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Complete List of Authors:	Lipshutz, Bruce; University of California, Department of Chemistry

On the role of surfactants: rethinking "aqueous" chemistry

Bruce H. Lipshutz*
Department of Chemistry and Biochemistry
University of California, Santa Barbara, CA 93106 USA

Abstract. Some of the latest technological developments involving chemistry in water are discussed**.** Although each advance bears little-to-no relationship to the others, in the composite they highlight the seemingly unlimited opportunities for discovering Nature's secrets using water as the reaction medium. Thus, in addition to the environmental aspects driving this research, the benefits to be realized in making this switch away from reactions run in organic solvents and into an aqueous medium are clearly indicative of the future of synthetic organic chemistry.

Introduction: What's in a title?

The title for this contribution focuses on: "…rethinking aqueous chemistry…" The likely implication, on the one hand, is that a major change is needed; that organic chemistry as currently practiced in waste-generating, petroleum-based organic solvents should be converted into a sustainable discipline performed routinely in water. That notion implies quite a challenge, especially since modern organic synthesis has been remarkably successful doing chemistry in organic media. That's just reality, and we were certainly a contributor to these advances for over a quarter of a century, with the *12 Principles of Green Chemistry* only first appearing in the late 1990s.[1] But most realize that the world of chemistry is in a very different place today; that "business as usual" is no longer appropriate nor acceptable with the future in mind. As climate change has become part of our everyday lives, organic chemists cannot continue to consume and then burn (in large measure) non-chlorinated solvents and related downstream products. But there is no longer the opportunity to ignore the fact that organic chemistry is a major contributor to this worldwide problem, since the incineration of carbon-based materials leads to the greenhouse gas, CO_2.

Alternatively, "…rethinking aqueous chemistry" can also lead to recognition that modern organic chemistry in organic solvents has only *ca.* 200 years to its credit, while Nature has been doing chemistry in water for billions of years. And while a true appreciation for geological time is tough to grasp, it would be hard to argue, ignoring all the negative environmental issues associated with using organic solvents for synthetic gain, that the future favors any other reaction medium over water.

At issue in making this essential transition away from organic solvents is the traditional "thinking" that prevails to this day: water is the "enemy."[2] Whether it's the solubility issue of organic substrates in water, its pK_a that is too low for use of reactive and/or "water-sensitive" reagents, or the high boiling point for its supposedly essential removal as part of any reaction workup: it has been ingrained in organic chemists independent of location to avoid H_2O unless doing reactions where it is beneficial or essential (*e.g.,* hydrolyses). How unfortunate that such claims permeate the textbooks. But are the

textbooks "right"? Of course, they are correct, …*but only in part*! If water is present in an organic solvent, or what is commonly referred to as "adventitious" water, then it can certainly be problematic. But in pure (100%) water, or even mainly water, the story is quite different, and in many ways, counterintuitive. As examples, acylations with acid chlorides,[3] peptide synthesis,[4] and even *in situ* formation and use of water-sensitive reagents such as organozinc halides[5] required for Nobel Prize-winning Negishi couplings: all are doable in water. But, what about the solubility issue; most organics are not soluble in water! How can this issue be tackled? What does Nature do about this seemingly fundamental inconsistency? One need only look to the human body for unequivocal evidence that chemistry in water involving water-insoluble biomolecules was solved long, long ago. And so, how did evolution deal with lipophilic vitamins (*e.g.,* K_2, the menaquinones), essential coenzymes (*e.g.,* CoQ_{10}) and fatty acids (EPA and DHA), as well as the variety of polypeptides, etc. needed for life as we know it? The answer is that these lipophilic compounds are localized in the membranes, vesicles, and micellar arrays. In other words, Nature has been showing us, unequivocally and essentially, forever, how to do chemistry in water: engineer "biomolecule-like" nanoreactors in which modern organic reactions take place. Yes, it really is that simple.

A Quick Background: Chemistry *in Water,* and not… with Water or on Water

Ever since Blackmond's paper questioning (in part) the various terminologies that are being used rather "loosely" when water is present,[6] it has become important to differentiate terms such as "on water", "with water", and "in water." They are not the same, and need be understood when rethinking "aqueous" chemistry. Chemistry on water dates back to early observations by Breslow and co-workers,[7] and is far from a forgotten technology, as reviewed in 2020 by Kobayashi.[8] The experimental approach here, and unlike the variety of seemingly complex explanations behind its use,[9] is to add water-insoluble reaction participants (*i.e.,* substrates, catalysts, etc.) to pure water and stir. That's it; nothing is present to assist with the solubilization of reactants (such as co-solvents, surfactants, etc.). The temperature of reaction might be varied (*e.g.,* by heating in a microwave), or the time, but this chemistry is clearly happening "on water." Interestingly, although outside the scope of this opus, what about the related concepts of doing chemistry in the future "on *dirty* water", or "under water." Are these possible, and if so, what is to be gained, and learned, from these atypical situations?

Chemistry "with water" is very well known to organic chemists at virtually any level. Every hydrolysis reaction involving solubilization of a substrate in a water-miscible organic solvent to which is added a percentage of water, keeping everything in solution, is a "with water" phenomenon. So, what is meant by "in water", the remaining of these three terms, that differentiates it from "with water" and is the basis for all of the discussion surrounding "chemistry in water"? The difference is that "in water" chemistry relies on water-soluble "bio-like" molecules, most notably nonionic amphiphiles such as TPGS-750-M, also a pegylated amphiphile with a methylated terminus, and Savie, a newly introduced and biodegradable amphphile, where a polysarcosine has replaced the hydrophilic MPEG portion. Several and several others that have appeared over time (see Figure 1). Each forms nanomicelles thereby creating hydrophobic interiors in which water-insoluble substrates, catalysts, etc. are solubilized, and within these "nanoreactors" chemistry happens. This concept, known for decades as micellar catalysis,[10] has been converted from a "hit or miss" approach as used in the past[11] into a better defined, and general entry to effective modern synthetic chemistry performed with use of either none, or at most minimal organic co-solvent. Thus, by engineering nano-sized micelles (from nonionic surfactants) to be more

effective than the simpler biomolecules used by Nature throughout time (*e.g.,* phosphatidylcholine derivatives), seemingly all types of catalysis, *e.g.,* based on palladium, are amenable to reactions "in water."

