned out to be also the first example of 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  
 50 of DBSA, the longer ester was produced in 81% yield, while the shorter in only 4% yield.<sup>51</sup>

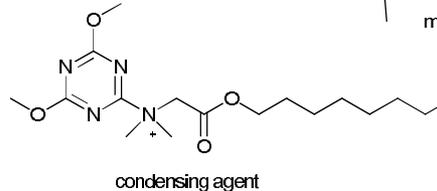
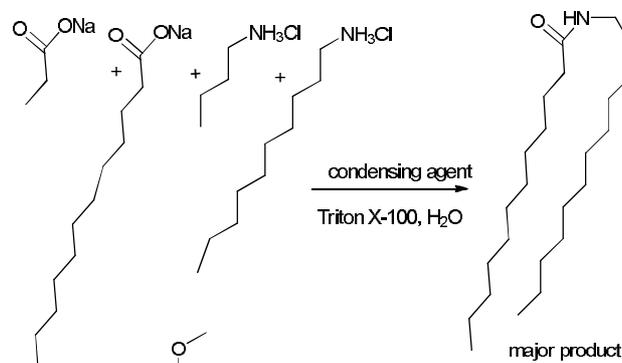
A



R1, R2= Alkyl



B



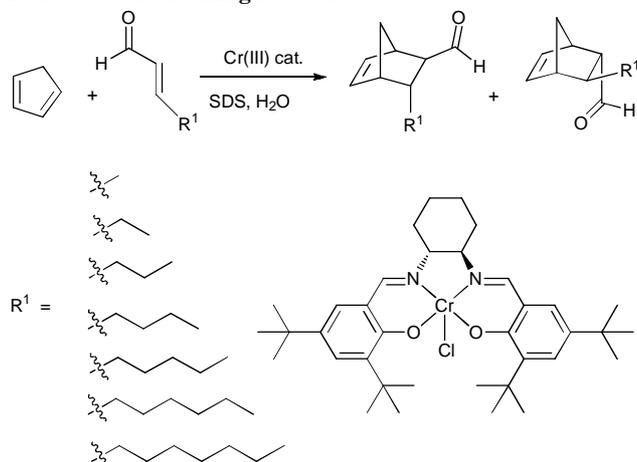
**Scheme 60.** A) Substrate selective bimolecular dehydrocondensation reaction mediated by micelles of fatty acid  
 55

salts. B) Substrate-selective dehydrocondensation at the interface of micelles of common surfactants.

A few years ago Kunishima and coworkers developed an amphiphilic dehydrocondensing agent based on 1,3,5-triazine for amide formation between carboxylic acids and amines and tested it in water. When lipophilic acids were used in combination with more lipophilic condensing agents, the system worked under micellar conditions observing a drastic rate enhancement due to local concentration and pre-orientation of the polar head groups on the surface of the micelle (Scheme 60A).<sup>126</sup> When sodium butyrate and laurate were tested in competitive experiments, only the longer amide was detected with >99% selectivity and 88% yield.

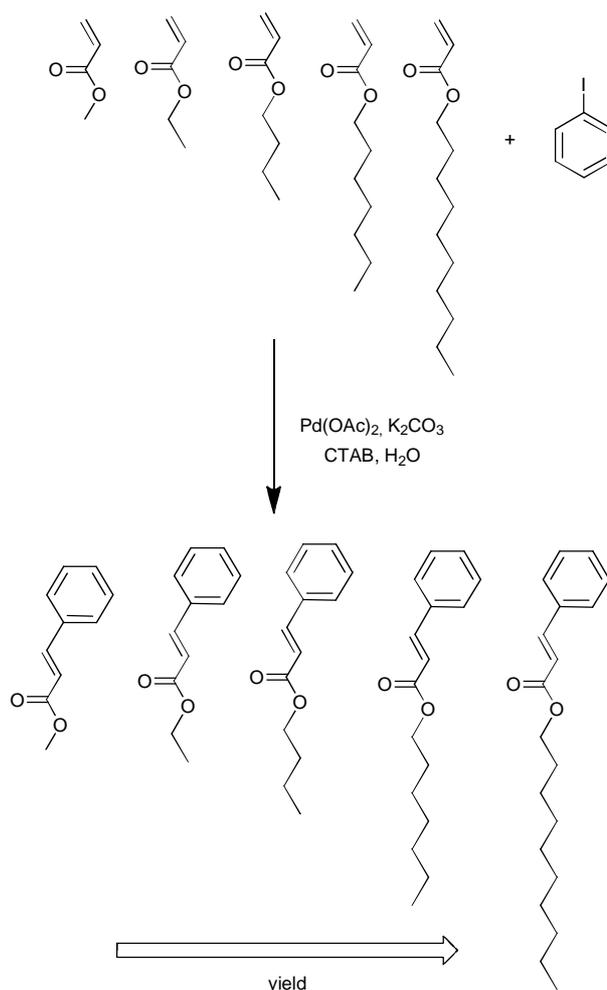
The authors further development the substrate selective version of the reaction under micellar conditions. The condensation reaction showed inhibition by traditional cationic surfactants due to repulsion with the cationic condensing agent while both non-ionic and anionic surfactants dramatically promote the reaction of carboxylates and the amphiphilic dehydrocondensing agents by generation of micelles. The reaction between butylamine and three carboxylic acids C<sub>6</sub>, C<sub>8</sub> and C<sub>12</sub> with the amphiphilic condensing agent and Triton X-100 led to the corresponding amides in 25%, 44% and 74% yield, respectively in agreement with the lipophilic character of the carboxylic acids employed (Scheme 60B).<sup>127</sup> Analogous competitive reactions between decylamine and butylamine with laurate with the condensing agent in the presence of Triton X-100 the longer amide was obtained in a 99:1 ratio with respect to the shorter *N*-butyldodecanamide. In the presence of two carboxylic acids and two amines, each including substrates with both long- and short-chain alkyl groups, the catalytic system showed to prefer the longest amide with 97% selectivity among four amides in water containing Triton X-100, while no significant selectivity was observed in methanol.

### 2.3.2 C-C bond forming reactions



**Scheme 61.** Substrate-selective Diels-Alder cycloaddition between cyclopentadiene and unsaturated aldehydes mediated by Cr(salen)Cl catalyst in SDS micellar media.

Substrate selectivity has been also demonstrated for metal catalyzed reactions employing micelles as supramolecular nanosized reactors where the preferable selection of a given substrate in a mixture of several ones, allowed its interaction with the catalyst. In the Diels-Alder reaction between cyclopentadiene and unsaturated aliphatic aldehydes from C<sub>4</sub> to C<sub>10</sub> mediated by Cr(III)(salen)Cl complexes in chloroform comparable activities for all substrates was observed. In water/SDS the catalytic system displays substrate selectivity with an up to 3.5 increase in activity in favor of longer substrates compared to shorter ones (Scheme 61).<sup>128</sup> The apolar core of the micelles forces the apolar cyclopentadiene and longer unsaturated aldehydes to get in contact with the catalyst within the micelle. The substrate selective systems discussed in this section, even if very simple from a chemical point of view, underline the importance of and the effect imparted by hydrophobic interactions that are the same observed with natural catalysts such as enzymes.



**Scheme 62.** Competitive Micellar Induced Substrate Selectivity in the Pd Mediated Heck Coupling Between Iodobenzene and Linear Acrylic Esters in Water.

As an example of a typical C-C bond forming reaction, Scarso and Strukul showed also that the simple use of palladium acetate as metal precursor in the presence of the cationic surfactant CTAB allows to run substrate selective Heck coupling reaction

between a lipophilic aryl iodide and a series of acrylate esters from methyl to lauryl. Short acrylate ester substrates were characterized by lower activity and lower formation of the corresponding coupling products. Increasing the length and hydrophobicity of the substrate caused a substantial increase of the amount of the corresponding coupling products (Scheme 62).<sup>129</sup> The same substrates did not show any difference in activity when working in organic media. The substrate selectivity observed is a direct consequence of the selection rules imparted by the micelles that host the metal species and discriminates the acrylates on the basis of their lipophilic character.

e l'idrogenazione delle aldeidi  $\alpha,\beta$ -insature???

### 3. Designer surfactants

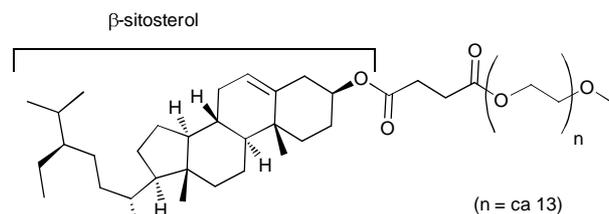
In the last decade, thanks to the intuition of Lipshutz and coworkers, the nature of the surfactant started to become subject of in depth investigations. This led to the design, synthesis, development and application of new surfactants in catalysis. In fact, while traditional surfactants have been developed focusing on the cheapness of the starting materials employed and looking at their properties as dispersing agents, recent tailored surfactants are specifically designed to exploit the nanoreactor properties of micelles. This is the case of polyoxyethanyl- $\alpha$ -tocopheryl sebacate (PTS, Chart 1) that is a non-ionic surfactant composed of racemic vitamin E as apolar portion, sebacic acid, and PEG-600 as hydrophilic portion. Neither PTS, that actually is a pro-vitamin molecule, nor any of its three components is of any environmental concern clearly showing for the green design of the molecule.<sup>130</sup>

An evolution of PTS is polyoxyethanyl- $\alpha$ -tocopheryl succinate (TPGS) that represents a second example of designer green surfactant. It is composed of a lipophilic  $\alpha$ -tocopherol moiety, a succinic spacer and a hydrophilic poly(ethyleneglycol) methyl ether chain (PEG-750-M) of average molecular weight of 750 u.m.a. The proportion between lipophilic and hydrophilic portions has been tailored in order to allow a broader array of chemical reactions in water.

