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Selectivity in micellar catalysed reactions: The role of interfacial dipole, compartmentalisation, and specific interactions with the surfactants

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Abstract

Micellar catalysis is playing a major role in green chemistry with ever increasing applications in the efficient and sustainable preparation of natural compounds, drugs, and more recently organic semiconductors for printed electronics. Most of the contributions in the field focus on the developments of surfactants and suitable formulative conditions capable of reproducing – and often improving – the yield of reactions commonly performed in organic solvents. The real ambition of the micellar catalysis approach goes beyond the improvement in the sustainability of existing methods and aims at mimicking not only the efficiency but also the selectivity of enzymatic catalysis. This review summarizes relevant examples of micellar catalysis enabled, efficient, and selective transformations, and discusses the different kind of processes impacting on the product distribution depending on the details of the formulative state achieved.

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Keywords

Micellar catalysis, Selectivity, Compartmentalisation, Interfacial dipole, Sustainability.

Introduction

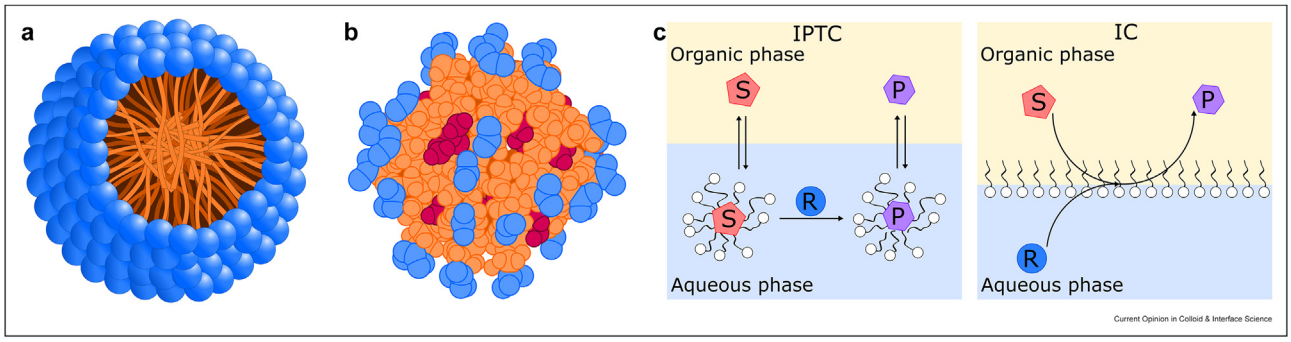
The advent of green chemistry, or sustainable chemistry, represents one of the most relevant developments of the chemical industry of recent decades. Nowadays, all chemical processes are finely tuned during the precompetitive phase to reduce the amount of wastes, reduce the energy consumption and the resources depletion both in terms of feedstocks and catalysts. Unfortunately, even though the advancement towards sustainability is constant, the chemical industry still cannot compete with biological transformations having essentially no waste, very limited energy intake and supremely efficient catalysis. The vast recurrence to toxic and often flammable organic solvents is at the same time contributing to the hazardousness of chemical transformations and to the production of large volumes of wastes [1].

Water is in many ways the perfect solvent to carry out organic reactions. It is available in large quantities, it is not toxic, not flammable and can be stored indefinitely without any hazard occurring. Also, its high thermal capacity and latent heat of evaporation give advantages in controlling exothermic reactions when upscaling preparations [2–4].

The fact that most organics are hydrophobic severely limited the number of processes compatible with an aqueous environment, yet the common wisdom that reagents require to be dissolved in a common phase to efficiently react is getting increasingly challenged. The literature of the last 20 years describes an impressive number of reactions involving lipophilic species, being efficiently and selectively performed in water as the prevalent solvent, provided that a suitable surfactant is employed [5–12].

Surfactants are amphiphilic molecules possessing a hydrophilic and a hydrophobic domain. They are capable of sizably reducing the interfacial energy associated with the presence of hydrophobic derivatives in an aqueous environment. Above a certain concentration, most surfactants self-assemble in a variety of association colloids, the most common of whom is the spherical micelle. At higher concentration, depending on the temperature and/or the ionic strength of the water solutions, more complex structures the like of microemulsions, lamellae, vesicles, and tubules can also be observed. The common characteristic of all such micro-heterogeneous environments is the formation of lipophilic pockets within a polar environment where either additional surfactant or other lipophiles can be accommodated [13–15]. Nature, to whom chemist should aways look for inspiration, uses association colloids for chemistry involving

Figure 1



a) Idealised structure of a spherical micelle obtained by the self-assembly above CMC of a general surfactant possessing a polar head (in blue) and a lipophilic tail (in orange); b) Realistic representation of a spherical micelle highlighting the prevalent distribution of polar heads in the corona and of apolar tails in the core. The red portions represent the chain terminal methyl groups. Picture inspired from Ref. [43]. c) Principles of an inverse phase transfer catalysis (IPTC) and interfacial catalysis (IC) with a surfactant as catalyst (S, substrate; R, reactant; P, product). Picture inspired by ref [44].

non-water-soluble reactants in the human body, which is not based on 100% water [16].

In the early 80's synthetic chemists started realising that association colloids are a simplified analogous of enzymes: reagents can be hosted and selectively localized in an environment with specific polarity, possibly leading to improved yield and selectivity. The selection of the correct surfactant is key to the success of the methods, as demonstrated in the impressive body of work of Prof. Lipshutz [11,17–27]. The field boomed in the last 10 years, with impressive results already thoroughly reviewed. The vast majority of C–C and C–N bond forming reactions employing Pd, Cu, Ni, Ru, Rh and Au catalysts can be performed efficiently, generally outperforming in terms of yields and sustainability the corresponding organic solvent-based protocols [28–34].

Surfactant enhanced chemistry is leaving the research laboratory and impacting on scaled up industrial productions, with several major players including Novartis seriously investing in further development [9,17,19,35,36].

The focus of the field is the improvement in the sustainability of known reactions and processes, through a progressive reduction of wastes, catalysts loading, and energy intake via reduction of reaction temperature and time, as well as recycle of surfactants and catalysts. This review focuses on a different aspect, directly correlated with the nature of the confined space where micellar reactions happen and most directly responsible of the popular analogy between micellar catalysis (MC) and enzymatic catalysis: selectivity [37,38]. Indeed, literature shows examples clearly demonstrating that the chemical nature of the interphases formed by surfactants in the reaction mixture can strongly influence the product distribution in competitive reactions. Moreover, the preferential compartmentalization of reagents having different polarity in the heterogeneous multiphase system characteristic of association colloids promoted reactions dramatically reduces parasitic reactions.

The review is organized in three sections. The first one summarizes the main features of surfactant enhanced reactions, giving an overview of the most popular surfactants and of the two main concentration regimes at whom micellar reactions are performed. The second section addresses explicitly selectivity in micellar reactions according to three main effects: 1) regioselectivity induced by dipoles at the water/lipophilic core interphase; 2) product selectivity induced by specific surfactant/substrate interaction; 3) product selectivity due to compartmentalization effects. The topic of stereoselectivity induced by chiral surfactants has been already recently reviewed and will not be covered in the present article. The third section will summarize the main results so far described and give an outlook at the main challenges the field of micellar chemistry is facing.

Water as a reaction medium

Water is cheap, largely available, non-toxic, non-flammable, and possesses a high thermal capacity. All such features are particularly favourable when looking at the ideal solvent where to perform chemical reactions. In addition, water offers both acid (Brønsted) and basic catalysis (Brønsted and Lewis), it is a very small molecule, and it is not particularly volatile. The surface of water is an excellent catalytic site to carry out a vast range of reactions, collectively defined as "on water" reactions [23,39,40]. Although clearly a protic solvent, water can efficiently be employed for green chemistry compliant reactions involving strongly reactive organometallic species like Grignard and even organolithium reagents [40–42]. Unfortunately, the solubility of most organics in water is very poor. Even though this feature alone does not preclude the possibility to perform reactions using water as the dispersing medium –

frequently under mechanochemical conditions — the heterogeneous nature of reactions mixtures severely limit the scope of such reactions, preventing an efficient contact between the different reacting species.

