

MINI REVIEW

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Recent designer surfactants for catalysis in water

Tommaso Lorenzetto,^{id} Giacomo Berton,^{id} Fabrizio Fabris^{id} and Alessandro Scarso^{id}*Received 24th May 2020,
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The use of water as a solvent for chemical transformations and catalysis is not only a counter-intuitive original approach with respect to catalysis in traditional media, but thanks to micellar catalysis and the recent development of new designer surfactants, it is becoming an important real benchtop alternative to the employment of organic solvents. Micellar catalysis has received new focus thanks to the recent introduction of the so-called designer surfactants by the group of Lipshutz as surfactants specifically designed and tested for catalysis in water. In particular, the advent of the benchmark **TPGS-750-M** has really revolutionized chemical synthesis and catalysis in aqueous media, leading also to important positive outcomes suitable for industrial scale applications. The present contribution covers the preparation and the applications in chemical transformations and catalysis of very recent new designer surfactants. These are readily available and economic amphiphiles, mostly prepared from renewable resources, that are specifically designed and tested for catalytic reactions in water. In particular, different neutral designer surfactants are covered and critically classified and discussed.

Introduction

The hydrophobic effect¹ is a powerful driving force to perform catalysis in water,² on water,³ under microemulsion conditions^{4,5} or in the presence of micellar aggregates, which has further spurred the use of water as a solvent for chemical and catalytic transformations. The latter field of research, namely micellar catalysis,⁶ has been largely dominated for many years by the fruitful combination of traditional commercially available surfactants with metal catalysis, emphasizing the positive effects observed in terms of recycling of the catalyst, easy product isolation and improved activity and selectivity (regio, stereo and enantioselectivity) as a consequence of the compartmentalization effects induced by the micellar aggregates. This field of research had the positive effect of trying to make the scientific community less “hydrophobic”, underlying the positive effects of the use of water as the only solvent for chemical transformations. Micellar catalysis was firstly introduced in the 70's, but only in the last decade has it become popular, and this specific field of research has been reviewed several times over the last few years.⁷ More specifically, some contributions further analyzed specific trends, like visible light photo-redox catalysis in micellar media,⁸ the application to multicomponent reactions⁹ and the use of metal nanoparticles associated with micellar media.¹⁰ In parallel, the development of metallo-surfactants as transition metal

complexes bearing hydrophilic ponytails to promote aggregation in water leading to metallo-micelles for catalysis and other applications in water was reported and some specific aspects were recently reviewed.^{11–13}

A milestone in the field of micellar catalysis was reached when Lipshutz first introduced the concept of designer surfactants as new amphiphile molecules specifically designed and developed for catalytic applications in water. The first surfactant was DL- α -tocopherol alkoxy polyethylene glycol sebacate¹⁴ (Chart 1), obtained through a rather straightforward synthesis from mostly renewable resources like racemic vitamin E, sebacic acid and a polyethylene glycol

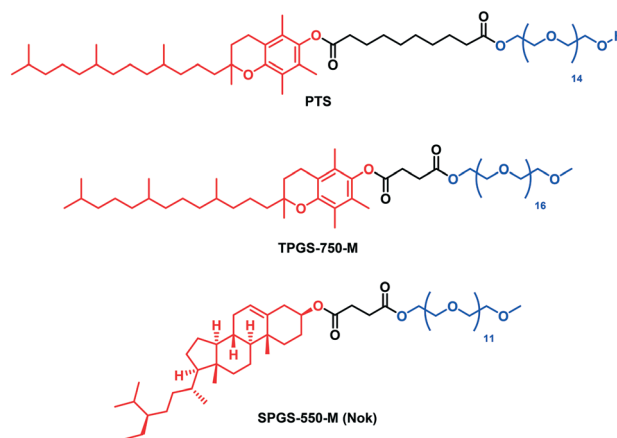


Chart 1 Chemical structure of the first introduced designer surfactants: first generation PTS, second generation TPGS-750-M and third generation SPGS-550-M Nok for catalysis in water.

Dipartimento di Scienze Molecolari e Nanosistemi, Università Ca' Foscari Venezia,
via Torino 155, 30172, Venezia, Italy. E-mail: alesca@unive.it

derivative with a terminal hydroxyl unit as a hydrophilic moiety.¹⁵ This surfactant enabled unprecedented catalytic performances in reactions like metathesis, Sonogashira, Suzuki–Miyaura, Heck, amination, silylation reactions and many other Pd-catalyzed transformations at room temperature.¹⁵

Further developments through a series of intermediate surfactants, based on the employment of a shorter linker between the hydrophobic and hydrophilic portions, eventually led to the introduction of DL- α -tocopherol methoxypolyethylene glycol succinate **TPGS-750-M** as a second generation amphiphile. This surfactant is characterized by the presence of succinic acid as a shorter spacer between the hydrophobic and the hydrophilic portions, and with the PEG unit capped as a methyl ether terminal group. The success of the latter designer surfactant enabled its application to a very wide range of chemical transformations,¹⁶ in particular for organometallic catalysis in water at room temperature,¹⁷ with metal nanoparticles,¹⁸ or with ppm amounts of metal catalysts,¹⁹ and also in combination with bio-catalysis.²⁰ The versatility of this surfactant further spurred several other research groups to investigate the potential of **TPGS-750-M**,^{21–23} and also as a drug carrier candidate.²⁴ Moreover, this designer surfactant attracted the interest of the pharmaceutical industry²⁵ reporting applications for the synthesis of active pharmaceutical ingredients,^{26,27} thus representing a real example of academic research that reaches large scale production projects.

In the meantime, to prompt the widespread application of designer surfactants, the group of Lipshutz developed a much more cost effective alternative to the second generation designer surfactant, replacing the hydrophobic unit with the less expensive β -sitosterol. The third generation designer surfactant β -sitosterol methoxypolyethylene glycol succinate **SPGS-550-M**, also called **Nok** (Chart 1),²⁸ enabled comparable catalytic properties to **TPGS-750-M** for several Ru and Pd catalyzed reactions at room temperature, thus representing a more economically viable alternative.