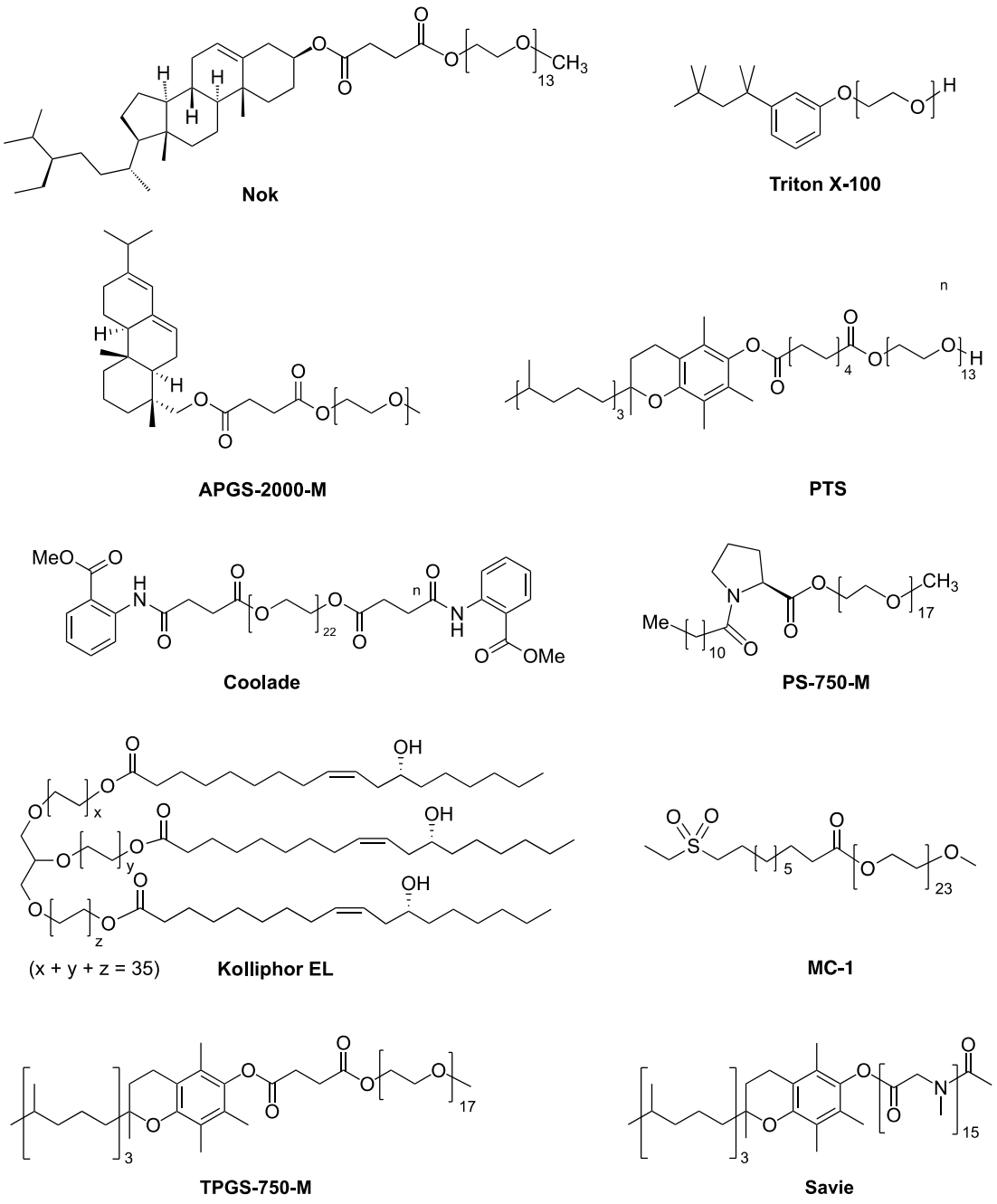


Figure 1. Representative nonionic surfactants that form nanomicelles in water

And unlike enzymes (which are also nano-sized catalysts), namomicelles are not discriminating; they accept most uncharged lipophilic educts, catalysts, and additives, suggesting that they are generally applicable to many types of unrelated chemistry. In essence, therefore, "designer" surfactants represent

a modern-day version of a *very* old concept. Why has it taken so long to develop synthetic chemistry in water? Whatever the explanation, not only is chemistry in water essential in order to minimize its contribution to climate change; not only is it crucial for preserving and extending the planet's limited supplies of natural resources and minimizing our investment in energy, but it also encourages alternative ways of thinking about doing organic synthesis. Judging from the reviews of late,[12] it sure seems that Nature remains patiently waiting for chemists to continuously discover, apply, and profit from its "secrets", just by switching to water.

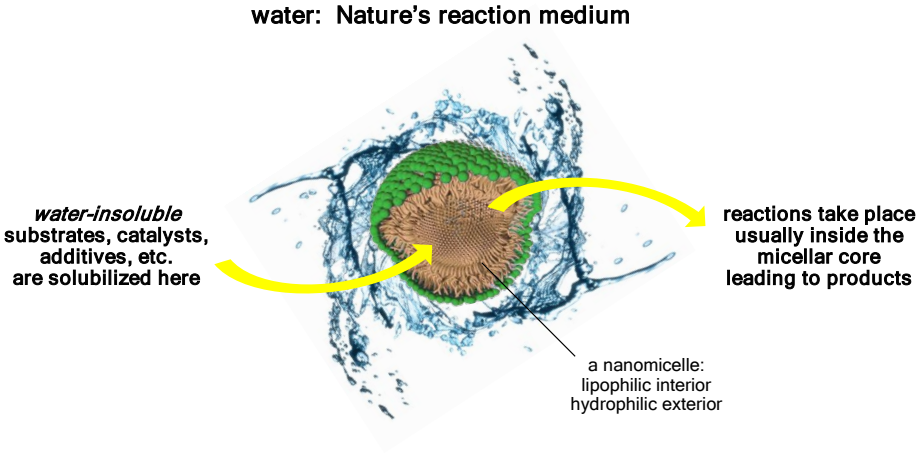
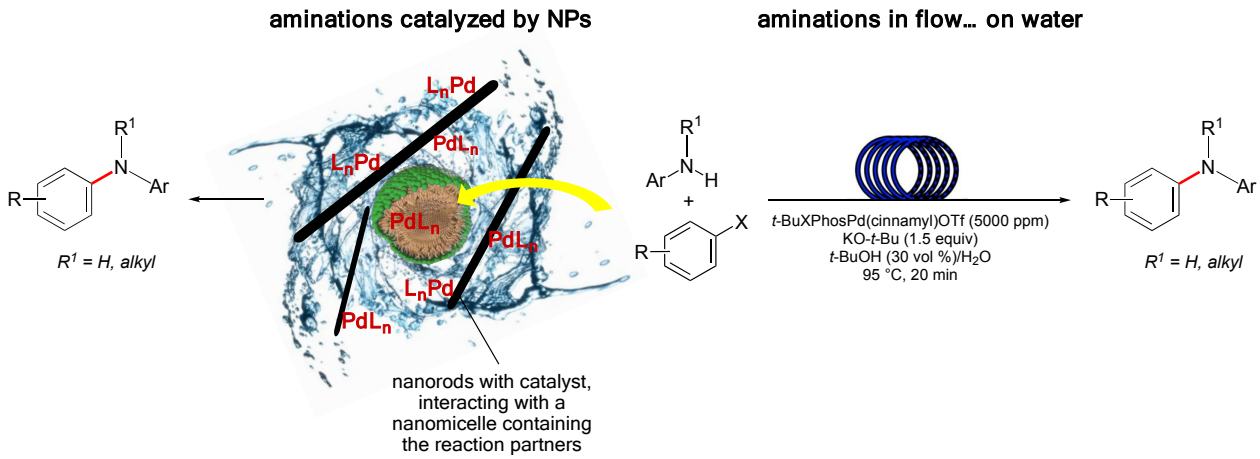


Figure 2. Modern organic synthesis in water, using one of Nature's "reactors" for water-insoluble compounds: a nanomicelle