Features of surfactant-enhanced reactions

Formulation chemists are well accustomed at the task of producing homogeneous mixtures of mutually incompatible components. Whereas the aim of formulations is to preserve the chemical identity of the different constituents of a complex mixture to benefit from the individual features of any one of them, micellar chemistry aims at finding a common ground within a micro-heterogeneous environment for reagents having different polarity to meet and react. The key concept of micellar catalysis is the association colloid, which is the self-assembled structure that amphiphilic molecules forms in water above a specific concentration defined as the critical micellar concentration (CMC). The most common kind of association colloid is the spherical micelle (Figure 1a), whose main characteristics are: a) a water swollen, polar external corona mainly constituted by the polar portions of the surfactants; b) an interphase between the polar and hydrophilic region and the nonpolar, hydrophobic one and c) a lipophilic core constituted by the packed apolar chains of the amphiphilic constituents. The spherical micelle is not the only possible spontaneous association colloid but just the simplest. Depending on the structure and concentration of the surfactant, worm-like micelles, 2D like lamellas and tubular structures can also form.

It is important to point out that spherical micelles (as well as the other association colloids) are not as well packed and organized as they are generally represented. Figure 1b shows a more realistic representation highlighting the presence of nonpolar chains also at the surface, breaking up the packing of polar heads. Such feature is relevant as it makes it easier for the various district of the association colloid to exchange material with the surrounding medium. Micelles have long been used as carriers of lyophobic organics, like drugs and cosmetic active components, and in the last 30 years demonstrated to be also very performing as self-assembled nanoreactors within a water environment.

The behaviour of micellar catalysed reactions is generally rationalised according to the lipophilic effect. Organics that are poorly soluble in water have an energetic driving force to localise within the apolar district of the micelle. The high effective concentration thus achieved makes it possible to reduce both the reaction time and temperature. For reactions requiring the use of a metal catalyst, the efficient colocalisation of all reaction species also allows to sizeably reduce catalyst loading. Such simplified model is helpful in explaining a good deal of the behaviour of organic reactions but holds limits.

Bone fide micellar reactions benefit from the catalytic effect observed in a homogeneous single-phase nanodispersed medium formed by the self-assembly in water of a surfactant above the corresponding CMC [45]. The self-assembly of micelles enables a steep increase in solubility of lipophilic organics. The details on the localization of such species within the different compartments of the micelles depends on the nature of the surfactant employed and on the polarity of the different reagents/catalysts. Recent computational evidence suggests that lipophilic materials tend to localize at the interphase between the lipophilic core and the hydrophilic corona, in a region even smaller than the micellar core thus further enhancing the increase in the effective concentration of reagents [46].

The simple micellar model is only valid when the nominal concentration of reagents is smaller than the maximum additive concentration (MAC). That is the maximum loading concentration still enabling the formation of a single isotropic solution. The use of concentrations lower than 10^{-4} M, far below MAC, are typical of earlier kinetic studies [47—49]. The more recent literature significantly deviates from such proof-of-concept approaches, pushing the limit of surfactant-enhanced reactions towards nominal concentrations in the order of 0.5—1.0 M, much more appropriate for practical synthetic purposes [50]. Working at concentrations orders of magnitude higher than MAC leads to the formation of complex multiphase systems. An impressive body of work, dedicated to a vast range of organic transformations, clearly demonstrated that the formation of such complex systems does not preclude efficiency. Yet, the insurgence of reproducibility issues and non-ideal behaviour of formulations is documented [51], and generally addressed through the addition of small quantities of suitable solvents [52,53]. It should be noted that the addition of a cosolvent changes very much the picture by changing the dimensions and the structure of the association colloid. The topic is of interest both fundamental and practical, but it falls out of the scope of the present review [52].

In such multiphase systems, the surfactant plays several different roles at the same time. It can still form aggregation colloids, but it also stabilises phase boundaries, lowering the interfacial tension and allowing the formation of very small, kinetically stable, droplets/particles. The basic micellar catalysis process we previously described is still operating, in competition with other surfactant-mediated processes like interfacial catalysis (IC) and a hybrid inverse phase transfer catalysis (IPTC) [44]. The latter involves a dual role played by the surfactant: enhancing mass transport of reagents to the water phase and therein promoting the micellar catalysis of the chemical step (Figure 1c shows a cartoon representation of the two processes).

The fact that MC, PTC, IC and IPTC are competitive and interrelated processes while working above MAC is a somewhat overlooked feature of modern micellar catalysis approaches and yet it has profound consequences in a key aspect: the choice of the correct surfactant(s) for a specific transformation. A suitable surfactant must be able to form micelles of a certain dimension and aspect ratio, but it also needs to enable efficient mass transfer through different phases during the whole chemical process. In the following sections we will show relevant examples of selective micellar reactions operating both below and above MAC. We will highlight the differences between the two regimes whenever relevant. It should be stressed that, even when MC, PTC, IC and IPTC are operating at the same time, the "micellar" regime remains distinct form phase transfer reactions in two critical aspects: the surface to volume ratio of the association colloids and the effective concentration of reagents within the lipophilic pockets of the same. Indeed, in the absence of any organic solvent the surfactant assembles in structures minimising the volume, thus enhancing the surface (where the selectivity mechanisms are mainly active). For the same reason, the effective concentration of hydrophobic reagents is maximised, thus promoting reaction rates.

Industrial and designer surfactants (with distinction between passive and active surfactants)

The selection of the appropriate surfactant is obviously of key importance for reactions carried out under micellar catalysis conditions [15]. Surfactants can be classified according to presence or not of a net charge, linear or branched structure and molecular weight. However, for the purpose of micellar catalysis the most important classification is between industrial and designer surfactants. The first class comprises all derivatives that are commercially available on an industrial scale and that have been optimized having in mind the purposes of formulation chemistry. Rather than being designed to perform chemistry, they are aimed at providing stable formulations of a given composition.

Within this context, surfactants are generally classified and selected according to the corresponding hydrophilic lipophilic balance (HLB), a dimensionless number correlated with the mass ratio between the hydrophilic and lipophilic portions of a surfactant. The HLB scale enables to distinguish between neutral lipophilic (HLB < 10) derivatives, prone to form water in oil emulsions, hydrophilic ones (HLB > 10), suitable for oil in water emulsions, and balanced (HLB $= 10$) surfactants. Charged surfactants have HLB values higher than 20. Formulations chemists select surfactants according to the affinity principle, so that the best derivative is the one matching the characteristics of the material to be dispersed. As we will discuss, the affinity principle can lead to peculiar selectivity effects. Scheme 1a shows a selection of industrial surfactants having documented applications in micellar chemistry [54].

On the opposite side of the spectrum, designer surfactants are specifically designed to enhance reactivity in water, in some cases for the widest possible range of reagents and in others having in mind specific classes of transformations and/or regents. The concept of designer surfactant was originally introduced by Prof. Lipshutz, who demonstrated that under the appropriate conditions chemistry in water outperforms reactions in organic solvents in terms of yield, catalyst loading, reaction temperature and time and thus ultimately efficiency and sustainability [22,26]. Such pioneering work inspired other synthetic chemists to develop additional designer surfactants for specific purposes [23,55,56]. Scheme 1b shows representative examples of efficient designer surfactants.

A subclass of designer surfactant that is worth mentioning consists in derivatives contributing to the outcome of the reactions by means additional to the formation of association colloids. Examples of such "active" surfactants comprehend amphiphilic derivatives whose lipophilic portion acts as the sensitiser in photoredox reactions [57], a very versatile and resourceful recently emerged approach (derivatives S−PTh and PQS-Ir of Scheme 1b) [24,58]. As photoredox reactions are one of the paradigm examples of selectivity induced by compartmentalisation effects, it is here worthwhile to single them out as a specific typology.

