Nanoconfinement Effects of Micellar Media in Asymmetric Catalysis

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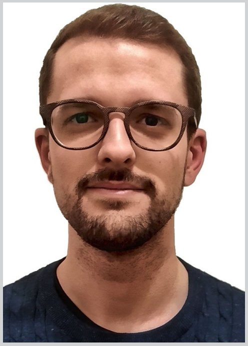
Abstract: Replacement of organic solvents, in particular chlorinated, aromatic, and polar aprotic ones, is an emerging issue that can find a solution in the development of catalytic reactions in water. Nature performs a multitude of chemical transformations in water under mild conditions mediated by enzymes. In particular the nanoconfinement effects of the enzymes ensure high activity and impressive stereoselectivities. Micellar catalysis is nowadays a real alternative approach to catalysis in traditional organic media, enabling good activity under mild conditions, with the advantage of possible catalyst and micellar medium recycling. Micellar media emerged also as good nano-environments for stereoselective reactions, with many examples of chemical transformations mediated by metal and organo-catalysts for which improvements of stereoselectivity were observed with respect to the same reaction under homogeneous conditions in traditional organic solvents. More specifically, both the catalytically active site and the micelles provided by the surfactant can contribute to the asymmetric induction, partially resembling what known in terms of stereoselectivity imparted by the active site of enzymes and metallo-enzymes.

Keywords: Asymmetric Catalysis; Water; Stereoselective Reactions; Surfactants; Organocatalysis

1. Introduction

Solvents are fundamental species involved in most chemical reactions, in particular to favor good contact and mixing between all the reagents and catalysts, to control heat exchange and homogeneity of the temperature, and to facilitate all the post-reaction manipulations. Solvents are also fundamental in the selectivity issues of chemical transformations, stabilizing reaction intermediates and transition states thus steering the chemo-, regio- and in particular stereo-selectivity.[1] Therefore, solvents have a prime role in chemical transformations, and for many years in the last century solvents were ubiquitously employed, even though not always unavoidable. Chemical transformations from academia to pharmaceutical synthesis in large plants is witnessing a revolution spurred by several factors like stringent safety and environmental requirements,[2] growing awareness of the public opinion about sustainability, and the desire to re-invent chemistry for the future generations. With the increasing implementation of the 12 principles of green chemistry in everyday chemical practice, more attention has been paid to the minimization of the use of toxic solvents favoring the flourishment of solvent-free reactions. The well-known concept "Best solvent is no solvent!"[3] introduced by Sheldon some years ago was initially a counterintuitive approach, while today it



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represents one viable option in particular in industrial applications thanks to the development of mechanochemistry.[4] Solvents in fact represent almost 60% of the mass of chemicals in the pharmaceutical chemical industries and they also contribute heavily to the waste amount formation,[5] negatively affecting green metrics like E factor, PMI[6] and others.[7]

Proper solvent selection is the first target of every process aiming at the improvement of the sustainability; in fact, over the years a series of review articles discussing different approaches for solvent picking were published,[8] favoring the real replacement of toxic solvents like chlorinated and aromatic ones with others less harmful,[9,10] especially under the impulse provided by pharmaceutical companies.[11] Green solvents[12] have been proposed over the years like ionic liquids,[13] deep eutectic solvents,[14] biobased solvents to improve defossilization,[15] some of which leading also to industrial applications. Among all, thanks to its low cost, large availability, high heat capacity and non-flammability, water is gaining momentum as a true sustainable solvent for chemical transformations,[16] and in general as medium for organic chemistry.[17] Confinement effects are also gaining momentum in catalysis, in particular under the point of view of sustainable chemical transformations,[18] due to the peculiar features that the control of the second solvation sphere of the catalyst can provide. Catalysis in water under micellar conditions[19] is a direct evolution of catalysis in water or on water,[20] in which surfactants are added to cope between the low solubility of organic reagents and metal catalysts.[21] Micelles and specifically many other aggregation systems provide self-assembled nanoenvironments and nanoreactors[22] in which higher local concentration, peculiar solvation properties and unique features are possible (Figure 1),[23] for chemical as well as photochemical transformations.[24] Surfactant aggregates are morphologically reminiscent of nanoparticles, in terms of radial organization, but with a much less defined structure. In this class of nano-reactors and nano-environments substrate distribution is affected by

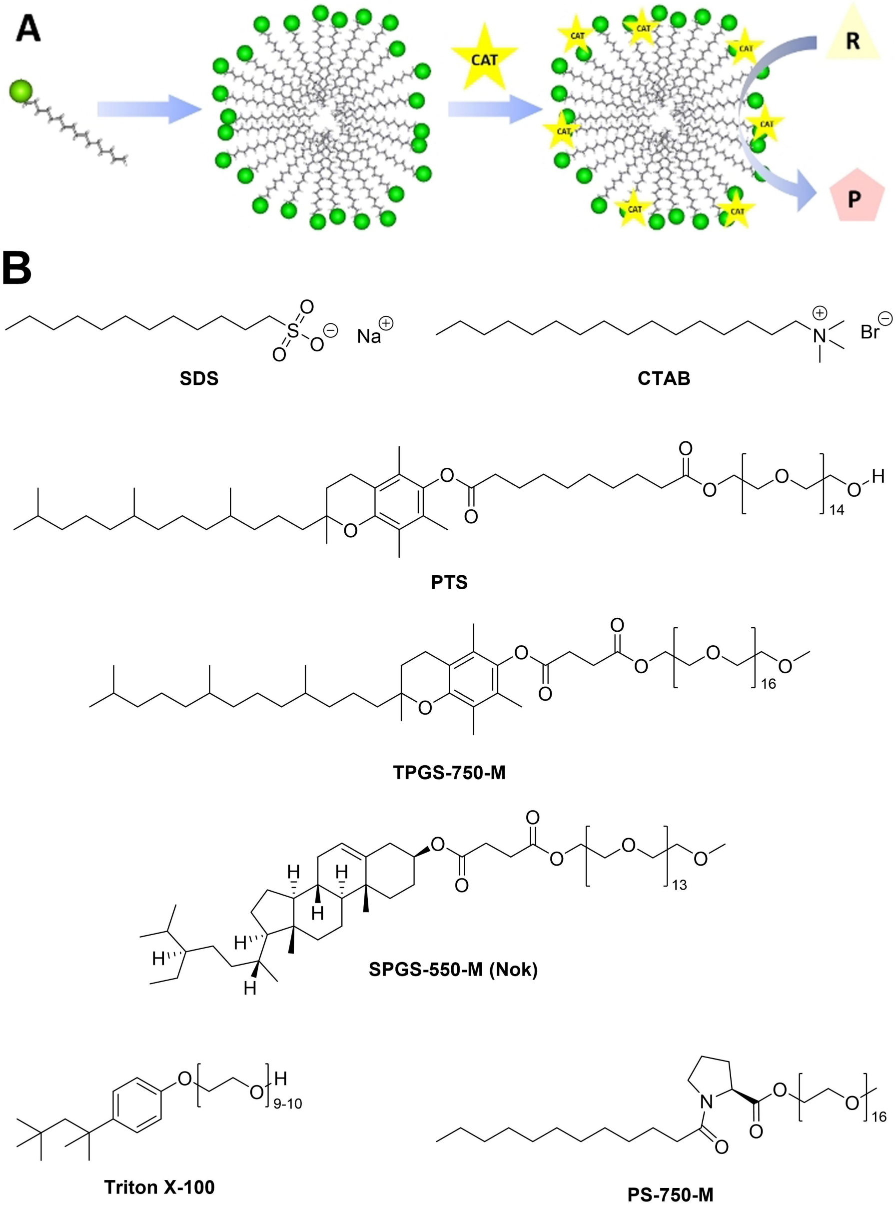


Figure 1. A) Self-aggregation in water driven by the hydrophobic effect of amphiphilic surfactants provide micelles and other aggregates that represent the nano-environment in which substrates and catalyst are in close contact; B) examples of commercially available traditional surfactants and recent designer surfactants employed for asymmetric catalytic reaction under micellar conditions.

many parameters like micelle size, concentration and many other leading to a large variability of media.[25] Micelles present the better cost-benefit ratio since surfactant synthesis is usually straightforward and aggregates formation simply requires the mixing of the components.The hydrophobic effect, as the most powerful driving force for aggregation in water,[26] promotes confinement effects, drives proper orientation and substrate selection that resemble, albeit in a much simpler system, enzymes. In fact, micellar catalysis can be considered one of the many strategies of supramolecular catalysis[27,28] for which recognition and confinement effects[29,30] are fundamental tools for mimicking enzymatic catalysis. In the recent years many kinds of chemical transformations are possible under micellar conditions[31] and the scientific community is becoming more and more aware of the opportunities offered by the use of surfactants in water for chemical transformations, in particular under the green chemistry and sustainability point of view.[32]

The use of micellar media not only entails the advantages arising from water, being an environmentally benign solvent, but also other advantages of micellar catalysis[33,34] are related to the opportunity to recycle the catalytic system especially for reactions involving products that are more hydrophobic than the reagents, or the micellar medium, thus improving largely the sustainability of the process.[35,36] More importantly, the field of micellar catalysis has been further spurred to real possible industrial applications also by the development of the so-called designer surfactants introduced by Lipshutz some years ago[37] as amphiphilic compounds, mostly from renewable resources, specifically designed and successfully applied in catalysis in micellar media[26,38,39] leading to unprecedent improvements in terms of efficiency under simplified and milder experimental conditions. Examples of successful commercialization of designer surfactants are TPGS-750-M,[40] Nok[41] and PS-750-M[42] (Figure 1B) thanks to their versatility in a wide range of metal catalyzed reactions in water. In the very recent years many more designer surfactants have been proposed[43] making the transition from organic media to water based media even more straightforward. Micellar catalysis is nowadays a real green alternative[44] to the use of organic media, in fact examples of large scale applications and involvements of pharmaceutical companies in the development of robust methods is a today's reality,[45,46,47,48] also in the context of waste-water management.[49] Micellar media have been successfully explored recently also for the synthesis of some drug candidates[50] specifically on workhorse reactions like Suzuki-Miyaura and Sonogashira couplings, Miyaura borylation, transition-metal-catalyzed CAr–N coupling, SNAr, amidation, and nitro reduction.

One specific field of micellar catalysis that has been so far only marginally investigated is catalytic stereoselective reactions (Figure 2). Stereoselective catalysis is in fact a fundamental field of research that finds large applications in the pharmaceutical industry, in fact 56% of the drugs currently in use are chiral products.[51] Although they have the same chemical structure, most enantiomers of racemic drugs exhibit marked differences in biological activities such as pharmacology, toxicology, pharmacokinetics, metabolism. After the tragic event of thalidomide in the 50's, all the stereochemical aspects of drugs are deeply investigated for all new drugs developed and released in the market.[52] Although many methods are possible for the preparation of enantio-enriched molecules, pharmaceutical industries often prefer to obtain the racemic mixture and resolve the enantiomers with the aid of chiral resolving agents. In better and most atom economic cases, the desired enantiomers are prepared from prochiral reagents using stereoselective catalysis, with the great economic and technical advantage of using minimal amounts of chiral species. Stereoselective catalysis has reached outstanding targets and in the recent years it is evolving taking into consideration sustainability and green principles.