These two designer surfactants, even if sharing similar lipophilic structures, lead to different outcomes in several catalyzed reactions. This is likely due to the different kind and shape of micellar aggregates formed. While PTS forms both 8–10-nm spheres and larger worm- or rod-like particles with overall average size of 25 nm, TPGS in water provides very sharp 12–13-nm spherical micelles. In the following part contributions from the Lipshutz group concerning the application of these tailored surfactants are described.<sup>131</sup>

Very recently the same group developed the latest designer surfactant SPGS-550-M called "Nok" based on a  $\beta$ -sitosterol methoxypolyethyleneglycol succinate structure, prepared in two steps from  $\beta$ -sitosterol with succinic anhydride and PEG-550-M (Scheme 63).<sup>132</sup> Third generation surfactant was tested in a wide series of reactions and compared to the performance observed with TPGS-750-M. In most of the cases, the new surfactant led to similar or better yields than those typically obtained with TPGS-750-M. The main advantage of SPGS-550-M consists in its

much lower cost that will favor its use in micellar catalysis in the near future.

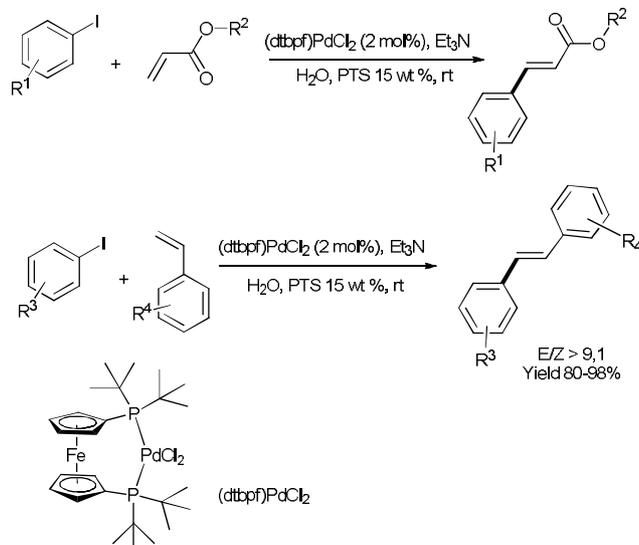


**Scheme 63.** Structure of SPGS-550-M "Nok" as new designer surfactant.

#### 3.1 Cross-coupling reactions at room temperature

The peculiar application of these new surfactants covers several aspects of palladium-catalyzed cross-coupling reactions specifically carried out under mild room temperature conditions in water. In the following examples of Heck, Suzuki-Miyaura, Sonogashira, and Buchwald-Hartwig aminations and others are reported.

##### 3.1.1 Heck

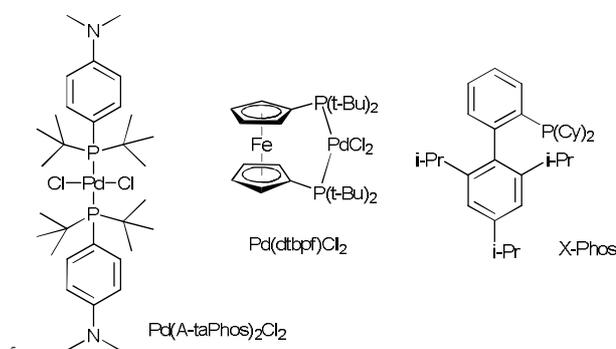
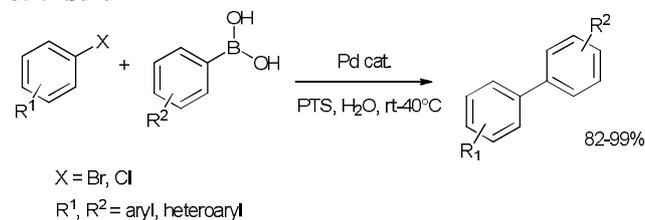


**Scheme 64.** Heck Couplings at Room Temperature in Nanometer Aqueous Micelles.

One of the first achievements of the employment of designer surfactants in traditional coupling catalysis was the room temperature Heck coupling (Scheme 64).<sup>133</sup> Even though Pd mediated couplings usually take advantage from cationic tetralkyl ammonium additives, Lipshutz and coworkers found that the neutral surfactant PTS provides a suitable environment to couple aryl iodides and acrylate esters or styrene derivative with reaction times up to 24h at room temperature. When aryl bromides were investigated, increase of the reaction temperature to 50°C was necessary. In particular, enhancement of the yield with aryl bromides at room temperature was possible simply adding 3M NaCl to the reaction system containing 5% w/w of PTS.<sup>134</sup> The effect of the increased ionic strength of the solution is to modify

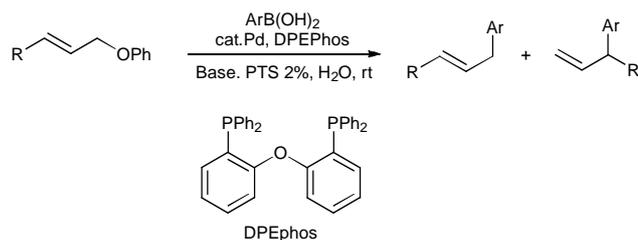
the aggregation of the surfactant leading to fully interconnected, extended network of aggregates.

### 3.1.2 Suzuki



**Scheme 65.** Suzuki-Miyaura cross-couplings in PTS micellar media.

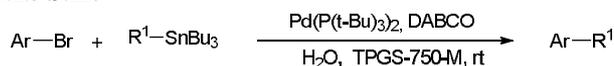
PTS nanomicelles showed excellent properties in the catalysis of the Suzuki-Miyaura Pd-catalyzed couplings between several heteroaromatic halides (bromides and chlorides) and boronic acids employing Pd(II) precursors (Scheme 65).<sup>135</sup> In all cases, "on water" conditions in the absence of surfactant led to much lower activity with respect to the use of PTS 2% as surfactant. When aryl chlorides were used as coupling partners, reaction temperature had to be increased up to 40°C. As an example of the great advantage offered by PTS micellar catalysis in this reaction, the coupling between the electronically deactivated 2,6-dimethylchlorobenzene and 3-thiophenylboronic acid was investigated. The reaction is usually carried out in organic solvent with several equivalents of inorganic salt as base at 100°C leading to 77% yield, while with PTS only gentle heating to 38°C was necessary, leading to 90% isolated yield of the corresponding coupling product. This protocol for Suzuki-Miyaura coupling demonstrates how micellar catalysis contributes to simplify and green up traditional cross-coupling reactions contributing to minimization of the use of organic solvent and, at the same time, reducing the energy involved in the process.



**Scheme 66.** Allylic ethers as substrates for Suzuki-Miyaura couplings in water at room temperature.

Organoboronic acids are familiar reagents that can be used for a broad range of cross-coupling reactions with several electrophiles including alkyl, aryl, alkenyl, and alkynyl groups, while examples of applications with allylic partners bearing acetates, carbonates, halides and pseudohalides, are rare. Exploiting the peculiar features of PTS as surfactant, Lipshutz disclosed the first example of Suzuki-Miyaura couplings between boronic acids and functionalized allylic ethers in water at ambient temperatures. The reaction employed a Pd(II) precursor with DPEPhos as bidentate phosphine ligand leading to efficient coupling between aryl boronic acids and cinnamyl phenyl ether largely favoring the formation of the linear product (Scheme 66).<sup>136</sup> Several boronic acids can be coupled with allylic ether under micellar catalysis conditions. In particular even *ortho*-substituted boronic acids reacted smoothly with a wide range of cinnamyl ethers bearing dibenzylamine-, aminoacid-, and malonate ester-substituents, in all cases leading to good to excellent yields at room temperature within few hours.