The success of the currently commercially available first three generations of designer surfactants, stimulated the Lipshutz group, and several other research teams, to create new classes of designer surfactants. In fact, many are the possible combinations of hydrophilic and hydrophobic units, preferably from renewable resources and from inexpensive materials, that can be combined providing gram scale amounts of new surfactants to be tested in water for many different reactions.

The present contribution covers the preparation and the applications of very recent new designer surfactants, that are critically classified and discussed based on their molecular structure, properties and applications to catalysis. This is clearly a fast growing field of research that will certainly give new achievements in the near future. A critical selection of the papers reported in the literature is presented, classifying the contribution based on the structure of the surfactant

rather than on the kind of chemical transformation promoted by the corresponding micellar aggregates. Another applied selection is based on the true role of the surfactant and of the corresponding micellar medium (Scheme 1); in some cases, the micellar aggregate is intrinsically catalytically active, while in others the micellar aggregates act as a nano-environment that hosts the real catalyst, imparting specific selectivity features or properties.

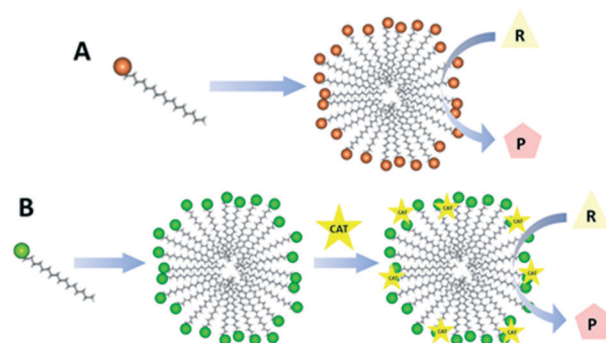
Direct catalysis by micelles of new designer surfactants

Examples of catalytic reactions imparted directly by the micellar aggregates are classified on the basis of the polar head group for ionic and neutral surfactants, since often the catalytic activity is provided directly by such head groups or possibly by the counterions present in the Stern layer on the surface of the micelles.

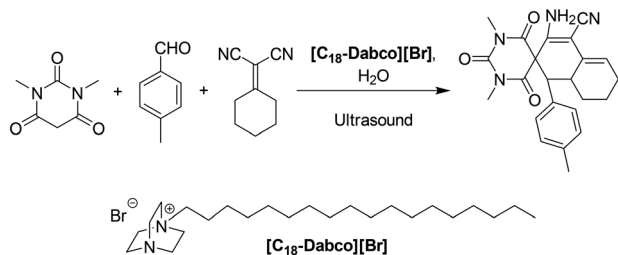
Regarding ionic surfactants, a novel DABCO-based cationic surfactant ($[\text{C}_{18}\text{-Dabco}][\text{Br}]$) was easily synthesized by the reaction of DABCO and octadecyl bromide in acetonitrile at room temperature in excellent yield (Scheme 2).²⁹ This new surfactant was exploited in the one-pot synthesis of spirocarbocycle derivatives under ultrasonic conditions in water. The reaction proceeded through a vinylogous Michael addition of cyclic nucleophiles, vinyl malononitrile and aldehydes.

The long alkyl chain of $[\text{C}_{18}\text{-Dabco}][\text{Br}]$ promoted its aggregation in water with a critical aggregation concentration (CAC) of 9.3 mM, while the free tertiary amine on the polar cationic head of the surfactant acted as a base, favouring the deprotonation and formation of anionic nucleophilic species from the 1,3-dimethylbarbituric acid and vinyl malononitrile stabilized by the cationic charge of the surfactant, thus favouring the catalytic activity. Overall, the designer surfactant enabled yields up to 88% for the final products under mild reaction conditions, with a much shorter reaction time compared to other commercially available surfactants.

Cationic surfactants are commonly used for reactions involving the hydroxyl anion as a base due to its ion pairing



Scheme 1 Different examples of catalysis by micelles of designer surfactants: A) the micellar aggregate directly promotes a chemical transformation; B) the micellar aggregate hosts the real catalysts and imparts specific properties and selectivities.



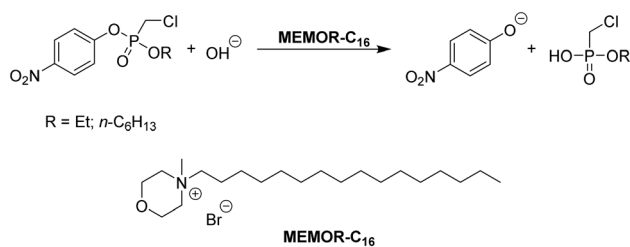
Scheme 2 Application of $[C_{18}\text{-Dabco}][\text{Br}]$ to the multicomponent synthesis of spirocarbocycle compounds in water under ultrasound conditions.

on the surface of the micelles that enhances the local concentration and increases the local pH. This effect has been exploited for the hydrolysis of toxic organophosphorus ester pollutants in water mediated by a combination of methyl-morpholinium surfactant **MEMOR-C₁₆** and polystyrene sulfonate (Scheme 3).³⁰

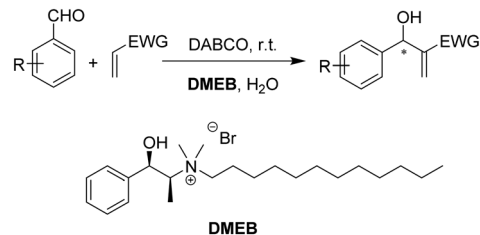
This cationic designer surfactant showed pronounced substrate selectivity in the hydrolysis of organophosphorus compounds characterized by different hydrophobicity and demonstrated acceleration of the hydrolysis reaction of phosphonates up to 50 times in comparison to the reaction in water.