The stereoselectivity of reactions is often very sensitive to solvent and temperature conditions. Even though examples of stereoselective catalytic reactions

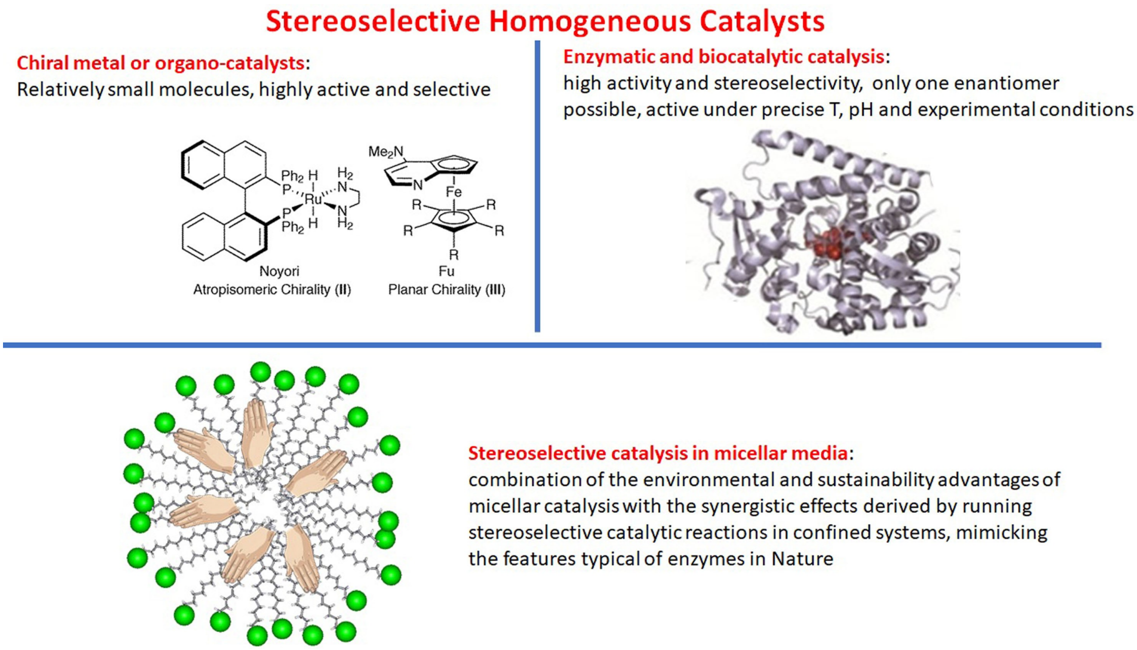


Figure 2. Comparison between stereoselective metal catalysis, enzymatic and biocatalytic stereoselective catalysis and stereoselective catalysis in micellar media.

under solvent free conditions are known,[53] the use of solvents for this kind of selective reactions remains the simplest approach to better control all reaction parameters and to ensure reproducibility and high stereoselectivity. When dealing with stereoselective catalysis, one highly efficient approach consists in the use of biocatalytic methods that ensure high enantiomeric excess often under aqueous conditions or using less harmful solvents. Nevertheless, traditional stereoselective metal or organic catalysts rival with biocatalytic methods due to the intrinsic advantage to be in many cases available in both enantiomers leading to both possible configurations of the new stereocenter created in the reaction. Furthermore, biocatalytic stereoselective methods often can be carried out with rather low substrate concentrations, which limits the productivity of the process. Overall, it is estimated that in the pharmaceutical industry stereoselective reactions are carried out preferably with chemical methods. It is also important to remark that for large scale stereoselective catalytic productions in industry organic solvents are still fundamental.

Examples of stereoselective catalytic reaction in micellar media are therefore covered in this perspective article, whose content has never been thoroughly reviewed in the literature. One of the main aims of the article is to convince about the great improvements in sustainability offered by the micellar media in place of organic media, also underlying the frequent synergy that exists between the confinement effects provided by micelles and the level of observed stereocontrol. In fact, other examples of organized media that influence the stereocontrol of chemical transformations are known, for instance reaction under liquid crystal or gel conditions[54] or reactions within supramolecular systems.[55] Among all, the intrinsic simplicity of micellar catalysis and the wide combination of catalyst, surfactant, experimental conditions, represent a still largely unexplored field of research that is fundamental to disseminate in the scientific community. Moreover, synergistic effects could be advisable using also chiral surfactants, in which the chirality of the hydrophobic nanoreactor resembles the chirality of the active site of enzymes. In this perspective this review classifies the literature since 2000 concerning stereoselective catalytic reactions under micellar conditions based on the chirality of the catalyst, surfactant, and furthermore on the nature of the catalyst either metal or organic, with a particular focus on new directions in the field.

2. Classification of Stereoselective Reactions in Micellar Media

Micelles represent the nano-environments where catalytic reactions take place; depending on the size, shape, polarity, and functional groups of the substrates as well as those of the catalyst, the reaction takes place in different positions of the aggregates. For instance, charged catalysts tend to be easily solubilized in water by surfactants, that may act as counter-anions, thus operating on the surface of the micelles. On the contrary, catalysts endowed with largely apolar ligands are more easily accommodated in the apolar core of the self-assembled nanoreactors, where they operate in a different surrounding. For asymmetric induction, the chiral unit usually is positioned on the active metal center, therefore most of the examples discussed in this perspective are related to stereoselective catalysis in micellar media using achiral surfactants. Nevertheless, chiral surfactants provide chiral micelles in which the asymmetry provided by the aggregate can induce a certain level of stereoselectivity also using achiral catalysts, or synergistic effects are possible with chiral catalysts. Stereoselective catalysts can be classified in terms of metal containing or purely organic nature of the catalyst and a further possibility to enhance the catalytic performance under micellar conditions consists in covalently conjugating active chiral catalyst, either organic or metal based species, with hydrophobic tails leading to amphiphilic metallo-surfactants or organo-surfactants that provide the corresponding chiral micelles (Figure 3). All these different approaches are described and discussed.

It is worth to notice for instance that micellar media, thanks to their ordered nanoenvironments, showed good selectivity also in reactions that provide diastereoisomeric products.

3. Achiral Surfactants with Chiral Catalysts

The first classification regards asymmetric catalytic reactions with achiral micelles. This is the most widely investigated class of stereoselective reactions under micellar conditions in which chiral catalysts are used in water with often commercially available achiral surfactants. As a driving force for the solubilization in water of the chiral catalysts, often developed to operate in organic media, charged surfactants that act as counter-anions for the chiral metal catalysts were employed. In most cases, anionic micelles are adorned with chiral cationic metal catalysts as counter-ions. Alternatively, when the chiral ligands are characterized by extended aromatic surfaces the catalyst can be more deeply hosted in the apolar core of the micelles.

3.1. Chiral metal catalysts

The green enantioselective reduction of aryl/heteroaryl ketones with PMHS was efficiently performed in an aqueous micellar medium via copper-catalyst bearing a dodecamethoxy-modified (*R*)-MeO-BIPHEP as chiral

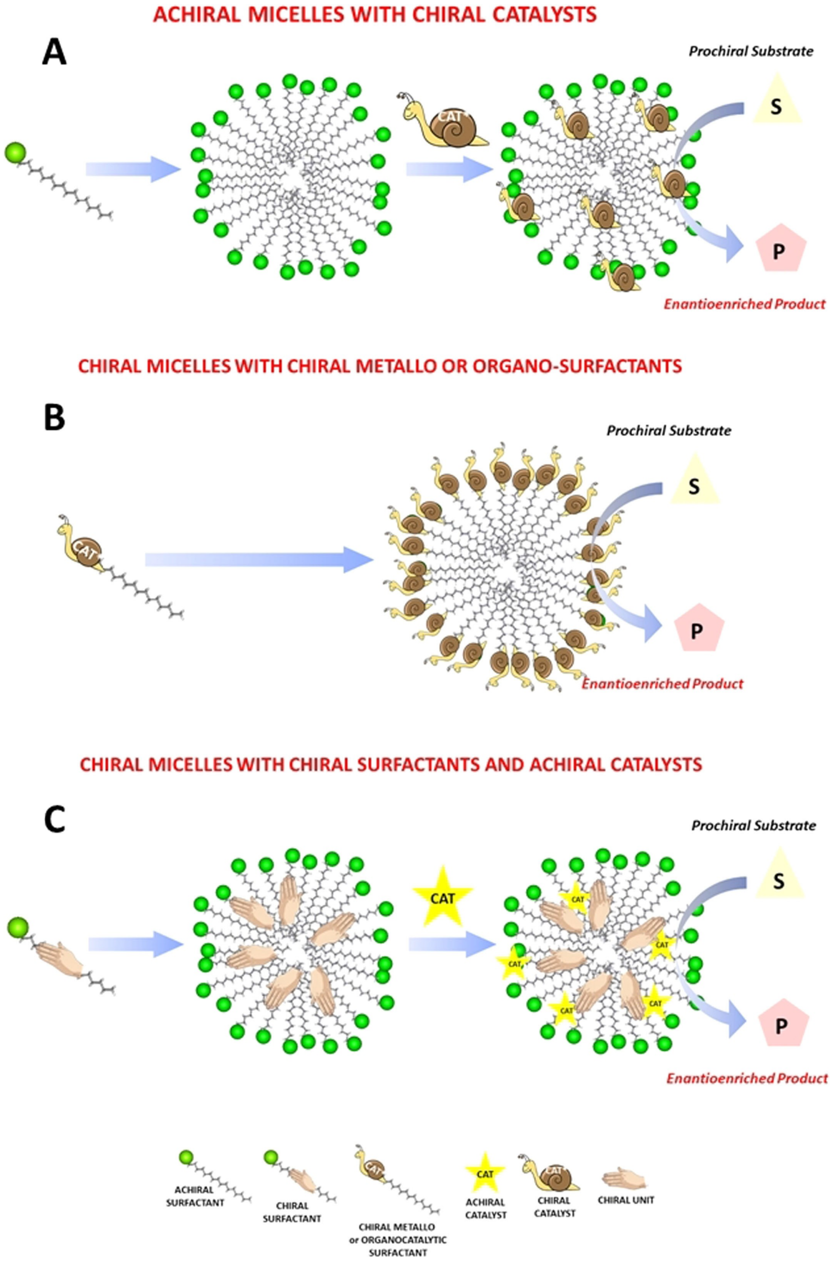
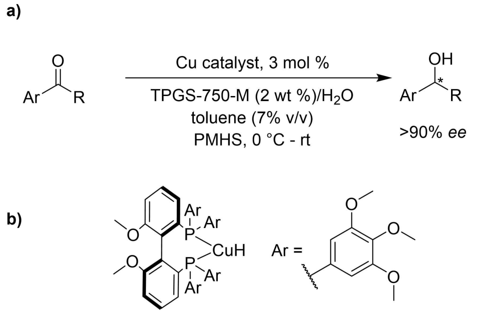


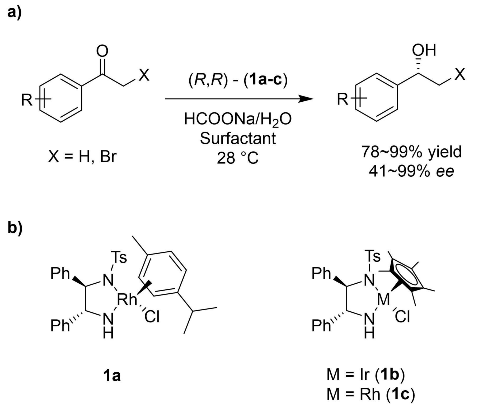
Figure 3. Different approaches to stereoselective catalysis in micellar media: A) chiral micelles with achiral surfactants and chiral catalysts; B) Chiral micelles with chiral metallo- or organo-surfactants; C) Chiral micelles with chiral surfactants and achiral catalysts.

ligand under mild experimental conditions using PMHS as inexpensive hydride source using TPGS-750-M as surfactant, in the presence of small amounts of toluene as cosolvent (Scheme 1).[56] The conversion of prochiral aryl and heteroaryl ketones bearing either electron-donating or electron-withdrawing groups to the corresponding enantioenriched secondary alcohols was performed with yields higher than 90% and *ee* > 90%.