New Chemistry *in Water*

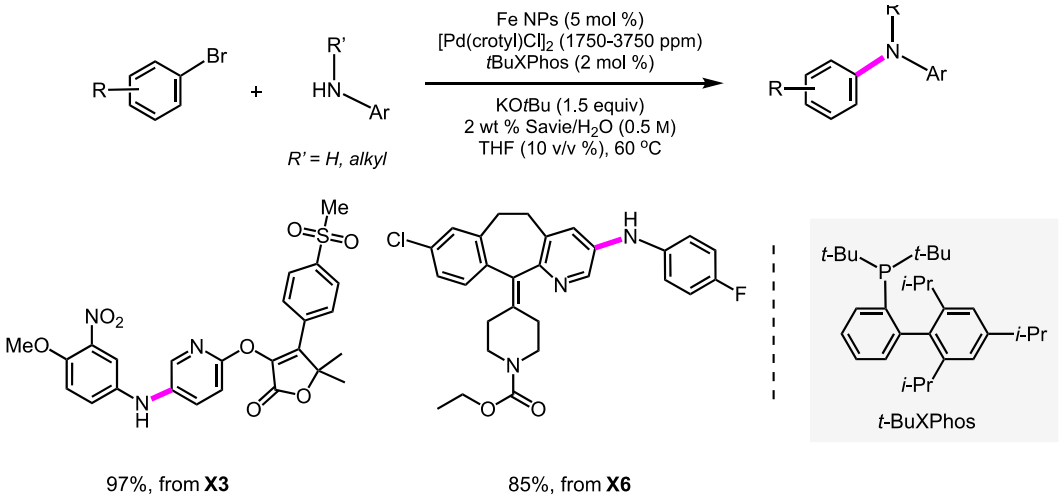
Aminations

Since Pd-catalyzed aminations are so important to the fine chemicals area, and the pharma industry,[13] in particular, detailed studies have continued that address C-N bond forming reactions under both batch[14,15] and flow conditions,[16] in or on water (Scheme 1). The former effort was designed to include aromatic / heteroaromatic halides in combination with either aliphatic or aromatic / heteroaromatic primary and secondary amines. These cross couplings contain sufficient functionality in each reaction partner such that the resulting products represent the potential of these new technologies to be useful at either the discovery or process research level.[17,18] In terms of substrates, the work focuses on examples of consequence, including late-stage functionalization and cases selected from the Merck Informer Library,[19] with each amination done under green chemistry conditions (*vide infra*).



Scheme 1. Aminations in water, catalyzed via new nanoparticles (NPs), or in flow, on water.

Initially, a heterogeneous catalyst was envisioned along the lines used previously for several C-C bond formations using aqueous micellar catalysis conditions.[20] In developing nanoparticles as catalysts (*i.e.,* NP rods; Scheme 1, left),[15] the search focused on finding the ligand (L in L_nPd) to be localized within both the nanomicelles in the water and on the surface of the Pd catalyst. The one that "matched" the aqueous nanomicellar and heterogeneous NP conditions for C-N couplings is the combination of precursor $[Pd(crotyl)Cl]_2$ with *t*BuXPhos, each commercially accessible (Scheme 2). Noteworthy is the amount of palladium required: only 0.125 mol %, which translates into 2500 ppm (0.25 mol %) for this dimeric cluster. Also, use of Savie as a biodegradable designer surfactant[21] (in *recyclable* water; Figure 2) plays a role, being far more polar than previously introduced TPGS-750-M[22] (*i.e.,* with the MPEG in the latter being replaced by the polypeptoid, specifically the 15mer, derived from sarcosine). Thus, under optimized (heterogeneous) conditions, a remarkably broad array of aminated products can be formed, including drug derivatives and targets derived from educts labeled, *e.g.,* **X3** and **X6**,[18] thus equating to late-stage derivatization. Also included in this study is the use of ocean water,[23] which is a viable alternative medium to more commonly used purified water. Lastly, a 5-step sequence run in 1-pot in an aqueous medium is described, representative of the opportunities that now exist for designing synthetic pathways that benefit from both improved time[24] and pot economies.[25]

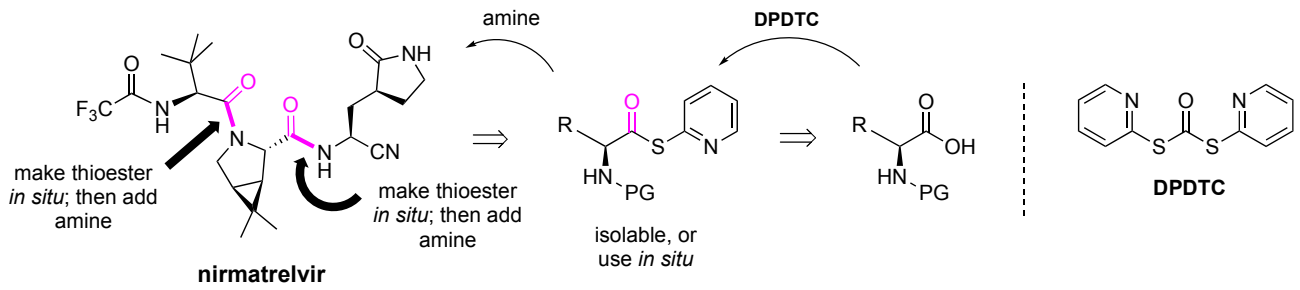


Scheme 2. Representative examples of NP-containing ppm levels of Pd for aminations in water

Lesson learned from Nature: *Is it really that surprising that important Pd-catalyzed C-N bond formations can be accomplished under mild conditions, and with only ppm levels of (in this case) precious metal catalysts akin to Nature's use of nanoreactors (e.g., enzymes, although in this case, micelles) in which to do chemistry? Or, is this to be expected, in line with so many other types of both Pd and even Ni-catalyzed couplings*[26] *performed in water. The bottom line seems to be that while aminations require different conditions (mainly involving changes in catalysts and temperatures) than those associated, e.g., with C-C couplings, they are amenable to chemistry in water. Thus, a remaining fair question might be: is there still sufficient justification for running aminations in organic solvents under more harsh conditions that require an investment in energy, and with unsustainable amounts of Pd?*

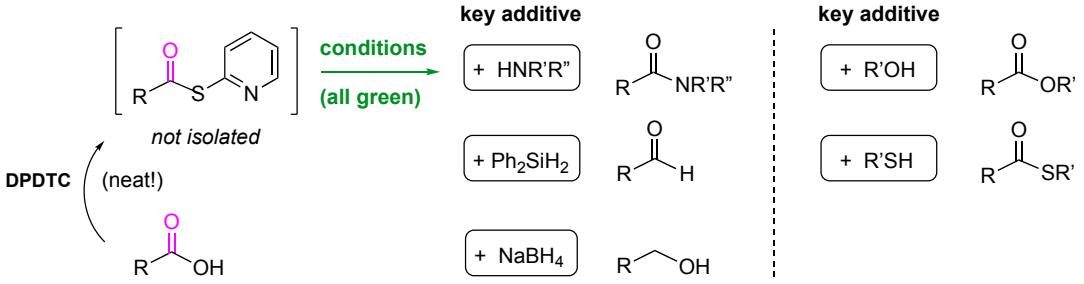
Do we really need commonly used peptide coupling reagents?