### 3.1.3 Stille

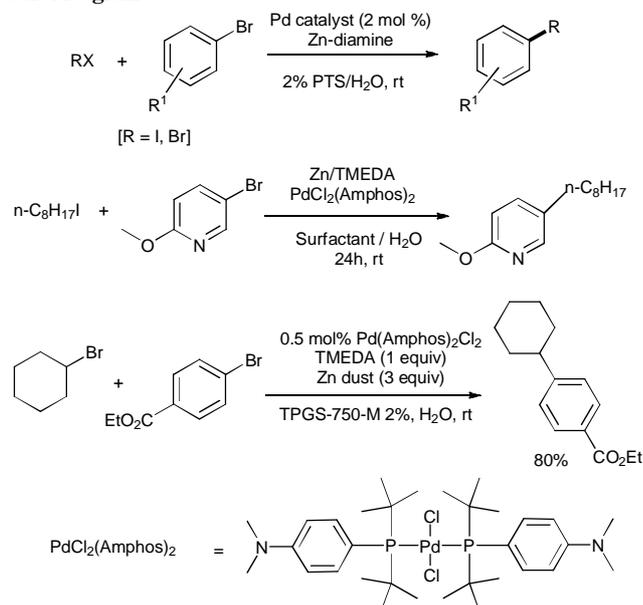


**Scheme 67.** Stille couplings in water at room temperature in micellar media.

Stille couplings are known to be compatible with aqueous media usually at medium high temperatures with limited variation in substrate type. Improvement both of the experimental conditions and on substrate scope of the reaction was proposed by Lipshutz employing TPGS-750-M as surfactant in water, in most cases at room temperature using a combination of Pd(P(t-Bu)<sub>3</sub>)<sub>2</sub> and DABCO (Scheme 67).<sup>137</sup> The use of one equivalent of NaCl was crucial, presumably because of the enlargement of micelles offering increased surface area as well as increased binding constants for substrates and catalysts. Aryl bromides coupled smoothly at room temperature while the analogous reactions of aryl chlorides, not surprisingly, were more sluggish. Proper tailoring of catalyst loading and small increase in temperature enabled good product formation in considerably higher yield, done in water at room temperature, and in a shorter time frame with respect to other traditional Stille couplings run in organic

solvents at 80 °C. Unfortunately, due to the apolar character of the Pd(II) catalyst, extraction with hexane at the end of the reaction led to partial extraction of the catalyst as well disabling in flask recycling.

### 3.1.4 Negishi

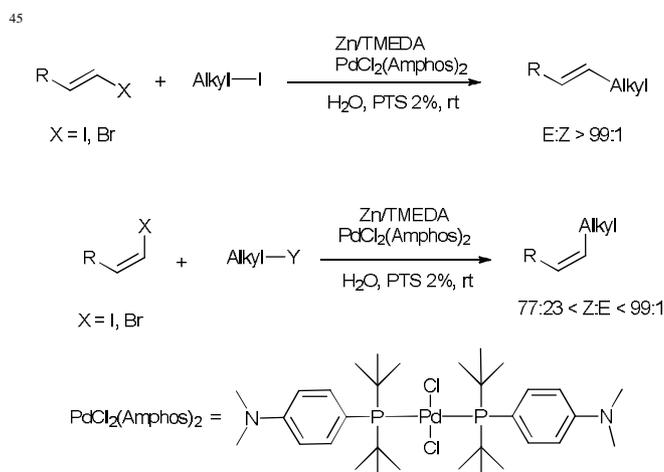


**Scheme 68.** Pd catalyzed Negishi-like cross-coupling between alkyl halides and aryl or heteroaryl halides in water mediated by PTS and TPGS.

Exploiting the intrinsic advantages of the use of PTS surfactant for cross-coupling reactions, in 2009 Lipshutz disclosed a very straightforward method for an alternative Negishi-like cross-coupling reaction between aromatic bromides and alkyl iodides in the absence of a stoichiometrically preformed organometallic coupling partner. The reaction avoids the prior synthesis of Zn-based reagents, known to be moisture sensitive, and uses directly alkyl halides in water in the presence of Zn all performed in 2 weight % PTS/H<sub>2</sub>O at room temperature (Scheme 68).<sup>138</sup> Other non-ionic surfactants (e.g., TPGS, Brij 30, and Solutol) can also be used with roughly comparable efficiencies. The reaction worked well with primary alkyl iodides using *N,N,N',N'*-tetramethylethylenediamine as ligand for the metal center. With secondary iodides the more bulky *N,N,N',N'*-tetraethylethylenediamine was essential to ensure good yields while tertiary iodides turned out not to be suitable substrates. Crucial roles were played by the diamine that favors the *in situ* formation of the alkyl-Zn species and by the surfactant since switching to organic media led to modest product formation (20%).

This catalytic Zn-mediated, Pd-catalyzed cross-coupling reaction was further extended to the use of different substrates. In particular the reaction proceeded smoothly with water-insoluble heteroaromatic bromides like substituted bromo-pyridines in combination with *n*-octyl iodide (Scheme 68).<sup>139</sup> Analogously, benzo[*b*]thiophene, thiophene, furane, pyrrole, indole, and quinoline derivatives all led to good product formation in

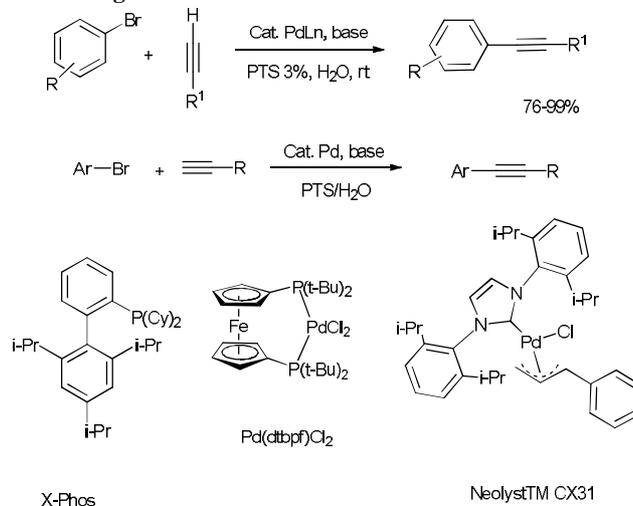
combination with functionalized primary and secondary alkyl halides bearing functional groups such as aliphatic and aromatic ketone, ester, ether, chloride, Boc, TBS, and benzyl-protected alcohols. All transformations occurred at room temperature in pure water using a commercially available Pd catalyst and PTS with *in situ* formation of organozinc halides.



**Scheme 69.** Stereoselective Negishi-like coupling between alkenyl and alkyl halides in water with PTS at room temperature.

Negishi cross-couplings involving *E*- or *Z*-alkenyl substrates was achieved subsequently in water with PTS simply mixing up Zn(0) with tetramethylethylenediamine (TMEDA) as ligand, a very electron rich Pd(II) catalyst and the *E*- or *Z*-alkenyl halide with the alkyl halide partner at room temperature (Scheme 69).<sup>140</sup> The reaction is almost completely stereoselective with retention of configuration of the original alkenyl halide in the coupling product. The corresponding coupling products were obtained in good to excellent yields even in the case of 2,2-disubstituted alkenyl halides, also in this case with complete retention of configuration.

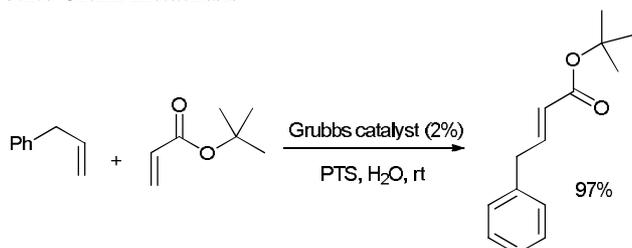
### 3.1.5 Sonogashira



**Scheme 70.** Sonogashira couplings of aryl bromides in the absence of Cu in water with PTS as surfactant.

The application of PTS surfactant to the Sonogashira coupling reaction between terminal lipophilic alkynes and less reactive aryl bromides led to efficient formation of the corresponding products again with the extra advantage of avoiding the presence of copper species and under mild conditions. (Scheme 70)<sup>141</sup> For instance, the presence of PTS in the coupling between phenyl acetylene and bromobenzene led to 83% of isolated product, while without surfactant only 34% conversion was possible. With this protocol more than 20 different combinations of terminal alkynes and electron rich as well electron poor aryl bromides led to the corresponding acetylenic disubstituted products in good to excellent yields, requiring in some cases optimization of the base employed.

### 3.1.6 Olefin metathesis

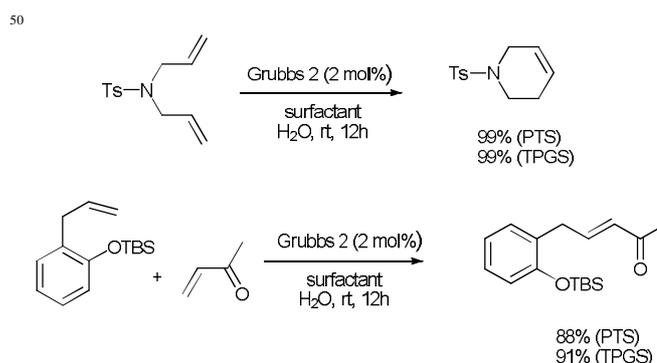


**Scheme 71.** Olefin cross-metathesis reactions at room temperature in water with the non-ionic surfactant PTS.

Metathesis reactions have been often investigated in water as solvent.<sup>142,143</sup> One of the earliest approaches in the use of micellar catalysis in metathesis reactions was provided by Lipshutz and coworkers that disclosed the positive combination between Grubbs 2 catalyst and neutral PTS surfactant that allowed 97% yield in the products between allylbenzene and *tert*-butyl acrylate in 12h at room temperature (Scheme 71).<sup>144</sup> The key aspects of this catalytic system are the mild experimental conditions, the *E/Z* ratios comparable to those typically observed in organic media, the compatibility with the presence of other functional groups, and last but not least the easy product isolation. The system was applied to a wide range of terminal alkene substrates demonstrating that intermolecular cross-couplings can be carried out in high yields without requiring the modification of catalyst or substrate to enhance their water solubility and no special techniques or handling procedures of the materials are necessary.