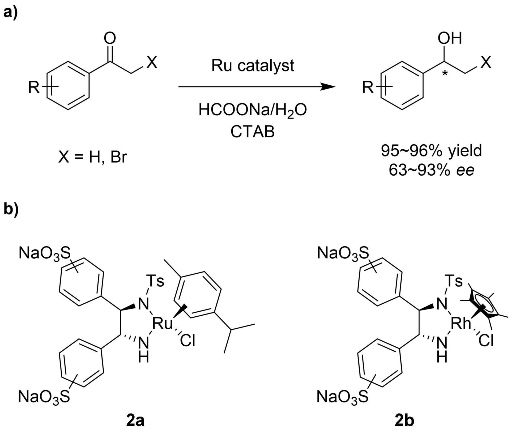
An interesting example of asymmetric transfer hydrogenation of ketones, especially α-bromomethyl aromatic ketones was achieved employing sodium formate as hydride donor, the hydrophobic transition metal-amido chiral catalysts TsDPEN–M (**1 a**–**c**), in the presence of surfactants (Scheme 2).[57] The chemical nature of the micellar medium influenced heavily the reaction, with anionic surfactant like SDS leading to lower reactivities, as compared to the control reaction without surfactant, because of the electrostatic repulsion between the charged polar head of the micelles and the reagent formate anion. On the other hand, the employment of CTAB showed an increase of



Scheme 1. Copper-catalyzed asymmetric reduction of aryl/heteroaryl ketones to the corresponding secondary alcohols mediated by TPGS-750-M in water.



Scheme 2. Asymmetric transfer hydrogenation of aryl-ketones (a), catalysts structures (b).



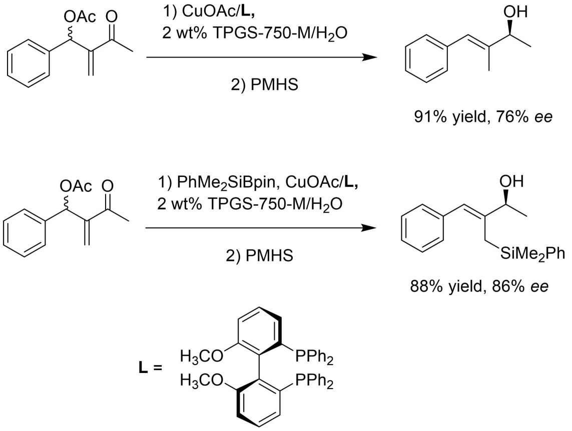
Scheme 3. Asymmetric transfer hydrogenation of aryl-ketones in cationic micellar media (a), Ru catalysts structures **2a** and **2b** (b).

TON thanks to the proximity of the cationic portion of the surfactant and the hydride donor, due to their opposite charges. The reactions were carried out in aqueous medium containing micelles and vesicles of CTAB and SDS (1:2 molar ratio respectively) that proved to be the best combination. This procedure allowed to obtain products with significant enhancement of chemo-selectivity, yields up to 97% and *ee* up to 99%. Moreover, the hydrophobic catalyst embedded in micelle formed by the surfactants, could be separated from the organic phase along with the products and recycled for at least six times. This work showed that micellar systems can be tuned appropriately, even combining different types of surfactants in order to optimize the overall efficiency.

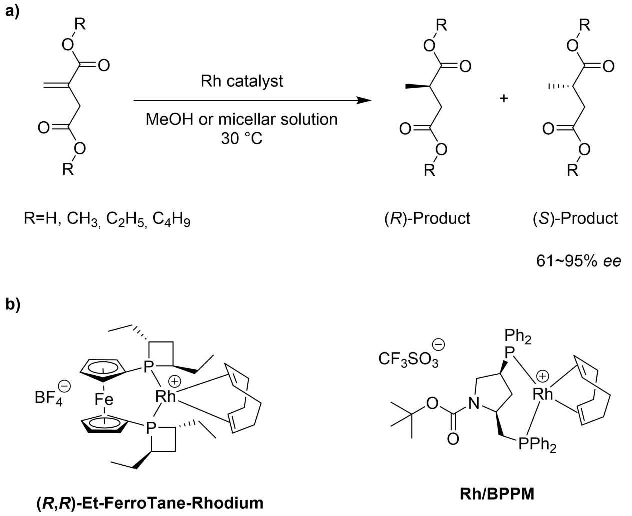
As a further example of asymmetric transfer hydrogenation in micellar media with cationic surfactant, the Rh catalysts bearing a sulfonated derivative of the chiral ligands reported in Scheme 2 allowed to achieve a considerable enhancement of activity with excellent catalytic performance and broad scope of aromatic ketones (Scheme 3).[58] Moreover, when employing α-bromomethyl aromatic ketones, the system allowed to maintain the bromine group intact, with excellent enantioselectivities (up to 96% *ee*). This may be caused by accelerated displacement of formate ions from aqueous solution to the micellar phases. The water-soluble ligands employed in the work were successfully and easily prepared via classical sulfonation and successive tosylation. The *bis*-meta-sulphonated ligand was detected as the major product, but mixture of ligands displayed equal catalytic performance compared with the pure one, avoiding an unnecessary purification. The catalyst could also be reused at least 21 times without loss of conversion and enantioselectivity further demonstrating the great advantages of the micellar media for catalyst recycling.

An example of efficient asymmetric tandem allylic substitution/1,2-reduction of racemic Morita-Baylis-Hillman acetates was effectively performed employing copper hydride coordinated with enantiopure chiral ligands (Scheme 4).[59] In this reaction it was possible to obtain enantio-enriched allylic alcohols under TPGS-750-M micellar conditions, using PMHS as hydride source, with similar yields albeit with lower stereoselectivity respect to organic media.

As a further example of reduction reaction, the catalytic hydrogenation of itaconic acid and dimethyl itaconate was successfully performed in water rather than in methanol exploiting the use of several surfactants like SDS and Triton X-100 using Rh/BPPM and (*R*,*R*)-Et-FerroTane-Rhodium as catalysts (Scheme 5).[60] The selectivity achieved is comparable to the traditional procedure performed in methanol (up to 95%). Repetitive semi-batch runs demonstrated the possibility to achieve a high TON of over 1000 without any deactivation of catalyst, that was further recycled using micellar enhanced ultrafiltration. Inhibition effects were observed for instance with Triton X-100 due to the presence of functional groups that could act as competitors for the binding site of the catalyst.



Scheme 4. Copper hydride tandem allylic substitution/asymmetric 1,2-reductions of racemic Morita–Baylis–Hillman substrates leading to chiral allyl alcohol derivatives in TPGS-750-M micellar media.



Scheme 5. Hydrogenation reaction of itaconates (a) and Rh(I) catalyst structures (b).

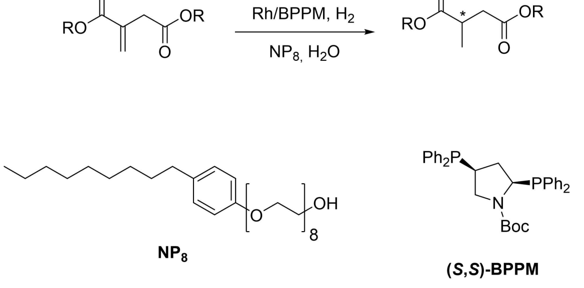
Using the Conductor-like Screening Model for Real Solvents (COSMO-RS) it was possible to predict the partition coefficient in order to optimize the different performances of the various tested micellar systems. Therefore, it was possible to choose the right surfactant as alternative reaction medium to reach good performance. In fact, more hydrophilic substrates are suitable to be treated with classic micelles, while reverse micelles were convenient when working with hydrophobic substrates. The right selection between normal or reverse micelles is indeed essential due to the use of the membrane that allows ultrafiltration of just the products, leaving catalysts and micelles in the reactor.

An example of highly efficient recycling of a stereoselective catalyst was provided by the asymmetric reduction of itaconic esters with Rh-BMMP as catalyst. The employed surfactant was named $\mathbf{NP_8}$ and it consists in an aromatic central spacer connected to an hydrophobic alkyl chain and a hydrophilic PEG unit, which enabled cloud point extraction (CPE) of the reaction product from the aqueous micellar solutions containing the chiral catalyst with ~96% of metal recovered (Scheme 6).[61] The stereoselective hydrogenation was very efficient with quantitative yields and high enantiomeric excess 92–96%.

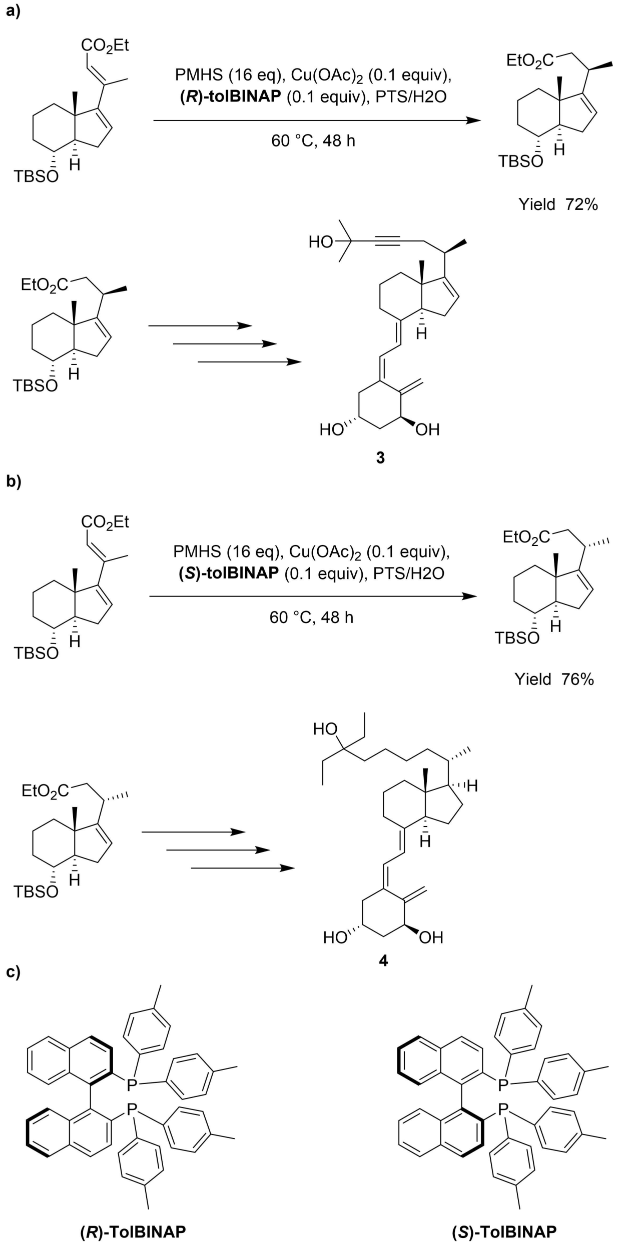
The employment of micellar condition was crucial to achieve two analogs of calcitriol (Scheme 7).[62] In this synthetic step which determines the stereochemistry of the methyl group of the target molecule, the asymmetric catalytic reduction of an *α,β,γ,δ*-unsaturated ester with CuH was performed employing polyoxyethanyl-*α*-tocopheryl sebacate (PTS) as surfactant. The catalyst employed was Cu-(*R*)-tolBINAP for the synthesis of **3** and Cu-(*S*)-tolBINAP the synthesis of **4** leading respectively to 72% and 76% yields.