One interesting example to promote stereoselective reactions under micellar conditions in the presence of achiral catalysts using chiral surfactants as the only source of asymmetry was recently reported for the asymmetric Morita-Baylis-Hillman reaction in water, reported in Scheme 4.³¹

Specifically, the cationic chiral surfactant (1*R*,2*S*)-(-)-*N*-dodecyl-*N*-methylephedrinium bromide (**DMEB**) was used for the formation of chiral micelles in water to induce asymmetry in the reaction between aromatic aldehydes and conjugated electron-poor alkenes mediated by the achiral DABCO tertiary amine. ¹H NMR studies suggested that the reaction occurs in the proximity of the polar head group of the **DMEB** micellar medium, close to the stereocenters of the surfactant that are responsible for the asymmetric induction. It is worthy of note that, in consideration of the mechanism of the reaction that involves anionic intermediate species, the surfactant designed is characterized by the presence of a positive charge to ensure stabilization of the intermediate that is held in close proximity to the stereocenters of the surfactants. This synthetic method led to high reaction rates, and enantiomeric excess up to 56%, with yields up to 78%,



Scheme 3 Cationic morpholinium based surfactant **MEMOR-C₁₆** for basic hydrolysis of toxic organophosphorus compounds in water.



Scheme 4 Stereoselective Morita-Baylis-Hillman reaction in water using achiral DABCO catalyst mediated by the chiral designer surfactant **DMEB**.

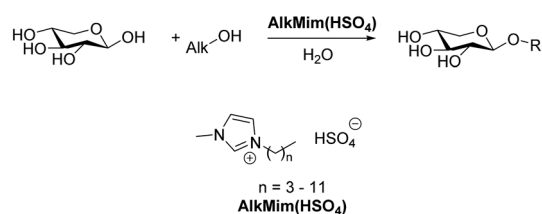
which represents better results with respect to the combination of chiral *L*-proline with achiral cationic cetyltrimethylammonium bromide (**CTAB**).

An interesting example of the formation of new C–O bonds is the reaction of the hydrophilic xylose with aliphatic alcohols in water for the formation of the alkyl xylosides through Brønsted acid catalysis by HSO_4^- as the counter-anion of cationic micelles formed by an amphiphilic cationic 1-alkyl-3-methylimidazolium species **AlkMim(HSO₄)** (Scheme 5).³²

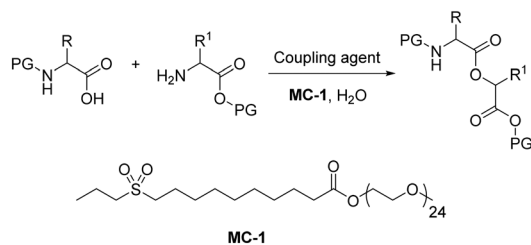
The desired products were obtained in good yields under milder conditions with respect to the traditional Fisher reaction, starting with the unprotected xylose and avoiding the formation of possible oligomers of alkyl xyloside.

As far as neutral designer surfactants with intrinsic catalytic activity are concerned, an interesting contribution by the group of Lipshutz was reported. The aim was to improve peptide synthesis in water taking inspiration from the reactions in DMSO as a common polar aprotic solvent, which is largely employed in synthesis. Lipshutz and collaborators disclosed the synthesis of **MC-1** as a new neutral surfactant comprising a sulfone unit in the apolar core of the structure, while for the polar hydrophilic portion a traditional PEG fragment was used (Scheme 6).³³

The use of **MC-1** avoided the use of any co-solvent to prevent precipitate formation, thus facilitating the overall peptide synthesis process and enabling a simple one-pot, two-step reaction. The implementation of the sulfone unit in the surfactant structure led to a series of advantages, like high yields and very importantly ease of handling of the reaction mixtures, better than **TPGS-750-M** and other commercially available surfactants. Moreover, it was proved that the use of this surfactant allowed gram scale syntheses, without affecting the overall yield observed. All these peculiar



Scheme 5 Etherification reaction between xylose and aliphatic alcohols mediated by amphiphilic 1-alkyl-3-methylimidazolium surfactant bearing a HSO_4^- counter-anion in water.



Scheme 6 Peptide synthesis carried out in water with the aid of the new designer surfactant **MC-1** bearing a sulfone unit in the apolar portion of the structure. PG: protecting group.

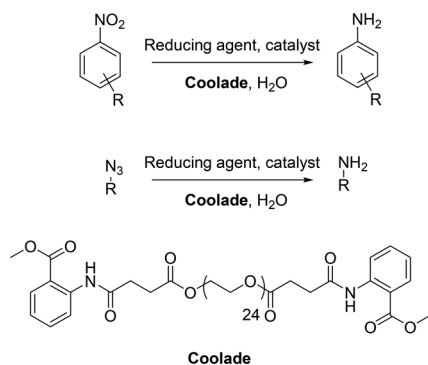
features speak for the potential industrial applications of this designer surfactant.

To address a common problem encountered in reactions performed in water in which gas evolution takes place, like for instance reduction reactions, a specifically designed surfactant named **Coolade** was proposed by Lipshutz, characterized by good anti-frothing properties in order to greatly mitigate the foaming effects in water (Scheme 7).³⁴

The surfactant was specifically designed with two identical lipophilic terminal aromatic units connected by a hydrophilic PEG spacer, aiming at easy isolation of the product without requiring column chromatography. **Coolade** was prepared in a two-step, single-pot process from methyl anthranilate as a lipophilic aromatic unit. Typical examples of successful applications of **Coolade** were the reduction of nitroaromatic compounds to the corresponding anilines or the reduction of organic azides to the corresponding amines. In all cases, the authors reported positive effects for reactions that are typically affected by production of large volumes of foam, especially those using sodium borohydride as a reducing agent. In particular, the absence of a long lipophilic portion in the surfactant, which is strictly connected with its foaming properties, produced little or no lasting foam.

Amino acid based designer surfactants

As simple, economic chiral units characterized by variable side chains, amino acids have spurred the development of



Scheme 7 Examples of the application of the new surfactant **Coolade** for chemical transformations in water to suppress foaming side-effects.

new designer surfactants. Apart from examples where the amino acid was used as a linker for the hydrophobic portion thanks to the presence of different functional groups, other approaches made use of oligopeptides where the chirality of this portion was exploited for stereoselective reactions.

An interesting new designer surfactant **FI-750-M**, also known as **PS-750-M**, was proposed recently by the Handa group based on the combination of a lipophilic ponytail connected to the nitrogen atom of a proline unit, further functionalized on the carboxylic moiety with a Me-PEG hydrophilic portion (Scheme 8).³⁵ **PS-750-M** was designed to mimic polar-aprotic solvents by introducing a greater degree of polarity into the micellar core.

