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Organic synthesis in Aqueous Multiphase Systems — Challenges and opportunities ahead of us

Pascal Hauk¹, Joanna Wencel-Delord¹, Lutz Ackermann², Peter Walde³ and Fabrice Gallou⁴

Abstract

Chemistry in water enabled by surfactants offers remarkable benefits from compliance and sustainability standpoints. It has consequently significantly grown and gained the major interest of synthetic organic chemists in the last decade. Rapid growth and adoption have mostly occurred through an increasing number of examples of successful, selective syntheses of desired products, although numerous and significant gaps remain in understanding the physico-chemical and mechanistic aspects of the applied surfactant-based aqueous reaction media. Further developments on these fronts should allow for a much larger impact in the future.

Addresses

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Keywords

Aqueous Multiphase Systems, Interface-rich aqueous systems, Surfactant, Water, Sustainability, C–C coupling, C–H activation.

Introduction

Triggered by various signals, whether the regulation and the potential ban of the reprotoxic polar aprotic solvents via the substance of very high concern process from REACH [1] or via the quest for Sustainable Development Goals as defined by the United Nations [2],

various neoteric solvents [3,4] or even applications of supercritical media such as water [5] have emerged. Water, which had been used sporadically mostly for biphasic processes, for in- or on-water chemistry [6], appeared as a viable sustainable option with the advent of a variety of so-called 'benign by design' surfactants. Such surfactants have emerged from Lipshutz's or Handa's laboratories in the last decade. At Novartis Pharma AG, we were able to rapidly capitalize on the breakthrough findings to push the boundaries of this chemistry and enable processes on both ends of the spectrum, whether very small (microgram scale) [7] or large (multi-hundred of kilograms) [8], while continuing the development of the chemistry with our academic partners. We were later followed by several other chemical and pharmaceutical organizations, evidenced by the formation of working groups within the ACS Green Chemistry Pharmaceutical Roundtable, and interest also grew in parallel within the academic field, thus leading to rapid development and successes in a plethora of transformations. Remarkable alternative approaches relying this time on hydrophobic effects generated by suitable polymers also appeared as viable options [9,10]. We have witnessed the impact of surfactant-based compartmentalization reaction mixtures (media) to enable more selective and productive transformations compared with conventional organic solvents because of the mild conditions associated with the (supra)molecular arrangement of the excipients, that is, their aggregate formation and microscopic phase separation. Taking advantage of this seldom-used supra- or poly-molecular assembly effect in water, significant benefits resulting from the use of water as the bulk reaction medium were observed, a significantly reduced environmental footprint, increased selectivities, improved productivities, and a sustainable alternative to undesirable solvents. Unfortunately, while we have been collectively largely succeeding in using a very pragmatic approach of trial and error, we left aside the physico-chemical and mechanistic aspects that are essential to the continued progress of the application of water as a bulk medium. However, reaching an additional level of complexity, that is, developing complex catalytic systems benefiting from this unique type of reaction medium, is far from trivial. To achieve this objective, the next major step will consist in increasing our

understanding of the physico-chemical phenomena and their improved control to enable better synthetic sequences and better processes. Such an advance can only happen by better upfront design, selecting reagents, catalysts and ligands more optimally in this desirable medium, with or even more optimally without recourse to the potential benefits of additives. Gathering in-depth knowledge on, and comprehension of, key factors allowing homogeneous or heterogeneous catalysis in water would bring exceptional benefits for both academia and industrial sectors, including many reaction types, such as metal-catalyzed cross-couplings, which are amongst the most used synthesis steps in the chemical and pharmaceutical industry.

Cross-coupling reactions involve reacting an organometallic reagent with an organic electrophile, typically in the presence of (a) transition-metal catalyst(s) to achieve a C–C, C–H, C–N, C–O, C–S, C–P, or C–Metal bond formation.

The following account is meant to emphasize our current limited understanding of the technology, highlighting the limitations and needs to bring the technology to the next level.

Background

To establish first the key factors governing homogeneous catalysis in/on the water *without added surfactant*, we will focus on the more rewarding but more demanding cross-coupling type of transformations. These require control over multiple components, namely the coupling partners (nucleophile and electrophile), the catalytic system, pre-catalyst (metal donor, ligand), and a base. They have, indeed, particular appeal for a variety of reasons, for as a class of reactions:

- they tend to be costly from a purely material standpoint and in terms of their environmental footprint because of the use of typically noble transition-metal extracted using scorching processes, applied routinely using high loadings, and/or enabled via sophisticated ligands;
- they often require high temperatures and polar media, pointing toward the use of the reprototoxic polar aprotic solvents (dimethylformamide, dimethylacetamide, *N*-methylpyrrolidone, *N*-ethylpyrrolidone);
- thus, they tend to suffer from reagent stability issues, more particularly of the metallated species that are prone to protodemetalation or oxidation; this point is typically being mitigated by increased stoichiometry that further increases the overall cost;
- being used at elevated temperatures, they exhibit limited or no selectivity (chemo- and regioselectivity, especially) and thus require synthetic adjustments, such as further usage of protecting groups, for example, or design of sub-optimal synthetic sequences.