The asymmetric hydrosilylation reactions of *β,β*-disubstituted Michael acceptors was achieved under mild conditions, at room temperature, exploiting micellar catalysis in water thanks to the combination of the rather inexpensive silane PMHS, atropoisomeric diphosphine ligand, and TPGS-750-M as amphiphile in the presence of CuH as catalyst (Scheme 8).[63] Under these conditions it was possible to obtain yields up to 94% and almost quantitative enantiomeric excesses for the optimized conditions. For these reasons, this newly developed synthetic route allowed for a greener and more environmentally acceptable pathway than the traditional method.

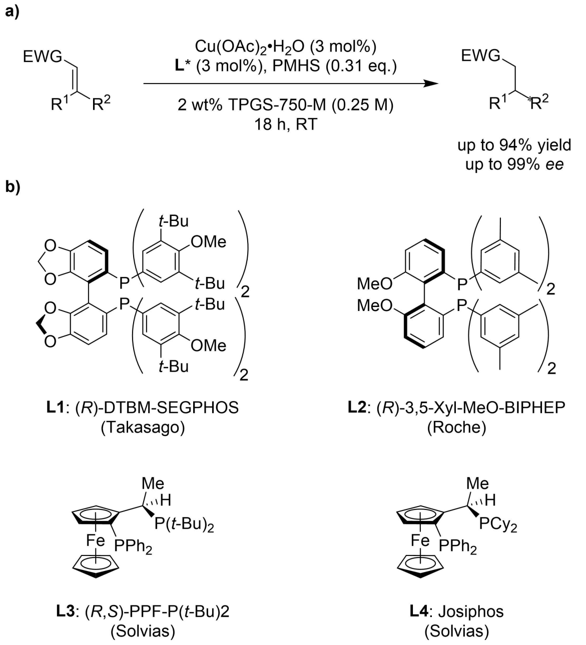
An intriguing example of stereoselective catalysis in water based on the use of supramolecular amphiphilic aggregates was achieved developing an advanced compartmentalized micellar nanoreactor. Such aggregate was obtained by cross-linking of multifunctional amphiphilic poly(2-oxazoline)s with spiropyran after micelle formation in water. This system allowed to perform incompatible tandem catalysis under aqueous conditions, thanks to its reversible photo-



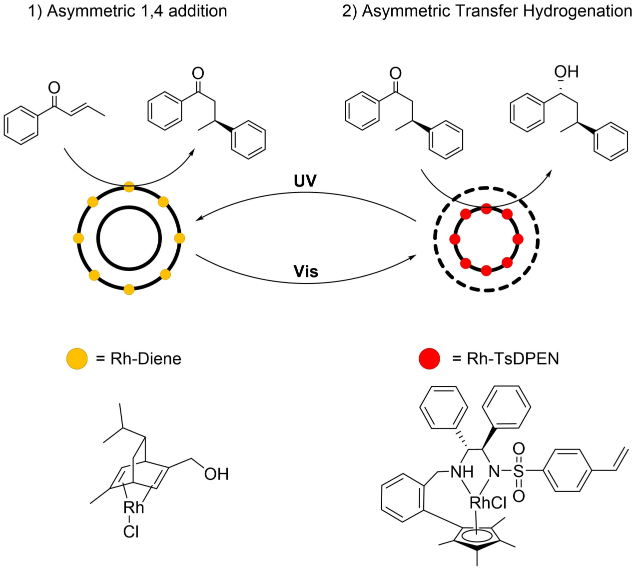
Scheme 6. Efficient catalyst recycling through cloud point extraction in the stereoselective hydrogenation of itaconic ester derivatives in water mediated by $\mathbf{NP_8}$ as surfactant.



Scheme 7. Asymmetric catalytic reduction of an *α,β,γ,δ*-unsaturated ester precursors of vitamin D analogs **3** and **4**, performed in micellar medium of PTS/H_2O (a and b) and structure of the catalysts employed (c).



Scheme 8. CuH-catalyzed enantioselective hydrosilylation of *β,β*-disubstituted Michael acceptors in TPGS-750-M micellar media (a) and structures of the chiral ligands employed (b).



Scheme 9. Schematic representation of the tandem catalytic process involving two stereoselective hydrogenation reactions to obtain multi-chiral products based on compartmentalized micellar nanoreactors.

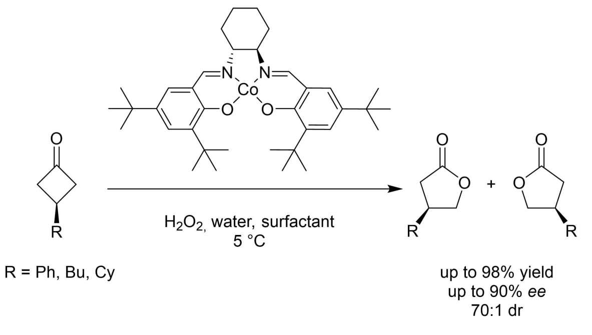
responsive properties that enabled to regulate the reaction pathway, switching its morphology in response to light irradiation. Two incompatible catalysts were spatially confined in the two portions of the nanostructure: in the hydrophilic corona a rhodium-diene complex catalyzed asymmetric 1,4-addition, while in the hydrophobic core a Rh-TsDPEN catalyzed asymmetric transfer hydrogenation (Scheme 9).[64] The overall process achieved multi-chiral products with high conversions and outstanding enantioselectivities in aqueous media (up to 99% *ee*, up to 98:2 d.r., yields up to 99%). The nanoreactor allowed to by-pass the intrinsic incompatibility between the catalysts employed via compartmentalization and enabled photo-regulation of the desired reaction pathway, mimicking the concepts of compartmentalization and responsiveness of natural streamlined metabolic processes.

Regarding stereoselective oxidation reactions in micellar media, the Baeyer-Villiger oxidation of cyclobutanones with hydrogen peroxide was performed in a catalytic, diastereoselective and enantioselective way in micellar media with surfactants like SDS, Triton X-100, Triton X-114 using the commercially available chiral Co(Salen) as catalyst (Scheme 10).[65] It is worth to note that this complex showed no catalytic effect in organic solvent, but once dissolved in water with the aid of surfactants moderate catalytic activity, high diastereoselectivity (up to 70:1 d.r.) and good enantioselectivity (up to 90% *ee*) were generally observed.

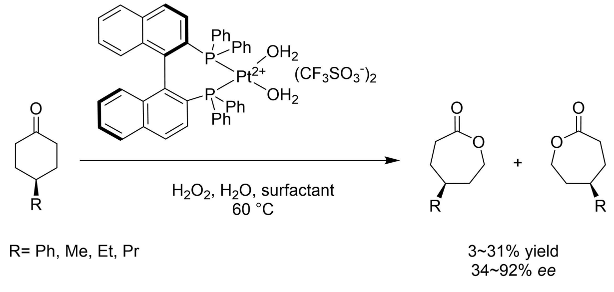
Another example of Baeyer-Villiger oxidation performed on cyclic ketones was carried out in water using moderate catalyst loadings (<5 mol%) of soft Lewis acid Pt(II) complex bearing chiral diphosphine using hydrogen peroxide as environmentally friendly oxidant (Scheme 11).[66] The addition of a wide range of surfactants, among which SDS allowed the best results, was crucial to afford high enantiomeric excess (*ee* up to 79%), which also in this case is higher than in organic solvents. Moreover, when applied to *meso*-cyclohexanones it was possible to enhance the enantioselectivity of the reaction up to 92% *ee.*

Regarding the stereoselective oxidation of prochiral aryl alkyl sulfides, this reaction can be achieved in water-surfactant medium such as SDS, involving chiral platinum diphosphine complex $\{[(R)\text{-BINAP}]\text{Pt}(\mu\text{-OH})\}_2(\text{BF}_4)_2$ in the presence of hydrogen peroxide (Scheme 12).[67] The interesting features of this procedure are several and make this method attractive: *i*) the separation of products from catalyst could be achieved via a simple diethyl ether/water-surfactant two phase separation, *ii*) high yields were achieved with low catalyst loading, *iii*) mild experimental conditions using hydrogen peroxide as green and inexpensive oxidant. Moreover, the reaction turned out to be highly chemo-selective providing the obtained sulfoxide to sulfone ratio up to 200:1, with high enantio-selectivities (up to 88%).

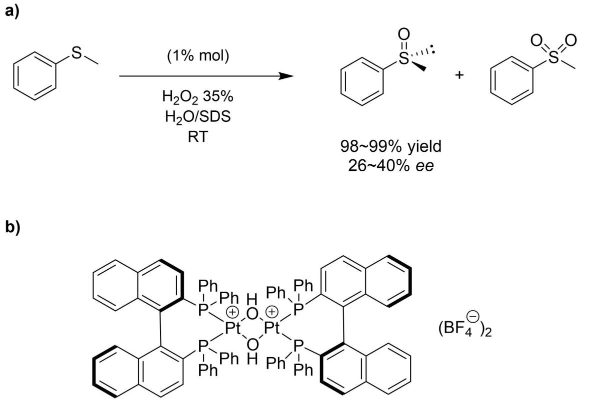
A remarkable example of recycling and improvements in enantioselectivity for the reaction of epoxidation of terminal alkenes was performed involving a chiral, electron-poor platinum(II) catalyst with hydrogen peroxide as terminal oxidant in water-surfactant media using SDS, CTABr, SPAN 60, Triton X-100, Triton X-114, and Triton X-405 (Scheme 13).[68] The reaction was conducted in extremely mild and environmentally friendly experimental conditions and the isolation of the enantio-enriched product could be achieved with a simple two-phase extraction. It is interesting to observe that the micellar media allowed



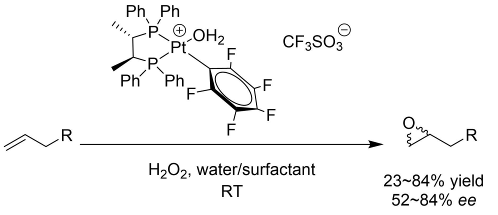
Scheme 10. Enantioselective Baeyer-Villiger oxidation of cyclic ketones with H_2O_2 mediated by Co(Salen) catalyst in water with different surfactants.



Scheme 11. Catalyzed Baeyer-Villiger oxidation of meso-cyclohexanones with H_2O_2 in micellar medium.



Scheme 12. Stereoselective oxidation of prochiral aryl alkyl sulfides in water/surfactant medium catalyzed by Pt(II) dimeric complexes (a) and structure of the catalyst employed (b).