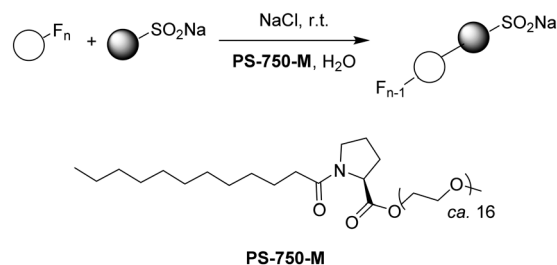
Proline-based surfactant **PS-750-M** in water enabled clean and selective sulfonylation of poly-fluoroarenes by sulfinate salts in water under mild conditions and under gram scale conditions, showing good yields and no formation of side products. It has been discovered that the **PS-750-M** linker region was best suited for mutual solubility of the polyfluoroarene and the sulfinate anionic nucleophile. This surfactant enabled recycling of the reaction medium and isolation of a pure product by simple filtration without the use of an organic solvent.

The application of this promising designer surfactant was extended successfully to photo-assisted selective oxy-halogenation of terminal alkynes, leading to the corresponding di-halo-methylketones under mild experimental conditions (Scheme 9).³⁶

Employing micelles of **PS-750-M**, it was possible to achieve the selective oxy-halogenations of alkynes in water under very mild conditions. The use of a photocatalyst and inexpensive reagents such as *N*-chloro and *N*-bromo succinimide in these reactions provided better yields compared to commercially available surfactants like **TPGS-750-M**, **Triton X-100** or sodium dodecyl sulphate (**SDS**), with no requirement of special precautions in the reaction setup, with the further advantage of the possible recycling of the reaction medium and catalyst.

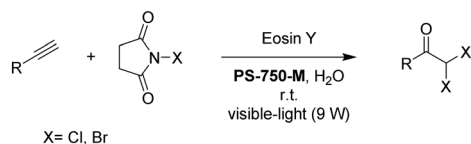
The same surfactant promoted the metal-free reaction between indoles and the fluorinating agent *N*-fluorobenzenesulfonimide (NFSI), providing 3-fluoro indoles in high yields in water (Scheme 10).³⁷

By using the benign surfactant **PS-750-M**, it was possible to develop an approach that allowed site-specific solubility of



Scheme 8 Application of the designer surfactant **FI-750-M** for the sulfonylation of polyfluoroarenes in water under mild conditions.

Mini review



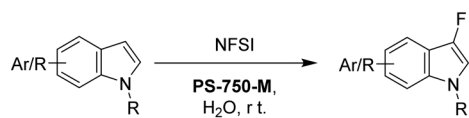
Scheme 9 Synthesis of di-halo-methyl ketones from terminal alkynes through photo-assisted selective oxy-halogenation mediated by PS-750-M in water.

the substrate and fluorine sources in the micelle, thus permitting highly selective direct mono-fluorination of indoles and arenes, with excellent functional group tolerance. It was observed that the polar-inner core of the spontaneously formed nanomicelles mimics polar aprotic organic solvents, while the relatively highly polar interface assists in dissolving the fluorinating reagent. This method was applied to gram scale reactions with good yields. It also allowed the recycling of the reaction medium for four overall cycles without globally affecting the outcome. Moreover, the low calculated *E* factor indicated that the process was suitable and environmentally friendly.

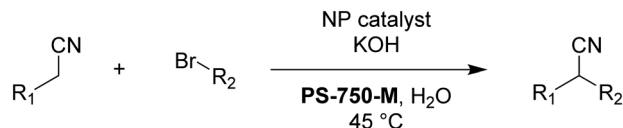
Surfactant PS-750-M was successfully employed in the preparation of ultrasmall palladium nanoparticles through reductive elimination of [XPhosPd(crotyl)Cl] under mildly basic aqueous conditions (Scheme 11).³⁸ The metal nanoparticles could then be stored preserving their catalytic properties or used *in situ*. Handa and co-workers exploited the obtained nanocatalyst in the α -arylation reaction of nitriles in aqueous micelles. Presumably, the micellar environment stabilizes the carbanion or keteniminate intermediates, shielding them from protonation by water.

Moreover, this method allows reactions between substrates bearing a wide range of functional groups with high yields (up to 92%), other than the possibility to accomplish multiple complimentary reactions in one-pot using the same catalyst, without the need to isolate the intermediates. By using water as a green reaction solvent, it was possible to avoid the use of hazardous organic solvents and to scale up the reactions, enabling the synthesis in large quantities of precursors for relevant pharmaceutical targets, showing the possibilities that this innovative synthetic pathway allows.

One important example illustrating the effect of the chiral properties of peptide-based designer surfactants is based on PRW-C₁₆, consisting of a sequence of L-proline, L-arginine and L-tryptophan with a hydrocarbon chain that was studied and applied for the stereoselective aldol condensation reactions between cyclohexanone and *p*-nitrobenzaldehyde in water (Scheme 12).³⁹



Scheme 10 Fluorination of indoles in position 3 of the aromatic compound by NFSI in water mediated by PS-750-M.



Scheme 11 α -Arylation of nitriles with aryl alkyl bromides in water catalyzed by ultrasmall Pd nanoparticles stabilized by PS-750-M.

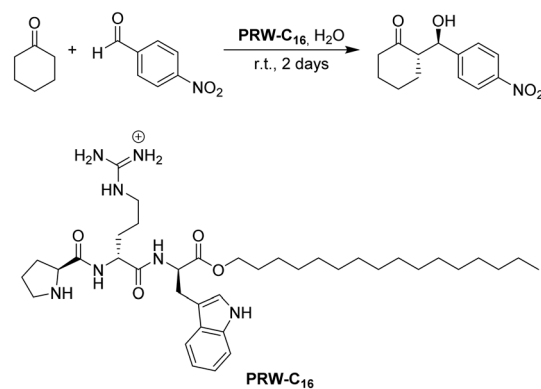
This surfactant showed the formation of spherical micelles with an average diameter of about 6 nm, where the peptide polar fragments are positively charged on the arginine amino acid. The catalytic activity of the lipopeptide-based micelles was tested observing that under optimized reaction conditions, high yields (up to >99%), good enantioselectivity (*e.e.* up to 85%) and high diastereoselectivity (*d.r.* up to 92:8) were obtained using as little as 5 mol% of catalyst. It was noted that the positioning of the catalytic groups at the lipopeptide/water solvent interface was responsible for the observed selectivity of the catalyzed aldol reactions.

