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Transitioning organic synthesis from organic solvents to water.

What's *your* E Factor?

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Traditional organic chemistry, and organic synthesis in particular, relies heavily on organic solvents, as most reactions involve organic substrates and catalysts that tend to be water-insoluble. Unfortunately, organic solvents make up most of the organic waste created by the chemical enterprise, whether from academic, industrial, or governmental labs. One alternative to organic solvents follows the lead of Nature: water. To circumvent the solubility issues, newly engineered "designer" surfactants offer an opportunity to efficiently enable many of the commonly used transition metal-catalyzed and related reactions in organic synthesis to be run in water, and usually at ambient temperatures. This review focuses on recent progress in this area, where such amphiphiles spontaneously self-aggregate in water. The resulting micellar arrays serve as nanoreactors, obviating organic solvents as the reaction medium, while maximizing environmental benefits.

1. Introduction

It seems like a very simple question: What's your E Factor? The reality is that the vast majority of chemists, including organic chemists, have no idea how to answer it, and yet the economic and environmental implications can be huge.[1] But unless one today is an experienced process research chemist, who calculates E Factors? While few are looking for such extra work, maybe this is one exercise in simple mathematics that ought to be done; one just needs to be prepared for the outcome, because as the saying goes, "it ain't pretty." An **E**nvironmental Factor, or **E** Factor, introduced decades ago by Sheldon,[2] has not only withstood the test of time, but has grown in relevance, as it represents one meaningful measure of "greenness" associated with any reaction.[3] By definition, it correlates the amount of waste created, by weight, divided by the weight of isolated product. Hence, the lower the E Factor, the more environmentally acceptable the process. By far, the major component leading to elevated E Factors is the organic solvent used as, or part of, the reaction medium.[4] Traditionally, the sequence to most reactions calls for the up-front use of an organic solvent, after which workup in the usual way includes dilution with water, followed by extraction with yet additional organic solvent (which is oftentimes different from the reaction solvent). And what is to be done with all the contaminated waste-water, the volume of which usually far exceeds that even associated with the organic solvents invested, that, typically at best, are only partially recovered?[5] Logically, this just doesn't sound like a sustainable, let alone environmentally responsible, approach to doing chemistry. This is the way it has always been taught, and how it is still practiced. But Nature does not do synthesis in organic solvents such as ethers or DMF, let alone in solvents that deplete our petroleum reserves; why have we not looked to Nature for insight and guidance as to how to avoid use of organic solvents as reaction media?

2. Getting organic solvents out of organic reactions

As previous reviews have discussed,[6] one option for minimizing organic solvents in organic synthesis is to design an amphiphilic species that contains a lipophilic portion that will function as the organic solvent, following dissolution in water and spontaneous self-assembly into micellar form. Of course, the major difference here is that there will be very little of this surfactant, and even less of its derived nanoparticles present in the water; indeed, the amounts required for a surfactant to form a micellar array (*i.e.,* the critical micelle concentration, or CMC) are typically on the order of 10^{-3} to 10^{-4} M.[7] Hence, with virtually no effort on the part of the synthetic practitioner, nanoreactors can be formed that function as the reaction vessel in which a desired transformation occurs involving otherwise water-insoluble substrates and catalysts. The "trick", in a sense, is to recognize that these nanoparticles are truly functioning as the reaction solvent, and that solvent selection can play a determining role in a reaction's outcome; it's not conceptually different from one's selection of an organic solvent in which to run any reaction: the choice matters. The nature of the amphiphile, therefore, can be crucial, and this was the rationale behind the development of "designer" surfactants.[6b] But unlike the choice of organic solvent as the reaction medium, the key parameter appears to date to be particle size and occasionally, shape, rather than specific content (*vide infra*).

The lead surfactant for many transition metal-catalyzed cross-couplings is TPGS-750-M (**1**),[8] which replaced its first generation precursor PTS (**2**, Figure 1).[6a, 9] As has been shown in just about every reaction studied in either medium, these amphiphiles provide a synthetically more attractive outcome than identical reactions run in most other surfactants that might be chosen simply by virtue of expedience; *i.e.,* they can be obtained from commercial suppliers. The impetus for development of second generation TPGS-750-M was predicated on the observation that micelles averaging 50-60 nm, as determined by Dynamic Light Scattering (DLS), appeared to afford yields that are equal to, or better than, those seen with PTS (average size 23 nm).[8]

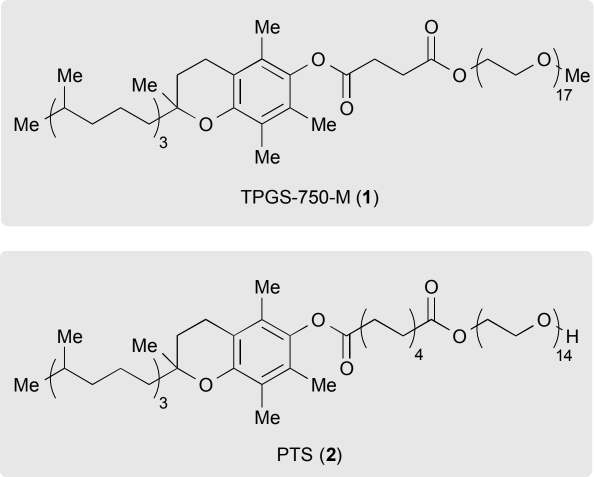


Figure 1 Structures of PTS, and the more recently engineered surfactant TPGS-750-M

Equally important, however, was the cost associated with their syntheses, which is far lower in the case of **1**. Taken for granted is the guiding principle that any new amphiphile should be "benign by design",[10] meaning that it would be of little consequence should it find its way into the environment. That is, just as TPGS-1000,[11] also commonly referred to as "vitamin E TPGS", is not only innocuous but is used routinely by pharma as an excipient, so are PTS and TPGS-750-M harmless variations; indeed, they are pro-vitamins (*i.e.,* another form of "ester-E").