For excipient-enriched, surfactant-containing aqueous systems, partitioning of the various reaction components and the supramolecular assembly behavior are key points and phenomena that remain to be controlled for improved overall output. Not doing so, unfortunately, can make us navigate in between various regimes with more or less control of selectivity, that is, then largely governed by the physico-chemical aspects of the reaction components, which will control more than just mass transfer between the different phases and hence, reactivity (see [Figure 1](#)).

In this review, we highlight the current unknown aspects of such chemistry. We hope to convince and attract experts in the community of colloid and interface scientists to contribute by bringing answers and insight to this profoundly radical yet sustainable approach to synthetic organic chemistry. We also wish to offer some guidance as to how and why to use one or the other additive (surfactant or polymer) and how to control the regimen under which the physical phenomena occur.

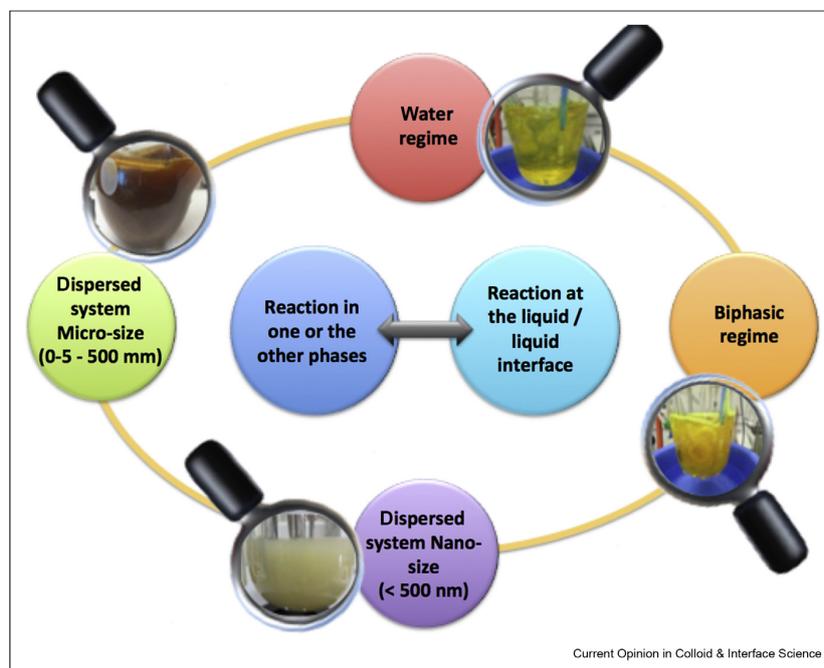
Of particular interest behind such an approach is the need to physically enable the necessary proximity of each of the reaction components to allow for the desired reactivity under mild reaction conditions while ensuring stability. In the subsequent sections, we evaluate systematically the requirements and current limitations associated with soft matter systems, mainly “micellar” approaches, (see below about the meaning of the term “micelle” used in this review and in the literature), and highlight their differences compared to in-water, on-water, or even biphasic phase-transfer processes illustrating the discussion using selected examples. Each case will be taken from the most readily encountered and promising synthetic strategies, namely Suzuki–Miyaura, Mizoroki–Heck, or Negishi cross-couplings, and more recent and sustainable, yet underdeveloped, C–H activation-type approaches.

We would like to direct the readers to a few recent and excellent accounts, such as for example, the one from Kobayashi, who recently describes several examples of in-water chemistry and clearly highlighted the importance of the intrinsic solubility of the various reaction components, recognizing the criticality of the dynamic interfacial phenomena, and offered valuable on-water models [12]. Other recent reviews describe various aspects and provide several examples of chemical reactions in water-based systems, where reaction localization in a dispersed phase — or in a pseudo phase (aqueous micelles or oil-in-water microemulsion droplets) plays an important role [11–18].