Combination between metal catalysis and designer surfactants

A more common use of traditional surfactants and designer surfactants consists in providing an appropriate nano-environment to promote the intimate contact between reagents and metal catalysts. In this section, examples of reactions catalyzed by metal complexes and metal nanoparticles in designer surfactant micellar aggregates are reported, focusing on the crucial role played by the surfactant on the catalytic performance. In this case, most of the reported designer surfactants are neutral and characterized by PEG hydrophilic residues.

Transition metal catalysts and designer surfactants

An interesting new surfactant bearing a sugar unit for metal catalysis in water was described connecting a lactose hydrophilic unit to an aliphatic alkyl chain forming the alkyl



Scheme 12 Structure of the designer amphiphilic lipopeptide PRW-C₁₆ and its application in aldol condensation reactions.

lactosamine **ALA-14**, easily synthesized and naturally degradable for applications like the Ullmann type C–S coupling reaction in water mediated by copper salt (Scheme 13).⁴⁰

The lactose had the additional role of chelating the catalytic metal center, forming metallo-micelles that can be recycled and reused. This system provided good to excellent yields of the desired sulfone products in the coupling between aryl iodides and benzyl sulfinates. **ALA-14** was shown to promote the copper-catalysed Ullmann C–S coupling reaction in water with moderate-to-excellent yields with the possibility to efficiently recover both the surfactant and the water.

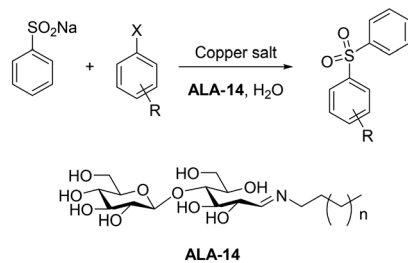
An interesting surfactant named **APGS-550-M** was recently proposed, characterized by an easily accessible hydrophobic portion available from the naturally abundant compound, rosin. The latter is isolated from exudates of pines, the production of which stands at one million metric tons per year (Scheme 14).⁴¹

The surfactant was successfully applied to the amidation reaction of alkynyl bromides catalyzed by copper in water, leading to the corresponding ynamide derivatives. In particular, the authors described the efficient and high yield synthesis of dozens of derivatives. The reaction was efficiently promoted, enabling the complete recycling of the surfactant and catalyst up to three times, thus promoting a marked decrease of the *E*-factor of the chemical transformation with average values between 5 and 11, including in the calculation of aqueous waste as well.

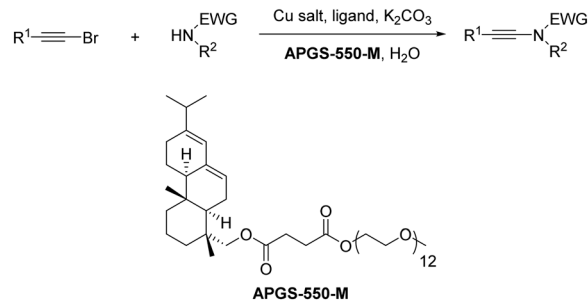
A similar derivative based on a slightly different hydrophobic rosin derivative, dehydroabietinol, and with a longer Me-PEG hydrophilic unit called **DAPGS-750-M** was also reported for oxidation reactions in water (Scheme 15).⁴²

This designer surfactant was specifically employed for the oxidation of tertiary alcohols to ketones in water through C–C β-scission in the presence of Bi(OTf)₃, AgNO₃ and K₂S₂O₈ under mild experimental conditions. The micellar catalytic method was extended to a wide range of possible substrates with the important advantage of simple product isolation and in-flask recycling of the aqueous phase.

The above reported neutral surfactant **PS-750-M** bearing a proline spacer in between hydrophilic PEG and hydrophobic C₁₁ portions, and that showed intrinsic catalytic activity, was tested also for applications in combination with transition



Scheme 13 Ullmann type C–S cross-coupling promoted by the new surfactant *N*-alkyl-lactosamine **ALA-14**.



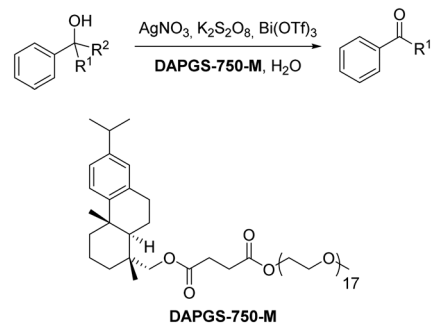
Scheme 14 Amidation reaction of alkynyl bromides catalyzed by copper in water in the presence of the new surfactant **APGS-550-M**.

metal catalysis in water with great success. Specifically, for C–C bond forming reactions, the new surfactant developed by the Handa group favored the Suzuki–Miyaura cross-couplings of 2- and 4-quinoline and isoquinoline substrates, showing interesting properties in terms of compatibility of the reaction with the presence of other functional groups (Scheme 16).⁴³

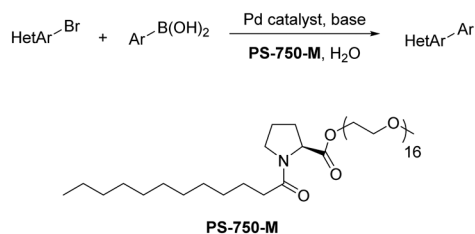
The authors investigated the self-assembly properties of the surfactants showing the formation of micelles with *ca.* 107 nm average diameter as confirmed by DLS analyses, with an increase in size up to *ca.* 229 nm when in the presence of 10 mM of 2-bromoquinoline. More importantly, the micellar aggregates stabilized the Pd complex with no decomposition even after several days at room temperature. Peculiar features of the micellar catalytic method were the low catalyst loading, the possibility to run reactions on a gram scale and the in-flask recycling of the π-allyl Pd catalyst and of the designer surfactant as well.