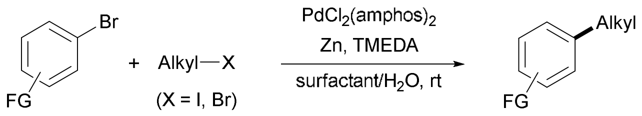
Since the appearance of prior reviews on the applications of PTS and TPGS-750-M,[6] much new chemistry has been enabled by these nanomicelle-forming species. Both continue to be items of commerce,[12] and a route to multi-gram quantities of **1** has been reported,[8] with additional details in the form of an *Organic Synthesis* procedure also of very recent vintage.[13] A third generation and less costly surfactant, called "Nok" (*vide infra*),[14] is discussed herein, and will soon be an item of commerce as well.[15]

3. New technologies in water

3.1 Reactive metal chemistry…in water at room temperature

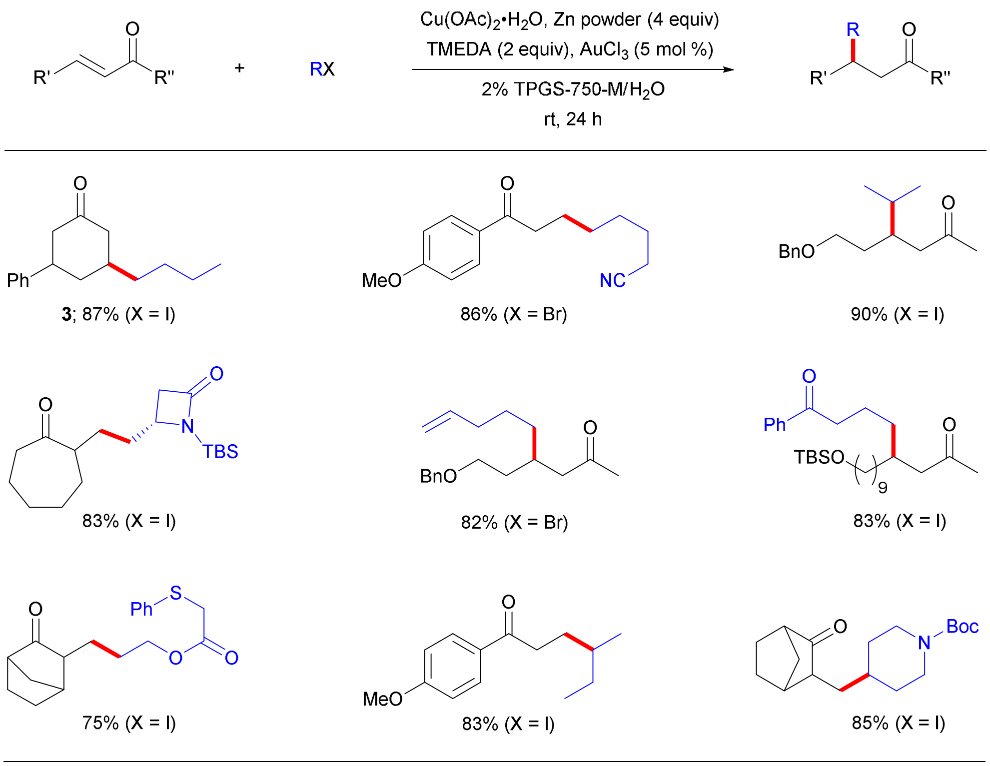
The Pd-catalyzed coupling between an alkyl zinc halide and an aryl or heteroaryl halide to arrive at an alkylated aromatic ring is considered a standard Negishi coupling.[16] But rather than using moisture-sensitive, pre-formed organozinc halides under strictly anhydrous conditions,[17] such "reductive cross-couplings"[18] can now be accomplished by simply mixing the precursor halides *in water*.[19] With the addition of a Pd catalyst, TMEDA, and zinc (dust or powder) the alkylated aromatic product is formed. The scenario of events envisioned for this seemingly textbook-prohibited reaction involving a presumed *in situ*-generated RZnX in water goes along the following lines:[6b] the "organics" (both halides, the Pd catalyst, and some of the TMEDA present) obtain maximum occupancy within the limited number of nanomicelles in water. These particles collide with the heterogeneous zinc in the medium, whereupon the zinc surface is cleaned by the TMEDA, leading to its selective insertion into the sp^3 C-X bond of the alkyl halide present within the micelle. The resulting water-sensitive RZnX, temporarily buffered from the surrounding aqueous medium by the micelle's exterior, is then exposed to both the catalyst and aryl bromide that are present within the nanomicelle in high concentrations, thus leading to net cross-coupling (Scheme 1). It is worthy of mention that aryl bromides can be used under such conditions at room temperature, whereas traditional Negishi couplings in organic (usually ethereal) media do not normally occur with such educts at ambient temperatures.[20]

