CHAPTER 12

Transition Metal Catalysis in Micellar Media: Much More Than a Simple Green Chemistry Promise

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12.1 Introduction

Spurred by the nowadays well-established environmental sensitivity, the new perspectives in organic synthesis and catalysis are strongly bound to the twelve principles of Green Chemistry. The latter is not just a young subdiscipline of Chemistry but also a new reference standard for research in the general field of synthetic organic chemistry. In the synthesis of fine chemicals or pharmaceuticals, solution chemistry is the standard approach, often performed with the aid of soluble catalysts using traditional batch reactors. Among the constituents of a liquid phase reaction, the solvent is by far the major component, representing about 80% of the total mass; regrettably, however, its recovery and recycle suffer from only moderate efficiency. This in turn imposes the problem of disposing large

amounts of exhausted solvents, particularly in the pharmaceutical industry where the final product is very often the result of numerous steps. According to an evaluation carried out on the Swiss chemical industry (based mainly on fine and pharma chemicals), at the end of a process, solvent recovery is barely above 30%, the remaining being simply burnt to recover heat.[1] This situation entails several economic as well as environmental drawbacks related to both new solvent supply and increased gas emissions into the atmosphere. In this context, the environmental acceptability of the solvent used becomes a key issue. This is the main reason why, in industrial practice, methanol, acetone, and toluene are the most common reaction media.

In a chemical reaction, the solvent fulfills several functions at the same time: (i) it ensures the contact between reagents of different polarities, (ii) it controls heat transfer, and (iii) it favors reactant interactions leading to the formation of the final product. Among the different possible solvents, water could be the most desirable option as it conjugates the lowest impact on the environment with other advantages. In fact, it is economic, non-toxic, non-flammable, it has tuneable acidity, high heat capacity and large heat of evaporation (which allows easy control of exothermic reactions), high polarity, the coexistence of both hydrogen bond donors and acceptors, it produces neither greenhouse emissions nor it requires synthesis, and finally its E-factor is assumed to be equal to zero.[2] In one word, it can be considered the green solvent *par excellence*. However, against these beautiful features, water suffers from the fundamental disadvantage of not being able to dissolve hydrophobic molecules, such as most organic molecules and organometallic catalysts used in homogeneous phase industrial processes for the synthesis of many commodities, fine chemicals, pharmaceuticals, *etc.* This behavior is due mainly to the so-called classical 'hydrophobic effect',[3] an example of entropic effect where the solvation by water of a hydrophobic organic reactant or the hydrophobic portion of a molecule spontaneously leads to the aggregation of the apolar surfaces, thus requiring a reduced number of water molecules for solvation and liberating several other water molecules with a large overall increase of entropy.

Nevertheless, organic chemistry in water has been successfully applied in several cases because the hydrophobic effect may result also in 'compaction' of the reagents in the transition state, increasing the reaction rates as observed for the first time by Breslow some forty years ago in a Diels–Alder reaction.[4] The most common approach in the use of water as the solvent has been the introduction of appropriate hydrophilic tags on the ligands of intrinsically hydrophobic catalysts and the use of water–organic two phase systems. In this way, the soluble catalyst remains confined in water and can be easily recycled at the end of the reaction by simple decantation, thus solving one of the major weak spots of homogeneous catalysis. This approach has been the basis for the well-known Ruhrchemie-Rhone Poulenc industrial process for the production of butyraldehyde *via* hydroformylation.[5]

Still, how does Mother Nature manage the problem? All enzymatic reactions occur in water and enzymes are amphiphilic macromolecules based on proteins containing both hydrophilic functional groups and large hydrophobic portions. Their compatibility with water is ensured by the hydrophobic effect, which forces the protein part of the enzyme to fold exposing the hydrophilic groups on the external surface in contact with water, thus endowing the enzyme with solubility. At the same time, the hydrophobic portions are confined inside and assume the enzyme characteristic structure, held together by weak interactions (H-bonds, dipole–dipole interactions, *etc.*), that are responsible for the extraordinary catalytic activity and selectivity of these macromolecules capable of picking up the right substrate in a complex mixture and transforming it into the right product. The inside part of an enzyme, where the active site is typically located, is therefore a hydrophobic nanophase separated from water and a suitable reaction medium for hydrophobic reagents.

Soaps, which have been used by man for about 2000 year to remove fats, operate by the same principle. Records on their preparation are reported by Pliny the Elder in his *Naturalis Historia*,[6] where he describes a strange practice by Gauls, who used to melt together tallow and wood ashes, obtaining upon cooling a solid material called *sapo*. Surfactants, the active ingredients of soaps, are amphiphilic molecules with a polar hydrophilic head and a hydrophobic tail that, above a certain concentration (the critical micellar concentration or cmc), self-assemble in solution to give nanometric aggregates (micelles) where the hydrophilic heads are concentrated on the surface in contact with water while the hydrophobic tails point inside. Similarly to enzymes, they constitute an organic nanophase dispersed in water capable of dissolving hydrophobic molecules (such as fats). Surfactants are a wide class of generally cheap chemicals largely available commercially as anionic (**A**), cationic (**C**), zwitterionic (**Z**), and neutral (**N**) molecules (see Figure 12.1 for some examples).
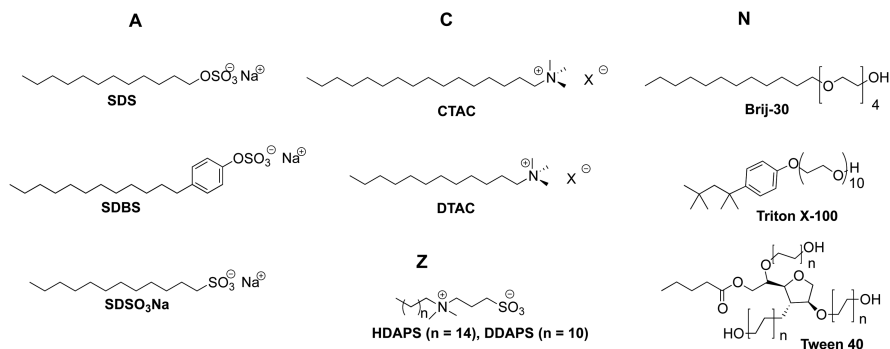
Figure 12.1   Some examples of commercially available surfactants: **A** (anionic), **C** (cationic), **Z** (zwitterionic), and **N** (neutral).
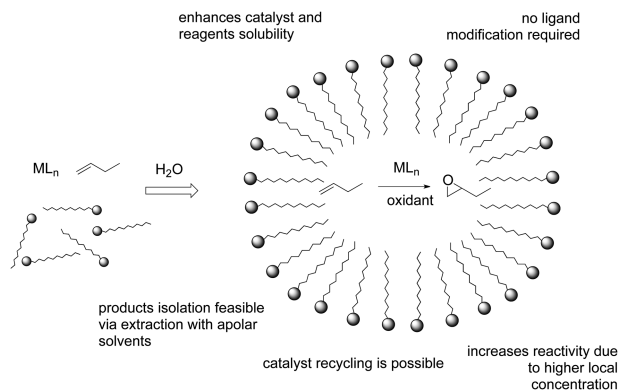
Figure 12.2   Scheme representing a micelle as a nanoreactor through self-assembly and dissolution of reactants, products, and catalyst in an epoxidation process. The advantages of this approach are also indicated.