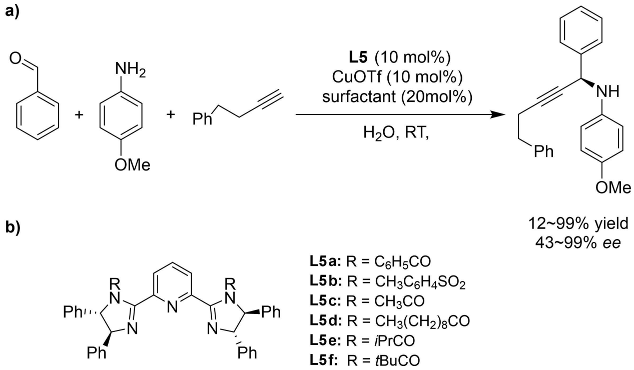


Scheme 13. Stereoselective epoxidation reaction of terminal alkenes in water/surfactant medium under mild conditions catalyzed by electron-poor Pt(II) complex.

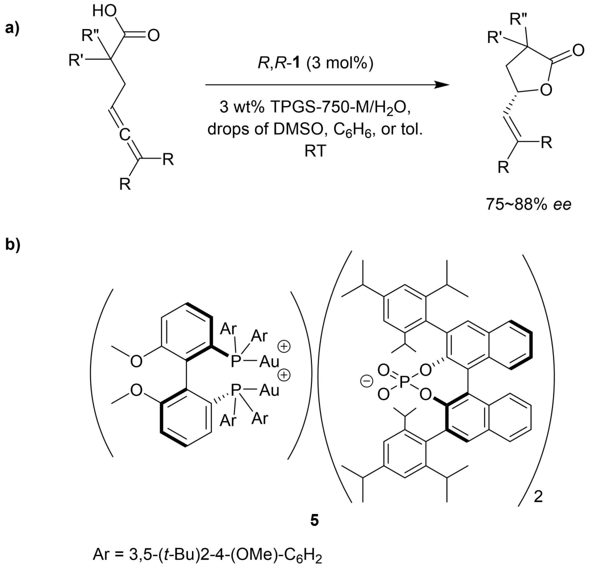
significant improvement in the asymmetric induction compared to the use of organic solvents (*ee* up to 58%).

Multicomponent reactions are particularly favored by the micellar conditions. An example is the three component reaction between aldehydes, amines, and alkynes that was carried out with *bis*(imidazoline)-Cu(I) catalysts in water with SDS as a surfactant (Scheme 14).[69] This procedure was applied on a large substrate scope of various aldehydes and alkynes to give optically active propargylamines with excellent yields and *ee* up to 99 %.

The hydrophobic effect characteristic of nanomicelles has been exploited in the intramolecular asymmetric gold-catalyzed hydrocarboxylations of allenes showing *ee* up to 88% of the lactone products (Scheme 15).[70] This stereoselective reaction is particularly interesting since the asymmetric induction may be ascribed to the tight ion-pair binding between a nonracemic cationic gold catalyst and its nonracemic counterion. Moreover, other intriguing aspects of this method are the possibility to recycle of catalyst, the absence of organic solvent due to the employment of the micellar medium and the very low E Factor.



Scheme 14. Stereoselective multicomponent aldehyde, amine and alkyne reaction catalyzed by Cu catalysts leading to chiral propargylamines under micellar media (a) and structure of the ligands employed (b).



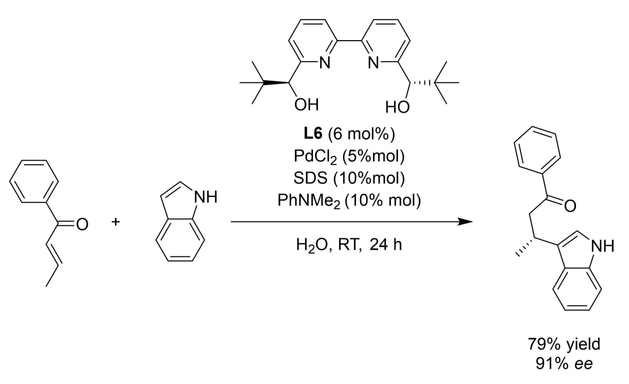
Scheme 15. Stereoselective lactonization of allenes catalyzed by Au(I) complexes in water/surfactant medium under mild conditions (a) and structure of the nonracemic catalyst **5** bearing chiral ligand and chiral counter-anion (b).

Considering C–C bond formation stereoselective reactions, the electrophilic palladation of indoles through C–H bond functionalization was achieved in water in the presence of SDS showing high enantioselectivities. The catalyst reacted with 2,2′-bipyridine-based chiral ligand rather than phosphine-based ligand, forming cationic catalysts that showed fruitful interaction with the anionic surfactant (Scheme 16).[71] The obtained catalytic system allowed the simultaneous activation of a carbonyl moiety and a π bond in water through the presence of the cationic Pd(II) complex.

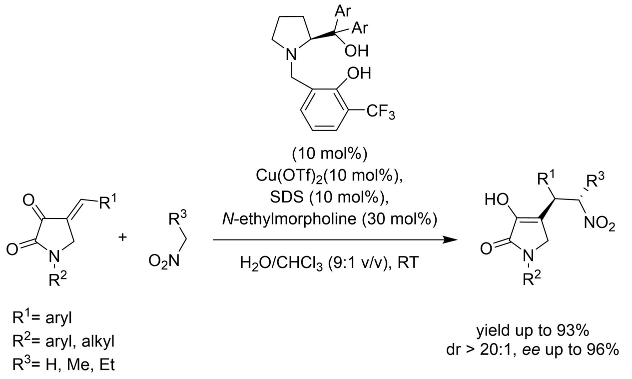
Employing SDS as surfactant in the presence of a chiral copper complex, the diastereo- and enantioselective 1,4-Michael addition reaction reported in Scheme 17[72] was achieved. This procedure is tolerant to air and water and allowed to have access to carbon-carbon bonds, obtaining a series of nitro-containing pyrrolidones. The obtained product showed a major stability in the enol form rather than in the ketone form. Moreover, this process was scaled-up to gram scale with 85% yield, 14:1 dr and 94% *ee.*

An interesting tandem nucleophilic addition/protonation sequence reaction of α-branched enones in water was achieved employing chiral copper(II) complex combined with anionic surfactants (Scheme 18). This process enabled to obtain optically active *α*-methyl-*β*-amino ketones, with good yields (up to 71%) and high enantioselectivity (up to 82% *ee*).[73]

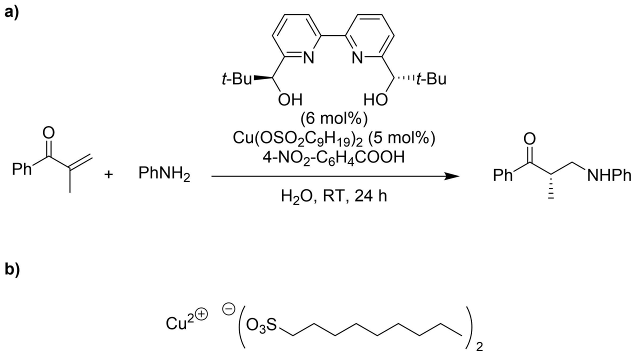
Another example of C–C bond formation is the asymmetric palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate which was carried out in



Scheme 16. Enantioselective functionalization of indoles in water under mild conditions catalyzed by Pd(II) catalysts.

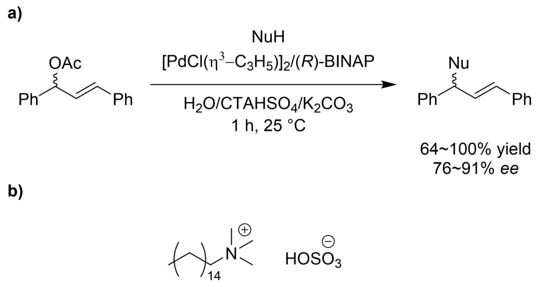


Scheme 17. Stereoselective Michael reaction in water with Cu catalyst in the presence of SDS.



Scheme 18. Stereoselective tandem nucleophilic addition/protonation reaction of α-branched enones in micellar medium (a) and structure of the surfactant employed (b).

water employing $CTAHSO_4$ (cetyltrimethylammonium hydrogensulfate) as surfactant in the presence of an inorganic base. The metal catalyst presented BINAP as chiral ligand (Scheme 19).[74] Enantio-selectivities up to 91% were obtained using carbon nucleophiles. Interestingly, extending the reaction to other allylic water-soluble acetates displayed lowered efficiency and enantioselectivity. Furthermore, testing the reaction with amines as nucleophiles, the same results was obtained with or without the surfactant, also in this case due to the good solubility of such reactants in water.

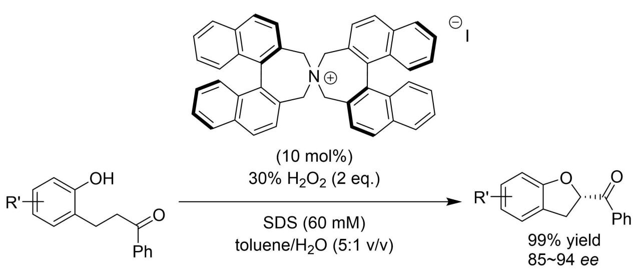


Scheme 19. Asymmetric palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate under micellar medium (a) and structure of the surfactant $CTAHSO_4$ (b).

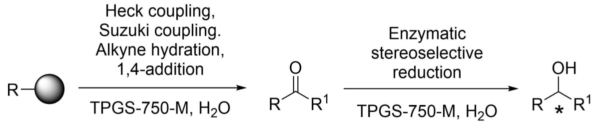
3.2. Chiral Organocatalysts and Enzymes

An example of combination of achiral micelles based on anionic surfactants with chiral organocatalyst bearing positive charge was reported. In this case electrostatic interaction was fundamental to ensure high activity and stereoselectivity. The enantioselective cycloetherification of keto phenols to the corresponding dihydrobenzofuran derivatives was carried out using hydrogen peroxide and chiral quaternary ammonium iodide in micellar media based on anionic surfactant SDS in water/toluene 1:5 (Scheme 20).[75] This procedure allowed to obtain the products starting from a series of substituted keto phenols (electron-rich and electron-poor) with good conversion rate which has been proven to be proportional to the concentration of surfactant. Moreover, the yield was improved by four times with respect to other known methods that do not involve the use of any surfactant. The proposed mechanism involves the formation of an oxidant species, $[R_4N]^+[IO]^-$, confined in an anisotropic closed environment enabled by the surfactant.

A remarkable example of the use of surfactant was reported by the group of Lipshutz, by matching the catalytic performances of enzymes with the solubilization properties of TPGS-750-M. In detail, they reported about the tandem syntheses of ketone-containing products through transition metal-catalyzed reactions based on Pd, Cu, Rh, Fe and Au, that was followed by enzymatic reductions mediated by alcohol dehydrogenases. Due to the full compatibility between the metal-driven reactions, the surfactant and the enzymes this is one-pot process can lead to high yields (up to 99%) of optically enriched products (up to 99.5% *ee*) (Scheme 21).[76] The presence of the surfactant in the reaction medium enhanced the catalytic activity of the enzymes, presumably because of the role of the micelles to act as reservoirs for the substrates, thereby moderating the degree of enzyme



Scheme 20. Asymmetric enantioselective cycloetherification catalyzed by quaternary ammonium salt in micellar medium.



Scheme 21. Compatible combination of metal catalysis and enzymatic bio-catalysis in water with TPGS-750-M for one-pot synthesis of ketones and the following highly stereoselective reduction to secondary alcohols.

saturation, allowing also to increase the productivity associated with large-scale applications.