In or on water chemistry

In and on water chemistry have been the first source of success in water-based chemistry. From the fundamental

Figure 1



Various regimes for reactions to occur in surfactant-based aqueous systems. The dispersed systems shown often are called 'micelles' or 'nanomicelles', although they do not correspond to the classical definition of micelles and are more of emulsion-type, see text for details. See more in-depth discussion on the various categorizations in the study by Pera-Titus [11].

viewpoint, these descriptors implied, in the former situation, either rendering all the reaction components as soluble as possible in the bulk medium or facilitating the interfacial process via additives, as in the latter case. The Ruhrchemie/Rhone-Poulenc oxo process via the hydrosoluble phosphine ligand triphenylphosphine-3,3',3''-trisulfonic acid trisodium salt process is probably the most notable example that enabled a variety of transformations, such as Sonogashira or Suzuki–Miyaura cross-couplings, for example [19]. A major limitation though is the limited substrate scope, as only the ligand, but not the organic substrates, can be tailored for solubilization in water as the bulk medium, leading to the overall experimental conditions being relatively harsh (temperature typically above 100 °C), thus leading to stability issues. Moreover, usage of problematic polar aprotic co-solvent resulting in the lack of selectivity and high catalyst loading further limited the potential of this elegant methodology. An alternative solution to further improve the catalytic system consists in using a three-phase medium, as reported by Nowothnick et al. [20].

Water chemistry enabled by surfactants

Numerous reports emerged in the last decade on the use of surfactants to enable chemistry in bulk water [12,21–23]. By in large, nonionic surfactants have

proven to offer the widest scope, both in terms of the type of transformation and substrate variation. We will, therefore, use for the discussion this specific class of surfactant. A variety of such nonionic benign by design surfactants is all considered PEGylated amphiphilic species, with or without a linker. TPGS-750-M [24], PQS [25], SPGS-550-M [26], Coolade [27], DAPGS-750-M [28], APGS-550-M [29], MC-1 [30], PTS [31], SMPS [32], BTBT-750-M, PiNAP-750-M [33], TPG-lite [34], or PS-750-M [35] are some of the most studied excipients (Scheme 1). They have been demonstrated to be extremely versatile, most notably TPGS-750-M and PS-750-M, and shown to function as suitable surrogates to reprotoxic polar aprotic solvents, thus offering a real opportunity to phase out such solvents. Their behavior in bulk water was studied, and the size and shape of the resulting supramolecular arrangements were disclosed [36]. One must here already acknowledge that in most cases, these data were acquired for the 'naked systems', not the 'real-life' ones that would contain all the reaction components and better reflect the regime under which the transformation can proceed. This aspect is particularly important if one or several of the reaction components can serve as solubilizers and co-solvent, thus potentially drastically changing the underlying physico-chemical phenomena. We, at

Scheme 1

Key surfactants		Key ligands		
Reaction	Conditions (reaction scheme)	Type of medium/type of transformation	Key concept	Advantage over classical reaction
Ruhrchemie/Rhône-Poulenc oxo process (industrial process)	<chem>CH2=CH-CH=CH2 + CO2 + H2</chem> $\xrightarrow{\text{Rh(TPPTS) cat}}$ <chem>CH3-CH2-CHO + CH3-CHO</chem> 45 °C	Aqueous biphasic catalysis	Biphasic solution; use of water-soluble catalyst	Easy separation of the catalyst → recycling energy balance, (process becomes a net steam supplier); constant pH → excellent selectivity excellent catalyst removal
Suzuki coupling in three-phase micro emulsions	<chem>c1ccc(C#N)cc1 + B(OH)2</chem> $\xrightarrow[\text{H}_2\text{O} / n\text{-heptane} / \text{surfactant}]{\text{Pd(OAc)}_2 (0.5 \text{ mol\%}), \text{TPPTS} (2.5 \text{ mol\%})}$ <chem>c1ccc(C#N)cc1</chem> 45 °C 60 °C 94%	Three-phase micro-emulsions	Addition of a surfactant to improve phase separation; - formation of the three-phase region once full conversion is active - easy separation of the product in the organic phase, salts in aqueous phase and reuse of the catalyst	Easy recycling and reuse of the catalyst reduced problems of the accumulation of salts accumulation increased turnover number and cost efficiency
Surfactant enabled Suzuki-Miyaura cross-coupling	<chem>Br-C6H4-CF3 + B(OH)2</chem> $\xrightarrow[\text{NEt}_3 (2 \text{ equiv})]{\text{Pd(OAc)}_2 (0.1 \text{ mol\%}), \text{HandaPhos} (0.1 \text{ mol\%})}$ <chem>NMe2-C6H4-CF3</chem> Nok in H ₂ O 45 °C 98%	Surfactant (Nok or TPGS-750-M), reaction in one or the other phases	Design of ligand particularly suitable for to promote reactions in micelles - increased lipophilicity of all components	Very low catalyst loading (typically 0.1 mol% and below) general catalytic system (functional group tolerance) mild reaction condition *in-flask* recycling of the surfactant, water and catalyst
	<chem>CHO-C6H4-Br + B(OH)2</chem> $\xrightarrow[\text{K}_3\text{PO}_4]{\text{Pd(OAc)}_2 (0.25 \text{ mol\%}), \text{HandaPhos} (0.5 \text{ mol\%})}$ <chem>CHO-C6H4-Br</chem> TPGS-750-M in H ₂ O 45 °C 97%			
	<chem>Br-C6H4-N + B(OH)2</chem> $\xrightarrow[\text{K}_3\text{PO}_4]{\text{palladacycle} (3 \text{ mol\%})}$ <chem>N-C6H4-Br</chem> PS-750-M in H ₂ O 45 °C 88%			
	<chem>Br-C6H4-S + B(MIDA)</chem> $\xrightarrow[\text{NEt}_3]{\text{Pd(OAc)}_2 (0.1 \text{ mol\%}), \text{HandaPhos} (0.1 \text{ mol\%})}$ <chem>N-C6H4-S</chem> Nok in H ₂ O 20 °C 90%	Organic solvent free-reaction, use of surfactant	Design of suitable coupling partner (in situ release of boronic acid in water)	No organic solvent potentially direct isolation of the product via filtration E factor close to zero
	<chem>Br-C6H4-CN + B(OH)2</chem> $\xrightarrow[\text{K}_3\text{PO}_4]{\text{palladacycle catalyst} (0.25 \text{ mol\%})}$ <chem>CHO-C6H4-CN</chem> TPGS-750-M in H ₂ O 55 °C 81%	Surfactant + additive effect (organic solvent)	Design of suitable coupling partners (Bpin), adjustment of the properties each coupling partner catalyst design (dtbpf as optimal ligand) choice of the base	High yielding reaction even for challenging substrates low catalyst loading