Scheme 1 Zn-Mediated, Pd-catalyzed cross-couplings with aryl bromides in water

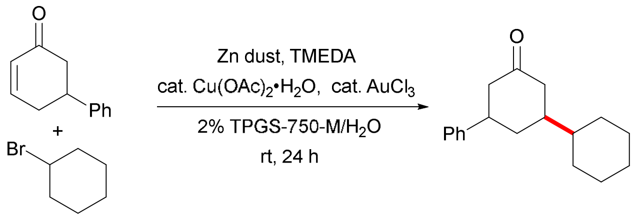


The crucial observation that a highly basic RZnX can be formed in a sea of water and yet has sufficient lifetime to effect transmetalation, in the above case to palladium, offers opportunities for its conversion to other organometallics. One such newly developed process focuses on organocopper complexes that can form *via* transmetalation from RZnX in the presence of a copper(I) salt.[21] When an α,β-unsaturated ketone is also housed within nanoreactors composed of TPGS-750-M, the desired 1,4-addition takes place. The resulting conjugate adduct, a copper enolate, is quenched by the surrounding water, leading to the product ketone and free copper available to re-enter the catalytic cycle. To enhance rates and drive these reactions to completion, the presence of a Lewis acid was found to be essential. While $BF_3{\bullet}Et_2O$ is the most common additive in organocopper conjugate additions[22] (recall Yamamoto's reagent, "$RCu{\bullet}BF_3$"),[23] the aqueous conditions preclude its involvement. Rather, use of $AuCl_3$ was found to be the most efficacious. Representative examples of C-C bonds made under these aqueous conditions are illustrated in Scheme 2. Given the functional group tolerance of organozinc reagents and the lack of a highly basic reagent needed for its preparation (*e.g.,* an RLi or RMgX), sensitive carbonyl groups including β-lactams are readily maintained. Noteworthy is the observation that while the surfactant is engineered to remain in the water, and hence, can be recycled, so does the gold; no additional $AuCl_3$ need be introduced upon recycling of the aqueous medium (Scheme 3). And as with all other reactions run in either surfactant **1** or **2**, the "workup" consists of nothing more than adding a small amount of a single organic solvent (*e.g.,* EtOAc, Et_2O, MTBE, hydrocarbon, etc.) to the reaction vessel, *gentle* stirring, and removal of the organic material. No additional water need be added, and the aqueous medium need not leave the reaction flask. As a further boost to reactivity, inclusion of a catalytic amount of Ag ion has been found to both accelerate these couplings and reduce the levels of alkyl halide required for full conversion.

Scheme 2 Conjugate additions of alkyl halides to enones



Scheme 3 In-flask recycling of TPGS-750-M and $AuCl_3$



cycle	conv. (%)	yield (%)
1	>99	89
2	>99	86
3	97	83
4[a]	95	84

[a] Reaction time 32 h.

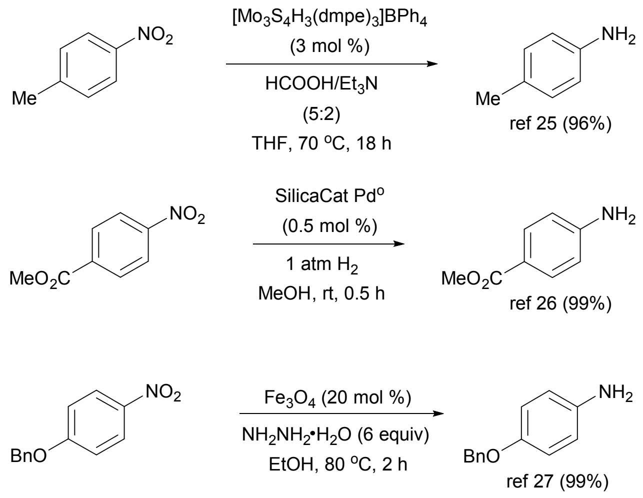
Representative Cu–catalyzed conjugate addition of alkyl halides in water. Preparation of 3-*n*-butyl-5-phenylcyclohexanone (3).[21]

A 5 mL microwave vial (oven-dried and under Ar) containing a stir bar was charged with zinc powder (66 mg, 1 mmol), $Cu(OAc)_2•H_2O$ (1.5 mg, 3 mol %), $AuCl_3$ (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 µL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodobutane (42 µL, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 42 µL of 1-iodobutane was added and stirring was continued for an additional 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo,* and the crude reaction mixture was analyzed by NMR, GC, and GCMS. Flash column chromatography using EtOAc/hexanes provided 3-butyl-5-phenylcyclohexanone (*trans* : *cis* = 85 : 15, 50 mg, 87%) as a colorless oil.

3.2 Zn-Mediated reductions of nitro-aromatics and -heteroaromatics

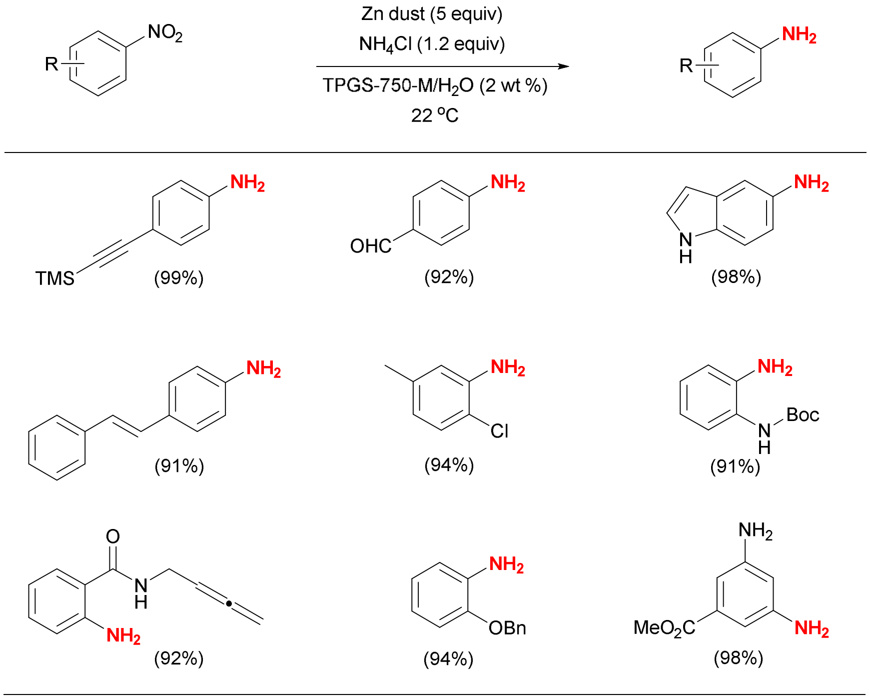
Use of a nitro group as an amine equivalent is a common strategy in organic synthesis, in particular when it is attached to an aromatic or heteroaromatic ring.[24] And although many methods of textbook status exist for its conversion to the corresponding free NH_2 residue, such chemistry is rarely utilized in the context of complex molecule syntheses as they tend to be rather harsh. This has not escaped the attention of synthetic chemists worldwide, and in the past few years alone a number of alternative procedures have appeared that address this seemingly simple reduction. Representative literature procedures are shown in Scheme 4.[25-27] Lacking in all known prior art on this subject is attention to "greenness"; none is likely to be viewed favorably under the auspices of the "12 Principles of Green Chemistry",[28] as these involve organic solvents, elevated temperatures, specialized experimental setups, and privileged ligands and/or catalysts. Moreover, few examples can be found of "real molecules" that would instill confidence in a researcher that the required chemoselectivity, or better, chemospecificity, might be anticipated.