The catalytic system was extended to a wide range of lipophilic substrates bearing terminal diene functional groups that led the corresponding cyclic 5-, 6- and 7-membered rings products in high yields<sup>145</sup> under very mild conditions, without requiring inert gas experimental conditions typical of the reaction.

Both traditional metathesis as well as ring closing metathesis (RCM) reactions with PTS proved to benefit from the addition of salt in solution. In particular small amounts of  $\text{KHSO}_4$  (0.02 M) had a much greater impact on the yield of the reaction, enabling facile recycling of the aqueous micellar medium that contains the catalyst for up to ten cycles with minimal loss of catalytic activity.<sup>134</sup> Alternatively,  $\text{CuI}$  added to the system ensured improvement of the yield for the metathesis reactions.

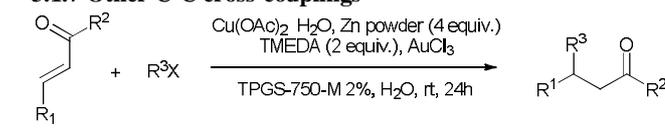


**Scheme 72.** Comparison between PTS and TPGS micellar media in Grubbs 2 RCM and CM.

Further surfactant optimization led to the preparation of surfactant TPGS-750-M characterized by easier synthetic access and at least the same catalytic impact, characterized by the presence of the same  $\alpha$ -tocopherol unit exploited in PTS but endowed with a longer methylated PEG chain. This change leads to larger nanoparticles in water and the new surfactant allowed extremely good catalytic activity in RCM and CM reactions (Scheme 72)<sup>146</sup> for a broad combinations of substrates. Moreover, the catalytic system showed to be sensitive to the pH of the system and the reaction repeated in the presence of  $\text{KHSO}_4$  enabled the coupling between allylbenzene derivatives and the unusual substrate methyl vinyl ketone observing a substantial improvement in yield from 74 to 91%. With the second generation of Grubbs catalysts (2 mol %) a variety of lipophilic substrates successfully undergo ring-closing or cross-metathesis in water at room temperature to produce high isolated yields of the desired products. Reactions were conducted in 2.5% TPGS-750-M/water, with yields equal to or slightly better than those obtained with other surfactant-water combinations.

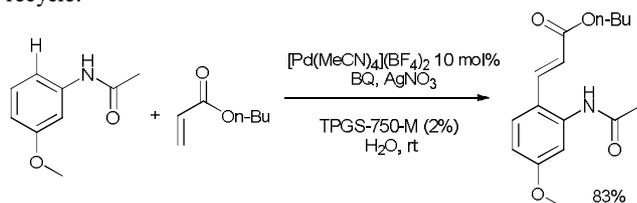
Charnay, Colacino and co-workers succeeded in monitoring a RCM reaction via  $^1\text{H}$  NMR measurements.<sup>94</sup> using Grubbs I pre-catalyst in the presence of *bis*-cationic surfactants for the reaction of *N,N*-diallyltosylamine and diethyl-diallyl malonate. They underlined that the surfactant forms micelles and dissolves the poorly water soluble substrate while the catalyst remains undissolved and surfactant molecules arranged around it creating a sort of adsorbed layer rather than a micellar building. This is sufficient to bring substrate and catalyst in close contact thus leading to formation of the product that being much more hydrophobic, separates from the reaction mixture. Overall, the reaction operates with a heterogeneous Grubbs catalyst.

### 3.1.7 Other C-C cross-couplings



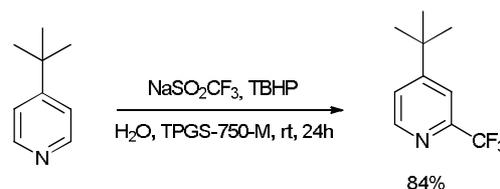
**Scheme 73.** C-C Bond formation via Copper-catalyzed conjugate addition reactions to enones in water at room temperature.

Among organometallic species, organocopper derivatives are standard reagents for conjugate Michael-type additions, but this kind of reagents need carefully dry conditions to ensure good product yields. As observed before, micelles provide apolar and "dry" nanoenvironments that enable water-sensitive reactions to be carried out using water as the bulk solvent, under absolutely counterintuitive and, at first sight, odd experimental conditions. This is the case of the organocopper addition of alkyl halides to enones disclosed by Lipshutz characterized by the use of  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (5 mol%),  $\text{AuCl}_3$  (5 mol%), Zn powder (4 equiv), TMEDA (2 equiv) and TPGS as surfactant in water at room temperature for 24h without requiring previous preparation of the organometallic species (Scheme 73).<sup>147</sup> The initially formed organozinc species subsequently transmetalate to Cu and eventually leads to conjugate addition to unsaturated ketones providing the corresponding  $\beta$ -substituted carbonyl compounds. Several cyclic and acyclic enones in combination with numerous alkyl bromides and iodides bearing functional groups can be utilized. The confinement of the catalytic metal species in the micellar phase enabled easy and efficient in-flask catalyst recycling for 3-4 runs achieved by simple hexane extraction of the reaction products and direct reuse of the aqueous phase. Moreover, different substrate combinations can be used in each recycle.



**Scheme 74.** Cationic Pd(II)-catalyzed Fujiwara-Moritani reactions at room temperature in water with PTS.

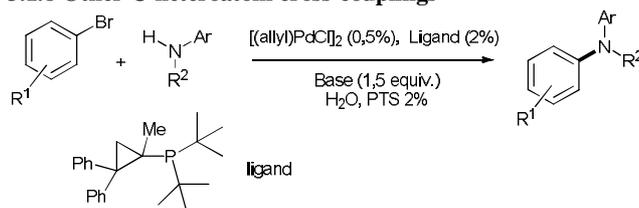
Aryl C-H activation reactions are valuable chemical transformations that are object of intensive studies by the scientific community. The reaction was extended to the use of water under micellar conditions by Lipshutz and co-workers that investigated the Pd(II)-catalyzed Fujiwara-Moritani reaction carried out without external acid at room temperature and in water as the only medium (Scheme 74).<sup>148</sup> The protocol for the Fujiwara-Moritani reaction promotes the *ortho*-directed C-H activation of anilides and requires the use of  $[\text{Pd}(\text{MeCN})_4](\text{BF}_4)_2$  that activates anilide derivatives at room temperature with PTS as surfactant in water as the only medium, with the addition of benzoquinone and  $\text{AgNO}_3$  but most notably without addition of external acid. It is worth noting that no products arising from a potentially competitive 1,4-addition pathway were observed as well as no double *ortho*-directed C-H activation occurred. 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.



**Scheme 75.** Trifluoromethylation of heterocycles in water at room temperature mediated by TPGS-750-M.

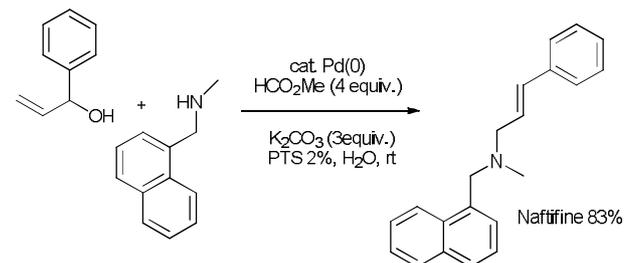
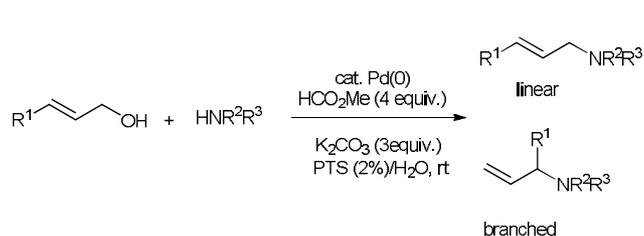
The use of surfactants in water is intrinsically useful form reactions between substrates characterized by high difference in polarity, for example between organic species and salts. A typical example is the combination of sodium trifluoromethanesulfinate ( $\text{CF}_3\text{SO}_2\text{Na}$ ) that with *t*-butyl hydroperoxide as oxidant is employed under the name of Langlois reagent for introducing trifluoromethyl groups onto electron-rich aromatic compounds (Scheme 75).<sup>149</sup> The reaction of this reagent with heterocyclic derivatives like pyridines, indoles and many others was found to greatly benefit by the presence in water of TPGS-750-M as surfactant. These radical reactions take place at ambient temperatures, and the aqueous medium could be recycled up to five times with minimal loss of catalytic efficiency.

### 3.1.8 Other C-heteroatom cross-couplings



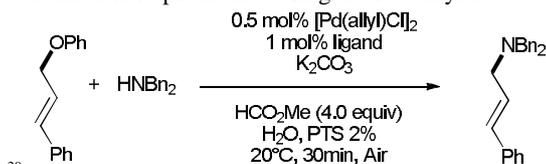
**Scheme 76.** Pd(II) catalyzed amination of aryl bromides in water at room temperature mediated by PTS as neutral surfactant.