Structure of select surfactants, ligands and select transformations in water.

Novartis, have, from our end, relied considerably on the use of TPGS-750-M that almost systematically benefitted from the use of an organic co-solvent, for example, acetone. The use of such a co-solvent was demonstrated to not only serve as a processing aid for physical transfer, scale-up [8,37–39] or scale-down experiments [7] but also indeed enlarge the initially formed (‘naked’) micelles, essentially doubling the inner diameter and facilitating the channeling of reaction components [36]. More insights have actually been well-described by Alexandridis, especially those who showed that an organic additive would promote ‘dissolution’ of the micelles and enable a transition from a co-surfactant to a co-solvent behavior depending on the amount of additive, thus facilitating a better reaction outcome [37]. Little is also known as to the dynamics of the supra-molecular system. This aspect is all the more critical as practitioners recognize that the benefits of such an approach rely largely on the rapid exchanges such a system promotes, enabling transfers from one phase to another once a chemical reaction has occurred, for example. Indeed, even from a practical viewpoint, reactions implying micellar conditions are not trivial, as the techniques allowing the formation of the desired micelles instead of the emulsions, that can be easily visualized, is crucial for a reaction’s success. Besides, several of the imaging techniques originate from microscopic measurements mostly based on cryogenic conditions, which may alter the system. We are currently working with partners to non-intrusively analyze and characterize these systems and should shed some light on them shortly. But the kinetics around their coalescence clearly will remain elusive and a challenge for the future.

Accordingly, to provide complementary solutions to biphasic systems used for homogeneous catalysis (see the Table in Scheme 1 with selected transformations in water), major advances were reached in metal-catalyzed cross-couplings, and in particular, Suzuki–Miyaura couplings, while implementing ‘micellar systems’. Remarkably, advances in terms of catalyst loading, mildness, and recyclability of the catalyst might be achieved while designing optimal Pd catalysts, able to react within this type of dispersed nano-sized aggregates (‘nanoreactors’) with appropriate coupling partners.