When the Bill & Melinda Gates Foundation asked us to make nirmatrelvir (the key ingredient in Pfizer's anti-COVID-19 polypeptide drug Paxlovid; Scheme 3)[27] in a cost-effective manner that does not rely on traditional peptide coupling agents, the question we asked was: "How would Nature do this"? Answer: thioester intermediates. This led to development of the dithiocarbonate, DPDTC,[28] which forms the corresponding 2-thiopyridine-derived ester under a variety of green conditions, including neat with mild heating (*i.e.,* 60 °C). The 2-mercaptopyridine released as by-product is recoverable and hence, recyclable. Also of note, although the initially formed thioesters are perfectly stable and thus, isolable, these can be made and used *in situ*, and readily converted to the targeted amide,[29] or in this case, peptide (Scheme 3).[30]



Scheme 3. Use of DPDTC-derived thioesters in place of traditional peptide coupling agents

The same 2-pyridyl thioester intermediates can be reduced to either the aldehyde, or perhaps more noteworthy, the alcohol, thereby avoiding use of potentially dangerous LAH, especially on scale (Scheme 4).[31] In addition to amides, aldehydes, and alcohols, both esters and thioesters appeared to be reasonable targets, and indeed, after some additional experimental work, both functional groups are now realizable using the same thioester precursors (see paper dedicated to solely this subject, herein).[32] Esters are formed under either neat conditions, or by adding the alcohol (1.05 equiv) to the *in situ*-formed 2-pyridyl thioester in highly concentrated and recoverable EtOAc (2 M). Thioesters, not surprisingly, are even easier to form, including under micellar catalysis conditions in water.[33]



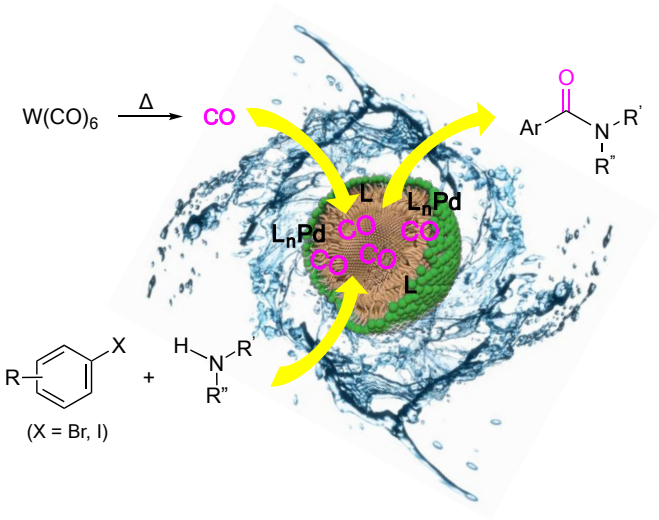
Scheme 4. Conversion from a carboxylic acid to multiple functionalities using a 2-thiopyridyl ester intermediate

Lesson learned from Nature: *Thioesters are used in vivo for a variety of biosynthetic processes (e.g., formation and degradation of fatty acids).*[34] *From the synthetic perspective, analogous 2-thiopyridyl esters serve as precursors to a variety of valued functionality, including generation of important amide and peptide bonds. This approach avoids waste-generating and potentially dangerous coupling reagents commonly used today in organic solvents.*

Pd-Catalyzed carbonylations of aryl halides (bromides and iodides)

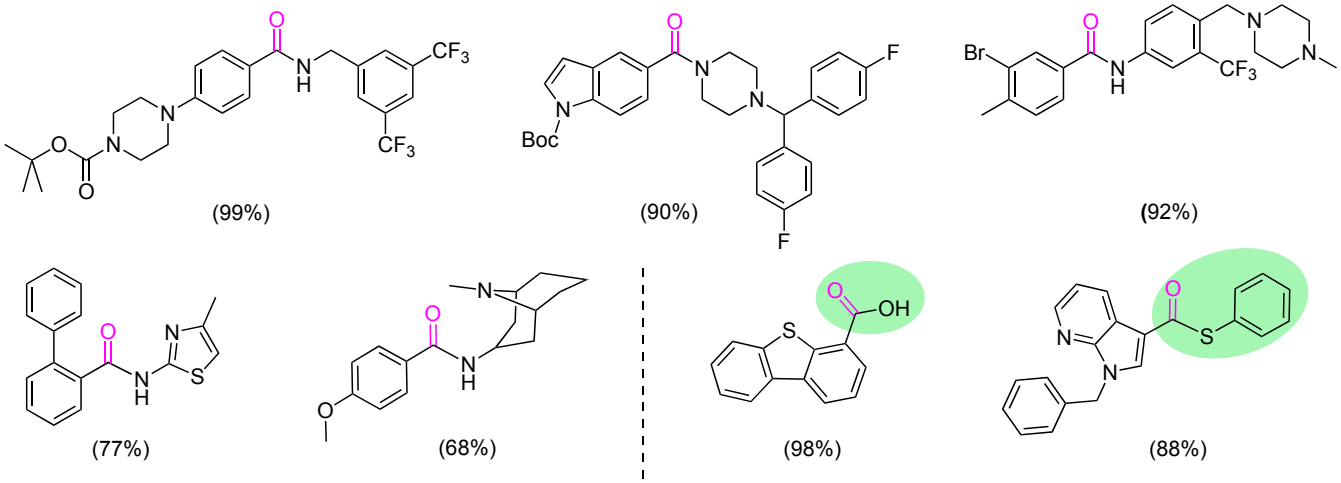
While important bond formations such as amides/peptides, esters, etc. tend to start with a carboxylic acid in place (*vide supra*), insertion of CO onto an aryl halide or pseudohalide is a well-known alternative.[35] Such processes, regardless of their history, have all been developed in organic solvents. Thus, it is also appropriate for this disconnection to be re-examined and potentially "upgraded" to

involve environmentally more forward-looking chemistry. Moreover, from just the purely synthetic perspective (*i.e.,* putting environmental issues aside), there are several improvements that can also be envisioned, including (1) development of a technology that is applicable to *both* bromides and iodides; (2) multi-step syntheses taking place in a 1-pot process; (3) use of milder reaction temperatures; and (4) the option to avoid dangerous CO gas and associated equipment. New procedures featuring these aspects are now available (*e.g.,* to make amides; Scheme 5), all being used under aqueous micellar conditions.



Scheme 5. Generation (from $W(CO)_6$) and localization of CO for carbonylations in aqueous micellar media

To ensure limited exposure to CO, $W(CO)_6$ (1 equiv by weight) was found to be an effective surrogate that releases CO, while loadings of the Pd catalyst were mostly in the 0.5 mol % range.[36] Using 2 wt % of the workhorse surfactant TPGS-750-M in water at 70 °C provided, overall, finalized conditions for carbonylation of both bromides and iodides, although the nature of the catalyst required for each showed some variation. Importantly, the aqueous medium is fully recyclable, and the investment of precious palladium is ten times lower than that typically used in carbonylations of this type…and that's before recycling. Net usage of ligated (L) Pd/carbonylation averages out to 0.25 mol %/reaction, which translates into a new standard for such processes. Mainly amides were prepared, although examples of both acid and thioester are included in this study (Scheme 6). Applications to highly functionalized products are included, as is a synthesis of the antitumor agent sonidegib involving amide formation that relies on carbonylation.