After an intensive screening of different P ligands, Lipshutz and coworkers found that efficient direct aniline formation was possible with aryl bromides in water at room temperature under micellar conditions due to addition of PTS to the reaction mixture (Scheme 76).<sup>150</sup> The protocol enabled direct synthesis of unsymmetrical di and tri-aryl amines with much lower catalyst loading than before. Tailoring the base was found to be crucial in order to achieve high yields for a broad combination of substrates leading to more than 20 aniline derivatives with yield in the range 72 - >99% even with sterically hindered 2,6-dimethyl substituted aryl bromide. Only careful degassing of the solution was required while the other experimental conditions were extremely mild for the kind of reaction under consideration.



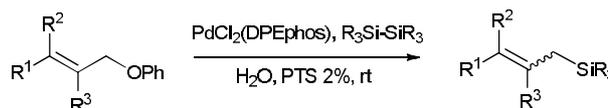
**Scheme 77.** Amination of allylic alcohols in water at room temperature under PTS micellar conditions.

PTS nano-micelles turned out to be very effective also in promoting a series of allylic substitutions. In particular, allylic amination requires either activated allyl alcohol derivatives or strong Lewis acids and anhydrous conditions when allyl alcohol is directly employed. Nevertheless, with 2% PTS in water and a Pd(0) catalyst the reaction between cinnamyl alcohol and dibenzylamine with an activating methyl formate led to the corresponding linear substitution product in 84% yield (Scheme 77).<sup>151</sup> This method enabled the facile allylic aminations of primary, secondary, and tertiary allylic alcohols all formed at room temperature and the same approach was applied to the synthesis of the antifungal agent nafifine reducing the overall number of steps and increasing the overall yield.



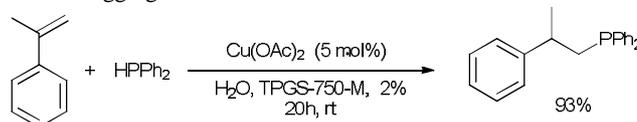
**Scheme 78.** Amination of allylic phenyl ethers via micellar catalysis at room temperature in water.

After reporting direct allylic amination of allyl alcohols, Lipshutz and coworkers disclosed a variant of the reaction employing allyl ethers as reactive substrates. Even in this case, micellar media formed by addition of PTS to water resulted crucial to activate a Pd(II) precursor for the reaction between cinnamyl-phenyl ether and dibenzylamine with methyl formate as activating group leading to the linear isomer in very high yield at room temperature. (Scheme 78)<sup>152</sup> Conversely, under on-water conditions the yield dropped down to only 53%. The catalytic system was applied to a broad combination of allyl ethers and nucleophilic secondary amines with generally high yields and selectivity. Moreover, the system turned out to be tolerant to the presence of other functional groups such as aryl bromides.



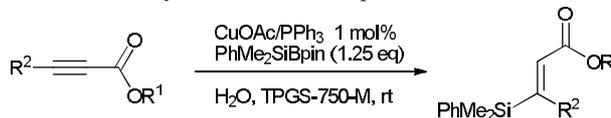
**Scheme 79.** Pd-catalyzed synthesis of allylic silanes from allylic ethers.

As a further variation of the allylic substitution reaction developed using PTS as surfactant, Lipshutz extended the reaction to the synthesis of allylic silanes from allylic ethers and disilanes as the stoichiometric source of silicon in water at room temperature (Scheme 79).<sup>153</sup> Of many Pd precursors, PdCl<sub>2</sub>(DPEphos) proved to be among the most active catalysts leading to high yields in the corresponding allylic silanes with preference for the linear over the branched derivative and high E/Z ratios. Among possible disilanes, hexamethyl disilane and diphenyl tetramethyl disilane were extensively investigated with good product formation in both cases. It is worth noting that the same reaction does not proceed at all in organic solvents like methanol, further confirming the pivotal role played by the micellar aggregate.



**Scheme 80.** Copper-catalyzed hydrophosphinations of styrenes in water at room temperature mediated by TPGS-750-M.

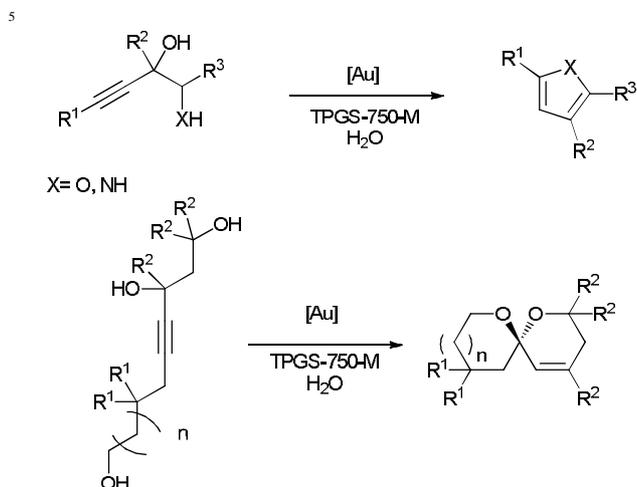
The use of TPGS-750-M favoured the hydrophosphinations of styrenyl systems with diphenylphosphine in water mediated by copper acetate rather than with more traditional Pd or Pt catalysts as recently disclosed by Lipshutz and collaborators (Scheme 80).<sup>154</sup> The reaction turned out to be practical with simple styrene and  $\alpha$ -methyl-styrene derivatives, with better results in particular with electron-poor and sterically unhindered substrates. Overall the use of micellar medium showed to be competitive with respect to the employment of traditional organic media both in terms of isolated yields and milder experimental conditions.



**Scheme 81.** Copper catalyzed stereoselective silylcupration of conjugated electron poor alkynes in water mediated by TPGS-750-M.

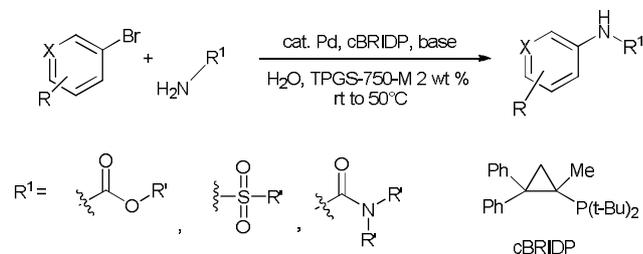
An extremely synthetically useful protocol was disclosed by Lipshutz and collaborators for the copper-catalyzed silylcupration of a variety of electron-deficient alkynes with silylborane forming isomerically pure *E*- or *Z*- $\beta$ -silyl-substituted carbonyl derivatives exploiting the micellar environment provided by TPGS-750-M in water (Scheme 81).<sup>155</sup> The reaction was rapid, tolerant of other functional groups present in the substrate leading high yields of vinylsilanes that are valuable compounds in organic synthesis. In particular, the catalytic system was optimized allowing to obtain good yields with catalyst loading as low as 1/10000 and scale up

on the orders of several mmoles of substrate was demonstrated. Moreover, the aqueous phase was recycled up to six times after extraction and substrates addition, without observing significant loss of catalytic activity.



**Scheme 82.** Gold-catalyzed intramolecular dehydrative cyclizations in micellar media.

The hydrophobic interior of the micelles is particularly suitable to promote dehydration and condensation reactions where water is a by-product. An example of the positive effect imparted by the use of micellar media of TPGS-750-M was provided recently for the gold-catalyzed cyclizations of diols and triols to the corresponding hetero- or spirocycles in an aqueous medium (Scheme 82).<sup>156</sup> In particular, because of the effect imparted by the surfactant, it was possible to efficiently transform acetylenic vicinal diols and amino alcohols to the corresponding furans and pyrroles with Au(III) precursors and properly substituted alkynes containing three hydroxyl residues could be converted to spirocyclic products in the presence of an Au(I) catalyst at room temperature.

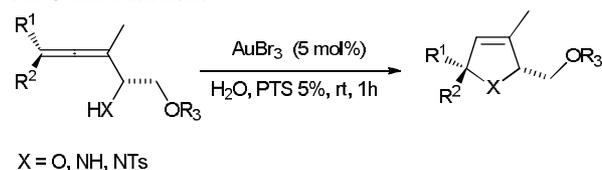


**Scheme 83.** Installation of protected ammonia equivalents onto aromatic and heteroaromatic rings in water enabled by micellar catalysis.

Palladium-catalyzed aminations of aromatic halides could be recently extended in micellar media thanks to the employment of TPGS-750-M. The surfactant provided the optimal environment to ensure close contact between the Pd precursor, the hindered monophosphine, the aryl and heteroaryl halide and an amine precursor such as carbamate, sulfonamide, or urea (Scheme 83).<sup>157</sup> Reactions were conducted at temperatures not higher than

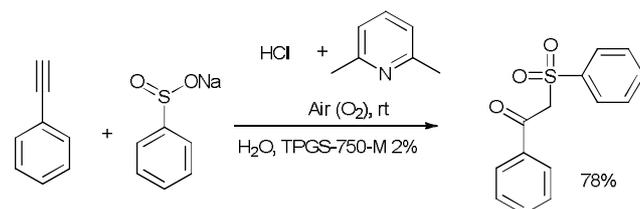
50°C under vigorous stirring leading to full conversion of the reagents and good isolated yields. The processes themselves take place within the nanoreactors formed spontaneously in an aqueous medium. The reaction media could be readily recycled, with a simple in-flask extraction using a minimum amount of a single, recoverable organic solvent thus drastically reducing the associated E factors.