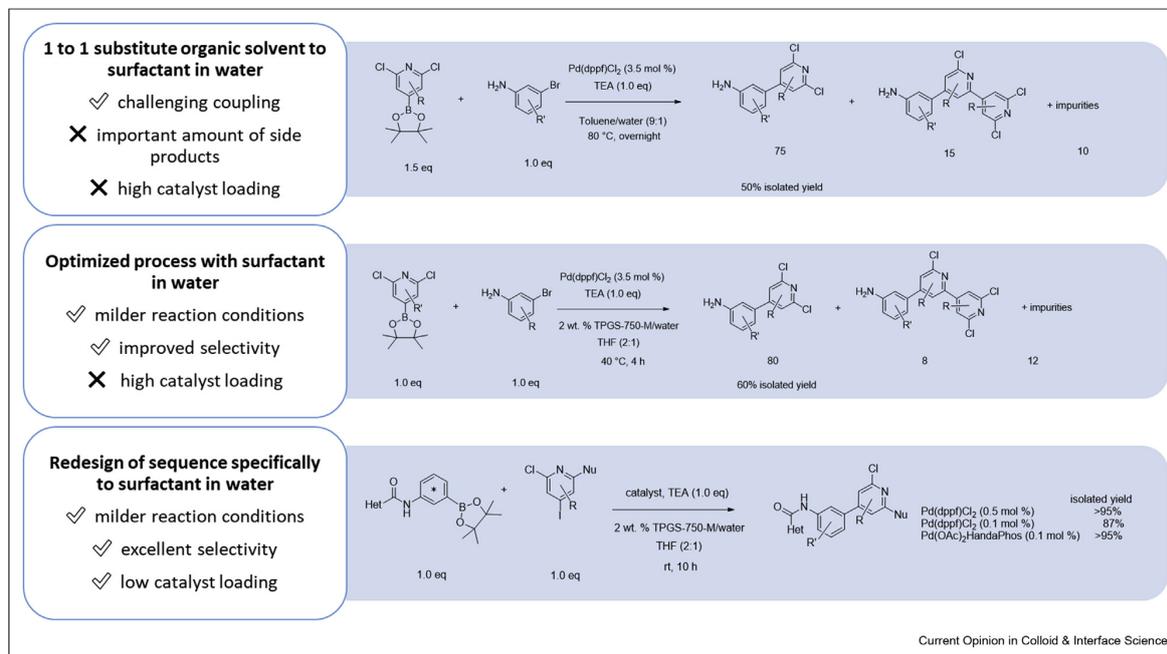
When the compartmentalization effect relies on the reaction happening in one phase or another, a good strategy for optimal performance may consist of increasing the lipophilicity of all the reaction components to the extent possible (e.g. coupling partners, ligand, metal donor, base). For example, after identification of the optimal surfactant for the specific substrates, use of ligands, such as HandaPhos [40] or EvanPhos [41], each designed with increased affinity for the interior of the surfactant-stabilized aggregates (‘micelles’) will greatly enhance the affinity for the

micelles. For the metal donor, more lipophilic species such as palladacycles can be used with further fine-tuning via an optimal choice of the counter-ion [42,43]. As for the base, testing an inorganic and an organic one can shed further light on their effect. When it comes to the coupling partners, however, fewer options are available, as the targeting end product requires a certain scaffold. One can, however, identify the best point of convergency in the synthetic sequence [8] with the optimal physico-chemical properties, and/or use of ancillary groups advantageously (e.g. methyliminodiacate-boronates or pinacol boronates instead of boronic acids [44]). This latter point illustrates the importance of the design of the synthesis; probably the most impactful aspect to envision the best outcome for any synthesis.

When the compartmentalization effect instead relies on interfacial liquid–liquid reactions, the guiding principle seems to be more the fine-tuning of the hydrophobicity of all the components of the reactions. For example, one can start by identifying the optimal surfactant, and/or stabilize it, for example, with nanoparticles as a catalyst; for the ligand, again, fine-tuning is possible to identify the most reactive and best fit for the system, for example,

1,1’-Bis(di-*tert*-butylphosphino)ferrocene (dtbpf) en lieu of 1,1’-Bis(diphenylphosphino)ferrocene (dppf) [45]. For metal and base, here again, a suitable metal donor and optimal base can be identified via standard screening. It is important to note though, that proceeding under such a regimen likely requires the formation of nanoparticles, which might require a critical process for their suitable preparation from a pre-catalyst. For the coupling partners, it is once again very important to understand the requirements in terms of physical properties to best design the nature of the coupling partners and that of the ancillary groups. Our experience over the last decade has thus been essentially empirical, mostly driven by trial and error, as we have not yet been able to predict the optimal approach and optimal design for our systems. In the case of nanoparticles, severe technical limitations have also been encountered, such as their characterization, or their robustness, which have impeded usage. The exact nature of the active species is also of great interest, although limiting our ability to ideally design a process that involves them. Scheme 2 illustrates how we evolved our synthetic strategy for an ultimate much superior performance via tailoring of the physico-chemical properties of all the reaction components to the medium itself. The fast pace of research and development in the pharmaceutical industry has made this particularly difficult, but we strongly believe that future significant advances in basic colloid and interface science will have a profound impact in the longer term. Of particular importance will certainly be the development of practical analytical techniques and the increased use of computational

Scheme 2



Toward successful development of industrially relevant Suzuki coupling in Aqueous Multiphase Systems.

tools. We would like to make an aparte at this stage and briefly comment on operations that occur after the reaction has taken place. Very often, as the complexity of the product increases, its solubility decreases which readily induces its precipitation from such media [46]. When the product is still partitioning in the various phases, a streamlined extractive work-up with a desirable and sustainable organic solvent enables isolation and purification in a practical manner, besides ensuring complete depletion of potential residual surfactant [47] (see Scheme 3).