The surfactant promoted also the Pd catalyzed sp²–sp³ cross-coupling of nitroalkane derivatives with aryl bromides under mild experimental conditions (Scheme 17).⁴⁴

PS-750-M proved to be a noteworthy and environmentally benign surfactant to mimic polar solvents such as DMF and 1,4-dioxane. Its application in palladium-catalyzed sp²–sp³ coupling of nitroalkanes to aryl bromides using a heteroleptic palladium catalyst provided good yields of products up to gram scale, under very mild reaction conditions. Besides using water as the reaction medium, the employment of this



Scheme 15 Oxidation of tertiary alcohols with β-scission and formation of ketones mediated by the new surfactant **DAPGS-750-M** in water.



Scheme 16 Suzuki–Miyaura cross-coupling between boronic acids and 2- and 4-quinoline and isoquinoline bromides mediated by Pd complexes in water with the aid of **PS-750-M**.

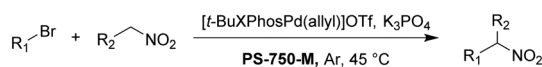
custom surfactant allowed in-flask recycling of the solvent and of the palladium catalyst as well.

One interesting application of the latter designer surfactant for C–N bond forming Buchwald–Hartwig aminations was reported using bimetallic micellar nanocatalysis (Scheme 18).⁴⁵

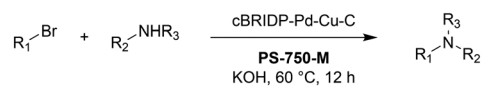
The role of the surfactant was to promote the synergy between Pd and Cu coordinated to the bulky phosphine ligand di-*tert*-butyl(2,2-diphenyl-1-methyl-1-cyclopropyl)-phosphine (cBRIDP) and the C surface, with positive effects on the catalytic activity related to their proximity on the solid heterogeneous support. Further analysis of the nanoparticles showed the association between the catalyst and the hydrophobic portion of the surfactant, which gave rise to a nest-like morphology of the aggregate. This method was found to be effective with a wide variety of substrates, allowing overall good-to-excellent yields. This custom catalyst has proven to be stable under ambient conditions for at least six months. Moreover, the possibility to recycle the catalyst and the reaction medium underlined the relevant utility of this approach.

An interesting effect of the specific micellar environments provided by **PS-750-M** was reported for the stabilization of Ni(0) species in water, which are usually incompatible with this medium. In fact, it was in the presence of **PS-750-M** that the formation of porous microballs containing Ni(0) nanoparticles was possible, thus further promoting highly selective micellar catalysis in water (Scheme 19).⁴⁶

These aggregates, aided by a minimal amount of Pd in water to prevent oxidation of Ni(0) nanoparticles, were applied in highly selective carbamate cleavage leading to the formation of secondary amines. It was observed that the proline-based **PS-750-M** plays a central role in achieving the microball architecture contributing to the *in situ* stability of such aggregates, with consequent desired catalytic activity. The catalytic system led to good solubility of hydrogen in the micellar interior, where metal nanoparticles are embedded,



Scheme 17 Cross coupling reaction between nitroalkane derivatives and aryl bromides catalyzed by Pd complexes in water mediated by **PS-750-M**.



Scheme 18 Buchwald–Hartwig amination mediated by Pd and Cu catalysts in water in the presence of **PS-750-M**.

thus enhancing the catalytic properties. It was shown that the use of sodium borohydride in place of hydrogen did not affect the overall yield, even though the formed reducing agent is not preferred due to a much lower atom economy. This novel nano catalyst showed high selectivity, not affecting other highly sensitive functional groups such as nitrile, carbonyl, olefin, and benzyl present in the substrate molecule.

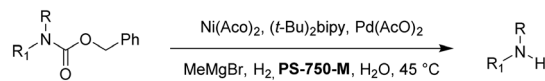
Even carbene based reactions could be promoted in water with the aid of **PS-750-M**, as disclosed in a recent example dealing with Pd nanoparticles in water (Scheme 20).⁴⁷

In this reaction, the role of the surfactant consisted in acting as a ligand for Pd nanoparticles, aided by inexpensive triphenylphosphine, to form aggregates suitable for exploring the reactivity of carbenes in aqueous nanomicelles. The additional role of the amphiphile **PS-750-M** was to shield the *in situ* generated carbene to prevent its dimerization, thus allowing it to be used to access useful precursors. The catalyst was highly selective for metal-carbene migratory insertion and it showed good yields for a wide variety of functionalised products such as cyclic olefins from different coupling partners, allowing large scale reactions. Moreover, no remarkable loss in activity was observed, therefore suggesting complete recovery of both the catalyst and micellar medium for up to four times.

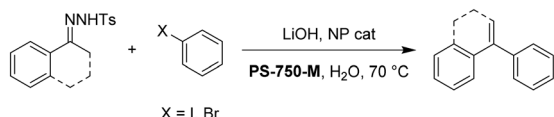
Very recently the group of Beverina introduced new neutral surfactants, **BTBT-750-M** and **PiNap-750-M**, based on extended aromatic units connected to aliphatic alkyl chains and PEG units as hydrophobic and hydrophilic portions of the surfactant (Scheme 21).⁴⁸

The new surfactants were specifically designed to be tested for the preparation of highly conjugated target derivatives of [1]benzothieno[3,2-*b*][1]benzothiophene (**BTBT**), a p-type organic semiconductor which is poorly soluble in water. With these new amphiphilic species, the efficient synthesis of organic semiconductors by Suzuki–Miyaura coupling in an aromatic micellar medium was reported, observing that **PiNap-750-M**, in particular, enabled the Suzuki cross-coupling reactions in the absence of a co-solvent, at room temperature, and widely decreasing the reaction times with respect to other known methods.