4. Chiral Micelles

Asymmetric induction in micellar media can also be achieved using chiral micelles in which every single surfactant molecule is chiral making the entire chiral aggregate in water a supramolecular self-assembled nano-environment. The surfactant can be endowed with catalytic function, like an active metal center or an organocatalytic moiety directly connected to the chiral portion of the surfactant leading to chiral metallo-surfactants or organo-catalytic surfactants. This class of chiral micelles are often inspired by traditional chiral metal or organo-catalysts developed to work in organic media and to which a hydrophobic side chain is covalently connected to obtain an amphiphilic species. Alternatively, even though much less investigated, are chiral surfactants lacking any catalytic portion, that give rise to chiral micelles in which achiral catalysts operate and where the asymmetric induction is due to the nano-environment and not by the catalyst itself. This very intriguing approach hardly provides very high enantioselectivity because of the highly dynamic character of micelles, where rapid exchange processes take place thus making more elusive the face recognition of prochiral substrates. Nevertheless, the investigation of chiral micelles especially derived from economic chiral units, for instance provided by the natural chiral pool, could represent an intriguing approach to improve the stereoselectivity of chiral catalysts. Examples of asymmetric induction in supramolecular catalysis due to chiral environments are known and the synergy between the chirality of both catalyst and micelle can really provide new hints in asymmetric catalysis.

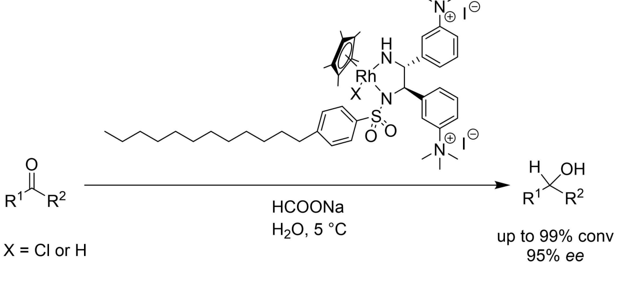
4.1. Chiral Metallo Surfactants

The direct covalent conjugation of catalytic units with lipophilic tails is a well-established strategy to ensure high catalyst loading in the micellar medium, with the great advantage of simple recycling of the chiral micellar catalysts by extraction of the product of the reactions with apolar solvents, while the micelles remain confined in the aqueous phase for future recycling. As a general drawback, a more complicated synthesis of the chiral catalyst bearing the lipophilic side chain is requested, sometimes with some detrimental effects in terms of enantioselectivity due to the presence of the side chain.

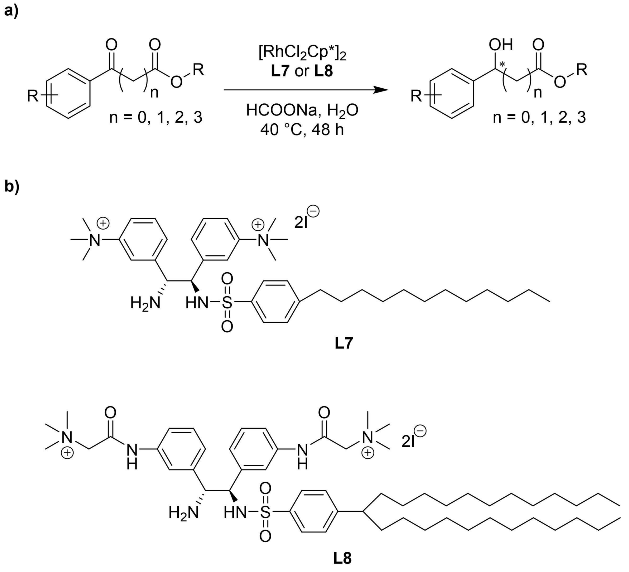
Interesting results concerning the asymmetric transfer hydrogenation were achieved employing a rhodium complex provided with chiral enantiopure ligand. This metallo-micelle catalyst was successfully employed in the asymmetric transfer hydrogenation on a broad range of aliphatic ketones in water. This procedure allowed for excellent conversions (up to 99%) and a remarkable enantio-selectivity up to 95% *ee* (Scheme 22).[77] The efficiency of the procedure was proved to be influenced by the solvent, temperature, and the nature of the aliphatic ketones. The proposed transition state involved the interaction between the Cp* ligand of the catalyst and the alkyl group of the substrate.

Another interesting alternative pathway for the asymmetric transfer hydrogenation was tested on a broad range of aromatic ketoesters using micellar catalysis. The reaction was accomplished with yields up to 99% and *ee* up to 99% employing metallo-surfactants bearing a rhodium active centre and a chiral double-chain surfactant-type ligand (Scheme 23).[78] This new designed catalyst has been employed also for the dynamic kinetic resolution (DKR) of bicyclic *β*-ketoesters in water with excellent enantio- and diastereo-selectivities. The architecture of the surfactant system was reported using TEM analysis with interesting outcomes: employing **L7** ligand the system assembles in a classic micellar manner, while using the double-chained ligand **L8** the system assembles forming a vesicle. This type of conformation enhances activities and enantio-selectivities.

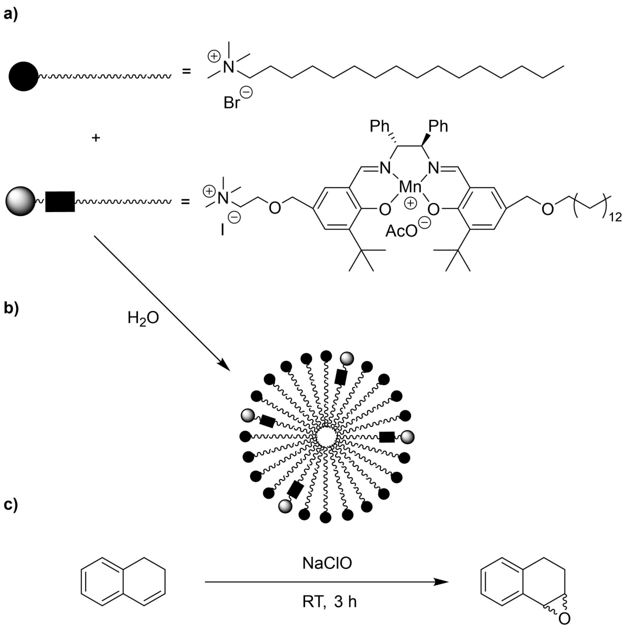
A new chiral Mn-salen catalyst, functionalized with a long aliphatic chain and a choline group, able to act as surfactant catalyst for epoxidation in water, was synthesized (Scheme 24).[79] It found application in the enantioselective green epoxidation of non-functional-



Scheme 22. Asymmetric transfer hydrogenation of aliphatic ketones catalysed by chiral metallo-micellar catalyst with additional trimethylammonium units.



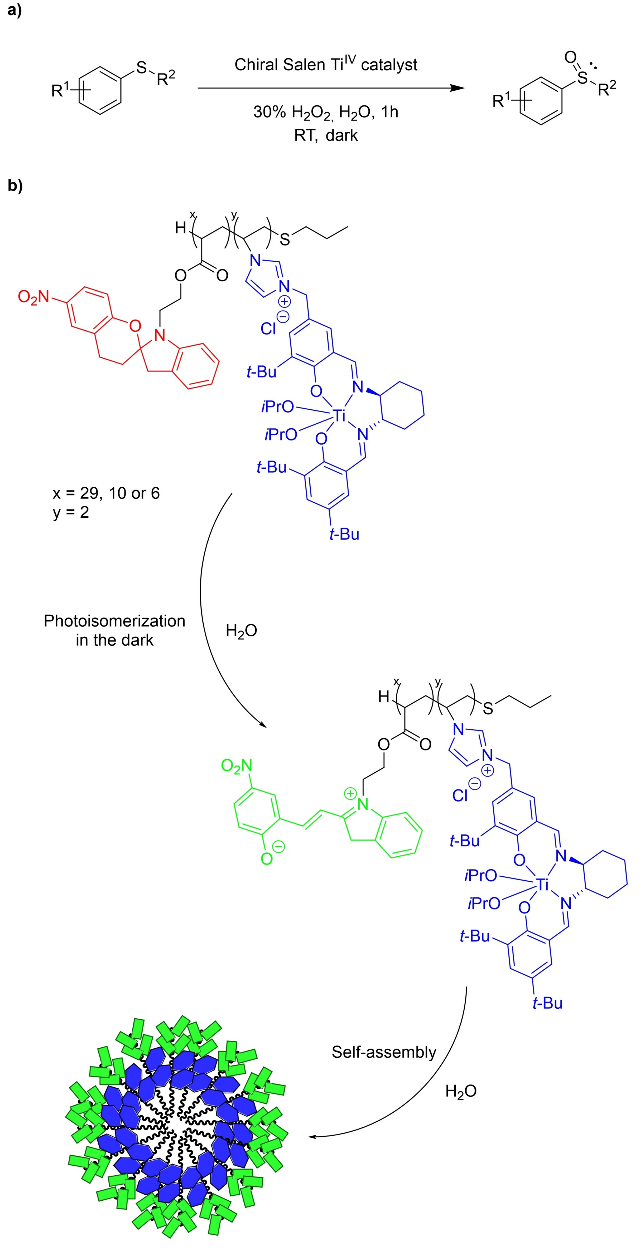
Scheme 23. Asymmetric ATH reaction catalyzed by chiral metallo-micelles or -vesicles (a) and structure of the ligand for metallosurfactants (b).



Scheme 24. Structure of the surfactants employed (a), schematic representation of the micelle in water (b) and example of catalyzed enantioselective epoxidation of 1,2-dihydronaphthalene.

ized alkenes in water, using NaClO as oxidant and CTABr as an assistant micellar medium to build a nanoreactor in which the reaction took place. It is noteworthy that the position of the catalytic metal center with respect to the micellar aggregate leads to different reactivities toward different alkenes: the length of the aliphatic moiety of the catalyst is crucial for improving the reactivity toward aliphatic alkenes. This method enabled to achieve high conversions and enantio-selectivity (over 80% *ee*) in the epoxidation reaction with 6-CN-2,2-dimethylchromene and 1,2-dihydronaphthalene.

A remarkable amphiphilic compound developing photoresponsive metallomicelles applied as asymmetric catalyst was recently reported (Scheme 25).[80] These systems, comprising a series of nitrospiropyran-containing di-block chiral hydrophobic salen Ti(IV)



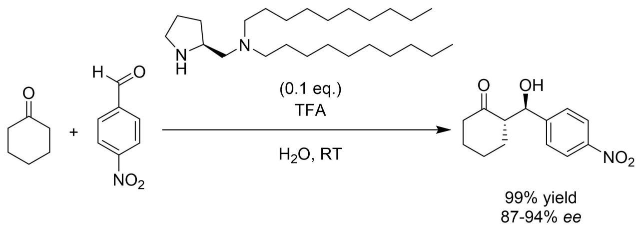
Scheme 25. Asymmetric sulfoxidation of aryl alkyl sulfides in water catalyzed by the polymeric photo-isomerization amphiphilic copolymer (a) and influence of light and water in the structure of the copolymer (b).

copolymers, combine the feature of homogeneous catalysts with the easy recovering proper to heterogeneous catalysts. By employing these new amphiphiles, asymmetric sulfoxidation in water using H_2O_2 as an oxidant of a broad range of aryl alkyl sulfides was performed, exhibiting significant rate acceleration (TOF over 1500 h^{-1}), remarkably high selectivity (up to 97%) and high enantioselectivity (up to 99% *ee*). Furthermore, when exposed to visible light, the aggregates were collapsed and precipitated from the aqueous system for easy recycling, thus avoiding further waste of the subsequent separation step.