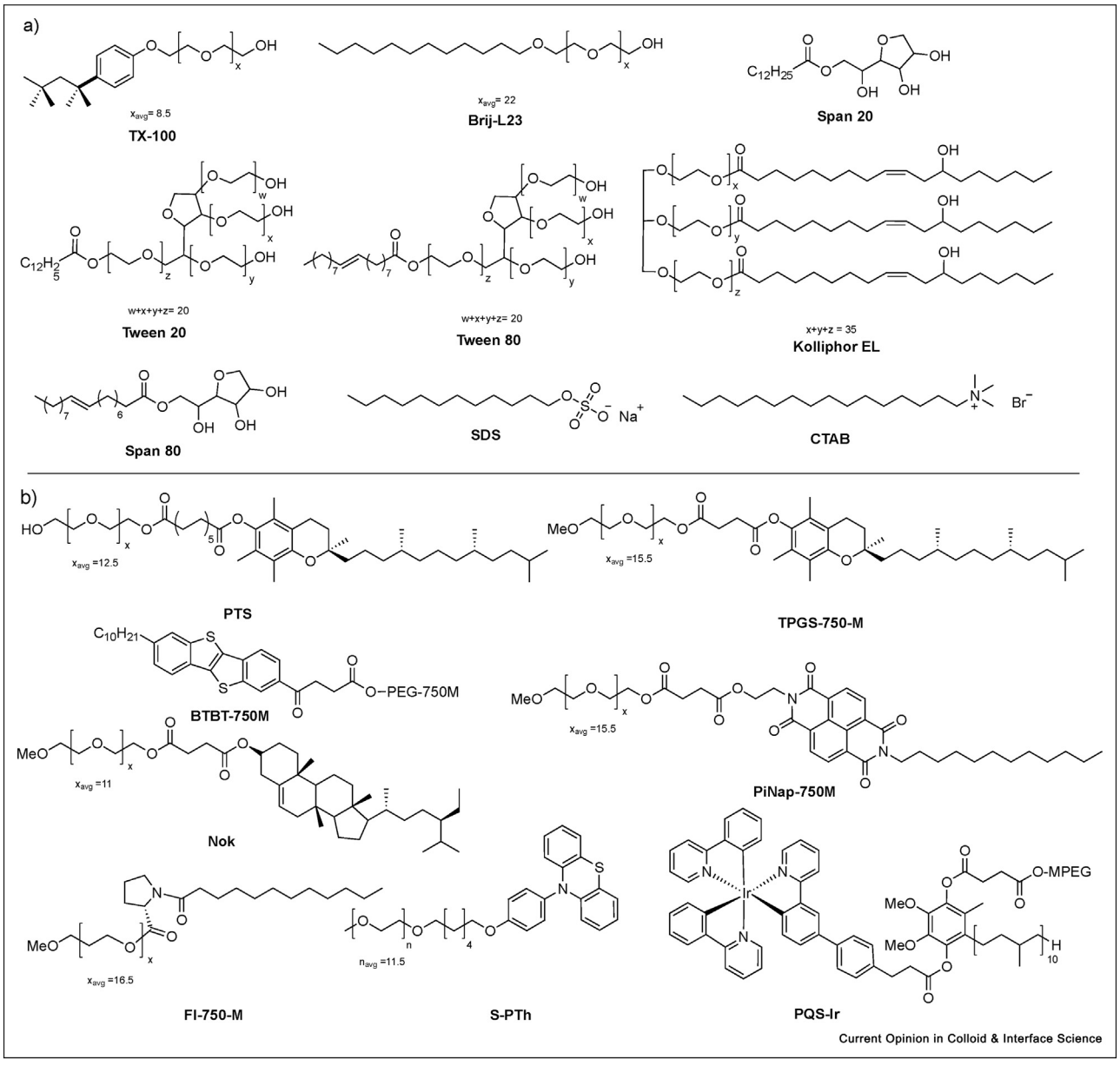
Selectivity at the water/oil interphase

The earliest examples of selectivity effects induced by micellar catalysis pertain to reactions performed under the MAC limit. In such cases, the simple micellar model holds true, and reaction can be rationalised assuming that reagents are quantitatively internalised in the micelles, with consequences on their specific reactivity.

A recent theoretical article devoted to the rationalization of Suzuki-Miyaura (S-M) reactions performed under MAC gave detailed information on the specific localisation within the various inter and extramicellar domains available while in a micellar solution [46]. The authors modelled the solution behaviour of the main components of the industrial surfactant Kolliphor EL (K-EL). As it is typical of industrial surfactants, K-EL is a complex mixture resulting from the epoxidation of castor oil with known equivalents of ethylene oxide. The main component of the resulting mixture is the epoxidated triglyceride depicted in Figure 2.

Using a molecular modelling approach, the authors demonstrated that the surfactant assembles in roughly

Scheme 1

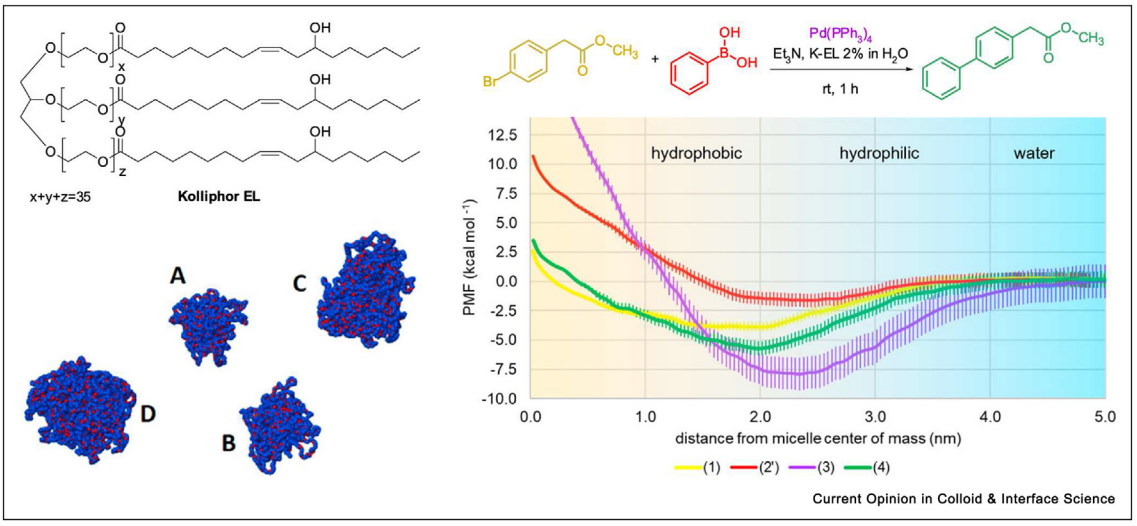


Chemical structures of representative a) industrial and b) designer surfactants.

spherical micelles having a lipophilic core and a hydrophilic water swollen corona. Calculations show that the various components of the prototypical S-M reaction between phenylboronic acid and 4-bromomethylbenzoate, in the presence of NEt_3 as the base and Pd tetrakis as the catalysts, colocalise at the interphase between polar corona and apolar core. This region is characterized by the presence of an interfacial dipole, having no role in the S-M reactions but responsible of the earliest examples of micellar catalysis induced selectivity in competitive reactions.

Sukenik and coworkers described the use an aqueous solution of the anionic surfactant sodium dodecyl sulphate (SDS) to catalyse the mercuriation of simple olefins and to control the selective monofunctionalisation of nonconjugated dienes, while promoting the effective partitioning of a reaction intermediate in a predictable and synthetically useful way [59]. Firstly, the authors demonstrated that the reaction carried out in a SDS solution at 2.5 times CMC works smoothly, with a behaviour similar to the one observed under the standard THF/H_2O control conditions. They then

Figure 2



Chemical structure of the industrial surfactant Kolliphor EL. Molecular dynamic model of K-EL micelles in water. Localisation of reactants, catalyst, and product in the S-M coupling of phenylboronic acid and 4-bromomethylbenzoate. Reproduced with permission [46].

moved to rigid, nonconjugated dienes, like limonene (**1**) shown in Scheme 2a, whose oxymercuration reaction in THF/H_2O leads to a distribution of 3 different products. The same reaction performed in SDS solution gives exclusively the alcohol **2** in 97% yield.

The selectivity induced by micellar catalysis became even more striking when mercuriating 4-vinylcycloexene **5** with one equivalent of $Hg(OAc)_2$. The reaction under standard THF/H_2O conditions gives a mixture of 8 different products, while the same reaction performed in SDS aqueous solution affords exclusively derivative **6** in 90% yield.