Scheme 4 Literature procedures for reduction of an aromatic nitro group



Here again, micellar catalysis is an enabling technology that, by definition, eliminates the organic solvent component. And when used at ambient temperatures, negates any investment of energy. One solution very recently introduced relies on inexpensive zinc dust, out of the bottle, in water at room temperature.[29] Adding a substrate to water containing TPGS-750-M-derived nanomicelles in the presence of Zn dust leads to the virtually quantitative reduction of nitro groups (Scheme 5). The surfactant is crucial in this process, as the corresponding "on water"[30]

Scheme 5 Zn-mediated reductions of aromatic nitro group at room temperature



alternative is not synthetically useful. Amphiphile **1** presumably in micellar form functions as the "solvent" for each educt. These particles, with the substrate in high concentrations therein, strike the surface of the metal facilitating facile and clean electron transfer. Anionic intermediates in search of neutralizing protons are readily accommodated by the surrounding water.

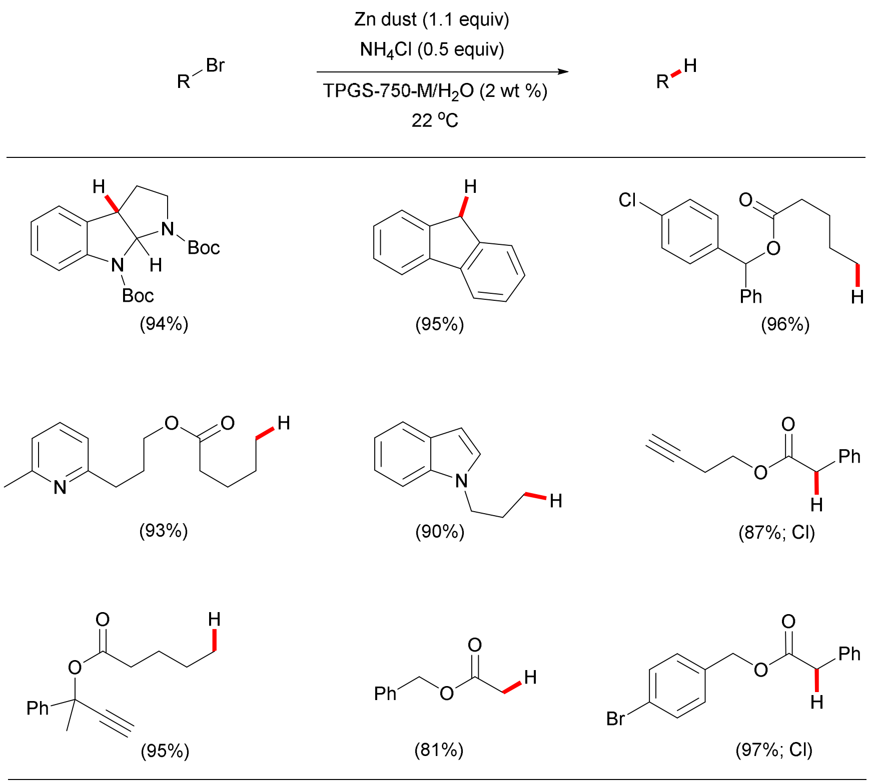
General procedure for Zn mediated reductions of nitroaromatics in water at room temperature.[29]
To a 5 mL round bottom vial equipped with a magnetic stir bar was added the nitroarene (0.5 mmol) and ammonium chloride (0.6 mmol, 1.2 equiv), followed by 2 wt % TPGS-750-M/H_2O (1 mL, 0.5 M) via syringe to the vial. The mixture was stirred for *ca.* 1 min to distribute and dissolve the starting nitroarene. Zinc dust (2.5 mmol, 5.0 equiv) was added in a single batch to the resulting stirred emulsion, and the reaction was allowed to continue stirring vigorously at rt. Reaction progress was monitored by TLC/GSMS. Upon complete disappearance of starting material and any nitroso or hydroxylamine intermediates (generally between 0.5 h and 6 h), the reaction was filtered through a 1 cm silica gel plug to remove water and zinc solids, and rinsed by a minimal volume of EtOAc. Alternately, the completed reaction was extracted via *gentle* stirring with a minimum volume of EtOAc or diethyl ether, and the extracts dried over anhydrous sodium sulfate. The resulting organic solution was concentrated *in vacuo*, and analyzed by GCMS and NMR spectroscopy, and generally required no further purification.