Micelles can be seen as nanoreactors[7] capable, in principle, of dissolving hydrophobic substrates and catalysts already known to work in organic solvents without the need for modifying the ligands to make the system compatible with water, thus being potentially applicable to a large array of processes. Dissolution inside micelles generally leads to higher local concentrations with respect to ordinary solvents, implying a possible increase in reactivity; moreover, the chance to extract reaction products with water-immiscible organic solvents at the end of the reaction opens the way to possible catalyst recycling with evident economic advantages and better perspectives for practical applications (Figure 12.2).

Clearly, the need for product extraction from aqueous phases raises some possible criticism about the green character of catalysis in water, because organic solvents are involved anyway and the resulting water becomes a water stream contaminated by organics subjected to restrictions before disposal that must be purified by common techniques, such as stripping under vacuum or adsorption on activated carbon.[8] However, as long as water provides extra performance in terms of activity and selectivity, the concerns about the use of limited amounts of traditional solvents at the end of the reaction are at least mitigated and, in the case of successful recycling, reduced to a minimum.

The general subject of micellar catalysis has been reviewed several times over the years since the 1970s.[7a,9] Furthermore, some recent papers have appeared on some new, specific trends in micellar catalysis such as the application to multicomponent reactions,[10] the use of metal nanoparticles associated with micellar media,[11,12] the combination with visible light photo-redox catalysis,[13] or the development of new surfactants endowed with new catalytic head-groups.[14] The present contribution will focus specifically on the use of classical transition metal catalysts, picking from the

authors' personal experience, and the advantages of their use in micellar media in terms of activity, selectivity, and ultimately green chemistry advances with specific reference to the synthesis of fine chemicals and pharmaceuticals.

12.2 Early Studies on Enantioselective Oxidation

When we first entered this topic 15 years ago, the most common approach to transition metal catalysis in water was inspired by the Ruhrchemie-Rhone Poulenc process for the synthesis of butyraldehyde by hydroformylation,[5] *i.e.*, *via* the introduction of hydrophilic tags on the ligands surrounding the transition metal center in order to make it soluble in water. Thus, having to decide what prototype reaction to investigate to test the limits of micellar conditions, we opted for enantioselective oxidation for two main reasons: first, because it is a key step in the synthesis of a variety of active pharmaceutical ingredients (APIs) such as omeprazole (anti-ulcer), taxol (anti-cancer), indinavir (anti-HIV), among others; second, because enantioselective oxidation with hydrogen peroxide as the oxidant and platinum(II) complexes as catalysts was a system that we had thoroughly studied for the previous 25 years. In fact, complexes of general formula $[(P\text{-}P)Pt(R)]_n(A)_n$, where P-P is a diphosphine; R = $-CF_3$, $-C_6F_5$, $-$OH; A is a weakly coordinating anion such as BF_4^-, ClO_4^-, or triflate; and n = 1 or 2, are stable catalysts for a variety of oxidation reactions such as epoxidation,[15] sulfoxidation, hydroxylation of aromatics,[16] and the Baeyer–Villiger oxidation of ketones,[17] showing peculiar selectivity properties and good activity. Two examples are reported in Figure 12.3.
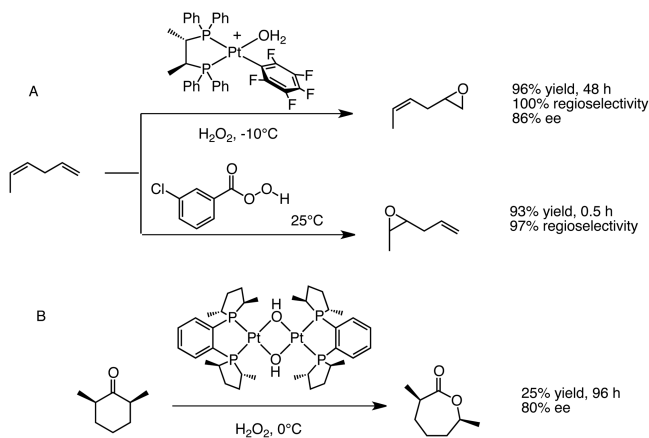
Figure 12.3 Two typical examples of enantioselective oxidation with hydrogen peroxide as the oxidant using chiral platinum(II) complexes as the catalysts: (A) epoxidation of a diene and regioselectivity comparison with *m*-chloroperbenzoic acid, and (B) desymmetrization of a *meso* cyclohexanone through Baeyer–Villiger oxidation.
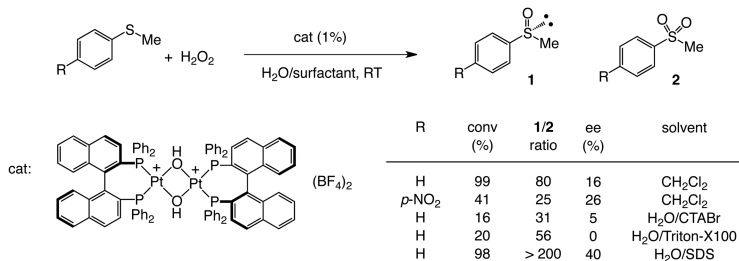
These systems allowed the first successful use of aqueous hydrogen peroxide as the oxidant in a variety of oxidations without any waste of oxidant in side-reactions using soluble transition metal complexes as catalysts. These properties, along with the high product yields, high product selectivity, and mild conditions required, make these systems a good example of Green Chemistry *ante litteram*, as their discovery dates back to the early 1980s, *i.e.*, several years before the twelve principles of Green Chemistry were established. This excellent performance is strongly linked to the choice of Pt(II) centers as catalysts for a number of reasons, some of which were clear only retrospectively: (i) ligands on Pt(II) are less labile than on, *e.g.*, Pd(II) or Rh(I), making the catalyst more stable under strong oxidizing conditions and allowing the safe use of phosphines as ligands with the consequent advantage of better tuning of the steric and electronic properties at the metal center; (ii) diphosphine Pt(II) complexes are inert to oxidative addition, reducing the number of oxidant activation steps and improving selectivity; (iii) Pt(II) does not undergo one-electron redox pathways imparting the oxidant with better stability; and (iv) Pt(II) is a slow catalyst in β-hydride addition/eliminations, preventing the occurrence of Wacker chemistry as is the case of, *e.g.*, Pd(II). In addition to that and with respect to the specific use of these systems in micellar catalysis, we can also add: (v) the observed high activity and selectivity at all levels (chemo-, regio-, enantio-) are important for testing the potential of micellar systems and evaluate all the *pro*'s and *con*'s with respect to a traditional solvent; (vi) water is already present in the system both as the solvent for hydrogen peroxide and as the reaction product; (vii) the catalyst is stable in water, a condition that does not occur with, *e.g.*, early transition metals being strongly Lewis acidic that readily decompose in the presence of water.