Authors pointed out that, despite the dynamic nature of the association colloids, the structure of the micelles imparts a net anisotropy to the substrate. On a time-average basis, the newly created polar end resulting from the reaction of the exocyclic double bond orients the molecule toward the hydrophilic compartment of the colloid, forcing the other double bond in a region not accessible to the polar $Hg(OAc)_2$. Such an interpretation was supported by the absence of selectivity observed in flexible nonconjugated terminal dienes lacking structural constraints in the reciprocal orientation of reacted and unreacted double bonds.

The same authors obtained kinetic data for the hydroxymercuriation reaction of 12-oxa[4.4.3.]propella-3,8-dien in THF/H_2O vs SDS solution, demonstrating that the observed chemoselectivity is due to the anisotropic solubilisation of monoreacted substrate molecules in micellar sites, differentiating the availability of the unreacted one to the aqueous compartment of the colloid [60]. Attempts at expanding the scope of the reaction to aromatic derivatives failed due to the known preferential solubilisation of aromatic molecules in hydrated environments with respect to simple aliphatic ones [61,62]. The oxymercuriation of p-diallylbenzene was in fact completely non-specific. While disappointing from the point of view of synthesis, the result clearly demonstrated the very limited penetration of water into the micellar core.

Grieco et al. observed similar results — rate acceleration and enhanced selectivity — in the Diels Alder reaction of **7** with diene **8** [63]. The reaction was performed in water alone, due to the self-emulsifying capabilities of sodium salt **8**. While comparing the results obtained using organic solvents (benzene and toluene, as well as neat reaction in the melt), the authors observed a steep increase in the reaction rate along with a remarkable selectivity towards derivative **9**. They ascribed the improved rate to the relative orientation of the reactants in a micelle, enabling a reduction of the entropy requirements for the bimolecular reaction. The selectivity in the formation of **9** over **10** was suggested to relate to the transition state volume. Derivative **9** transition state occupies a smaller volume than that leading to the adduct **10**, thus favouring better packing within the micelle.

Iacobucci et al. described the role played by SDS micellar solutions on the stereoselectivity of the acid-catalysed cyclization of the monoterpene (+)-citronellal (**11**) [64]. The control reaction was performed in dilute aqueous H_2SO_4 at a concentration just below the solubility limit of citronellal and gave the mixture of

products **12**–**15** shown in Scheme 2c. Derivatives **12** and **13** in a 2:1 ratio dominated the products distribution. When the same reaction was performed in SDS and below MAC for citronellal, the reaction became more efficient and the 2:1 ratio was increased to 5:1. Scheme 2c shows the reaction mechanisms leading to the formation of derivative **12** (path A) and **13** (path B). The observed selectivity in the formation of **12** can be connected to stabilising effect of the oxygen upon the tertiary carbocation formed in path A. The increased selectivity induced by SDS micelles was rationalized assuming that the reaction is occurring near the interface, where the high proton activity associated with the Stern layer promotes the acid-catalysed cyclization more effectively. As it is shown in the bottom part of Scheme 2c, the folded conformations **12a** and **13a** may orient themselves in the micelle so that the protonated carbonyls are pointing outwards. This arrangement favours the cyclization of **12a** but imposes an additional energy barrier to the reactivity of **13a**, both in the form of a more hydrophobic solvent (micellar core) for the incipient C-8 carbocation, and additional energy needed to expose the carbocation to water.

Bhagwat et al. exploited the interface dipole at the boundary of hydrophobic and hydrophilic districts of micelles to control the ratio between 1,2 and 1,4 reduction products in the reaction of isophorone with $NaBH_4$ in aqueous environment [65]. They observed that the use of ionic surfactants (SDS and CTAB) promotes the formation of the 1,4 products and that the rate of reduction depends on the surfactant concentration, according to increased solubility in the micellar solution.

The same research group later explored the regioselective oxychlorination of various activated and deactivated aromatic compounds in micellar media [66]. They used ^{1}H NMR spectroscopy to prove that the representative aromatic compounds 3,5-xylenol and benzoic acid feature a specific special orientation when in the presence of micellar media. Such results explained the observed ortho-selectivity in the corresponding chlorination reaction. The ortho-selectivity was found to be dependent on the solubility of the target in the micellar medium. The protocol was synthetically useful not only in improving regioselectivity, but also in promoting the conversion of deactivated aromatic compounds like chlorobenzene and iodobenzene.

Hydroformylation of alkenes is a further reaction benefiting from the specific orientation of the precursor within the micellar environment. Scarso and Strukul demonstrated that the use of anionic micelles formed by SDS improves both the catalytic performance and the regioselectivity of the hydroformylation reaction of alkenes mediated by the bis-cationic Pt(II) catalyst of the type $[P_2Pt(H_2O)_2](OTf)_2$ bearing large bite angle diphosphines [67]. The authors demonstrated that the use of surfactants is essential for the dissolution of the reagent. The improved selectivity was attributed to the positioning of the catalyst on the anionic surface of the micelle, enabling conversion of both linear and internal alkenes into the corresponding aldehydes with linear to branched ratios up to >99:1. The method proved to be particularly efficient for low polarity substates, thus further substantiating the interpretation of the results in terms of localization of the catalyst.

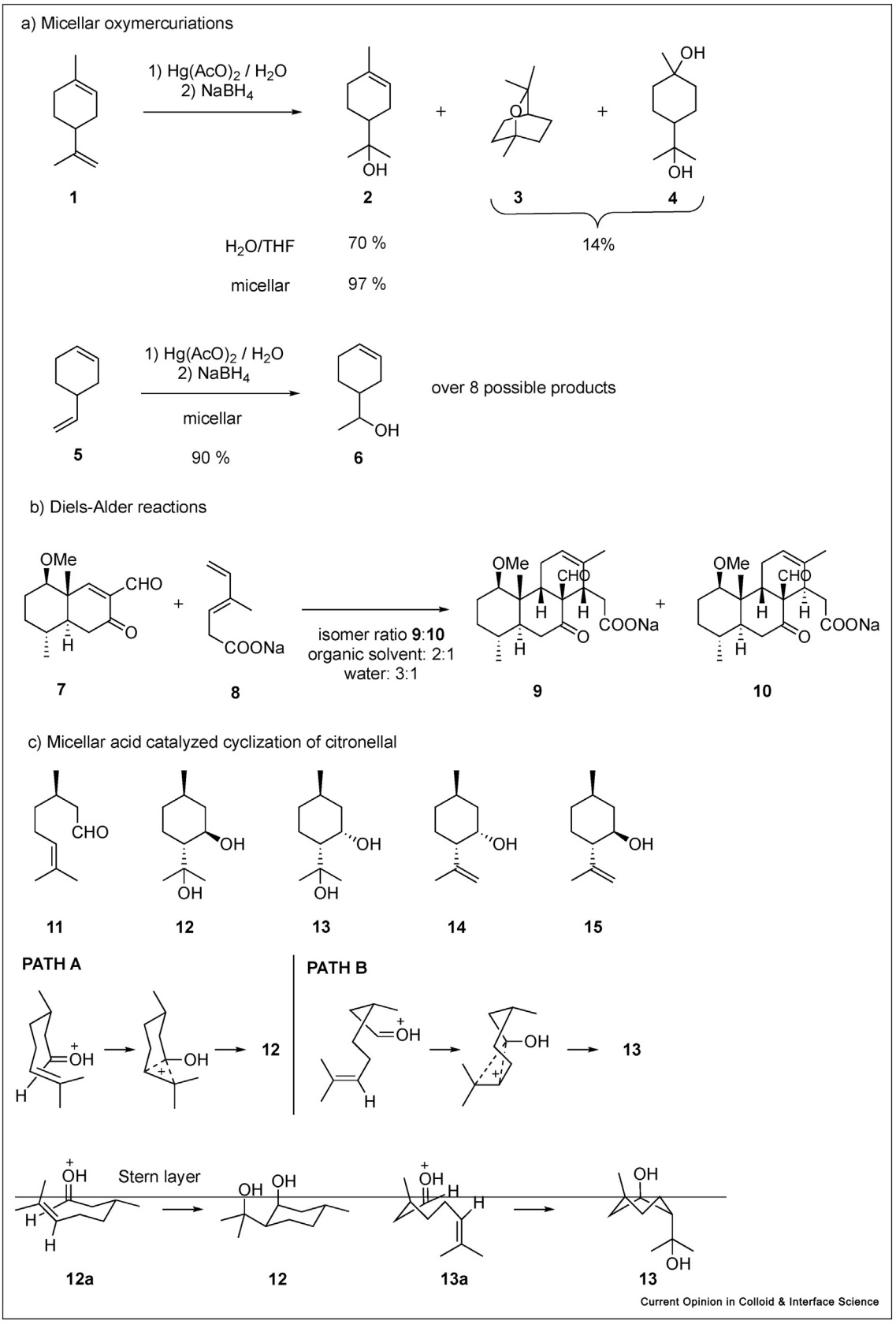
Selective interaction between surfactant and substrate: Towards surfactant induced chemo selectivity