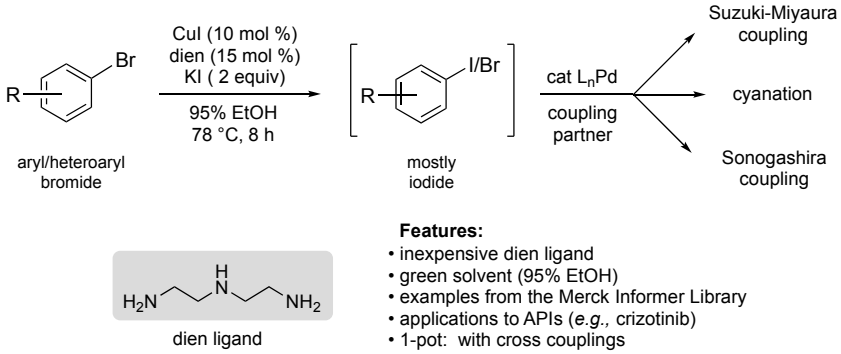
Scheme 6. Representative examples of products from carbonylations of precursor aryl bromides/iodides

Lesson learned from Nature: *Carboxylic acid-derived functional groups, perhaps most notably amides/peptides, can now be made in water via insertion of CO into an intermediate C-Pd bond, starting with an aryl halide (Ar-X). Conceptually, the micellar environment, used throughout evolution, localizes the CO released from $W(CO)_6$ in high concentrations within its inner cores relative to the surrounding water, leading to results that are as good or better than those expected in pure organic solvents.*

Especially challenging Pd-catalyzed cross couplings of aryl bromides… made easier

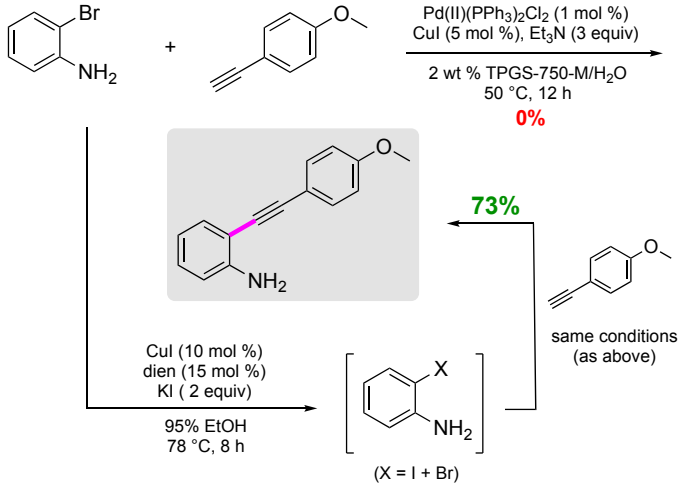
Consider a situation where molecular modeling indicates that a blockbuster drug might result from a single step using a seemingly straightforward Pd-catalyzed reaction of an in-hand aryl- or hetero-aryl bromide. In other words, a highly functionalized, available compound need only be converted to this new, highly active drug in a single step. However, all efforts to find conditions to negotiate this coupling led to failure. What are the options? Clearly, ignoring the potential for huge economic and medicinal gains is not one of them!

Faced with the prospect of having to re-design the entire route, a more palatable alternative is needed, and indeed, has been developed.[37] That is, the inactive or poorly participating bromide is converted, *in situ*, into the corresponding far more reactive iodide using copper catalysis (Scheme 7). Then, without isolation/purification, this newly formed iodide has a dramatically increased chance of participating in the desired coupling, in water. The bromide-to-iodide conversion is best achieved in the green and inexpensive solvent 95% EtOH, while the dien ligand used is a re-purposed waste material.

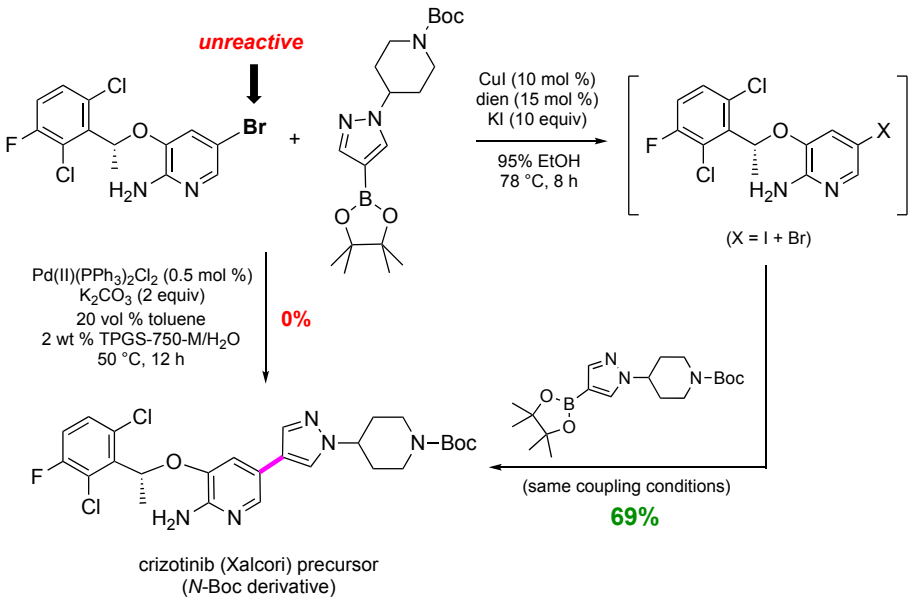


Scheme 7. Conversion of unreactive aryl/heteroaryl bromides to reactive iodides *in situ*, followed by cross couplings

For example, consider the case involving a seemingly straightforward Sonogashira coupling, but where an *ortho*-bromoaniline is experimentally found to be totally unresponsive towards reaction with an activated arylalkyne (*i.e.,* 0% yield; Scheme 8). However, by initially converting it to the corresponding iodide, and without isolation, it then smoothly couples to afford the desired unsymmetrical diarylalkyne in 73% *overall* yield. Perhaps more convincing is the attempted Suzuki-Miyaura coupling between the 3-bromopyridine and a boronate under mild conditions in aqueous micellar media, which does not form any heterobiaryl (*i.e.,* 0% yield; Scheme 9). However, upon preliminary conversion of the same bromide to (predominantly) its corresponding iodide, this new intermediate can then be used directly (*i.e.,* under the same coupling conditions, and without isolation) to afford the *N*-Boc-protected precursor to the antitumor agent crizotinib in 69% isolated yield.