12.3   Oxidation in Micellar Media

The first process investigated in soapy water was the enantioselective sulfoxidation of a variety of arylmethylsulfides with hydrogen peroxide using a $[(P-P)Pt(\mu-OH)_2]^{2+}$ catalyst, where P-P is a chiral diphosphine ligand.[18] The synthetic protocol is very simple: reagents and catalyst are placed in water, where (with the exception of H_2O_2) they are not soluble and, upon addition of a suitable surfactant at a concentration above the cmc, they readily dissolve. The reaction can be carried out in air at room temperature with excellent yield in short times. As shown in Figures 12.4 and 12.5, the choice of surfactant as well as its concentration are critical to maximize the reaction rate and enantioselectivity.

As can be seen under optimized conditions and in comparison with the reaction carried out in an organic solvent, high conversions are preserved while the enantioselectivity of the system is improved.

Similar results were observed in the enantioselective epoxidation of terminal alkenes[15e,19] and the Baeyer–Villiger oxidation of cyclic ketones[20] also

Figure 12.4 contains the reaction scheme and the following data table:

| R	conv (%)	1/2 ratio	ee (%)	solvent
H	99	80	16	CH$_2$Cl$_2$
p-NO$_2$	41	25	26	CH$_2$Cl$_2$
H	16	31	5	H$_2$O/CTABr
H	20	56	0	H$_2$O/Triton-X100
H	98	> 200	40	H$_2$O/SDS

Figure 12.4 Oxidation of thioanisoles with hydrogen peroxide using a chiral platinum(II) complex as the catalyst: performance in different reaction media showing how H$_2$O/SDS improves the chemo- and enantioselectivity.
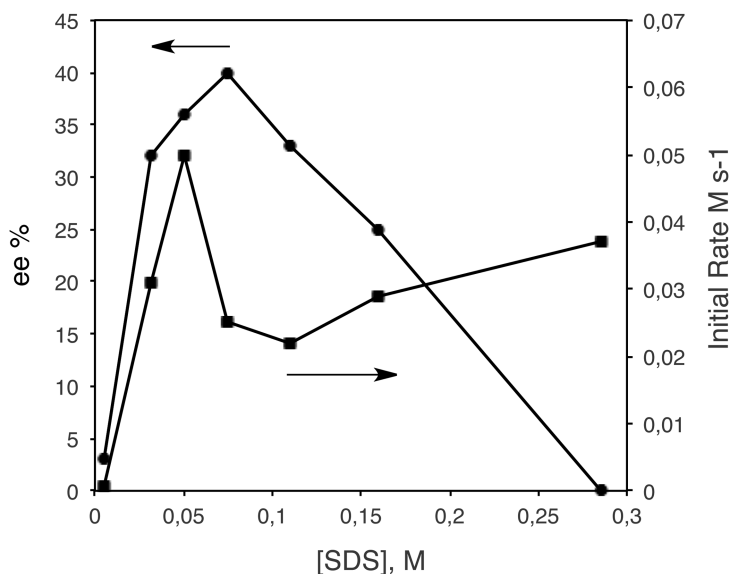

Figure 12.5 Effect of surfactant concentration on the initial rate of reaction (squares) and sulfoxide enantioselectivity (circles).

using hydrogen peroxide as the oxidant. In the former case (Figure 12.6), the use of Triton-X100 neutral surfactant allowed to significantly increase the enantioselectivity and also to separate and recycle the chiral Pt(II) catalyst for at least three times without loss of product yield and ee. A spectacular increase in both the yield and enantioselectivity was observed in the Baeyer–Villiger oxidation of substituted cyclobutanones using a Co(salen) complex previously reported by Katsuki and found virtually inactive in the same reaction.[21] As can be seen in Figure 12.7, the product yield increased from 15% to
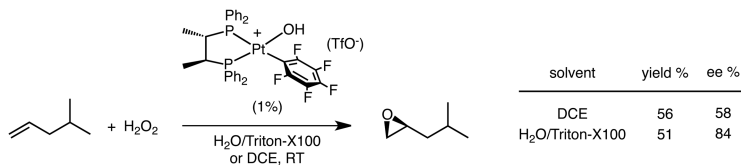
Figure 12.6 Effect of a micellar medium *vs.* DCE on the enantioselectivity of the epoxidation of a terminal alkene using a chiral platinum(II) catalyst.