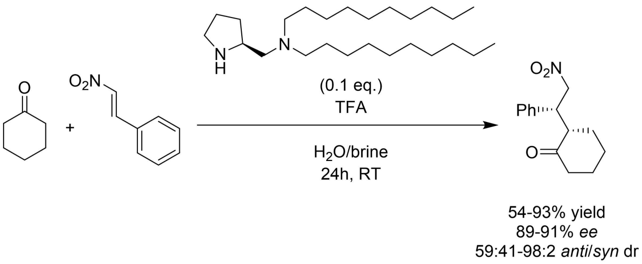
4.2. Chiral Organocatalytic Surfactants

Organo-catalysis is an extremely important field of stereoselective catalysis testified by the recent Nobel Prize awarded to List and Mac Millan. Organocatalysis rapidly intersected the use of water as solvent,[81] indeed, thanks to the covalent modification of traditional organocatalysts with long lipophilic alkyl chains, it is possible to obtain micellar aggregates in water with catalytic features.

A noteworthy example of organocatalytic surfactant was developed to achieve direct asymmetric cross-aldol reactions in water, without the use of any organic solvent (Scheme 26).[82] The diamine bifunctional catalyst provided with long hydrophobic alkyl chains enabled to obtain quantitative yield in the reaction between cyclohexanone and *p*-nitrobenzaldehyde. Interesting, high enantioselectivity (up to 94% ee) was observed when TFA was added to the reaction, even when employing equal molar ratio of the substrates.



Scheme 26. Direct asymmetric cross-aldol reaction performed in acidic micellar medium at room temperature catalyzed by the diamine surfactant.

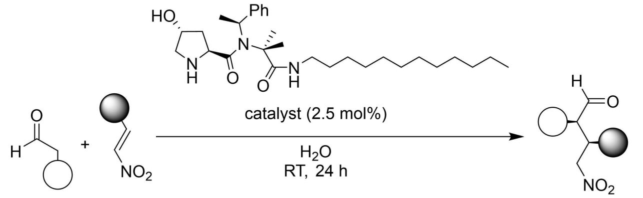


Scheme 27. Direct asymmetric Michael reaction of cyclohexanone with *β*-nitrostyrenes in brine at room temperature catalyzed by the diamine surfactant.

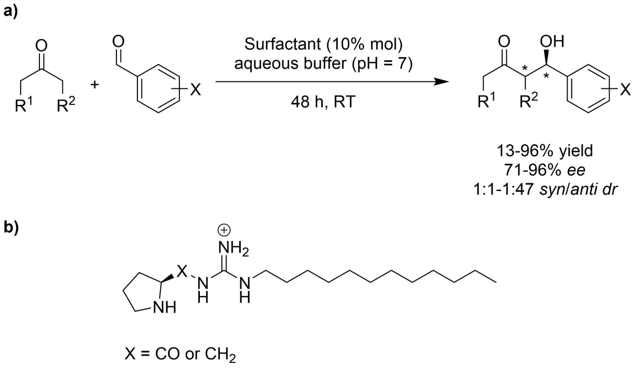
The same organocatalytic surfactant system was also employed in the direct asymmetric Michael reaction of aldehydes and ketones with *β*-nitrostyrenes with high yields (up to 67–99%), high enantioselectivity (32–97% ee) and good diastereoselectivity (59:41–98:2 *anti*/*syn* dr) (Scheme 27).[83] The peculiar feature of this process was the possibility to operate in brine or seawater, with better results than those obtainable when distilled water was employed. This was due to the favorable aggregation of the organocatalyst and the reactants, that reduced the contact with the polar aqueous medium, enhancing the performances of the catalyst. The results achieved with this diamine/TFA bifunctional catalyst system clearly underline the effective design strategy used for the development of aqueous organocatalytic systems.

A similar approach based on a new amphiphilic lipopeptide enabled the asymmetric Michael addition of aldehydes to *trans*-*β*-nitrostyrene in water, affording the product with excellent yields (up to 99%), diastereoselectivities up to d.r. 99:1, and enantioselectivities up to 99% *ee* using low catalyst loadings (Scheme 28).[84] The various *N*-alkylated lipopeptide organo-catalysts were obtained through an isocyanide-based multicomponent reaction after a complete tuning of the backbone of the organo-catalyst. The organocatalytic method in water could be easily scaled-up retaining good activity and selectivity, and more importantly the catalyst could be recycled for up to four cycles, with reproducible catalytic performances.

Another example of amphiphilic organocatalyst involving a proline unit connected to cationic guanidine as polar head group was proposed for the asymmetric aldol reactions of ketones in water at neutral pH (Scheme 29).[85] The reactivity of the system was strongly dependent on the electronic nature of the substrates, in particular on the aldehyde, that determined also the stereoselectivity of the products obtained. Further investigations highlighted the delicate combination of intermolecular and intramolecular interactions of the organocatalyst. Thanks to the hydrogen bonding features present in the acylguanidine



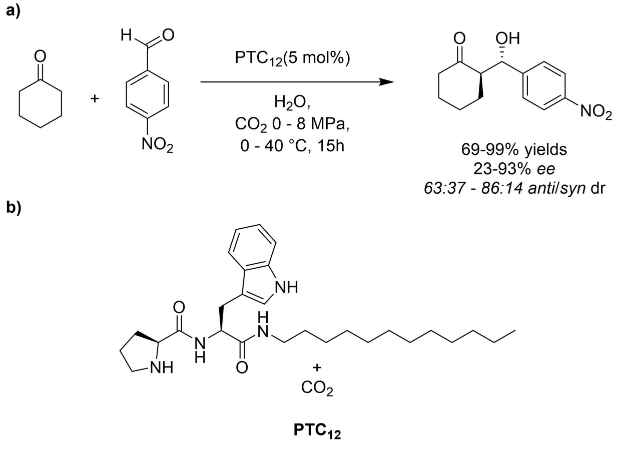
Scheme 28. Asymmetric Michael reaction of aldehyde and trans-*β*-nitrostyrene catalyzed by *N*-alkylated lipopeptides under micellar conditions in water.



Scheme 29. Asymmetric aldol reaction of ketones in water at pH = 7 (a) and structure of the amphiphilic guanidinium catalyst (b).

moiety, the organocatalytic surfactant favored a fixed conformation on the substrates which is responsible of the asymmetry imparted in the reaction. Tweaking these particular features, the organocatalytic surfactant enabled to achieve high yields up to 96% and ee (up to 96%, with dr that spanned from 1:1 up to 1:47 for the *syn*/*anti* product.

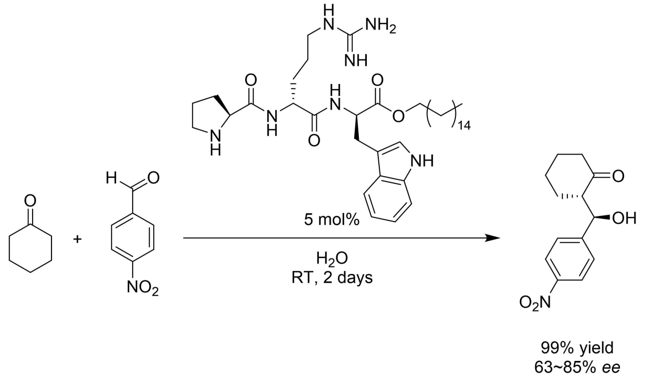
An interesting, albeit unconventional catalytic system for asymmetric aldol reaction was developed exploiting an amphiphilic proline derivative, for which supramolecular aggregation in vesicles was triggered by the addition of compressed CO_2 (Scheme 30).[86] The particular feature of such structure arises from the dynamic regulation of the size of the aggregates, which can be controlled by CO_2 pressure, influencing catalyst activity and selectivity. This method allowed for high yields (up to 99%) and high enantioselectivity (up to 93% ee), along with simple separation of products. Moreover, recycling of the catalyst was possible without any major loss in activity and enantioselectivity for up to five cycles.



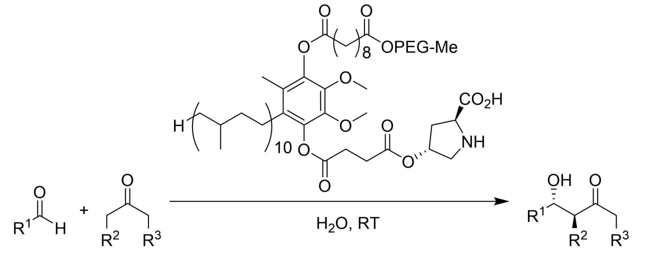
Scheme 30. Asymmetric aldol reaction in micellar medium under CO_2 pressure (a) and structure of the amphiphilic proline derivative (b).

A reference asymmetric aldol condensation reaction between cyclohexanone and *p*-nitrobenzaldehyde was performed by the amphiphilic organocatalyst based on a tripeptide sequence of L-proline, L-arginine and L-tryptophan with an aliphatic side chain on the terminal acidic moiety (Scheme 31).[87] The reaction in water using only 5 mol% of catalyst led to yields up to 99%, enantioselectivity up to 85% and high diastereoselectivity (d.r. up to 92:8). The self-assembly properties in water of this amphiphilic lipopeptide were investigated, determining a critical aggregation concentration in water of 0.17 mM with formation of spherical aggregates with 6 nm diameter as determined by cryo-TEM analyses, high-resolution SAXS and further confirmed by molecular dynamic simulations.

Asymmetric aldol reactions were also performed employing a new designer surfactant containing an organo-catalyst reminiscent to proline attached to a nanomicelle-forming amphiphile derived from the dietary supplement CoQ10 (Scheme 32).[88] The enantiomeric excess of the products was comparable to those obtainable with traditional methods operating in polar aprotic organic solvents with proline as organocatalyst. The confinement of the organocatalytic



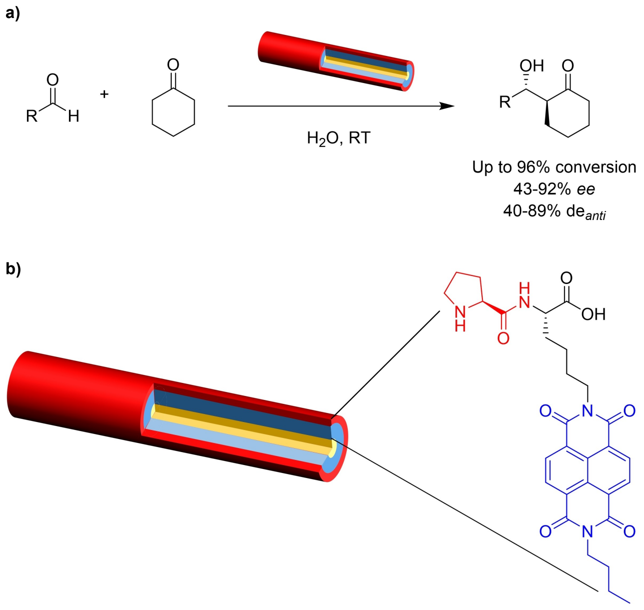
Scheme 31. Asymmetric aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde catalyzed by the amphiphilic lipopeptide in water.