Scheme 8. Example illustrating a reaction that fails to one that goes *via* initial *in situ* conversion to the iodide



Scheme 9. Application of the *in situ* bromide-to-iodide conversion *en route* to the antitumor agent crizotinib

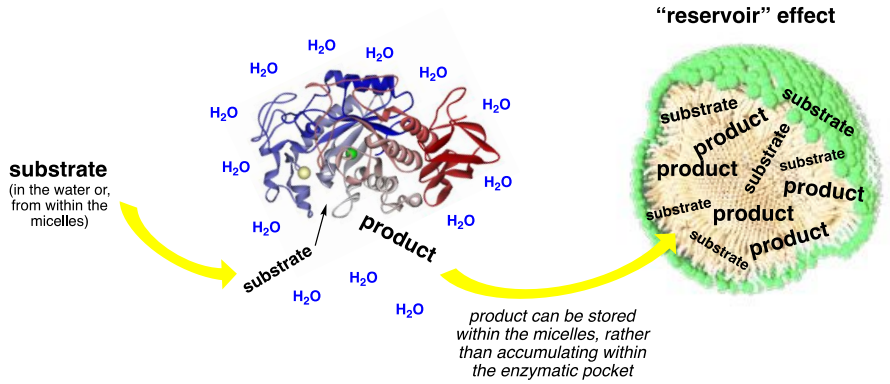
Lesson learned from Nature: *Highly derivatized educts containing normally reactive aryl/heteroaryl bromides (e.g., such as those found in the Merck Informer Library) oftentimes contain functionality that may compete with a ligand initially on a Pd-containing catalyst, thereby decreasing or even eliminating catalyst activity. One option is to convert the bromide in situ to a more reactive iodide, which (without isolation or purification) ultimately may significantly improve the yield of desired product. The chances for a successful transition metal-catalyzed conversion, or any reaction being run in Nature's "solvent", go up dramatically using aqueous micellar catalysis where the concentrations inside the nanoreactors (≥2 M) in water are usually ten times those typically used in organic solvents (which are limited due to practical considerations, such as stirring). This phenomenon, in general characteristic of aqueous micellar catalysis, has not yet been fully appreciated presumably because chemistry in water is not commonly utilized. Nonetheless, these likely increases in chemical kinetics especially important in industrial circles, remain for further "discovery."*

Chemoenzymatic catalysis: is this the future of organic synthesis?

The reviews routinely point to the same problems associated with "mixing" chemocatalysis, done in organic solvents, with enzymatic catalysis, typically run in an aqueous buffered medium.[38] That is, the "oil and water don't mix" mentality which has been the guiding principle overshadowing the many benefits to be realized by merging both approaches.[39] Up until recently, this notion, that these two approaches to synthesis occupy "two distinct worlds"[40] prevailed…but no longer. The very idea of changing enzymatic catalysis for use in organic solvents goes against evolution and nature's use of enzymes in water throughout time. That's clearly a losing proposition in both the short and long term, especially with all the environmental issues now before us, as well as the promise of enhancing an enzyme's reactivity and selectivity and the "new-to-nature" modifications that directed evolution offers.[41] Acknowledgement of these fundamental aspects of biocatalysis provides yet another reason to encourage chemocatalysis away from its use in organic solvents and towards water. And once

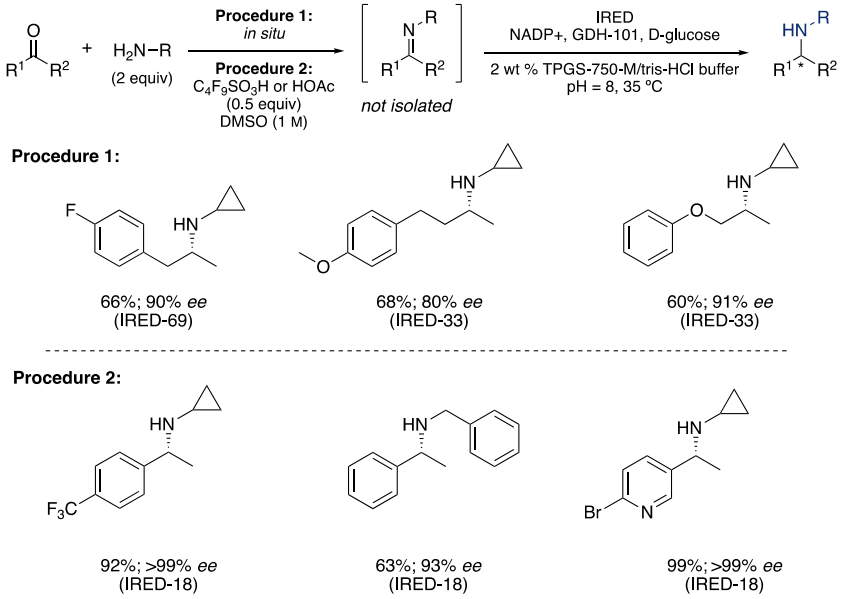
compatible, chemoenzymatic catalysis (which implies use of both sequentially and in 1-pot) becomes a very attractive option for doing synthesis, today and tomorrow.

From the recently disclosed examples discussed herein, which further add to the growing toolbox of technologies, chemistry "in water" is a viable option. But there's far more here for the taking: it also provides an exciting basis for uncovering nature's secrets that have accumulated over the millennia. In hindsight, having micelles in water that enhance *both* chemo- and bio-catalysis now makes sense: they function both as nanoreactors in whch chemocatalysis can take place, also benefitting biocatalysis simply from their presence as a temporary "reservoir" in which water-insoluble products resulting from enzymatic processes are stored that might otherwise accumulate and block substrate entry.[42] This phenomenon, typically falling under the blanket of enzymatic product inhibition,[43] can be a major obstacle to subsequent chemocatalysis, or even biocatalysis, especially with considerable amounts of starting materials remaining. Just having nanomicelles in the water can be a very simple "fix" (Scheme 10).

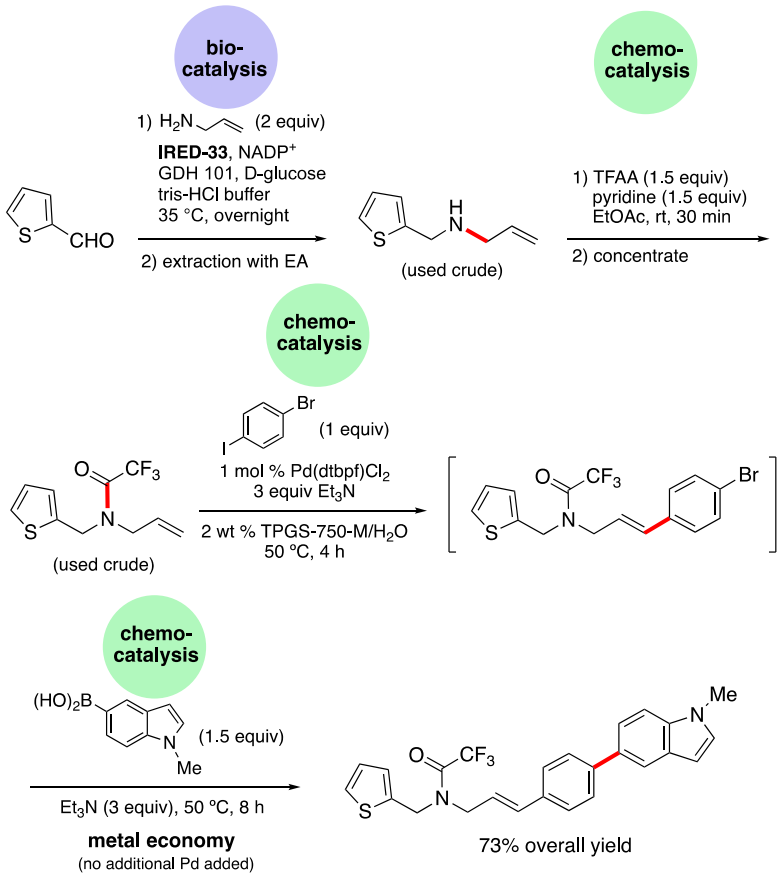


Scheme 10. The "reservoir" effect on biocatalysis due to nanomicelles in the water