| solvent	yield %	ee %
DCE	56	58
H$_2$O/Triton-X100	51	84
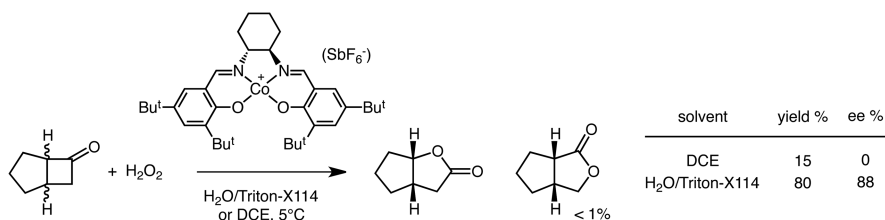
Figure 12.7 Spectacular amplification of the activity and enantioselectivity by a micellar medium in the Baeyer–Villiger oxidation of a substituted cyclobutanone using a chiral cobalt(III) complex as the catalyst.

solvent	yield %	ee %
DCE	15	0
H$_2$O/Triton-X114	80	88

80%, while the enantioselectivity increased from zero to 88%, an effect that is only due to the micellar medium.

12.4 Other Reactions

After this seminal work, many other reactions have been tested over the years, *e.g.*, Friedel–Crafts,[22] Stille,[23] Diels–Alder,[24] hydration,[25] hydroformylation,[26] nucleophilic aromatic substitutions,[27] indol functionalization,[28] alkyne hydroboration,[29] hydroaminomethylation,[30] isomerization,[31] hydrogenation,[32] C–H functionalization,[33] C–O bond formation,[34] and metathesis.[35] A comprehensive review of these processes is beyond the scope of this contribution; however, a few selected examples illustrating the synthetic potential and practical utility of micellar catalysis will be briefly summarized.

Figure 12.8A shows the asymmetric transfer hydrogenation of aromatic ketones to obtain the corresponding chiral alcohols, catalyzed by unmodified hydrophobic ruthenium, rhodium, and iridium chiral amido complexes.[36] This reaction was successfully performed with significant enhancement of activity, chemoselectivity, and enantioselectivity (up to 99% ee) in aqueous media containing micelles. The hydrophobic catalyst, embedded in micelles constructed from the surfactant cetyltrimethylammonium bromide (CTAB), could be separated from the organic phase along with the products and was recycled for at least six times.
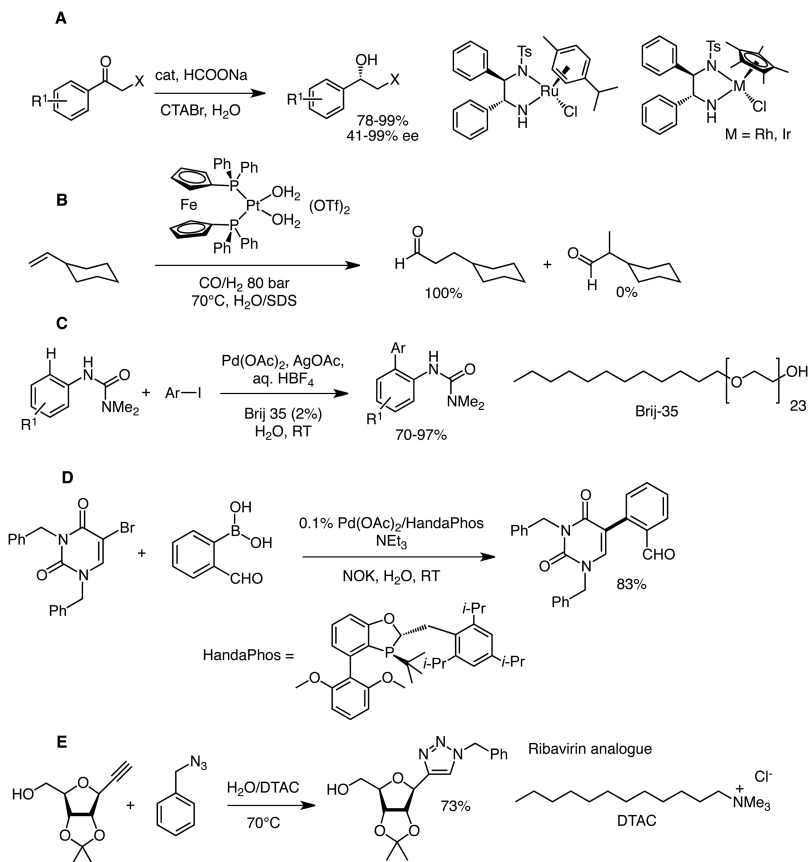
Figure 12.8 Some examples of catalytic reactions performed in micellar media:
(A) asymmetric transfer hydrogenation of aromatic ketones using
amido ruthenium, rhodium, and iridium catalysts; (B) hydro-
formylation of alkenes performed by cationic platinum triflate
complexes; (C) Pd-catalyzed arylation of anilides with aryl iodides
under mild conditions; (D) Suzuki–Miyaura cross-coupling carried
out with ppm levels of the catalyst; and (E) synthesis of a ribavi-
rin analogue *via* 1,3-dipolar cycloaddition between an alkynylated
riboside and benzyl azide.

The hydroformylation of a variety of terminal and internal alkenes was
efficiently performed by cationic platinum triflate complexes of the type
$[P_2Pt(H_2O)_2](OTf)_2$ under mild conditions in water/SDS as the micellar
medium (Figure 12.8B).[26] The use of surfactants is essential to ensure disso-
lution in water of both the catalyst and substrate, the former being positioned
on the anionic surface of the micelles. A large variety of diphosphine ligands
could be used; the best results were observed with the ferrocenyldiphos-
phine shown in Figure 12.8B that afforded linear aldehydes as the exclusive

products. The catalyst could be separated by extraction of the organic products with hexane and recycled for at least four times with only a modest loss of activity and no effect on the selectivity.