3.3 Zn-Mediated reductions of alkyl halides

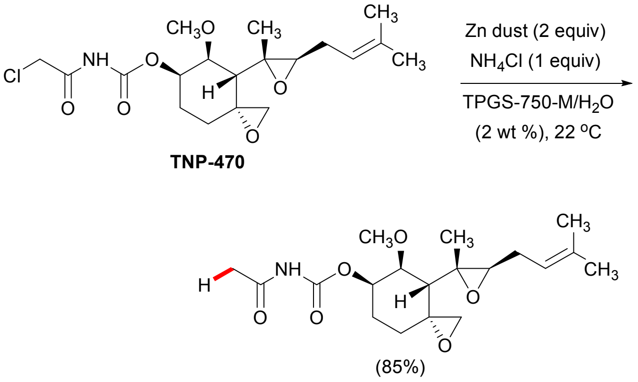
Textbook methods for the reduction of an alkyl halide are plentiful, suggesting that this is a solved problem in organic synthesis. While for simple cases this may be true, such is far from reality when it comes to complex molecules where functionality abounds. Recognition of this gap in methodology has led to several developments of late that offer selective conversion of the C_{sp3}-halogen bond to the corresponding C-H bond in the presence of numerous functional groups. Solutions to this problem include, *e.g.,* use of interesting NHC-borane complexes.[31] Perhaps of greatest efficiency and functional group tolerance is catalytic Ru-catalyzed photoredox chemistry.[32] While each has its virtues and disadvantages, none takes into account its impact on the environment; *i.e.,* at what environmental cost is a C-X bond being reduced?

One alternative that offers the equivalent transformation but does so in the absence of a transition metal and takes place in water at room temperature has recently been reported.[33] It follows from previously described (*vide supra*) net Negishi-like couplings in water that involve *in situ* alkyl halide conversions to organozinc halides on the surface of zinc metal, insulated from the surrounding water by the nanomicelle in which the halide is housed.[18] Since this RZnX is generated in the presence of an aryl halide (Ar-X) that presumably has been converted in part to its derived Ar-Pd-X given Pd(0) in the pot, cross-coupling ensues. However, in the *absence* of a coupling partner and palladium, the intermediate RZnX has no other option but to eventually gain exposure to water, resulting in net reduction of the C-X bond. The functional group compatibility of this process is excellent, given the nature of the metal involved: zinc.[34] As the examples in Schemes 6 and 7 illustrate, formation and quenching of the *in situ*-formed organozinc species is very effective. This trivial method takes advantage of the facile and preferential insertion of zinc into alkyl rather than aryl C-X bonds. Strong testimony to the green nature of this chemistry can be found in that the process occurs in water at room temperature, with the aqueous phase amenable to recycling, and with a low E Factor.

Scheme 6 Zn-mediated reductions of alkyl halides at room temperature



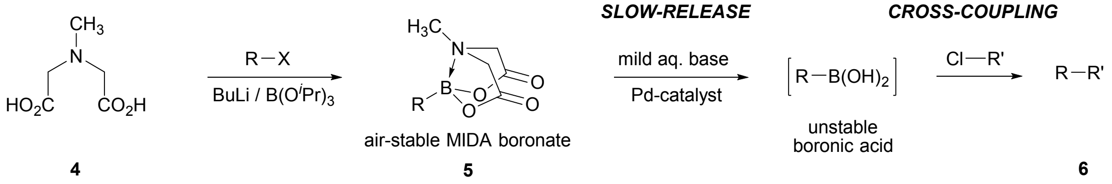
Scheme 7 A Zn-mediated reduction in a highly functionalized molecule



3.4 Suzuki-Miyaura couplings of MIDA boronates

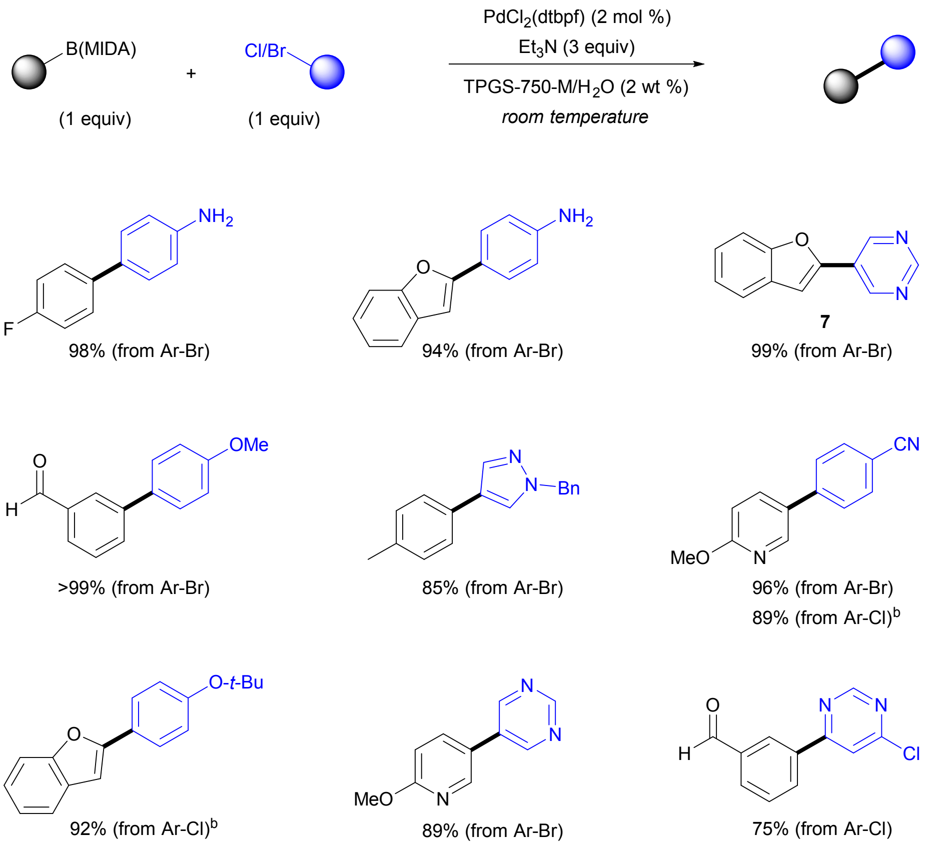
Boronic acids of many heteroaromatics are notoriously unstable, and hence, when used in anticipated cross-couplings, decompose to varying extents (*e.g.,* protio-deborylation) under the traditionally mixed aqueous solvent conditions that oftentimes require some level of applied heat.[35] This tends to necessitate super-stoichiometric levels of the boronic acid, which can be expensive and ultimately can create significant amounts of undesired organic waste. A solution to this problem has been developed in the form of a protected boronic acid derivative that, under the basic reaction conditions, gradually releases the reactive organometallic that then readily participates in the desired Suzuki-Miyaura cross coupling (Scheme 8). Use of *N*-methyliminodiacetic acid (MIDA, **4**) boronates (**5**; "MIDA boronates")[36] offers the community materials that are both stable and crystalline, and have excellent shelf life.[37] Importantly, they allow for couplings to products **6** that might otherwise not be possible, or at least that would not occur in synthetically useful yields. Due to the slow release of their corresponding boronic acids, close to stoichiometric amounts (usually 1.2-1.5 equiv) relative to the coupling partner are called for, adding to the attractiveness of these intermediates.