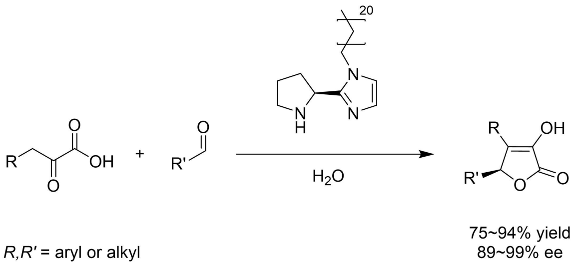
Scheme 32. Asymmetric aldol condensation between ketones and aldehydes mediated by designer surfactant containing proline in water.

surfactant in the aqueous phase enabled the in-flask recycling by simple product extraction with ethyl acetate, phase separation and reintroduction of the fresh substrates in the aqueous phase, leading to almost constant yields, diastereo- and enantio-selectivity.

A distinguishing example of a organocatalytic surfactant comprising a proline-lysine dipeptide zwitterionic head group connected to an hydrophobic 1,4,5,8-naphthalenetetracarboxylic acid diimide flat unit was proposed for the formation of self-assembled nanotubes that efficiently promoted aldol reactions in water (Scheme 33).[89] The self-assembly turned out to be promoted by the presence of the substrate, with enhanced catalytic activity observed for the nanotubes with respect to single monomers in solution. The catalyst could be readily recovered by ultracentrifugation to sediment the nanotubes from the aqueous layer and recycled for over five cycles.



Scheme 33. Asymmetric aldol reaction in water under mild conditions (a) and structure of the zwitterionic amphiphile that self-assembles into nanotubes in water (b).

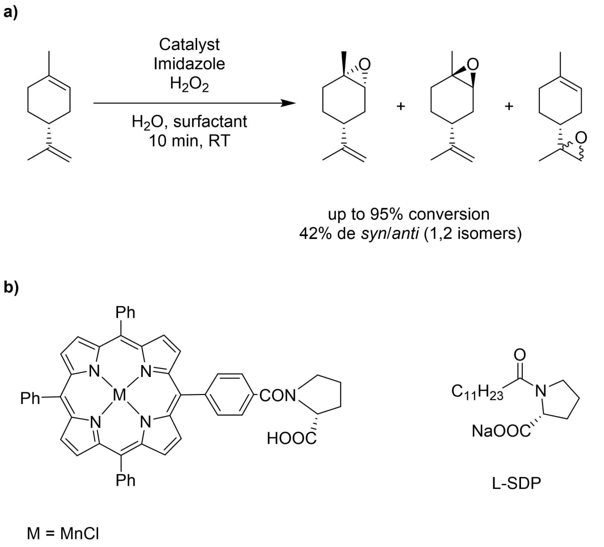


Scheme 34. Asymmetric synthesis of isotetronic acids from α-ketoacids and aldehydes catalyzed by imidazole/pyrrolidine amphiphilic organo-catalysts in water.

An example of the fruitful strategy leading by organocatalytic surfactants is reported in Scheme 34[90] consisting in the stereoselective synthesis of a wide range of optically active isotetronic acids from aldehydes and α-ketoacids in water. The organocatalytic surfactant was composed of an imidazole/pyrrolidine system that efficiently promoted the multistep reaction with yields up to 94% and enantioselectivity up to 99% *ee.* The authors investigated the aggregation properties of the organo-catalysts by fluorescent imaging, observing that catalyst molecules were localized on the surface of the emulsion, highlighting the fundamental role of the emulsion droplets in the process.

4.3. Chiral Surfactants with Chiral Metal Catalysts

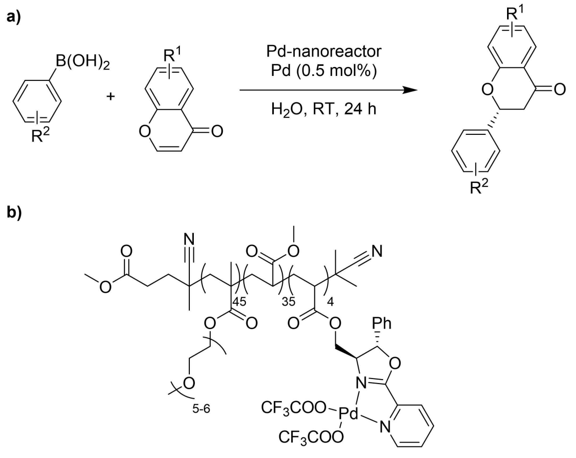
An example of improved diastereoselectivity in an oxidation reaction was reported based on the combination of anionic micelles, either achiral based on SDS or chiral using *N*-dodecanoyl-*L*-prolinate (L-SDP), with proline functionalized porphyrin derivative Mn catalyst (Scheme 35).[91] The micellar self-assembled system was tested in the regio- and stereo-selective epoxidation reaction of the chiral substrate (*R*)-limonene carried out in aqueous solution mimicking cytochrome-P450 biomimetic activity. The micellar systems allowed to achieve high substrate conversion when using L-SDP as surfactant (up to 95%) and good diastereomeric excess (42% de for the 1,2-epoxide isomers: *syn* vs *anti*), thanks to a preferred exposition of one of the unsaturated bonds to the metal catalyst, that is probably due to the rigid geometrical constraints of the substrate inside the self-assembled structures.



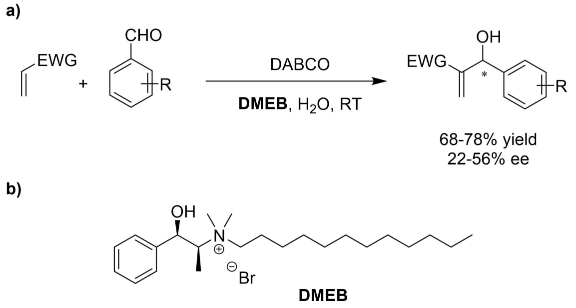
Scheme 35. Asymmetric epoxidation of (*R*)-limonene in water catalyzed by the micellar catalytic system (a) and structure of the chiral catalyst and surfactant (b).

4.4. Chiral Surfactants with Achiral Metal Catalysts

An interesting application of enantiopure polymeric micelles in water is the preparation of a wide range of natural products possessing relevant biological properties, such as flavonones. The generation of the catalyst involves the formation of polymeric core-shell micelles which coordinates palladium with a chiral pyridinooxazoline ligand (Scheme 36).[92] These amphiphiles cat act as nanoreactors to promote asymmetric conjugate addition of aryl boronic acids to chromones in aqueous media. The employment of the catalytic species allowed to increase catalyst activity, achieving yields up to 98% and enantio-selectivities up to 84% *ee* with low metal loadings and without any additive. Such performance was possible due to the higher local concentration of reagents inside the nanoreactor, caused by their confinement within the apolar core.



Scheme 36. Asymmetric conjugate addition of aryl boronic acids to chromones in aqueous medium to afford flavanones derivatives (a) and structure of the polymer employed to form the micelles (b).



Scheme 37. Stereoselective Morita-Baylis-Hillman reaction in water catalyzed by achiral DABCO mediated by the chiral designer surfactant **DMEB** (a) and structure of the chiral surfactant (b).

4.5. Chiral Surfactants with Achiral Organocatalysts

Examples of asymmetric induction for reactions with achiral catalysts based on the chirality present exclusively on the surfactant are rare, due in particular to the dynamic nature of micelles that hampers stereoselective induction. One very interesting example was recently reported for the asymmetric Morita-Baylis-Hillman reaction in water, reported in Scheme 37.[93] The specifically designed and synthesized organocatalytic surfactant was (*1R,2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB) that was efficiently tested in the reaction between aromatic aldehydes and conjugated electron-poor alkenes mediated by the achiral DABCO tertiary amine, allowing to achieve high reaction rates, yields up to 78% and enantio-selectivities up to 56% *ee.* It is worth to note that this catalytic system was characterized by better results with respect to other methods employing both chiral *L*-proline and achiral cationic cetyl-trimethylammonium bromide surfactant CTAB. A detailed ^{1}H NMR investigation revealed that the reaction occurs in proximity of the polar head group of DMEB micellar media and close to the asymmetric portion of the surfactant thus justifying the observed asymmetric induction. It is important to notice that the organocatalyst was specifically endowed with positive charges to ensure high contact with the common anionic intermediate of this class of reactions.

5. Conclusions and Perspectives

Like all homogeneous catalysis, also asymmetric catalysis is facing a revolution in consideration of the raising issues posed by sustainability and green chemistry practice. Organic solvent removal or proper solvent picking is a must, especially for processes that aim to large scale productions. Asymmetric catalysis in water under micellar conditions represent a natural evolution since traditional homogeneous catalysis already has been developed in this media with a rapid development in two decades from academia to pharmaceutical companies, leading to real examples of large-scale applications. Asymmetric induction under micellar media can be achieved by a wide combination of effects, depending on which component is chiral among catalyst and surfactant. What is new is the fact that micellar media often improve the stereo-selectivity of asymmetric reactions. Stereoselective catalysis in micellar media is a research topic that deserve a great effort to fully exploit the combination of the advantages offered by the use of water as solvent, in particular recyclability, and the less known advantages related to nano-confinement effects. Inspiration from what known for enzymes suggests that confinement effect of substrates in chiral environments further spur stereoselectivity. Nevertheless, a major difference exists between micellar catalysis and enzymatic catalysis: the latter is based on complex proteins made of chiral aminoacids, conversely micellar catalysis, apart a few examples, is characterized by the use of achiral surfactants. Nature provides an endless number of complex enantiopure molecules from the chiral pool that can be the base for new enantiopure designer surfactants. In particular, aminoacid and peptide based surfactants will certainly gain attention in the future years thanks to the versatility of the chiral units. It is therefore advisable an important effort in the design and exploitation of new chiral bio-sourced[94,95] designer surfactants from renewable resources to fully spur the field of asymmetric catalysis in micellar media. Development of such new surfactants will also provide a bridge between micellar catalysis and enzymatic catalysis giving rise to suitable chiral environments for achiral catalysts for the synthesis of chiral products, which are fundamental in particular for the pharmaceutical industry.

Looking into the system from the substrate point of view, micellar catalysis shares with enzymes the ability to isolate the substrate from the solvent, to de-solvate it, to complement most of its surface area and to preorganize it in order to facilitate its transformation into products. Moreover, the environment that surrounds the catalyst-substrate pair may provide extra stabilization or destabilization for intermediates and transition states through non-covalent interactions, thus spurring the catalytic activity. Overall, this results in a different interaction of the reagents with the catalyst leading to possible matching effects for the stereoselectivity of the chemical transformations considered. In particular, the use of chiral surfactants will enable i) the use of achiral catalysts that will influence the stereoselectivity of the reaction by operating in close proximity to the chiral apolar portion of the micelles; ii) the use of chiral catalysts that could enable matching effects with one enantiomer of the chiral surfactant, while mismatching effects could be possible the with the enantiomer of the surfactant. To this, the recently introduced strategy consisting in the preparation of imprinted micelles[96] for chiral recognition could further spur the stereoselectivity of future micellar media for catalysis.

As a general final perspective, in order to achieve a better control on micelles-substrate interactions for asymmetric induction, it is advisable the development of new rigid chiral surfactants bearing for instance large aromatic apolar surfaces. Such class of surfactants, inspired by the recent works of Yoshizawa,[97,98] will lead to the formation of micelles based on a small number of units. This will enable a better control of the reciprocal arrangement of the surfactant units, favoring positively the influence of the asymmetric environment provided by the aggregates in water. It is therefore clear that asymmetric catalysis will certainly provide a new lymph to micellar catalysis in water. Similarly to recent achievements in stereoselective catalytic reactions within coordination cages,[99] we are confident that this review will spur further this highly promising field of research, that will also provide a better understanding for the fundamental principles of stereoselective enzymatic catalysis.

Notes

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