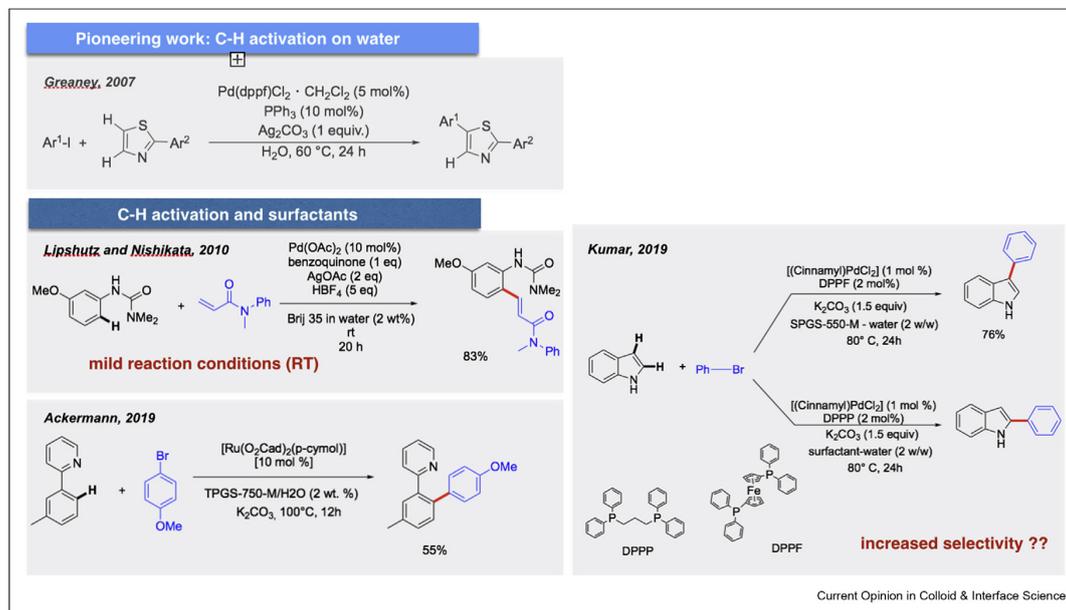
Drawing inspiration from the major advances achieved in the field of cross-couplings while using an in/on water approach, this strategy appears extremely appealing to adopt while developing more challenging C–H activation protocols. Surprisingly, despite the fact that pioneering efforts toward this goal were reported by Nishikata et al. [48,49] almost a decade ago, this field still remains poorly investigated. Only a handful of contemporary reports by Yetra et al. [50], Vaidya et al. [51], and Calascibetta et al. [52] that disclose remarkable findings is described; nonetheless, generalization and rationalization of the bulky aqueous medium are still, at best, preliminary.

In a seminal paper, Greaney reported the direct arylation of thiazoles on water [53]. The reaction was

reported to work under mild reaction conditions for a wide scope of aryl iodides, producing 2,5-diaryl thiazoles in excellent yields. Lipshutz and Nishikata later reported that remarkable yields and selectivity could be obtained using surfactants from various substituted aryl systems benefitting from the directing effect of carbonates or carbamates, using cationic palladium catalysis, but unfortunately saw limited success using a ‘micellar catalysis’ approach. In their hands, only the Fujiwara-Moritani coupling reactions in the water ended up being preparatively useful. The major C–H activation limitation, reaction temperature, could be overcome due to the use of “surfactant-based nano-reactors”; indeed, in general, high reaction temperatures are normally required to promote such a reaction. This surfactant-based protocol, however, is among the first examples of room-temperature C–H activation protocols. *While such findings can seem disappointing, it is actually very insightful and indicative of how high the bar is for such reactions.*

Kumar et al. reported a Heck-type of approach in water using the designer surfactant Nok [54], together with a palladium catalyst to selectively functionalize indoles in the C2- or C3-position. Moderate-to-good yields and excellent chemo- and regio-selectivity (C/N and C2/C3) were observed despite the elevated reaction temperature (80 °C), along with high functional group tolerance

Scheme 3



Recent applications of C-H activation involving water as a medium.

and robustness. While the report is limited to a purely synthetic discussion, the remarkable selectivities observed along with the ability to change the regioselectivity, in particular, via fine-tuning of the ligand shed some light on the role of the surfactant aggregates ('micelles') under aqueous conditions. In the absence of reported data, we will not extrapolate but would like to highlight that a careful evaluation in the subtleties going from 1,3-bis(diphenylphosphino)propane (dppp) to 1,1'-bis(diphenylphosphino)ferrocene (dppf) [54] as ligands and the fact that the reaction worked best using Nok could become especially insightful.