### 3.2 Other reactions



**Scheme 84.** AuBr<sub>3</sub> catalyzed intramolecular cyclization of various  $\alpha$ -hydroxy- and  $\alpha$ -aminoallenes in neutral micellar media.

Homogeneous gold catalysts are suitable for micellar media since they operate on substrates bearing functional groups that are also soft Lewis bases that do not suffer from competitive coordination to the metal by water. Lipshutz and Krause showed that neutral surfactants PTS and TPGS enabled in water efficient AuBr<sub>3</sub> catalyzed intramolecular cyclization of various  $\alpha$ -hydroxy- and  $\alpha$ -aminoallenes. These were converted into the corresponding heterocycles in high yields within 10-80 minutes at room temperature in air (Scheme 84).<sup>158</sup> Since addition of salts increases the average size and shape of the micellar aggregates, the reaction turned out to be faster by addition of NaCl. The high affinity of Au(III) for the micellar medium enabled efficient recycling of the catalytic system observing four complete runs with unaltered yield for the cyclized products simply extracted with hexane, limiting at the same time the overall metal leaching to less than 0.3%.

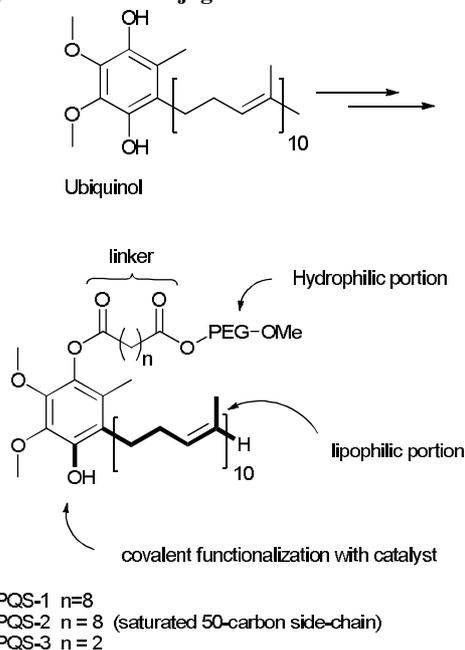


**Scheme 85.** Aerobic oxidation of arylalkynes and arylsulfinate salts to  $\beta$ -ketosulfones in micellar media.

The apolar environment present within micelles of TPGS-750-M surfactant favoured oxygen solubilization in water and greatly improved the metal and peroxide free aerobic oxidation of arylalkynes and arylsulfinate salts to  $\beta$ -ketosulfones (Scheme 85).<sup>159</sup> The reaction was applied to a wide range aromatic alkynes and aromatic and aliphatic sulfinic acids leading within few hours to good product yields. Moreover, after extraction of the products with an organic solvent, the aqueous phase was recycled up to three times. A detailed mechanistic investigation was provided confirming the role of molecular oxygen as terminal oxidant leading to a radical based process suggesting that the oxidation

was occurring within the lipophilic core of the nanomicelles of surfactant.

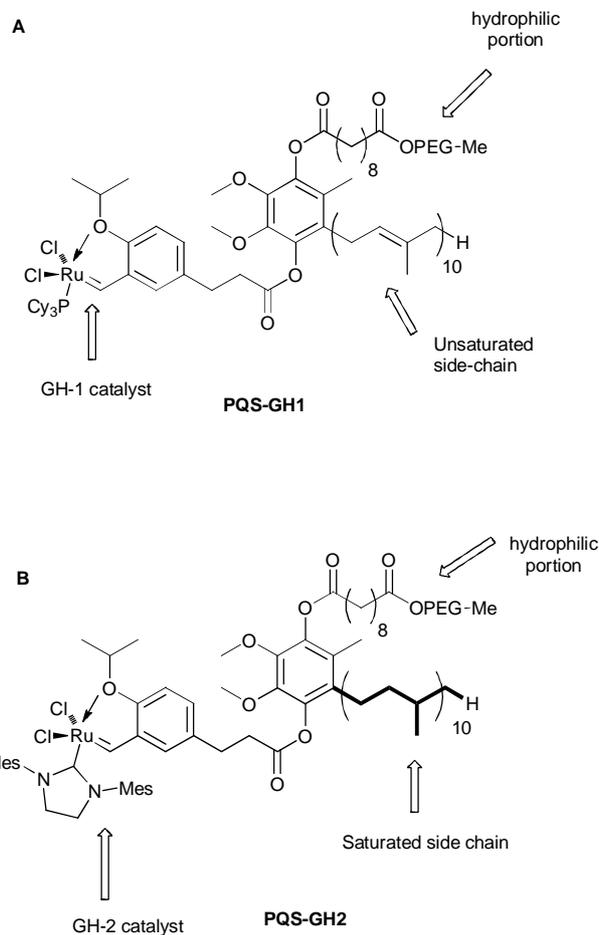
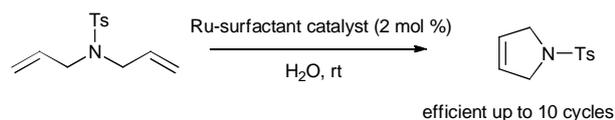
### 3.3 Catalyst-surfactant conjugates



**Scheme 86.** Modified routes to the “designer” surfactant PQS.

Aiming at exploiting the intrinsic recyclability of micellar catalysis, Lipshutz proposed a new designer surfactant polyethyleneglycol ubiquinol sebacate (PQS) that includes i) a lipophilic component based on the ubiquinol form of coenzyme Q<sub>10</sub> (2,3-dimethoxy-5-methyl-6-poly-prenyl-1,4-benzoquinol) bearing a poly-prenylated side chain of 9-10 units, that provides the apolar core of the micellar aggregates where apolar substrates are dissolved, ii) a hydrophilic portion to impart solubility in water and iii) a phenolic residue to which, through a succinic or sebacic spacer, it is possible to attach covalently different ligands for metal catalysis or organocatalysts (Scheme 86) Three versions of the surfactant were developed containing different spacers and saturated or unsaturated lipophilic chains whose synthesis was optimized.<sup>160</sup> The different surfactants showed similar behavior in terms of recyclability when covalently modified with Ru(II) catalysts for RCM.

#### 3.3.1 Metallo-surfactants



**Scheme 87.** PQS: a new platform for micellar catalysis. RCM reactions in water, with catalyst recycling.

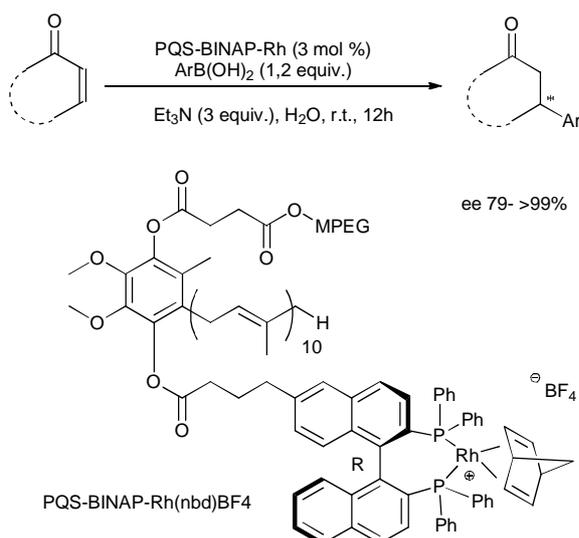
Initially the new surfactant system for catalyst recovery was endowed with a Grubbs Hoveyda 1 Ru(II) catalyst to investigate the ring-closing metathesis reactions of water-insoluble dienic substrates in pure water at room temperature (Scheme 87A).<sup>161</sup> The metal containing surfactant formed micelles of 44 nm average size in water and efficiently catalyzed the RCM of N, S and O containing lipophilic dienes leading to the corresponding five, six and seven-membered ring products in 79-96% yield. Overall the process showed to be extremely robust, enabling excellent isolated yields at room temperature without the exclusion of air and operating even in seawater. More importantly, the metal-surfactant system could be recycled by simple diethyl ether extraction of the products for ten recycles with minor loss of catalytic activity, while the typical Grubbs catalyst loosed its performance in few cycles.

The concept was extended to Grubbs Hoveyda 2 containing a carbene ligand to Ru(II) covalently connected to a variant of the PQS tenside bearing a completely saturated alkyl chain (Scheme

87B).<sup>162</sup> The evolved metallomicellar catalyst containing 2% w/w of catalyst enabled efficient RCM of heterocyclics and carbocyclics from five to seven membered rings as well as closing metathesis between acrylates and other alkenes. High level of recyclability was proved for both RCM and for heterodimeric CM.