In 2010, the group of Lipshutz reported for the first time a Pd-catalyzed C–H activation/cross-coupling at room temperature consisting in the arylation of anilides with aryl iodides to give biaryl derivatives in good yields.[37] The combination of Pd(OAc)$_2$ and HBF$_4$ allowed for reactions of aryl ureas with aryl iodides under very mild conditions using micellar catalysis (Figure 12.8C). This reaction was made possible using an *in situ* generated cationic palladium catalyst in the absence of phosphine ligands. Essential to drastically improve the yields of some 24 different substrates with respect to non-micellar systems was the use of the commercially available neutral surfactant Brij-35.

More recently, the same group reported a large series of Suzuki–Miyaura cross-couplings involving highly functionalized reaction partners for the synthesis of pharmaceuticals using monophosphine HandaPhos as the ligand for the Pd catalyst and operating in water containing NOK.[38] This enabled Pd-catalyzed reactions to be run at ppm levels of this pre-catalyst instead of the usual 5 mol% employed in the traditional synthesis carried out in organic solvents, thus reducing the level of residual Pd in the products to about 1 ppm (Figure 12.8D). The catalyst could be recycled up to four times without loss of activity and product yield.

Finally, Uziel and coworkers reported in 2009 the synthesis of carbonated analogues of ribavirin (an antiviral drug active against both DNA and RNA viruses) starting from carbohydrate derivatives obtained by an alkynylation reaction mediated by indium(0).[39] The C-ribosides were then engaged in a Huisgen 1,3-dipolar cycloaddition reaction in micellar medium (Figure 12.8E). It is noteworthy that here, the surfactant does not only provide the reaction medium but also catalyzes the click reaction. Under these conditions, the formation of 1,2,3-triazoles with control of the regioselectivity was observed.
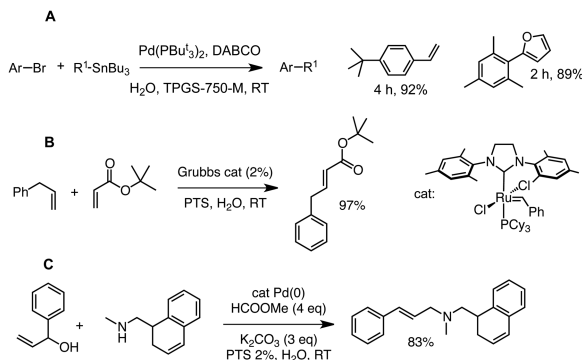
12.5 Designer Surfactants and Metallosurfactants

Given the importance of C–C bond forming reactions in drug synthesis, over the years, the group of Lipshutz has reported a series of especially designed unconventional neutral surfactants capable of improving the catalyst performance of a series of Pd-catalyzed transformations such as Stille, Suzuki–Miyaura, metathesis, allylic amination. *etc.* Some of these surfactants are shown in Figure 12.9.

They are all based on a PEG unit as the hydrophilic head, a natural product as the hydrophobic pocket (β-sitosterol in the case of PSS and NOK and tocopherol in the case of PTS and TPGS-750-M) and a variable length dicarboxylic acid as a spacer in between.
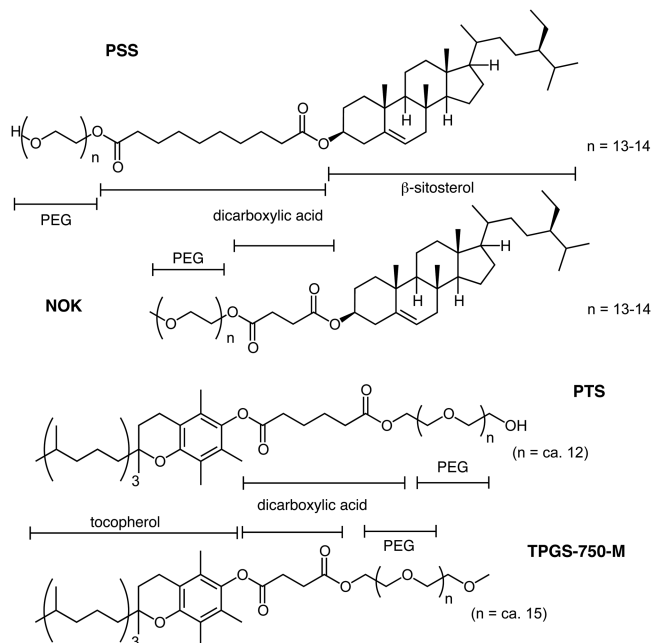
Figure 12.9   Designer surfactants reported by the group of Lipshutz.


Figure 12.10   Some examples of the use of designer surfactants in synthetically useful reactions: (A) Stille nucleophilic substitution, (B) metathesis between allylbenzene and acrylate esters, and (C) allylic amination.

Some examples on the use of these designer surfactants are shown in Figure 12.10 and they address some important features with respect to their possible practical applications. In fact, Stille nucleophilic substitution of arylbromides with organotin derivatives allowed the preparation of a variety of alkylaromatics working in water containing TPGS-750-M in short times and high yield under considerably milder conditions with

respect to those of organic solvent systems, where similar yields could be observed only at 80 °C, thus saving energy (Figure 12.10A).[40] Metathesis of allylbenzene and acrylate esters could be easily performed with Grubbs catalyst in PTS/water, proving a flexible system compatible with a variety of functional groups and allowing easier product isolation with respect to organic solvent systems (Figure 12.10B).[41] Finally, the antifungal Naftifine could be prepared *via* allylic amination under very mild conditions using traditional Pd catalysts operating in PTS/water media, allowing the facile amination of primary, secondary, and tertiary allylic alcohols (Figure 12.10C).[42]