A designer neutral surfactant stearyl methoxy-PEG-glycol succinate (**SMPS**) was recently reported comprising a C₁₈ long aliphatic alkyl chain connected through a bis-carboxylic acid



Scheme 19 Carbamate deprotection leading to amines mediated by Ni(0) metal catalysts in water enabled by the presence of **PS-750-M**.



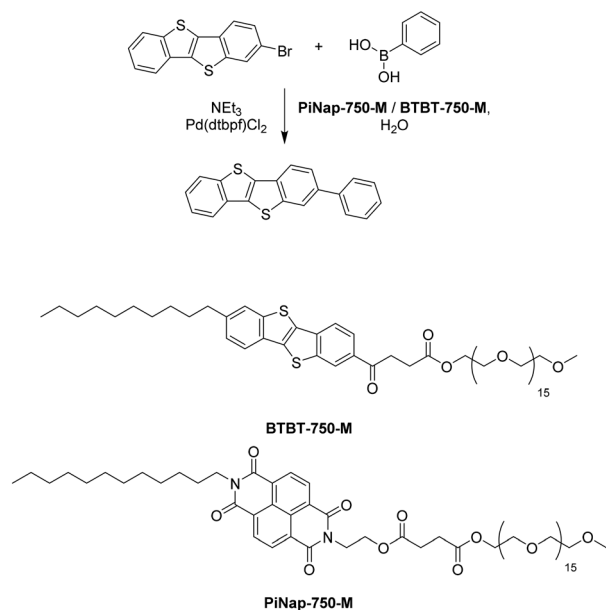
Scheme 20 PS-750-M promoted reaction between *N*-tosylhydrazones and aryl halides via formation of intermediate carbene species.

to a PEG unit for metal catalyzed organic transformations in water (Scheme 22).⁴⁹

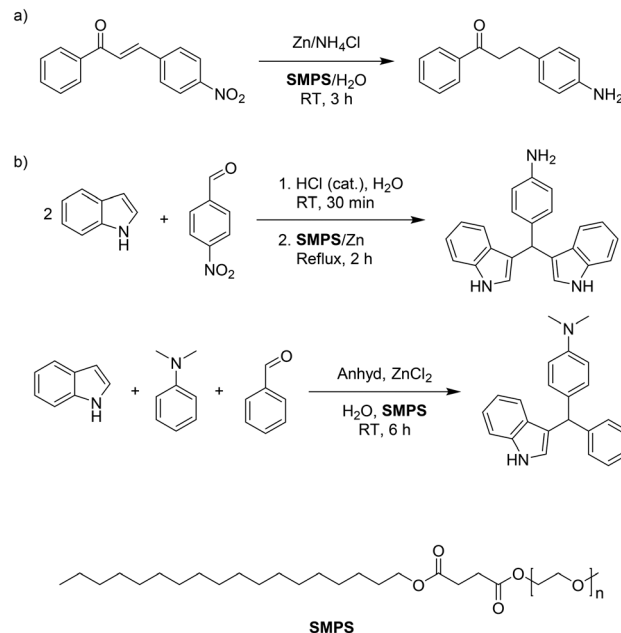
Excellence in organic transformation was reported through the reduction of lipophilic nitroarenes and through the syntheses of aniline tethered indole derivatives with good-to-excellent yields. Using this new methodology, iterative stepwise synthesis and the use of harmful organic solvents were circumvented. Moreover, **SMPS** was demonstrated to be non-toxic as a consequence of phytotoxicity, bacteria toxicity, and aquatic toxicity assays, thus further spurring its future uses.

Further successful applications of this promising new designer surfactant are the Pd catalyzed cross-coupling Heck reactions reported in Scheme 23.⁵⁰

Specifically, **SMPS** was explored for the transformation of a series of anilines to the corresponding densely substituted biologically relevant skatole derivatives in an aqueous medium via *5-exo-trig* cyclization reactions. The scope of the reaction was further extended to intermolecular Csp²-Csp² and Csp²-N bond forming reactions in water. Systematic investigations revealed that the increase of the hydrophobicity of the surfactant influenced positively the yield of both C-C and C-N bond forming reactions in water.



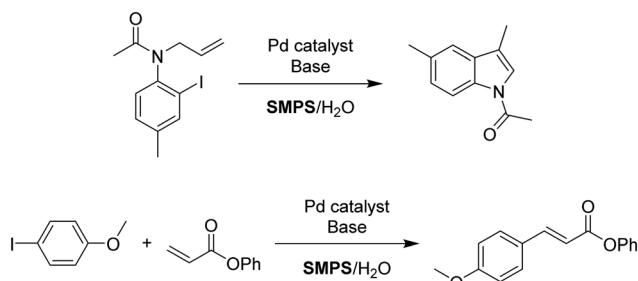
Scheme 21 Extended aromatic based designer surfactants BTBT-750-M and PiNap-750-M for Suzuki-Miyaura cross-coupling for the synthesis of p-type organic semiconductors in water.



Scheme 22 Applications of **SMPS** a) in the selective reduction of unsaturated ketones and b) in a multicomponent reaction for the preparation of mono and bis-indolyl derivatives.

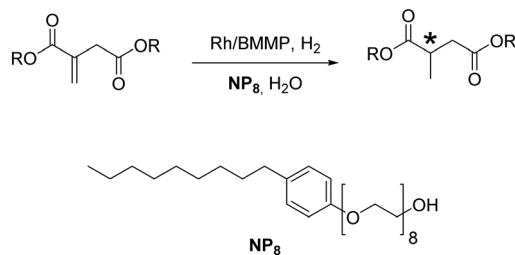
A further important advantage of the use of micellar media with transition metal catalysis consists of simplified catalyst recycling. An important example was recently reported for the stereoselective hydrogenation of itaconic acid and ester derivatives mediated by a Rh/BPPM catalyst. For this specific target, a new designer surfactant named **NP₈** was developed based on an aromatic central spacer connected to an aliphatic hydrophobic alkyl chain and a simple PEG hydrophilic portion. The chiral metal catalyst was efficiently recycled through cloud point extraction (CPE) from aqueous micellar solutions of the nonionic surfactant **NP₈** and reused in subsequent reactions (Scheme 24).⁵¹ While for substrates with free acid moieties the activity was severely affected, for itaconic esters the reaction was very efficient and recycling was almost quantitative, with ~96% of the metal recovered.