Scheme 8 Slow-release of unstable boronic acid from MIDA boronate



With stability, however, come changes in reactivity, not to mention that such reactions, as is true in general for Suzuki-Miyaura couplings done in aqueous organic media, are not considered especially green. A change to an aqueous medium, enabled by micellar catalysis, has been found to lead not only to the desired couplings at room temperature, but where the MIDA boronate *need not be used in excess*.[38] Another bonus to this technology is that the aqueous medium is recyclable, and remarkably, the palladium catalyst is retained in large measure in the aqueous phase. As shown in Scheme 9, coupling products that derive from both aromatic and heteroaromatic MIDA boronates are amenable, as are aryl and heteroaryl bromides and chlorides. Also among the salient features of this newly introduced technology is the opportunity to completely remove organic solvents from the equation; *i.e.,* an E Factor approaching *zero*. This is accomplished by simply diluting the aqueous reaction mixture upon completion of the reaction with water.[39] The precipitated coupling product is then filtered off, and the filtrate is prepared for recycling by

Scheme 9 Representative cross-couplings of MIDA boronates and aryl/heteroaryl bromide/chloride in water at room temperature[a]



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[a] Isolated yield after filtration; determined to be >95% pure by ^{1}H NMR. [b] 4 mol % Pd catalyst.

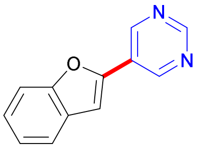
adding neat TPGS-750-M to bring its level to the original two weight percent. Thus, no organic solvent in the reaction mixture, no organic solvent in the workup, no organic solvent in the purification; as phrased by Steve Ritter in *Chemical & Engineering News*, a "cross-coupling triple play."[40] And, another bonus: no waste water.

Another particularly interesting aspect to MIDA boronate chemistry is that no formal study on their couplings with aryl *bromides* has as yet been reported. The implication associated with their established use in Suzuki-Miyaura couplings with aryl chlorides is that this is a "solved problem" insofar as other halides are concerned. But such a conclusion can be misguided, since it assumes that if oxidative addition of Pd(0) to an aryl chloride goes with facility, then the corresponding insertion into a weaker C-Br bond must be more facile; hence, the overall reaction should proceed as well with similar efficiencies. In fact, such is not always the case, and for good reason: that particular step (*i.e.,* oxidative addition) may no longer be rate determining, and hence the nature of the intermediates along the catalytic cycle that bear the ligands chosen to assist with the oxidative addition need not be ideal at that point or otherwise in the overall catalytic cycle. This situation has been observed previously with Miyaura borylations,[41] where conditions leading to facile C-B bonds derived from aryl *chlorides* in organic media[42] are not particularly useful under otherwise identical conditions when applied to aryl *bromides*.[43] In the case of MIDA boronates, as illustrated in Scheme 10, cross-couplings have been performed under micellar (entry 1) as well as traditional conditions on both types of halides.[38] The quality of the coupling to arrive at **7** using a

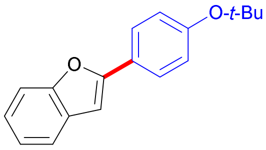
Scheme 10 Comparison reactions conducted at *room temperature*

entry	reaction conditions	**7**[a]	**8**[a]
1	$PdCl_2$(dtbpf) (2 mol %), Et_3N (3 equiv) TPGS-750-M/H_2O (2 wt. %), rt	99%	92% [b]
2	$Pd(OAc)_2$ **(2 mol %)**, SPhos (**2 mol %**) dioxane:H_2O (5:1), K_3PO_4 (**3 equiv**), rt	27%	12% [b]
3	$Pd(OAc)_2$ (**5 mol %**), SPhos (**10 mol %**) dioxane:H_2O (5:1), K_3PO_4 (**7.5 equiv**), rt	60%	24%

[a] Isolated yield. [b] 4 mol % $PdCl_2$(dtbpf)



7 (from Ar-Br)



8 (from Ar-Cl)

precursor aryl bromide in an organic medium (aqueous dioxane; entries 2, 3), albeit at room temperature, was poor (27%). Upon more than doubling the catalyst, ligand, and base, the yield was still only modest (60%). Reactions involving the corresponding chloride under either set of conditions were low yielding (12% and 24%). By contrast, under micellar catalysis conditions, *both* educts lead to good isolated yields of the desired biaryl products **7** and **8**.