The issue of catalyst permanent confinement in the micellar medium, sometimes a problem preventing catalyst separation and recycling, was addressed designing metallo-surfactants, where the catalyst is part of the surfactant structure, thus being not extracted from the micellar medium during product separation with organic solvents. Two examples are shown in Figure 12.11. A ring-closing metathesis reaction could be realized using the ruthenium catalyst shown in Figure 12.11A, where the metal is linked to the hydrophobic core (a ubiquinol unit) connected to a PEG chain with a dicarboxylic acid spacer using the same strategy adopted for the designer surfactants shown in Figure 12.9.[43] This strategy allows to recycle the catalyst up to ten times without loss of activity and selectivity. The opposite approach is shown in Figure 12.11B, where the rhodium catalyst is placed close to the hydrophilic head of a sulfonamide surfactant containing a variable length alkyl chain.[44] This was used for the asymmetric hydrogenation of a series of ketones to give the corresponding chiral alcohols with high conversion and enantioselectivity, observing that the latter could be increased upon increasing the surfactant alkyl chain length.
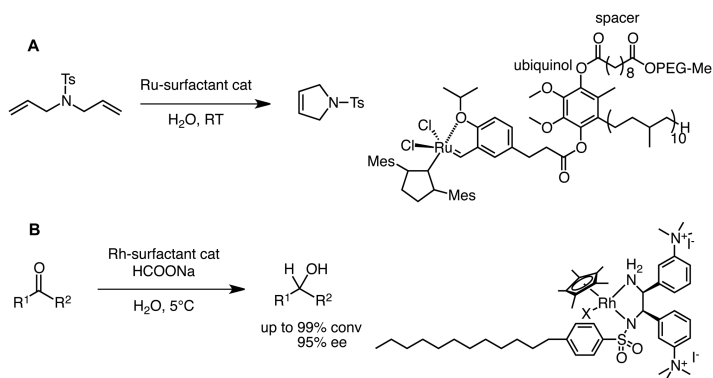

Figure 12.11　Two examples of the use of metallo-surfactants: (A) ring-closing metathesis using a ruthenium-surfactant catalyst, and (B) enantioselective hydrogenation of ketones using a rhodium-surfactant catalyst.

12.6   Importance of Catalyst–Surfactant Interactions

As evident from the examples reported in the previous sections, the use of micellar media not only entails the advantages arising from water being an environmentally benign solvent and the possibility to separate and recycle the catalyst, but also from the increase in yields and selectivity at all levels: chemo-, regio-, and enantio-. All that being related solely to the presence of micelles where the reaction takes place. In this respect, an important issue is the nature of the catalyst–surfactant interactions and how these can drive the course of the organic transformation under study. While it is easy to demonstrate by simple calculations that the reactant and catalyst concentrations inside the micelle are at least one order of magnitude higher than in a regular solution, which would account for the increased reaction rates, insight into catalyst–surfactant interactions has been almost completely neglected in the current literature in this field.

In a series of oxidation reactions, we reported a systematic study of catalyst positioning in a micellar medium using two-dimensional NMR techniques (NOESY, DOSY) to identify the interactions of the catalyst with different segments of the surfactant molecule. The surfactant was in all cases SDS.

In the sulfoxidation performed with the class of bis-cationic (diphosphine)Pt dimers shown in Figure 12.4,[18] the aromatic rings of the phosphine were clearly found to interact with the first methylene group adjacent to the SO_4^- hydrophilic head, suggesting that the bis-cationic catalyst, somehow expectedly, was likely sitting on the anionic surface of the surfactant, as indicated in Figure 12.12A. In the epoxidation of alkenes carried out with the (diphosphine)Pt(C_6F_5) catalyst shown in Figure 12.6,[19] the aromatic rings of
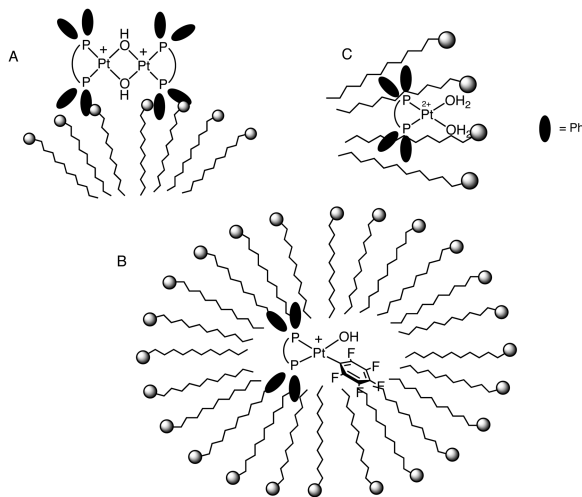
Figure 12.12   Positioning of bis-cationic (diphosphine)Pt complexes in SDS micelles in different oxidation reactions with hydrogen peroxide: (A) sulfoxidation, (B) epoxidation, and (C) Baeyer–Villiger oxidation.

the phosphine were found to interact with the terminal methyl group of the alkyl chain of SDS, suggesting that the catalyst was deeply buried inside the micelle, as represented in Figure 12.12B. Finally, in the Baeyer–Villiger oxidation of ketones with $[(diphosphine)Pt(OH_2)_2]^{2+}$,[45] the phenyl groups of the ligand were found to interact with the methylene groups of the central part of the alkyl chain of SDS, suggesting a third different catalyst positioning mechanism, as indicated in Figure 12.12C.

These observations clearly indicate that, even if the complexes are very similar (they all contain platinum, tetraaryl diphosphines, and they are all cationic) and catalyze oxidation reactions where hydrogen peroxide is the oxidant, in their interactions with SDS micelles (indeed a very simple structure), they occupy different positions and are surrounded by environments of different polarity. In fact, at variance with any homogeneous reaction medium where catalyst solvation is a random phenomenon, a micelle is an ordered, anisotropic aggregate where a polarity gradient exists from the surface to the core. This spontaneous positioning in differently polar environments will influence the electronic demand of the reaction transition state, often resulting in an increase in activity and, more importantly, in selectivity.