Only a few ionic designer surfactants have been described for catalysis attributed to metal species, as reported below. One example is based on polymer-colloidal complexes where



Scheme 23 Application of **SMPS** to the Pd catalyzed intramolecular and intermolecular Csp²-Csp² cross-coupling reactions in water.

Mini review

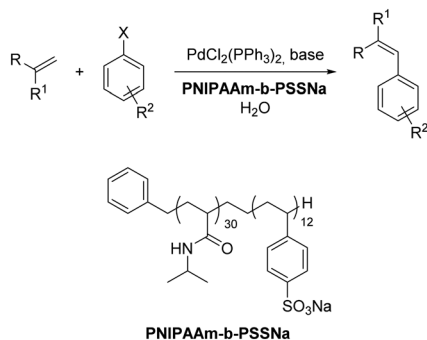


Scheme 24 Efficient catalyst recycling through cloud point extraction for the stereoselective hydrogenation of itaconic acid derivatives with chiral Rh catalysts in water mediated by NP₈ as a surfactant.

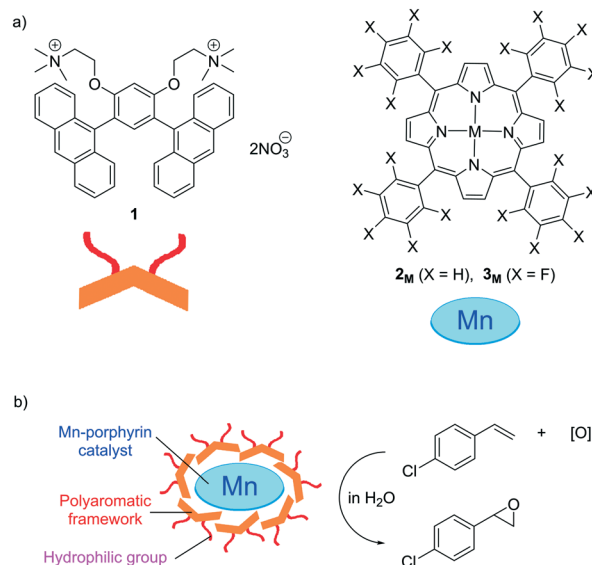
the polymer is composed by two domains characterized by opposite hydrophilicity and hydrophobicity. In some cases, block co-polymers are used in place of molecular surfactants to promote the contact between catalyst and substrates and to reversibly modulate aggregation to favor extraction and product separation. A recent example for the palladium-catalyzed Mizoroki–Heck reactions in water was reported based on thermo-responsive polymer micelles **PNIPAAm-*b*-PSSNa** containing sulfonate moieties (Scheme 25).⁵²

The micelles were generated from thermo-responsive block copolymers consisting of a poly(*N*-isopropylacrylamide) (**PNIPAAm**) segment and a hydrophilic segment such as nonionic poly(ethylene glycol) (PEG) and anionic poly(sodium *p*-styrenesulfonate) (**PSSNa**) leading to aggregation at higher temperature corresponding to the experimental conditions for the cross-coupling reactions, while at lower temperature efficient extraction of the products from the aqueous reaction mixture was possible, thus providing an extra feature with respect to classical surfactants.

Alternatively, while traditional surfactants are characterized by large polar head-groups and narrow apolar chains, a reverse approach has been introduced recently by the group of Yoshizawa, that disclosed a series of charged and neutral amphiphilic new molecules based on rigid large polycyclic aromatic panels connected to small polar side chains leading to a wide range of pseudo-spherical assemblies in water.⁵³ Such nanocontainers showed impressive host-guest properties towards apolar guests. In



Scheme 25 Palladium-catalyzed Mizoroki–Heck reaction mediated by a Pd catalyst in water in the presence of amphiphilic copolymer **PNIPAAm-*b*-PSSNa** in water.



Scheme 26 a) Chemical structure of the rigid aromatic amphiphilic cationic designer surfactant **1** and the Mn-porphyrin catalysts **2_M** and **3_M** tested; b) cartoon representation of the nano-capsule formed in water from **1** and the hosting of the oxidation catalyst to promote the epoxidation of styrene derivatives with enhanced TON.

particular, the group reported an interesting application of one of these nanocontainers based on a new cationic aromatic surfactant bearing a bis-anthracene framework **1** reported in Scheme 26, that was exploited to improve the catalytic activity of an epoxidation catalyst.⁵⁴

In particular, the reported Mn-porphyrin catalyst was encapsulated within the water soluble polycationic self-assembled capsule by grinding and subsequent water addition. The catalytic system showed enhanced catalytic activity with a turnover number of up to 1350 for 1 h, even without the aid of axial imidazole ligands under ambient experimental conditions. The role of the nanocontainer was to stabilize the catalyst and to promote through the hydrophobic effect its interaction with styrene as a substrate and to favour the release of the more hydrophilic styrene oxide product. Support of such mechanistic advantages was provided by means of spectroscopic studies and competitive-binding experiments.

Conclusions

In summary, we presented recent trends and achievements in the preparation and application of designer surfactants for catalytic transformations in water as a new promising direction in micellar catalysis. Surely, the near future will show many more examples in this specific research field, hoping that one day catalysis in water will surpass catalysis in organic media. Firstly, more effort is required also to design new surfactants from renewable resources,⁵⁵ in particular considering the chiral pool of molecules available from Nature and the possibility to obtain chiral surfactants. Future directions will consider the surfactant not any more

as a static unit but as examples of modulable surfactants in terms of aggregation properties as a function of external stimuli like temperature,⁵⁶ pH, light,⁵⁷ and electric and magnetic fields.⁵⁸ Another promising approach consists in the *in situ* formation of surfactants from combinations of sub-units,⁵⁹ thus largely amplifying the number of new possible surfactants. All these new ideas, applied to designer surfactants for catalysis in water, will help to truly transform micellar aggregates more and more into active nanoreactors,⁶⁰ with the aim of mimicking one day enzymatic catalysis.

Conflicts of interest

There are no conflicts to declare.

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