In the previous section we have reviewed reactions carried out at concentrations below MAC, where the simple micellar model is appropriate and satisfactorily explains the results. Modern literature on micellar catalysis quite significantly deviates from such ideal conditions, generally suggesting surfactant concentrations in the 2–5 wt% regime and formal reagents concentration between 0.5 and 1.0 M [50]. We have already discussed how the formulative state of surfactant enhanced reactions changes when the concentration of the surfactant becomes significantly smaller than that of reagents and products. Unregarding to the specific nature of the various association colloids that become possible and likely coexistent, reactions can still be rationalised on the basis of the selective localisation of reactive species within specific pockets of the employed surfactants. The parallel with enzymatic catalysis is frequently invoked when discussing selectivity in micellar catalysis.

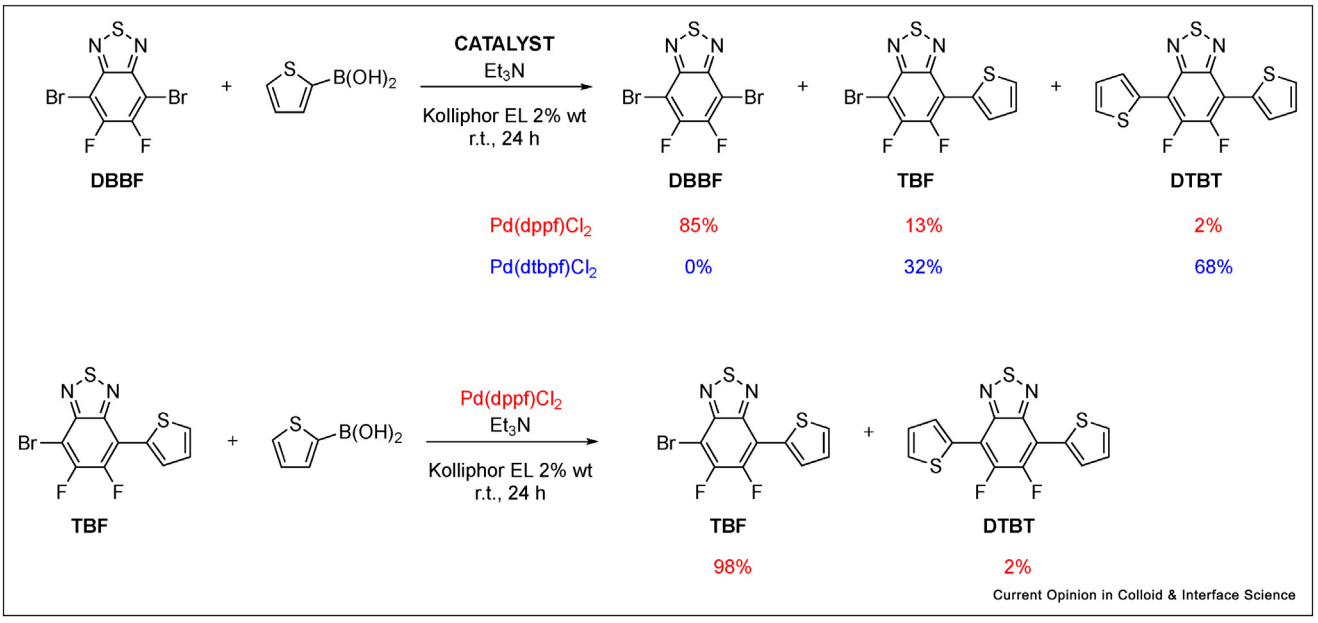
For a given reaction performed under relatively small surfactant concentration, achievement of complete conversion requires the assembly of reactive sites where reagents and catalysts can colocalise, efficiently convert into products, and eventually be released to be replaced by a new aliquot of fresh reagents. This process poses specific requirements to the surfactant to be employed [68]. The golden rule for the formulation chemist is to select a surfactant that mimics as much as possible the characteristics of the phase to be dispersed. For micellar reactions performed above MAC, this feature is not enough. It is paramount that the affinity of the surfactant for the product is inferior to that for the reagent to avoid saturation of the catalytic site by selective accumulation of the product. Such effects generally require change in the composition of the micellar solution but can also be exploited to control the product distribution in competing reactions.

Rathman et al. showed that it is possible to selectively monoalkylate aniline with 1-bromobutane to form N-butylaniline, strongly reducing the competitive double alkylation to N,N-dibutylaniline [69]. The authors observed that when performing the reaction in an

Scheme 2


a) Micellar oxymercuriations
1) Hg(AcO)2 / H2O
2) NaBH4
1
2
3
4
H2O/THF
70 %
14%
micellar
97 %
1) Hg(AcO)2 / H2O
2) NaBH4
micellar
90 %
5
6
over 8 possible products
b) Diels-Alder reactions
7
8
isomer ratio 9:10
organic solvent: 2:1
water: 3:1
9
10
c) Micellar acid catalyzed cyclization of citronellal
11
12
13
14
15
PATH A
PATH B
Stern layer
12a
13a
Current Opinion in Colloid & Interface Science

Scheme 3



Saturation of the catalytic site effects in the S-M cross coupling of 4,7-dibromo-5,6-difluoro-2,1,3-benzothiadiazole.

aqueous solution of surfactants, the use of excess aniline increased yield and selectivity towards monoalkylation. The use of an excess of bromobutane had the opposite effect. The lipophilic 1-bromobutane and both alkylation products are solubilised almost entirely in the micelles. The formation of relatively small amounts of N,N-dibutylaniline was observed to effectively inhibit further alkylation of N-butylaniline, leading to the observed increase in selectivity. In a control experiment, the authors observed that incorporation of small amounts of dibutylaniline in the micelles inhibits reaction between 1-bromobutane and butylaniline but not between 1-bromobutane and aniline. This work is a good example of selective interaction between components of the reaction mixture and surfactants can lead to synthetically useful results.

Sanzone et al. used a similar effect for the one pot synthesis of a series of unsymmetrically substituted 4,7-diaryl-5,6-difluoro-2,1,3-benzothiadiazole luminescent derivatives of interest for organic optoelectronics [70]. The authors observed that the S-M coupling of 4,7-dibromo-5,6-difluoro-2,1,3-benzothiadiazole (DBBF) and thiophene-2-boronic acid is surprisingly inefficient when carried out under micellar catalysis conditions using the neutral surfactant K-EL. The conversion of bromide was found to be insensitive to the excess of boronic acid employed. Under the very same experimental conditions, different boronic acids and/or dibromide derivatives gave near quantitative conversion of the double arylation product.

By reacting the mono arylation product TBF with excess thiophene-2-boronic acid, the authors observed minimal conversion of the starting bromide, with the formation of the double arylation products in 2% yield. Scheme 3.

The authors suggested that the double arylation product saturates the reaction site, thus preventing any further reaction. As the effect was believed to be specific of the selected surfactant, the authors explored the effect of blending K-EL with a lipophilic (Span 80) and hydrophilic (Tween 80) additional surfactant, observing that even when using very reactive catalysts, a more polar environment leads to preferential monoarylation over double arylation. They thus devised a two-step approach for the preparation of asymmetrically substituted double arylation products requiring a first monoarylation carried out in a polar surfactant mixture (K-EL:Tween 80 7:3), followed by a second one performed in a more balanced mixture obtained by further addition of the nonpolar Span 80 along with a second aliquot of a different arylboronic acid.