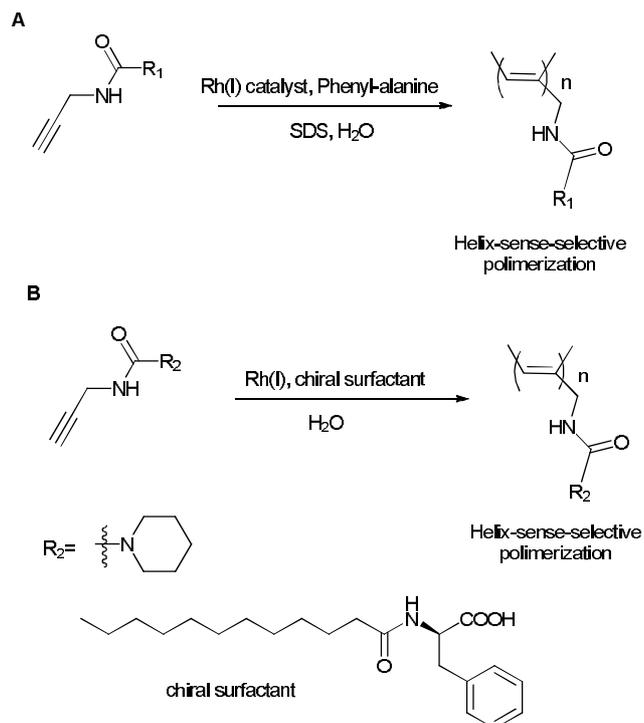
### 3.3.1.1 Chiral metallo-surfactants

Examples of chiral micelles are very few, often based on the employment of modified block co-polymers with chiral appendages or other intrinsically chiral natural polymers, both cases not considered in the present review.<sup>163</sup> Apart from early examples of catalysis with micelles,<sup>164</sup> in the foregoing we report a few recent systems that lay the foundations for future development in the field.



**Scheme 88.** Rhodium-Catalyzed Asymmetric 1,4-Additions, in Water at Room Temperature, with In-Flask Catalyst Recycling.

Covalent conjugation of the PQS scaffold to a BINAP-Rh(I) species provided efficient metallomicellar system to promote efficient 1,4-conjugate addition of aryl boronic acids to unsaturated cyclic and acyclic ketones in water at room temperature allowing easy isolation of the enantioenriched product by means of diethyl ether extraction (Scheme 88).<sup>165</sup> The products of the addition reaction were obtained in high yields and with enantioselectivity values comparable to what observed for related methodologies. As observed above, the PQS scaffold enabled easy recycling for up to four cycles of the catalytic system that remained confined in the aqueous phase.

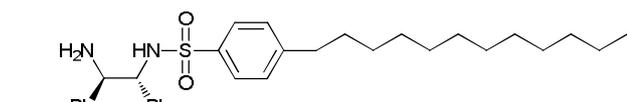
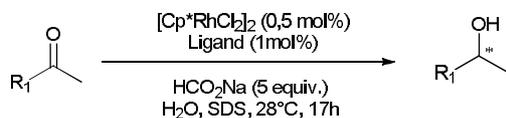


**Scheme 89.** A) Helix-sense-selective polymerization in SDS micelles with aminoacids; B) Helix-sense-selective polymerization in water with within chiral metallo-micelles.

Another outstanding example of chiral self-assembled micellar catalytic system was proposed by Deng, Yang and coworkers consisting in the formation of chiral SDS micelles by adsorption on the Stern layer of aminoacids like phenylalanine to provide chiral nano-environments to conduct asymmetric polymerization of propargyl derivatives by an achiral Rh(I) catalyst (Scheme 89A).<sup>166</sup> The authors observed that the stereochemistry of the aminoacid dictated the handedness of the poly-acetylene derivative that was obtained with number-average molecular weight in the 10000 to 56000 range and *cis* contents in the 96-98% range depending on the monomer employed. The chiral induction is provided by the interaction by H-bonding in the Stern layer between the incoming monomer and the aminoacid that covers the polar head-groups of the micelles. In fact, phenylacetylene being unable of forming hydrogen bonds with amino acid did not provide evidence of asymmetric induction in the corresponding polymer. Careful control experiments confirmed that the helicity induction was not dependent on interactions between the formed achiral polymer and the aminoacids and was just a consequence of chiral discrimination in the chain propagating process.

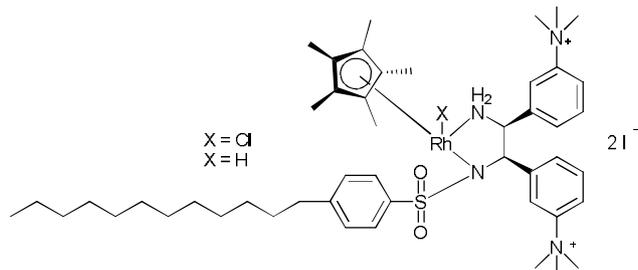
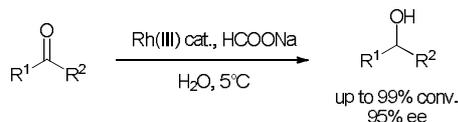
The same authors prepared an amphiphilic version of phenylalanine like dodecylphenylalanine and employed this surfactant aminoacid to generate chiral micelles in solution (Scheme 89B).<sup>167</sup> Addition of Rh(I) precursors led to the formation of chiral Rh(I) polymerization supramolecular catalysts that in the presence of an achiral substituted acetylene monomer led to helix-sense-selective polymerization and the resulting

polymer emulsions showed optical activity as a consequence of the predominantly one-handed helical conformation of the polymer.



**Scheme 90.** Rhodium-catalyzed asymmetric transfer hydrogenation of alkyl and aryl ketones in aqueous media.

In order to perform asymmetric hydrogenations of acyclic aliphatic and aromatic ketones in water, Adolfsson and coworkers prepared an amphiphilic version of a Ru(II) catalyst bearing a chiral lipophilic mono-sulfonated diamine ligand that in the presence of SDS as surfactant forms micelles of about 33 nm (Scheme 90)<sup>168</sup> as determined by means of NMR diffusion techniques. The mixed micellar system allowed the enantioselective transfer hydrogenation of ketones observing in some cases an increase of enantioselectivity due to the presence of SDS in water with respect to the reaction in pure water. In particular, cyclohexyl methyl ketone as substrate led to excellent conversion and enantioselectivity that is the highest ever observed under transfer hydrogenation with formate in water. SDS favors the solubilization of highly lipophilic substrates where the polar carbonyl end of the molecule points towards the surface, thereby facilitating stereochemical induction. Aryl alkyl ketones turned out to be excellent substrates leading to the corresponding alcohols with excellent conversion and enantioselectivity.

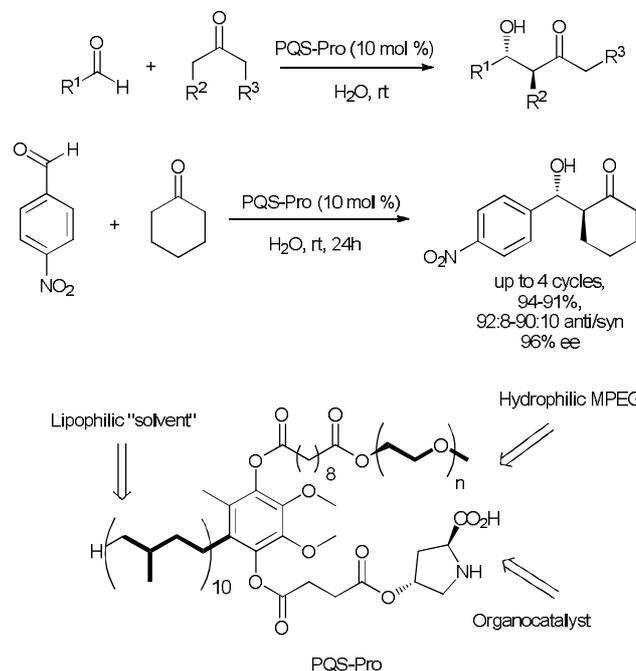


**Scheme 91.** Chiral Rh(III) metallo-surfactant micelles for efficient transfer hydrogenation of aliphatic ketones.

After investigating the use of cationic surfactants to improve the asymmetric transfer hydrogenations of aromatic ketones, Deng and coworkers moved further preparing the chiral ligand reported in Scheme 91 bearing a long alkyl chain to be used for the preparation of the corresponding Rh(III) complex, similar to

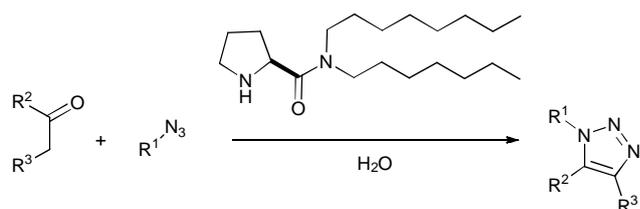
that reported in Scheme 90 but further functionalized with positive ammonium charges on the hydrophilic portion of the ligand. The obtained chiral metallo-surfactant self-assembles in water leading to chiral metallo-micelles<sup>169</sup> that catalyzed the efficient asymmetric transfer hydrogenation of aliphatic ketones with high enantioselectivities for a wide range of substrates. This is a rather challenging reaction compared to the transfer hydrogenation of aromatic ketones. The formation of metallo-micelles of  $67 \pm 16$  nm average diameters was confirmed by TEM analysis. The asymmetric reaction showed to be highly dependent on the length of the aliphatic ketone with longer substrates showing higher enantioselectivity (2-hexanol 76% ee and 2-tridecanol 94% ee) and substrate-to-catalyst ratios as high as 100. Synergistic effects between the catalytic metal center and the hydrophobic microenvironment present in the core of the metallo-micelle were considered pivotal to ensure high enantioselectivity.