Ackermann followed up on this seminal work, using the thiocarbonyl functionality of ferrocenyl ligands to introduce a variety of aryl and heteroaryl fragments. Excellent selectivity was obtained owing to the dispersion-donor thiocarbonyl, in addition to good-to-high yields. The reactions proceeded in TPGS-750-M in water and required both high (unoptimized) ruthenium catalyst loading (up to 10 mol%) and elevated reaction temperatures. While high catalyst loadings are not at all unusual for such demanding C–H functionalization transformations, the aspiration is clearly to truly enable 'micellar catalysis' that would proceed under a contained and compressed environment under much milder reaction conditions, obviously not the case here. The study was nicely complemented with DLS

studies on the size of the aggregates ('micelles') involved, showing that they went from ca. 52 nm–130 nm upon reaction completion.

By now, readers very likely have realized they often improper use of the term micelles within the synthetic community. Our synthetic community, and that of pharma especially which picked up on many applications very rapidly, has indeed associated the notion of micelles to the mere use of a surfactant in bulk water, without necessarily referring to the supramolecular objects that would result. While semantically false in a lot of cases, it reflects the very limited understanding at this time and has been one of the key drivers behind this assay. It must be noted, however, that measurements were not carried out under the conditions of the reactions, namely at 100 °C, and thus leave unclarity as to the actual regime of the emulsion (nano or micro-size). This aspect explicitly highlights our current situation and experimental challenges to measure and understand the reactive systems in a non-intrusive and unambiguous manner, leaving uncertainty on the actual regime of the transformations. This, in turn, does not allow us to control the systems and improve them to the next level of efficiency.

Despite these remarkable and rapid developments, very little is yet understood as to the regimen of reactivity, the extent of nanodispersion, and the size of the soft

matter objects, or even if reactions truly proceed under a single physical regimen. It remains a fantastic opportunity to design novel ligands for custom-made ruthenium C–H activation catalysts for use under “micellar catalysis” conditions. Could we, for example, imagine better control of compartmentalization, with a chance to enhance selectivity? This is the opportunity created with the template generated by the proline-derived surfactants brought to fruition by Brals et al. [35].

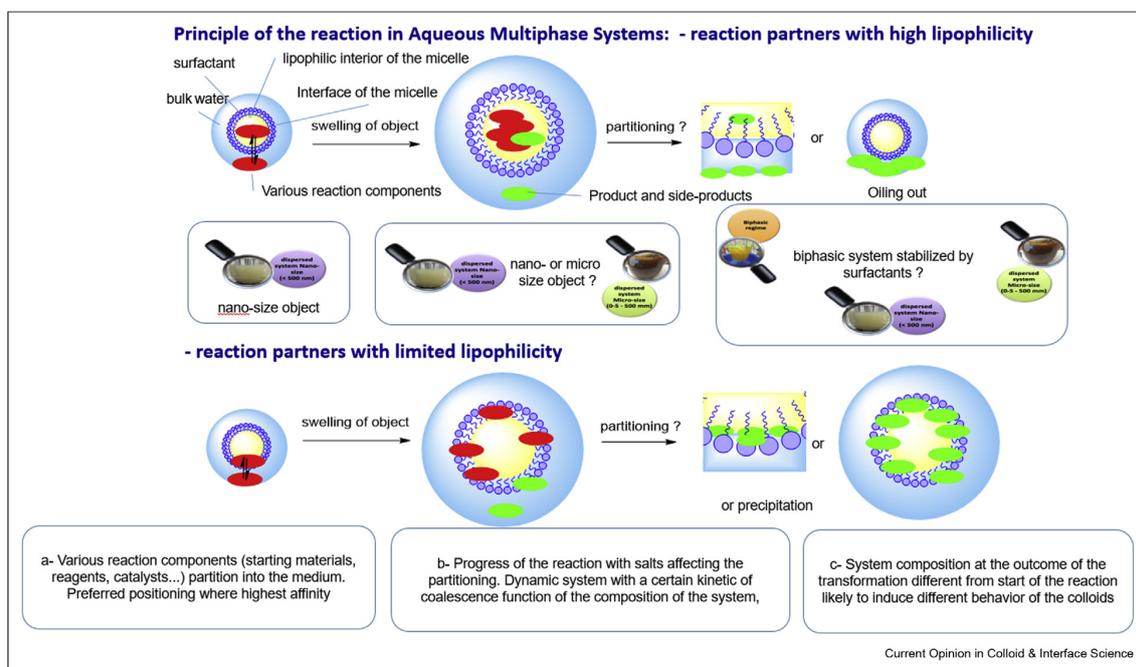
The emulsion system generated by Beverina et al. is a lot more complex, requiring an additional phase transfer catalyst to the extent of 30 mol% and elevated temperature above 130 °C. Because of this increased number of elements of complexity, understanding and rationalization is made even more challenging and will not be discussed here.