The formation of selective interaction between surfactant and reagents/products was also exploited by the

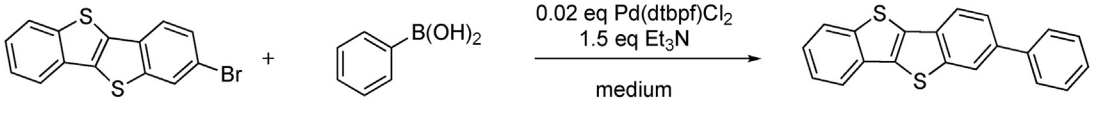
a) SDS induced selective mono oxymercuriation of limonene; b) Selective Diels-Alder reaction promoted by self-emulsification in water; c) acid catalysed cyclization of citronellal under micellar conditions.

same authors in a later study dedicated to the synthesis of molecular semiconductors of the [1]benzothieno[3,2-b][1]benzothiophene (BTBT) family [56]. Industrial and designer surfactants share the same set of noncovalent interactions while interacting with themselves and the lyophobic phase: dipole−dipole and Van der Waals. Some industrial surfactants feature unsaturations and/or benzene rings, thus introducing mild π-stack interactions. The authors demonstrated that the extension of the micellar catalysis methods to the manufacturing of molecules featuring an extended conjugation requires that the surfactant itself possesses a more extended π-conjugated structure. They also demonstrated that the specific electronic features of such π-systems have an impact on the conversion and distribution of products. In particular, the authors compared the performances of PiNap-750M and BTBT-750M (Scheme 1b) in promoting the S-M coupling of 2-bromo-[1]benzothieno[3,2-b][1]benzothiophene and phenylboronic acid using the industrial surfactant K-EL as the benchmark.

As it is shown Scheme 4, the otherwise generally performing K-EL is very inefficient in promoting this reaction. Visual inspection of the reaction mixture evidenced poor dispersion of the bromide and only with the addition of organic cosolvents and raising of the reaction temperature from 25 °C to 80 °C the reaction could be pushed to completion. Conversely, both BTBT-750M and PiNap-750M efficiently promoted the reaction at 25 °C and without the need for an organic cosolvent. Very remarkably, the reaction in BTBT-750M required 48 h to reach complete conversion, whereas the one in PiNap-750M only required 1 h. From the standpoint of selective interaction, PiNap-750M is expected to form stronger donor−acceptor π-π interactions with both bromide and product than BTBT-750M. Moreover, due to steric interaction, the arylation product is less planar than the corresponding bromide, thus negatively impacting on packing capabilities. It is thus expected that the reaction in PiNap-750M proceeds smoothly according to better solubilising capabilities and preferential affinity for reagents with respect to products. PiNap-750M was also suspected to interact with the palladium catalyst, thus possibly contributing to the catalytic cycle. In this sense, it can be considered as a catalytically active surfactant, i.e. a surfactant directly involved in the mechanism of the reaction.

The proline containing FI-750-M (Scheme 1b) is another surfactant capable of establishing selective interactions leading to enhanced selectivity. With respect to both industrial and saturated designer surfactants like TPGS-750-M, FI-750-M features a more polar lipophilic phase and it is thus particularly suitable to carry out reactions requiring polar derivatives and/or transitions states [71]. The proline linker is strategically placed at the boundary between apolar and polar pockets within the association colloid, a feature that turned particularly useful in the photoassisted selective oxyhalogenation of alkynes. When performed in homogeneous phase, the photoassisted reaction of terminal alkynes with N-bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) gives − alongside with the target α,α-dihaloketone - a mixture of products including α-haloketones and vinyl halides [72,73]. The authors demonstrated that NBS and NCS, due to selective binding to the proline residue, tend to accumulate at the boundary between water and oil phase. Such an effect is responsible for the steep increase in selectivity in the reaction of phenyl acetylene and NBS promoted by the photocatalyst eosin Y [74]. The cartoon on the right part of

Scheme 4

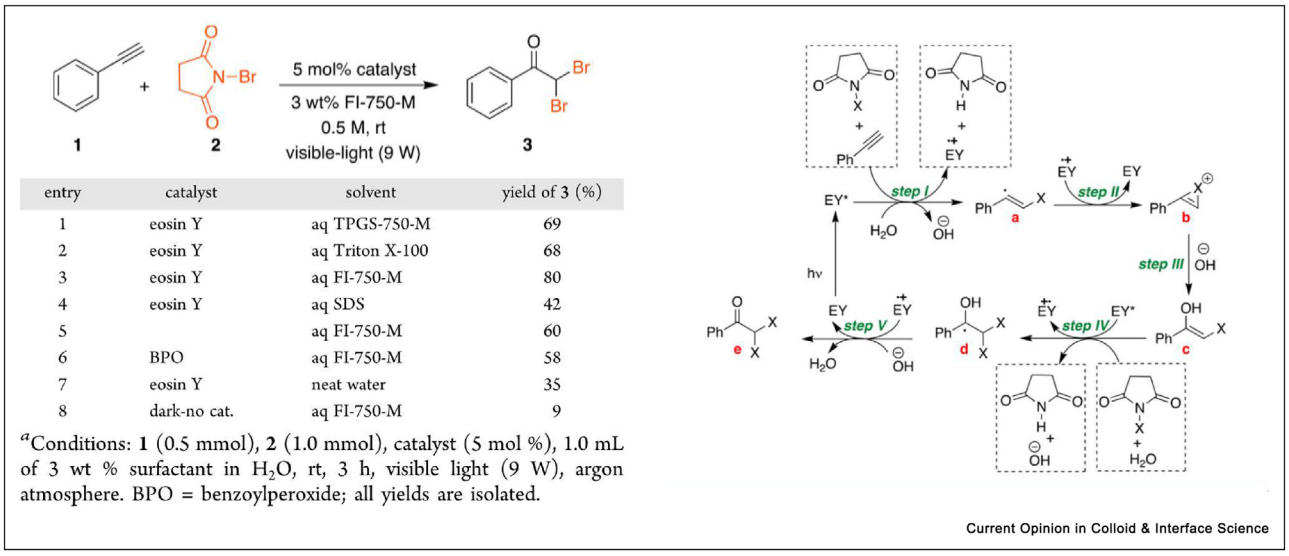


Entry	Medium	Atmosphere	Temperature (°C)	Time (h)	Yield (%)
1	K-EL 2%	Air	25	6	26
2	K-EL 2%:THF 9:1 v/v	Air	25	6	50
3	K-EL 2%:toluene 9:1 v/v	Air	25	6	45
4	K-EL 2%:toluene 9:1 v/v	Air	80	1	90
5	BTBT-750M 2%	Air	25	24	73
6	PiNAP-750M 2%	Air	25	1	78
7	BTBT-750M 2%	N_2	25	48	97
8	PiNAP-750M 2%	N_2	25	1	97

Current Opinion in Colloid & Interface Science

Selectivity induced by dipole-dipole interactions in the synthesis of π-extended molecular materials.

Figure 3



entry	catalyst	solvent	yield of 3 (%)
1	eosin Y	aq TPGS-750-M	69
2	eosin Y	aq Triton X-100	68
3	eosin Y	aq FI-750-M	80
4	eosin Y	aq SDS	42
5		aq FI-750-M	60
6	BPO	aq FI-750-M	58
7	eosin Y	neat water	35
8	dark-no cat.	aq FI-750-M	9

[a]Conditions: **1** (0.5 mmol), **2** (1.0 mmol), catalyst (5 mol %), 1.0 mL of 3 wt % surfactant in H_2O, rt, 3 h, visible light (9 W), argon atmosphere. BPO = benzoylperoxide; all yields are isolated.

Left. Selective oxyhalogenation of alkynes in FI-750-M aqueous solution. Right. Possible explanation of the observed higher selectivity. Reproduced with permission [61].

Figure 3 shows a rationalization of the observed selectivity, based upon the accepted mechanism of such reaction when in the presence of eosin Y [75].