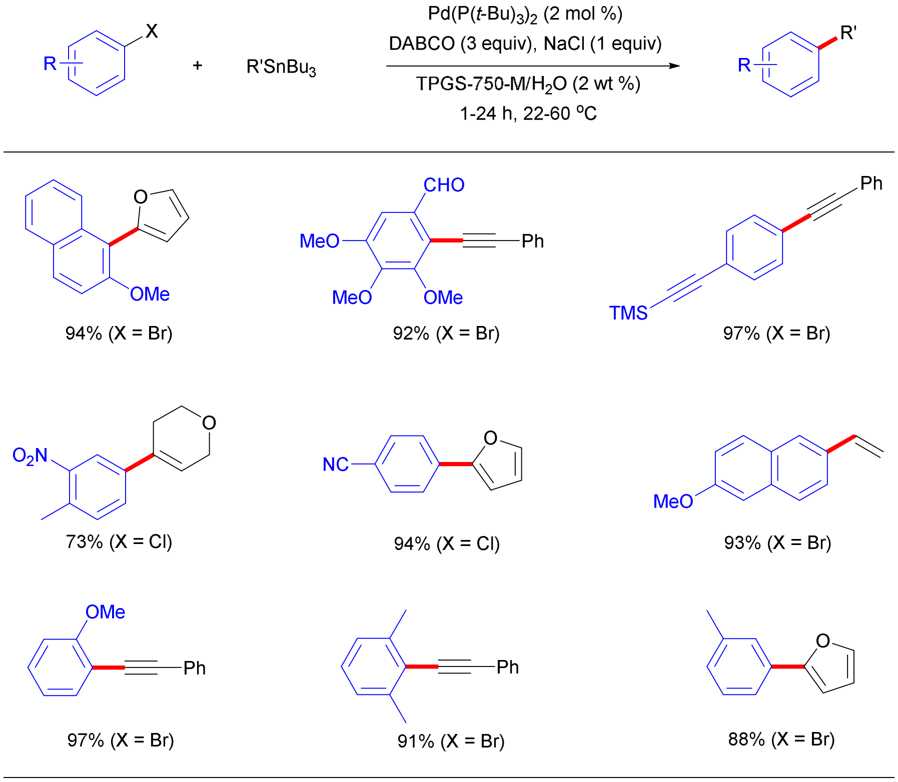
Representative Suzuki-Miyaura cross-couplings of MIDA boronates in water; preparation of 5-(benzofuran-2-yl)pyrimidine (7).[38]

Into a 10 mL screw top vial, (dtbpf)$PdCl_2$ (6.6 mg, 2.0 mol %), 5-bromopyrimidine (79.5 mg, 0.5 mmol, 1.0 equiv), 2-benzofuranylboronic acid MIDA ester (136.5 mg, 0.5 mmol, 1.0 equiv), and a Teflon stir bar were added and the vial was then capped. The vial was degassed with argon for less than 1 min. Et_3N (0.21 mL, 1.5 mmol, 3.0 equiv) was then added followed by 2 wt % TPGS-750-M/H_2O (1 mL, 0.5 M) via syringe. The vial top was wrapped using Parafilm and allowed to stir vigorously at rt for 24 h. Upon completion, 5 mL of 26.5g/mL aq. NaCl was added to the vial and the contents were briefly stirred and then transferred to a separatory funnel and extracted with EtOAc (3 x 25 mL). The organic phases were collected and the solvent removed via rotary evaporation with the water bath temperature at or under 40 °C. The crude material was purified by silica gel filtration (eluent: 20% EtOAc/heptane w/ 1% Et_3N (100 mL), 1.9 g of silica gel, ~1 inch diameter glass frit) to provide the desired compound **6** as a peach-colored powder (96.7 mg, 99% yield). Alternatively, upon completion of the reaction, the product can be precipitated by addition of water and then filtered to obtain the biaryl coupling product.

3.5 Stille couplings of alkenyl and aryl halides

Notwithstanding the tainted reputation that organostannanes tend to have with respect to the toxicity of tin, the fact of the matter is that Stille couplings were the fourth most heavily used type of cross-coupling reaction of the past decade.[44] Their stability towards air and moisture, which affords them significant shelf life, is noteworthy and attractive, and with good synthetic access to most types of stannanes, such couplings are not uncommon.[45] But with their stability comes the need to oftentimes use dipolar aprotic solvents such as DMF and NMP, along with heat, two factors that add up to processes that are egregious from the environmental perspective. The former solvent may soon be disallowed for use in the EU.[46] One alternative that takes advantage of the fundamentally lipophilic nature of organotin species utilizes micellar catalysis in water.[47]

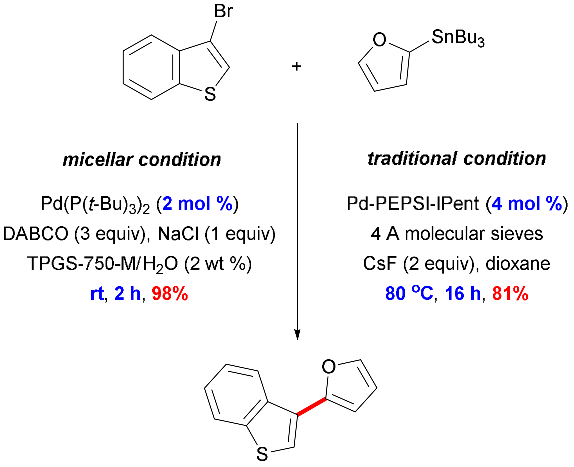
Scheme 11 Stille couplings of aryl halides in water



The penchant for organic molecules to reside within the hydrophobic, organic interiors seems like a natural fit for this chemistry, and indeed, a variety of Stille couplings can be run in water at temperatures between ambient and 60 °C, depending upon the halide. Again, TPGS-750-M (2 wt. %) serves admirably as the nanomicelle-forming amphiphile, while the commercially available catalyst $Pd(P(t\text{-}Bu)_3)_2$[48] in the presence of DABCO was determined to be the most effective combination. The presence of NaCl (1 equiv) in the aqueous mixture[9] assisted in driving reactions to completion. Aryl bromides couple smoothly at room temperature, while aryl chlorides tended to require mild heating to between 40-60 °C. Several representative examples are illustrated in Scheme 11.