### 3.3.2 Chiral organocatalyst-surfactants



**Scheme 92.** Organocatalysis in water at room temperature with in-flask catalyst recycling.

Extension of the PQS system to the covalent linkage of a proline derivative led to the development of a micellar catalyst that efficiently operated enantioselective aldol condensation of water soluble or insoluble substrates in pure water (Scheme 92).<sup>170</sup> Several combinations of aromatic aldehydes and cyclohexanones led to high yields in the aldol products with good *anti/syn* ratios and high level of enantioselectivity. Simple extraction with ethyl acetate enabled isolation of the product and reuse of the aqueous phase that maintained almost the same catalytic performance for up to four in-flask cycles.



**Scheme 93.** Organocatalytic 1,3-dipolar cycloaddition reaction between ketones and organic azides leading to 1,2,3-triazoles mediated by prolinamide-derived surfactant.

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The prolinamide derived surfactant reported in Scheme 93<sup>171</sup> allowed to conjugate the typical enamine organocatalytic cycle between secondary amines and carbonyl compounds with the micellar effect imparted by its amphiphilic nature leading to an efficient example of 1,3-dipolar cycloaddition between cyclic and acyclic ketones with organic aromatic azides. The Huisgen 1,3-dipolar cycloaddition reaction provided substituted 1,2,3-triazoles in water at 80°C in high yields.

#### 15 4. Summary and future perspectives

In this review advances in molecular catalysis within micelles have been described, focusing on the supramolecular aspects of this kind of catalysis that has proved suitable for almost all classes of chemical transformations, ranging from the use of organometallic species or dehydration reactions usually requiring strictly anhydrous conditions, to asymmetric reactions with both chiral metal catalysts and organocatalysts.

Like in Nature, the ideal micellar medium working well in all cases simply does not exist. Rather, the chemical nature of the surfactant, its concentration and molar ratio are all parameters with a profound influence on the outcome of the catalytic reaction and they deserve careful optimization. A critical balance between catalyst, substrate and surfactant properties must be analyzed in detail in order to ensure high yield, selectivity and recyclability. The wide availability of surfactants and their generally low cost are definite benefits that clearly speak for their potential towards practical synthetic methods and also in the possible scale up of suitable industrial productions. Micellar catalysis offers the great advantage of using catalysts already developed for use in organic media, where the tuning of subtle electronic and steric effects associated to the use of ligands has been already optimized, without the need to perturb these properties modifying the ligands to make the catalyst compatible with water. What is still largely under-investigated is a deeper look into the positioning and the interactions between the catalyst employed and the surfactant aggregates. Only with a larger interdisciplinary approach it would be possible to shed light onto these aspects of micellar catalysis thus greatly helping to understand the reasons for improved selectivities and activities.

Among several possible future directions in micellar catalysis, some are reported below all suggested by very recent literature where micellar aggregates are enriched with new functionalities, properties, features.

The development of new surfactants, with the auspice to be made with renewable sources, is one of the next challenges for micellar catalysis, together with the development of chiral

micelles from economic natural sources able to impart high levels of stereocontrol possibly acting as self-assembled organocatalysts themselves or in combination with achiral metal catalysts.

55 The self-assembly strategy that lies at the base of micellar catalysis recently suggested the preparation of hydrophobic core-hydrophilic shell-structured heterogeneous catalysts that showed good catalytic performance in pure water<sup>172</sup> opening the way to metal-supported catalysts based on the same strategy for reactions in water. Catalysis with dendrimers shares similar concepts. Once again, this clearly speaks for the versatility of micelles that have the great advantage of not requiring synthetic modification of the catalytic system because self-assembly of the structure is spontaneous.

65 Very recently Yoshizawa and coworkers reported a seminal work where micellar-like aggregates of very definite structures with 4-6 monomers were prepared exploiting aromatic-aromatic interactions present in purely aromatic surfactants rather than the classical use of surfactants endowed with long alkyl chains.<sup>173</sup> This opens the way to the design of new surfactants based on extended rigid aromatic surfaces having the further advantage to act as photoactive hosts able to transfer energy to the encapsulated guest molecule. This represents a cross-point between micellar catalysis and supramolecular recognition that may have far reaching implications.<sup>174,175</sup>

Another cross-contact is possible between micellar catalysis and heterogeneous catalysis especially for the stabilization of catalytically active metal nanoparticles. Recent report on Ag nanoparticles stabilized by traditional surfactants<sup>176</sup> opens to the employment of surfactants and micellar conditions for tailoring shape and properties of metal nanoparticles to be exploited in catalysis.<sup>177</sup>

Reversibility is another important feature in catalysis to implement control over catalytic activity and catalyst recovery. For instance, recent findings showed that by addition of carbon dioxide it is possible to reversibly modify the aggregation properties of surfactants.<sup>178</sup> It is therefore advisable that in the near future recovery of the surfactant or separation of the catalytic system from the reaction mixture would be feasible using this approach.

In summary, micellar catalysis is nowadays a well established green alternative to traditional homogeneous catalysis in organic media and will certainly benefit of new features in the coming future that will favor its larger diffusion especially in fine chemical production.

#### 5. Acknowledgements

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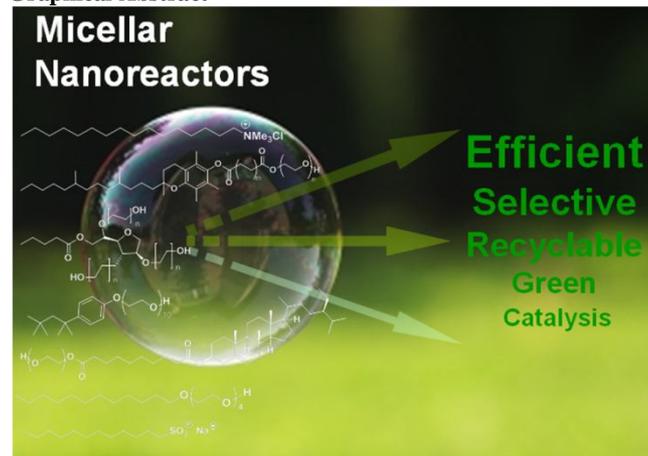
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#### 6. References and Notes

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## Graphical Abstract

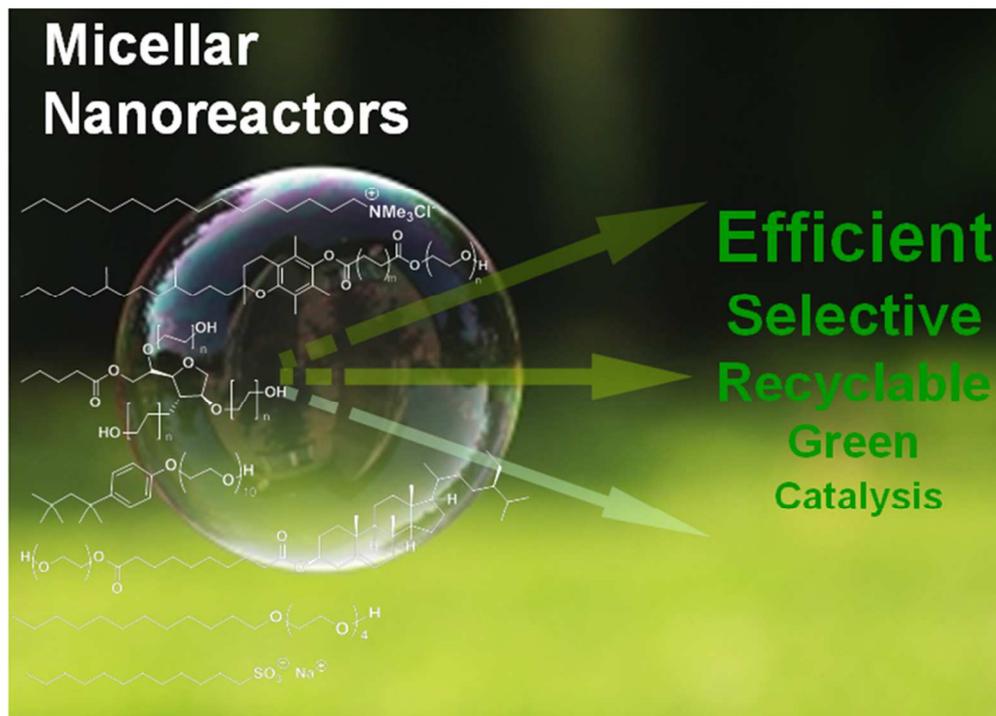


Micellar catalysis is nowadays a well established approach to convert traditional catalytic reactions commonly run in organic solvents into more efficient, selective, recyclable green catalytic reactions.

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