Enantioselective reactions allow the evaluation of the extent of this effect on the transition state. In fact, the ee is the result of the difference in energy between the two diastereomeric transition states leading to the formation of *R* and *S* products ($\Delta\Delta G^{\neq}$). The difference in ee observed when comparing the same reaction carried out in either an ordinary solvent or a micellar medium represents the ability of either medium to exert a better discriminating influence on the stabilization of the two diastereomeric transition states. Hence, in Figure 12.6, the 58% ee observed in DCE means $\Delta\Delta G^{\neq} = -3.23$ kJ mol^{-1}, while the 84% ee observed in Triton-X100 means $\Delta\Delta G^{\neq} = -5.95$ kJ mol^{-1}, the difference (2.72 kJ mol^{-1}) being due to the peculiar 'pocket' found in the micelle by the substrate when interacting with the catalyst. Similarly, in the Baeyer–Villiger oxidation reported in Figure 12.7, Triton-X114 is able to increase the $\Delta\Delta G^{\neq}$ by -6.82 kJ mol^{-1}, while no difference was observed in DCE, a huge discrimination effect solely due to the micelle.

These properties of micelles emphasize the already mentioned parallelism with enzymes (see Section 12.1), where the kinetic acceleration on the reaction under consideration is the result of the interactions (steric and/or electronic) exerted on the transition state by the polypeptide functional groups surrounding the 'pocket' where the active site is located.

A typical property of enzymes is substrate selectivity. This consists in the ability to pick up from the external reaction medium only the substrate that has to be transformed out of a large number of molecules (the well-known 'lock and key' concept). This peculiar property is generally not shared by ordinary catalysts, especially homogeneous, except for zeolites where the regular structure of channels and pores is able to select substrates on the basis of their size and shape (shape selectivity). Micelles can do the same, as has been demonstrated in a few cases even if on a different discriminating

basis. For example, in the Cr(salen)-catalyzed Diels–Alder reaction between cyclopentadiene and a series of α,β-unsaturated aldehydes of the type R–CH=CH–CHO (where R was a series of linear aliphatic chains from $-CH_3$ to $-C_7H_{15}$),[24b] it was found that the product yield was completely insensitive to the R-chain length when the reaction was performed in chloroform. Conversely, when the catalyst was embedded in SDS in water, the yield in the case of the longest aldehyde (R = C_7H_{15}) was 3.5 times higher than that for the shortest aldehyde (R = CH_3). The aldehydes were not tested individually but fed all together into the reactor in a real competitive test, thus proving certain substrate selectivity properties of the micellar system. Similarly, when the same aldehydes were hydrogenated with a Pd metal catalyst generated *in situ* by reduction of palladium acetate with hydrogen, again in a fully competitive test, when the reaction was tested in THF, the initial rate was found to be 3.6 times higher in the case of the shortest aldehyde with respect to the longest one. Conversely, when the Pd particles were embedded in SDSN (sodium dodecylsulfonate), not only were the longer aldehydes preferred to shorter ones, but the initial rate for R = C_7H_{15} was found to be 330 times higher than that for R = CH_3.[46] These results indicate that even simple structures like those of SDS or SDSN micelles are able to impart the catalyst with substrate selectivity, the driving force likely being the substrate hydrophobicity, *i.e.*, its affinity with the micelle inside, thus marking a not too surprising similarity with enzymes. This important property of micelles has huge practical potential, but has not been adequately addressed in the literature and deserves further insight.

12.7 Improvement of the E-factor and Practical Applications

In general terms, micellar media can be defined as green because they make possible the use of water as the reaction medium. They offer extra advantages such as the ability to improve the activity and selectivity of a variety of catalytic organic transformations and also entail the concept of substrate selectivity, as shown in the previous section. The crucial point however, implied in the title of this contribution, is: How green are these processes? Can we provide some metrics? And finally, are they amenable for practical application?

Speaking about metrics, it has to be pointed out that recent advances in the field are suggesting the replacement of classical concepts such as the Atom Economy or E-factor with other, more informative ones.[47] In the pharmaceutical industry, particularly useful to evaluate the industrial production of APIs is the Process Mass Intensity (PMI) proposed by the ACS Green Chemistry Institute.[48] The PMI is the ratio between the quantity of raw materials input (in kilograms) and the quantity of bulk API output (also in kilograms). An important difference with respect to the E-factor is that the water used in the processes is assumed as a raw material in the PMI. However, in the open

literature, no examples of PMI comparisons between classical and micellar routes have been reported to date. Hence, for the purpose of this contribution, the E-factors will be considered in the following.

The group of Lipshutz analyzed a series of C–C bond-forming reactions (Heck, Suzuki–Miyaura, Sonogashira) involved in the synthesis of some APIs and evaluated the E-factor of the traditional, organic solvent-based synthetic protocols according to published procedures as compared to the parallel use of micellar media.[49] As the examples in Figure 12.13 illustrate, the E-factors for each of the above reactions can be drastically reduced, in some cases by greater than an order of magnitude. Since these were run in water on a much smaller, laboratory scale, the corresponding drop in E-factor would likely be even more pronounced at larger scales, where small losses will have lesser consequences. Moreover, in most cases, cross-coupling reactions take place at room temperature while, in traditional organic media, heating might be necessary to initiate and/or drive reactions to completion. Heating, especially in high boiling solvents such as DMF, usually causes the unavoidable formation of varying amounts of side products, with potential complications in the subsequent product purification and decrease in yields of the desired products. Conversely, reactions run in water at room temperature are typically very clean with better product yields, as seen in each of the cases reported in Figure 12.13. Furthermore, running reactions in water greatly simplifies the set up, execution, and especially the workup procedures. When the reaction is complete, no
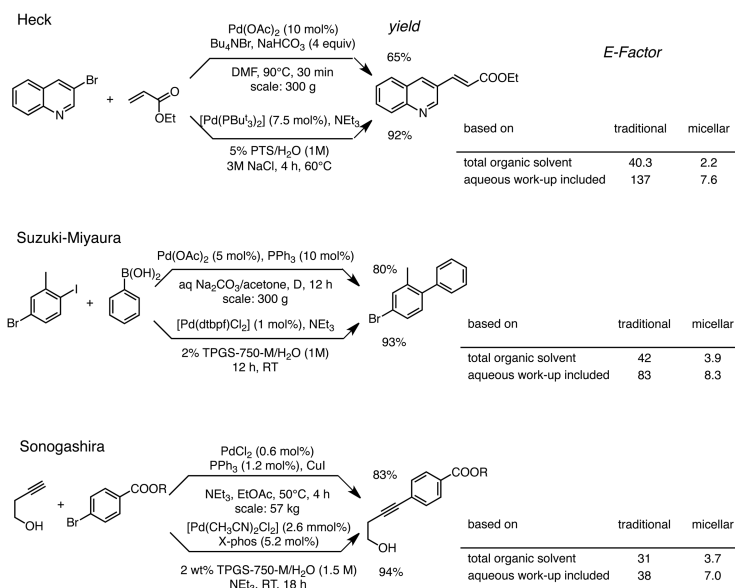
Figure 12.13 Some examples of C–C bond forming reactions carried out either in traditional organic or micellar media: comparison of the E-factors calculated in both cases for Heck, Suzuki–Miyaura, and Sonogashira reactions.