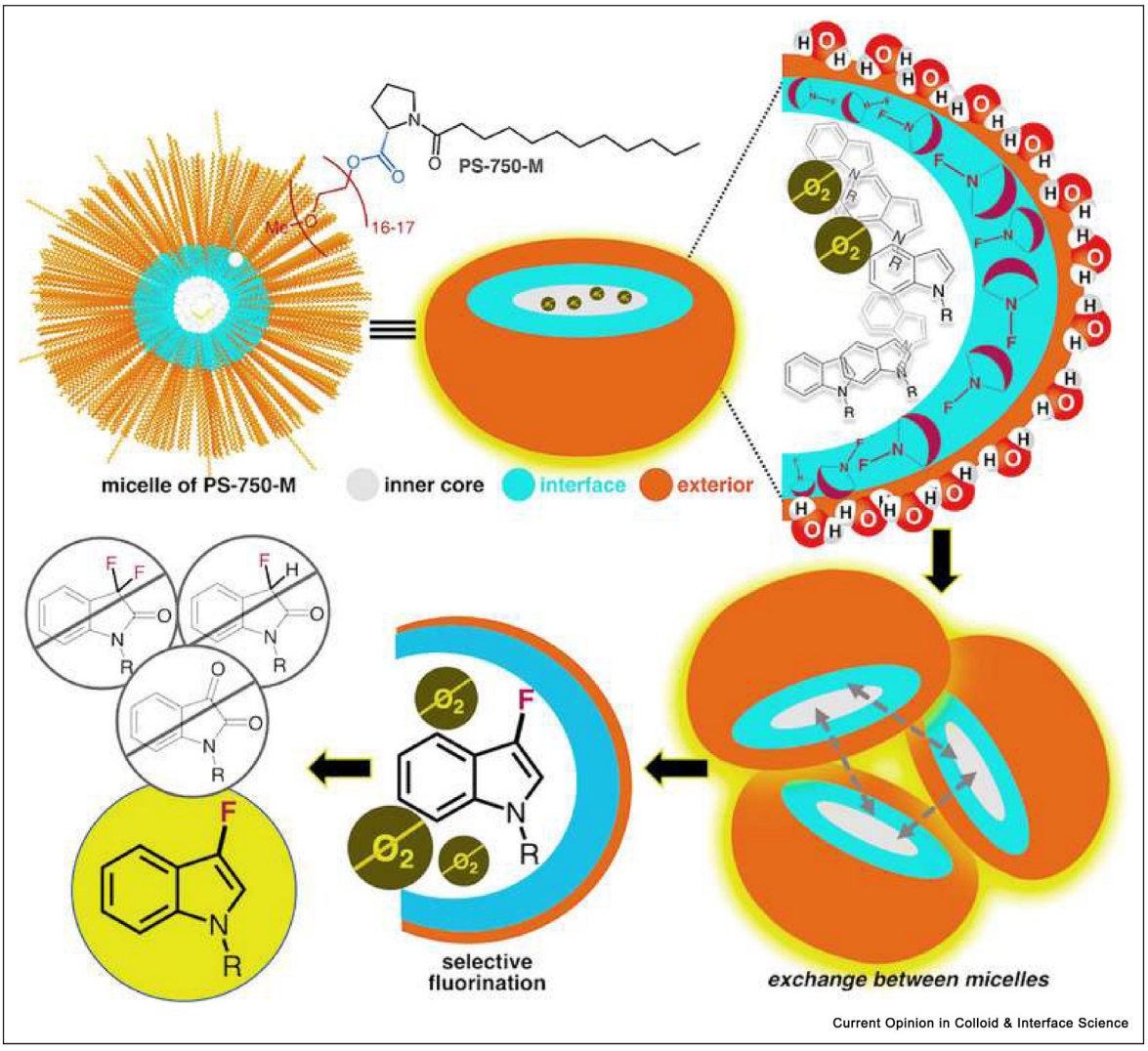
In the first step, the eosin excited state (EY^*) photoreduces the alkyne and NBS (or NCS) mixture with the formation of a halovinyl radical. The eosin radical cation than oxidises the halovinyl radical with the formation of the strained intermediate b (step II), which readily reacts with the hydroxide generated in step I to form α-hydroxy halostyrene intermediate c (step III). Another photoinduced electron transfer from EY^* leads to the formation of the α-hydroxy dihaloradical d (step IV). The hydroxide ion generated in step IV and radical cation of EY mediate the formation of e as the final product. As no unstaurations are left, the reaction does not proceed any further. Selectivity thus results by a combination of two effect: the selective interaction of the proline residue with NBS and NCS defining where the reaction effectively happens, and the solubility of eosin only in the outer polar phase. The boundary between the two phases is the only place where all reagents are present and additional reaction pathways not requiring the copresence of all reagents are silenced.

Compartmentalisation effects: Two reactions in the same flask

Aqueous surfactant solutions are micro-heterogeneous environments where hydrophilic, lipophilic, and amphiphilic compartments coexist, and chemical species can migrate. This feature offers a powerful control tool, as reactants having large partition coefficients between water and oil phase can be considered as interacting only at the interphases. Such compartmentalisation effects can be very resourceful in controlling the selective interaction of a given chemical species with only one of the several possible counterparts that are simultaneously present in the same reaction flask. The group of Handa gave particularly convincing evidence of the impact on selectivity of micro-heterogeneous over homogeneous phase reactions.

The selective monofluorination of indoles is a challenging task as generally electrophilic fluorination of the preformed heterocycle results in the formation of 3,3-difluoro-2-oxindoles [76] and 3,3-difluoro-3H-indole [77]. The use of a micro-heterogeneous environment, allowing for site-specific solubility of substrate and fluorine source in a specific compartment of the association colloid, makes it possible to dramatically improve selectivity over the monofluorination product [78]. As it is graphically schematised in Figure 4, the approach is based on the differential solubility of indole, monofluoro indole and fluorinating agent (Selectfluor™) in the various compartments of the micro-heterogeneous reaction environment. Slectfluor™ is polar and is thus preferentially localised in the hydrophilic portion of the micelles. Indole is more soluble in the lipophilic district, a feature even more pronounced in its monofluorination product. As such, Selectfluor™ and indole can only react at the boundary between hydrophilic and hydrophobic regions, and as soon as the first fluorination proceeds, the monofluoro indole migrates into the inner core of the micelle, thus preventing any further reaction. The low concentration of oxygen within the micelle also prevents the formation of oxindole and isatine, other common by-products of electrophilic fluorination. The

Figure 4



Selective monofluorination of indole according to a compartmentalization effect. Reproduced with permission [78].

generality and scope of the process was extensively investigated in over 20 examples of indole derivatives as well as on substituted benzenes, naphthalene, and pyrene derivatives.

The selective sulphonylation of polyfluoroarenes is another example of micellar method exploiting selective solubilisation of different reaction partners in different portions of the micellar micro-heterogeneous environment. Nucleophilic aromatic substitutions are amongst the many examples of reactions particularly efficient under micellar catalysis [79]. Yet, the sulphonylation of polyfluoroarenes via S_NAr poses specific challenges due to the water solubility of the peculiar nucleophile required, a sulphinate salt. As already described, the FI-750-M amphiphile forms micelles with different binding sites, capable of selectively interacting with polyfluoroarenes and sulphinate salts. The proline linker mimics the structural features of aprotic dipolar solvents like DMF and NMP, and preferentially dissolves the sulphinate nucleophile. Conversely, the perfluoroarenes will preferentially localise in the inner lipophilic core. The selective solubilisation of the different counterparts was also computationally characterised [80]. Most remarkably, not only the method enabled the synthesis of a wide range of sulphonated polyfluoroarenes, but was also efficient in the synthesis of polymeric membranes.

The effect of compartmentalisation effects in improving selectivity is particularly evident in photoredox arylation

reactions [81,82]. Such transformations are gaining increasing interest as possible alternative to more establishes metal-mediated cross coupling reactions, as the absence of a metal is advantageous in the purification, particularly for pharmaceuticals where metal traces must be particularly low. Even though powerful and gaining in generality, the method is still hampered by the need for over stoichiometric reagents to avoid the formation of by-products. Understanding of the issue requires a brief description of the catalytic cycle.