That several *nonionic* surfactants (other types, such as anionic and cationic surfactants have not been evaluated in this context) act in this "reservoir" manner can been seen from studies using numerous kit-based enzymes, including KREDs,[42] EREDs,[44] ATAs,[45] and selected lipases that make esters…*in water*.[46] Here, just the presence of nanomicelles in the water provides an alternative location for the (especially) lipophilic products from enzymatic catalysis to be stored, away from the entryway thereby allowing more substrate participation. Yet another type of important enzyme, imine reductases (IREDs), has only recently been evaluated and, likewise, found to enhance the extent of conversion associated with several carbonyl/amine combinations.[47] Thus, as shown in Scheme 11, secondary nonracemic amines are readily formed in somewhat variable overall ee's using the benefits derived from the presence of TPGS-750-M (2 wt %). In general, the amphiphile can impact the extent of conversion, and hence, yield, either quite substantially (*e.g.,* >40% relative to that obtained using the aqueous buffer alone), or be of little-to-no effect, indicating that screening of the surfactant can be an important parameter. Here again, an IRED-catalyzed ketone-to-amine conversion allows for a chemoenzymatic catalysis sequence, in this case involving 4-steps, outlined in Scheme 12. Aside from the initially formed *N*-allylated, thiophene-containing adduct that can be used "crude", the concept of "metal economy"[20e] is also highlighted. Thus, after conversion to the amide, a Mizoroki-Heck reaction is followed directly by a Suzuki-Miyaura coupling



Scheme 11. IRED-catalyzed conversions of ketones to nonracemic secondary amines



Scheme 12. Chemoenzymatic 4-step sequence including an illustration of "metal economy"

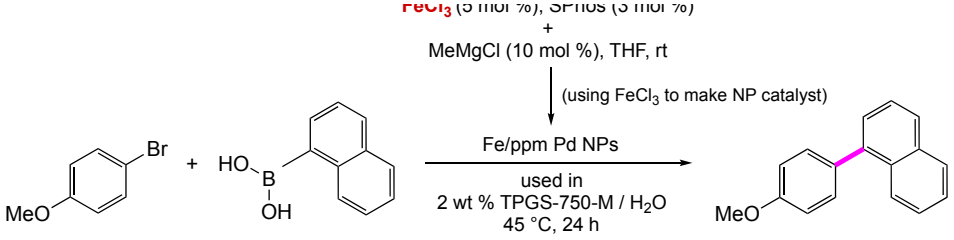
using the Pd present in the aqueous reaction mixture for both steps. Hence, this process is another example featuring, in addition to metal economy, time [24] and pot economy.[25]

Lesson learned from Nature: *Both chemocatalysis and biocatalysis are now usable for synthetic gain in nature's chosen reaction medium, water. So, why maintain a distinction in terms of the type of reagent involved; doesn't nature see this chemistry as just "catalysis"?*

More of Nature's secrets…just waiting to be "discovered"

The finding that by simply having nanomicelles in the aqueous medium associated with an enzymatic process may alter the natural balance associated with product formation was unexpected. Nonetheless, in hindsight, it seems quite reasonable to consider surfactants, or surfactant-like species and related biomolecules (such as simple vesicles and membranes) as likely contaminants (or "dirt")[48] in the water throughout evolution. Their presence can dramatically enhance the extent of enzymatic conversion to product and thereby, provide options for multi-step processes in the same pot (see Scheme 10).

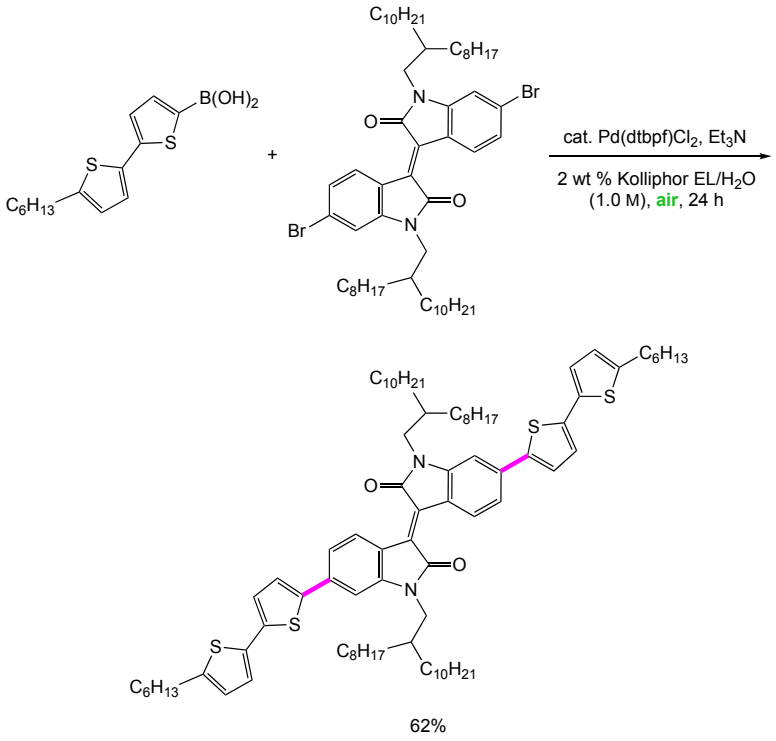
Another "gift from Nature" focuses on the origin of the nanoparticles (NPs) used for ppm Pd-catalyzed aminations in recyclable water (*vide supra*). These NPs derive from treatment of inexpensive $FeCl_3$ in THF with MeMgCl (Scheme 13). The message from Nature, however, was the finding that since $FeCl_3$ originates with mined iron ore from different locations in the world, the iron is mixed naturally with other metals (mainly base metals, such as Cu, Ni, Co, etc.) to varying extents. But since these sources of iron are not the same (why should they be?), one "impurity" in the iron happens to be palladium, which is processed into the targeted ferrous and ferric salts. ICP-MS analysis reveals the relative amounts involved, and as in the case reported,[20a] sufficient Pd was present (>350 ppm) in the resulting NPs to catalyze Suzuki-Miyaura couplings. In other words, Nature is providing Pd, hidden within iron salts, at no cost. Where else might such precious metals be found, without formally mining for them, that can be parlayed into catalysts for organic synthesis under green chemistry conditions? Such opportunities might be all around us; are we really paying attention?[49]



commercial source of $FeCl_3$	amount of Pd in $FeCl_3$	yield of biaryl product (%)
Sigma-Aldrich	8	4
Alfa Aesar	10	9
Fisher	3	NR
Chem-Impex	**320**	**93**