Discussion

In experiments with the surfactant PS-750M (Scheme 1), a wide spectrum of analytical techniques was used to ascertain that proline was the most polar portion of the surfactant and served as a stable ligand for metals (Pd, Ni, Cu), thus ensuring control of the location where catalysis would take place. Control experiments also showed that PS-750-M tended to contain all reaction components within the interior of the aggregated

state of this surfactant, as proven by the increase of the size of the ‘micelles’. Dynamic light scattering (DLS) experiments were indeed conducted and showed that at ambient temperature, the average diameter increased from ≈ 130 nm with the naked system to ≈ 550 nm when the nanocatalyst was dispersed in the aqueous solution of PS-750-M, indicating the binding of the nanocatalyst with either interface or inner core of the micelles, to a size of ≈ 1.2 μm when all reaction components were present. Interestingly, the same measurements carried out at 60 °C exhibited a similar trend, but with much greater swelling up to ≈ 1.8 μm upon dissolution of 1-bromonaphthalene, and even to ≈ 3.6 μm upon dissolution of both the catalyst and 1-bromonaphthalene. While there seems to be here controlled on the compartmentalization effect, one can hardly envision a genuine nano-effect rather than a micro-effect here. These observations seem to correlate with the slightly higher need in metal catalyst required to achieve full conversion in comparison to genuine micellar catalysis that can be observed to proceed at the ppm level under very mild reaction temperatures [55]. This does not detract from the merits of this approach and even bodes well for the future when a better understanding of the system exists, leading to alternative designs that are more optimal. Such experiments contribute to our understanding of the necessary salient

Figure 2



Simplified sketch of the fate of the aggregates, and the compartmentalization effect.

features associated with such processes and how to best master them.

More recently, water chemistry enabled by polymers has led to several remarkable advances [9,10,56,57] with researchers at Abbvie, led by Braje, who, in partnering with Handa, demonstrated spectacular rate enhancements during reactions performed in water. The key additive is the readily available and biodegradable polymer HPMC. These observations certainly offer significant prospects in the near future, but because of our limited understanding, we will not comment at this stage (see Figure 2).

In all these examples, the reaction mixtures are not micellar according to the definition of micelles as surfactant aggregates that form an isotropic phase without any turbidity. The systems are rather ‘complex multiphase systems’, emulsion-like, as mentioned by Ceriani et al. [58]. In the case where there is a ‘mismatch’ of the various reaction components, poor performance is expected because of the localization of the various reaction components in the various compartments of the systems. In practice, this translates into lower yield or increased required stoichiometry, or increased reaction temperature to facilitate the transfer of the components from one phase to the other or all of the above. For the other cases, whether the reaction partners have high or limited lipophilicity, a simplistic visualization consists of the localization of the reaction partners within the interior of the aggregates or at the interface, respectively. The addition of a high amount of reacting species results in a transformation of the micelles into swollen ones, emulsion-like systems, or heterogeneous multiphase systems. Whether the aggregate consists of a single object or multiple smaller ones is not entirely clear yet and probably differs from surfactant to surfactant [35]. The overall challenge is to understand the structure, molecular organization and dynamics of these heterogeneous systems, and how the chemical structure of the amphiphiles influences the properties of the systems and - what is most important — the performance of the reactions carried out. It is all the more complex as the system composition evolves over time, with to name just one the effect of salts side-products that can radically change the solubilities and hence the partitioning. Under these circumstances, the art relies on finding the right ‘micellar’ regime and surfactant not just for the system at the onset of the transformation, but also throughout the reaction. The chemical structure of the surfactants used is obviously important, but it is not clear which surfactants systems are good for a given reaction or reaction partners, and why they are good. The role of the surfactant is to provide an optimally dispersed system, a ‘complex multiphase system’. To understand this correlation between surfactant structure and reaction, performance would tremendously accelerate development of the

chemistry in water and would be a highly impactful goal for future studies.

In conclusion, while we have started witnessing increasingly sustainable advances in synthetic chemistry using water as the bulk medium, there is still very limited physico-chemical and mechanistic understanding, which prevents the unleashing of the full power of such an approach. Only a handful of reaction partners can be engaged productively in synthetic transformations as such in water, while the vast majority requires the use of an additive stabilized emulsion in water, whether via a surfactant or a polymer. In our hands, and via the growing amount of literature, we strongly believe that surfactants bring the required generality to enable physico-chemical phenomena in bulk water, making dispersed system in water as viable sustainable option for the long-term. The ultimate goal being is to rapidly switch toward not only better technologies but also more resource-efficient practices moving away from fossil feedstocks. This paradigm shift represents an undeniable asset to exploit optimally and collectively to have a chance to respond to the future needs of society. A strong collaborative effort between synthetic organic chemists and physico-chemical or colloid and interface scientists will be required to embark on such a journey, looking to unleash the full potential of micellar catalysis. We do hope such an account will entice the best minds to delve into this fascinating field; after all, it is our ticket to sustainability.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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