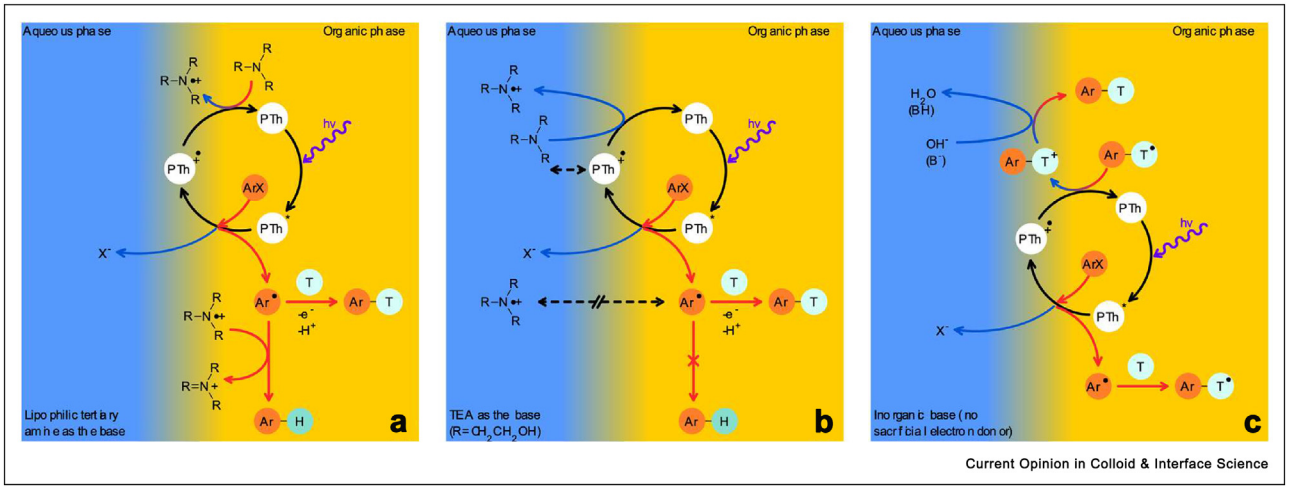
In the prototypical reaction, an aryl halide (Ar—X) is photoreduced to the corresponding radical ($Ar^{\bullet}$) by a photo induced electron transfer operated by a suitable photosensitiser in the corresponding excited state (Cat^{*}). The photosensitiser act as a catalyst and is immediately reduced to ground state (Cat) by a sacrificial tertiary amine (NR_3), consequently forming the corresponding radical cation ($R_3N^{+\bullet}$). The $Ar^{\bullet}$ radical can either intercept the coupling partner (T), with subsequent formation of the product (Ar—T), or react with $R_3N^{+\bullet}$ to give the hydrodehalogenation side product (Ar—H). The reaction selectively gives Ar—T only if T is used in large excess (typically 20—50 equivalents), which clearly limits the synthetic usefulness [75]. In the absence of NR_3, only the relatively diluted radical $^{\bullet}$Ar—T can reduce the Cat^{*} intermediate, thus seriously slowing down the reaction [83]. The use of poorly soluble tertiary amines ensures both the presence of the required reducing agent (necessary to regenerate the catalyst) and the swift removal (by precipitation) of the unwanted corresponding radical cation, thus establishing a trade-off between the selectivity and reaction speed [84]. However, such an approach requires custom-made amines. The use of micellar catalysis offers a simpler and cheaper alternative.

The key to selectivity is the efficient removal of the $R_3N^{+\bullet}$ intermediate from the reaction site, while at the same time ensuring the presence of the parent amine. According to the same mechanisms proposed to explain the enhanced selectivity in the monoarylation of indoles described by Handa et al., the micellar environment is ideal to fulfil both conditions in the same reaction flask.

Indeed, different amines can have different partition coefficients so that lipophilic amines like tributylamine will preferentially localise in the micellar apolar core, whereas hydrophilic amines like triethanolamine will preferentially localise in the water phase. In both cases, however, the $R_3N^{+\bullet}$ formed while regenerating the photocatalyst is an ionic species, and will leave the micellar region, where both the target arene and bromide are localised. As it is shown in Figure 5, this process fulfils the conditions for selective and efficient photoredox coupling as, provided that an amine with suitable partition is selected, the sacrificial donor will be available within the micelles, but the corresponding $R_3N^{+\bullet}$ species will be immediately removed from the reaction site thus preventing the hydro dehalogenation pathway [58].

The authors further improved on the method by incorporating the photocatalyst within the structure of the surfactant (derivative S—PTh shown in Scheme 1b).

Figure 5



Cartoon of the accessible paths of the oxidative catalytic cycle in emulsion, depending on the nature of the base employed. (A) Lipophilic tertiary amine: the amine closes the catalytic cycle in the oil phase, thereby turning into $R_3N^{\bullet+}$. Such species localises preferentially at the aqueous/organic interphase, thus being still able to interact with $Ar^{\bullet}$, and promoting the formation of Ar—H. (B) Hydrophilic tertiary amine (like TEA): the catalytic cycle can still be closed by the tertiary amine, but in this case the $R_3N^{\bullet+}$ is hydrophilic and migrates in the aqueous phase, thus being unable to interact with $Ar^{\bullet}$ and form Ar—H. (C) No sacrificial electron donor present: the catalytic cycle can only be closed by Ar—$T^{\bullet}$, which transforms into Ar— T^{+}, eventually being deprotonated to Ar—T in the water phase by the action of a mineral base. Reproduced with permission [58].

According to such method, pyrrole and indole derivatives can be efficiently arylated with a variety of bromides in good to excellent yield, while completely avoiding the formation of the hydrodehalogenation of the employed bromide and without recurring to neither large excess of pyrrole/indole partner nor the use of specialised amines.

Conclusion and outlook

The field of micellar catalysis has evolved enormously in the last 20 years, after the discovery that reactions can be performed efficiently even at formal concentrations exceeding MAC by orders of magnitude. Such fundamental finding enabled the development of a plethora of surfactant enhanced reactions of high practical value for preparative chemistry. The scope, efficiency and overall operational simplicity of micellar catalysed reactions are so impressive that one really wonders why such methods are not even more widespread than they already are. As mentioned through the text, efficiency is not the only feature of such reactions. Selectivity is another very relevant characteristic that further supports the analogy between micellar and enzymatic catalysis. The field has been reviewed many times, even recently, mostly highlighting sustainability, efficiency, and generality. This review offers a different perspective by focusing on selectivity, highlighting contributions coming both from relatively old articles, describing reactions below MAC, and new ones, performed well above MAC but showing features that can be rationalised following similar arguments. The formation of association colloids enhances selectivity according to three fundamental mechanisms, non-necessarily independently operating. The first one is the consequence of the formation of an interface dipole between water and oil phase. The second one relies on the compartmentalisation of species featuring different partition coefficients. The third one arises from specific interactions between reagents and products with surfactants. This latter phenomenon can also be exploited to control the stereochemistry of reactions using enantiomerically pure surfactants, a topic we did not cover as an exhaustive review on the topic was recently published [85].

The field is further evolving in several, equally relevant directions. The quest for the development of new and improved designer surfactants [86], the development of heterogenous catalysts — mostly in the form of nanoparticles — that are compatible with micellar approaches [87,88], the reduction of metal catalysts to ppm level [89—91], and at the forefront of the whole field, the cooperative exploitation of micellar and enzymatic biocatalysis [37,92]. Joining the dots of all such promising approaches becomes increasingly difficult, yet the main message of the contributions summarised in this and other recent excellent reviews is that the features of the bona fide, below MAC, micellar approach are mostly preserved even when working not only above MAC but under emulsion and even dispersion conditions. Moreover, supported, and heterogeneous catalysts can be employed and remain advantageous, both in terms of efficiency and ease of operations. Within this exciting and rapidly evolving panorama, one missing topic still seems to remain unexplored, perhaps the one most directly leading to real artificial enzymes. We have discussed examples where selectivity stems from the presence of an interface dipole, and others where it stems from specific polar interaction with the chemical species involved in the reactions. One wonders whether it would be possible to define stable catalytic sites where interface dipoles, direct and directional dipole—dipole interaction with the surfactants and compartmentalisation can coexist thus creating an analogue for the active pocket of an enzyme. Examples of such stabilised nanoreactors are appearing in the most recent literature [93]. The development of heterogenised and molecularly imprinted catalysts could lead to such a remarkable result and is likely worth exploring.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Luca Beverina reports financial support was provided by Ministero dell'Università e della Ricerca (2017YXX8AZ PRIN grant).

Data availability

No data was used for the research described in the article.

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