additional water needs to be added. Product extraction is simply performed by adding a limited amount of an organic solvent to the reaction vessel with subsequent in-flask extraction and product removal.

This procedure makes catalyst recycling quite straightforward. The surfactant and catalyst remain in the aqueous phase, in the reaction vessel, and are ready for reuse. As calculated by the authors, even a single recycle of the medium can result in a further reduction of the E-factor of over 50% (down to 2.8 for Heck and to 1.9 for Suzuki–Miyaura).

These results point further out the huge practical potential of micellar catalysis and justify its green character on a quantitative basis, even if the metrics are applied to a single reaction and not to an entire process. However, having potential is not the real thing, and so the answer to the third question raised at the beginning of this section came from industry. In 2016, an industrial research group from Novartis Pharma published the industrial synthesis of an API by comparing the organic traditional route to a micellar one by evaluating the yields, costs, and cycle time.[50] The synthetic procedure (Figure 12.14), carried out at kilogram scale, consisted of five different steps: (1) a nucleophilic aromatic substitution, (2) a

Step	Conditions	Yield (%)	Cycle time (hr)	Cost difference
1 S_NAr	reactant 1.2 eq, i-PrOH/toluene, 80°C, 5h	87	104	+4%
	reactant 1.0 eq, TPGS-750-M/water, RT, 12-16 h	75	61	
2 Suzuki-Miyaura	reactant 1.4 eq, Pd, t-AmOH, 85°C, 6h	=	61	-38%
	reactant 1.0 eq, Pd, TPGS-750-M/water, RT, 4-6 h	=	24	
3 hydrolysis	NaOH, MeOH/water, RT, 8h, MeTHF	70	137	
	NaOH, RT, 4-6 h	87	53	
4 amide bond formation	reactant 1.2 eq, acetonitrile, 50°C, 10h	76	105	-7%
	reactant 1.0 eq, TPGS-750-M/water, RT, 10-12 h	80	76	
5 final deprotection	HCl, MeOH/water, 0°C to RT, 16 h	92	62	0%
	HCl, MeOH/water, 0°C to RT, 16 h	92	62	
	Overall organic traditional	42.5	469	-17%
	micellar	48	276	

Figure 12.14 Multistep synthesis of an active pharmaceutical ingredient: comparison between the organic traditional (highlighted in grey) and micellar routes.

Suzuki–Miyaura C–C bond formation, (3) an ester hydrolysis, (4) an amide bond formation, and (5) a final deprotection to eventually release the API. The specific nature of the targeted drug substance and of the intermediates through the sequence were masked with stars, diamonds, circles, *etc.* for commercial sensitivity reasons.

The table in Figure 12.14 summarizes both the reaction conditions as well as product yields, the cycle times (the time necessary to carry out the operation), and the cost savings for each individual step comparing the organic traditional and micellar routes. As can be seen, the latter was performed in TPGS-750-M (where appropriate) at substantially milder conditions, using fewer reactants, in shorter times, overall reducing costs by 17% and the total cycle time to three fifths, which means that the multipurpose facilities employed could be used for other operations for that equivalent time.

Another important issue concerns the quality of the final compound and is of paramount importance in the pharmaceutical industry. In all steps described, very high quality of the crude intermediate products was claimed. The intermediates could simply be isolated and purified by crystallization, the purity of the targeted API turned out to be 99.5% or greater, even better than the routine purity obtained in the original process conducted in organic solvents.

12.8   Conclusions

As we have tried to demonstrate in this outline, the micellar approach, whose major feature is the possibility to operate in water as the reaction medium, is already a major tool in the hands of synthetic organic chemists and is on the way to become an important green technology with ubiquitous fields of application.

Surfactants are self-assembling auxiliaries, widely available on the market, that need no special technique to be used but are simply added to water. They allow the use of transition metal complexes developed for work in organic solvents, already optimized by ordinary synthetic elaboration without any special modification to make them compatible with water. Their use does not require any significant plant design or operational changes in the industrial practice while simplifying the separation processes.

The activity and selectivity are strongly bound to the different catalyst (and substrate) positioning within the micelles because of the existence of a polarity gradient, affording a local 'pocket' that can influence the outcome of the reaction with different levels of selectivity (chemo-, stereo-, enantio-). In enantioselective transformations, the steric constrain and anisotropy of the medium can amplify the free energy difference of the diastereomeric transition states, bearing interesting similarities with enzymes including their substrate selectivity.

The range of reactions in which micellar media can be successfully used is already very wide. Micelles can improve yields, selectivity at all levels,

reaction conditions, product separation, and catalyst recycling, ultimately decreasing the costs of operation and energy input. The surfactant choice is a key issue that, in specific cases, can be optimized with especially designed surfactants and metallo-surfactants. Practical examples provide some metrics demonstrating that micellar catalysis can indeed reduce the E-factor and in industrial practice also improve the yields, reduce the energy consumption, shorten the cycle times, and ultimately reduce production costs. In short, catalysis in micellar media is much ahead of a mere Green Chemistry promise and can be already considered a profitable industrial opportunity.

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