Scheme 13. Variations in levels of Pd as an "impurity" in $FeCl_3$

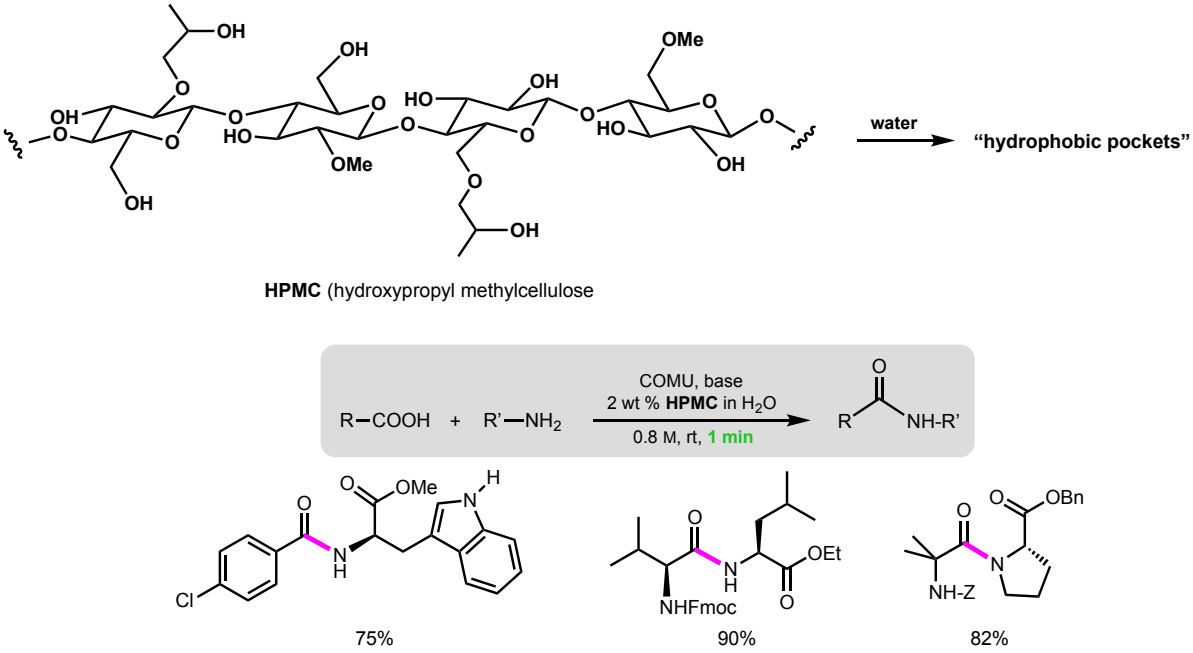
Secrets associated with chemistry in water have been found by others as well. As noted herein, nonionic surfactants enable chemocatalysis in water, and in addition, can play a beneficial role in biocatalysis. Although most nonionic surfactants used in synthesis contain PEG, with perhaps the exception of Savie (Figure 1),[21] the individual properties of each PEGylated surfactant need not be the same. Such is the case regarding cremophor, now referred to as Kolliphor EL (Figure 1), a well-known polypegylated product derived from ricinoleic acid (the main ingredient in castor oil), available in quantity from the BASF.[50] Data on this amphiphile does not include an unexpected, seemingly to date unique property, first discovered and reported by the Beverina group.[51] That is, notwithstanding the characteristically highly preferred dissolution of gases, such as oxygen, in hydrocarbon media relative to water,[52] nanomicelles derived from Kolliphor EL can be used to great advantage in cases where the presence of oxygen can be tough to remove, or is particularly disadvantageous in terms of the chemistry involved. Or maybe, reactions (*e.g.,* Suzuki-Miyaura couplings) involving oxygen-sensitive group such as most phosphines can now be run under aerobic conditions (Scheme 14).[53] What is Nature telling us about surfactants?



Scheme 14. Use of micelle-forming Kolliphor EL in a Pd-catalyzed cross coupling, *in air*

Another spectacular discovery developed by the joint industrial/academic team of Braje (AbbVie) and Handa (now at Missouri) concerns the use of an inexpensive, *biodegradable* sugar (and very little of it per reaction), hydroxypropyl methyl cellulose (HPMC; Scheme 15). When dissolved in water it enables remarkably rapid reactions to occur. Several types (*e.g.,* aminations,[53a] amide formations,[53a,b] click,[54] S_NAr,[55] etc.) are amenable to the purely aqueous conditions involved.[56] The results are attributed to formation of "hydrophobic pockets" in which reactions happen, usually within seconds-to-minutes.

What is known about these pockets themselves, and why do they form using this particular cellulose derivative? What are the concentrations of substrates and how do they find their way so quickly into these pockets? Should this phenomenon be thought of involving porous liquids that are best known[57] for accommodating *gases* but potentially in modified form may offer extensive additional applications to organic synthesis? In brief, is this yet another example of Nature's secrets at a very early stage of development?



Scheme 15. Very rapid reactions, such as amide/peptide bond constructions, in aqueous solutions of HPMC

Summary & Conclusions

While the theme for this focused contribution may be "Rethinking aqueous chemistry…", in reality, "re-thinking" began well over 15 years ago leading to the first publications in back-to-back-to-back fashion in *Organic Letters* in 2008.[58] Since the technologies available today include many of the most commonly used processes in organic synthesis, the implication is that there are no technical hurdles preventing chemistry from being done in nature's "solvent", water, thereby replacing waste-generating and in many cases, toxic and flammable organic solvents. In this regard, "re-thinking aqueous chemistry" seems long overdue, as the world is beginning to recognize the essential transition away from petroleum, a move mandated by existential factors such as climate change.

In this brief review some examples of more recently added processes to the growing toolbox are discussed. These might bear no obvious relationship to each other, other than that they share the commonality of their reaction medium. Hopefully, together they provide an enticing case for making additional discoveries that lie in wait, having accumulated over the millennia. After all, with most of modern organic chemistry having been developed in organic solvents, one could argue that much of this

fundamental science needs to be re-evaluated, and perhaps, re-done *en route* towards a more sustainable discipline. To help make these needed transitions all the more apparent, also available and used frequently are the metrics associated with green chemistry. These all started with environmental, or E Factors from Sheldon years ago. And while there are today numerous versions (*e.g.,* cE Factor, etc.),[59] the pharma industry has adopted, in general, use of process mass intensity (PMI).[60] Neither of these are as indicative of the entire picture, which is why a full life cycle assessment (LCA) is actually the preferred approach.[61] Unfortunately, this method of analysis is quite labor and time intensive, and takes a definitive level of "know-how" and insight not commonly available to industrial labs, let alone academic groups. Ideally, therefore, a collaborative approach is one attractive path forward. After all, we may not have a choice.

The good news, in part, is that as the field "re-invents" itself, the "two worlds" of chemocatalysis and biocatalysis are now merging (*i.e.,* into "chemoenzymatic catalysis") with the help, to varying degrees, of nonionic surfactants that enable utilization of both in water.[39,42] Thus, on the one hand, the oftentimes exquisite selectivities offered by enzymes, used in water, should increase in appeal and eventually, applications. On the other hand, nanomicelles in the same aqueous medium, as nanoreactors, are indiscriminate, welcoming all types of substrates and catalysts, thereby enabling an array of chemical reactions. Thus, the hope is that the community sees the unlimited possibilities for chemistry in water, which is exactly how Nature planned it long ago.

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