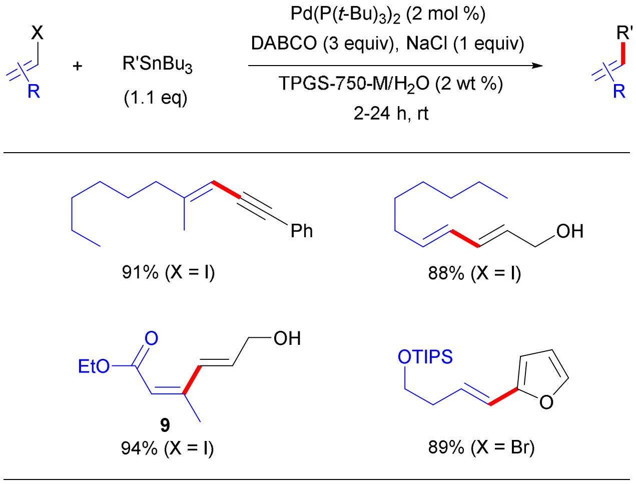
By way of comparison citing a literature example of a coupling between a heteroaromatic bromide and heteroaromatic stannane (Scheme 12), traditional conditions involving an organic solvent (dioxane) and heat (80 °C) led to the targeted biaryl in 81% yield after 16 hours.[49] Under micellar catalysis conditions, the same product could be formed in close to quantitative yield (98%) at room temperature in only two hours, and with half the level of palladium in the pot.

Scheme 12 Comparision of Stille couplings in micellar *vs.* traditional conditions.



Yet another important distinction between Stille couplings in organic solvent versus aqueous nanoparticles is found in reactions of alkenyl halides (iodides and bromides), where retention of olefin geometry is an important consideration. Given the proper choice of ligand in the aqueous reaction medium, such cross-couplings maintain stereo-integrity, even in cases of *Z*-β-halides associated with conjugated carbonyls (*e.g.,* **9** in Scheme 13). Such is far from the case in related reactions run in organic solvents such as NMP, where isomerization from *Z*-to-*E* can be a major problem.[50]

Scheme 13 Stille couplings of alkenyl halides in water at room temperature



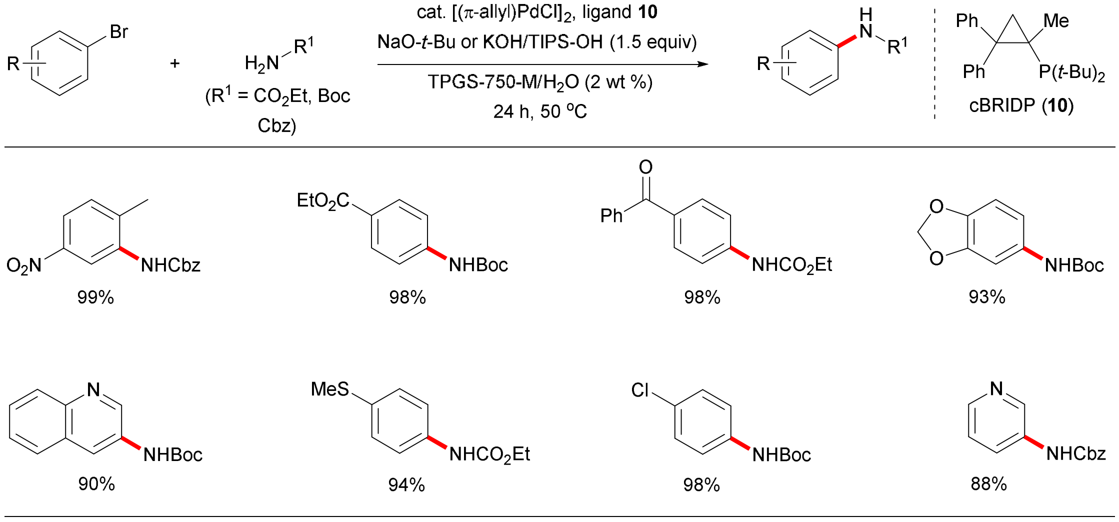
General procedure for Stille couplings in water.[47]

The palladium catalyst (0.005 mmol), organohalide (0.250 mmol), DABCO (0.750 mmol) and NaCl (0.250 mmol) were weighed into a microwave vial at rt. The organotin reagent (0.275 mmol) and 2 wt % aqueous TPGS-750-M solution (1.0 mL) were then added by syringe (liquid organohaildes were also added by syringe). The resulting solution was allowed to stir vigorously at rt (slight heating was required in some cases) and monitored by GC or TLC. Upon completion, the reaction mixture was then diluted with NEt_3 (0.3 mL) and EtOAc (4.0 mL), filtered through a bed of silica gel layered over Celite. The volatiles were removed *in vacuo* to afford the crude product. The extent of conversion and *Z*/*E* ratios were determined by GC. Further column chromatography on silica gel afforded the pure desired product.

3.6 Aminations of aromatic and heteroaromatic rings

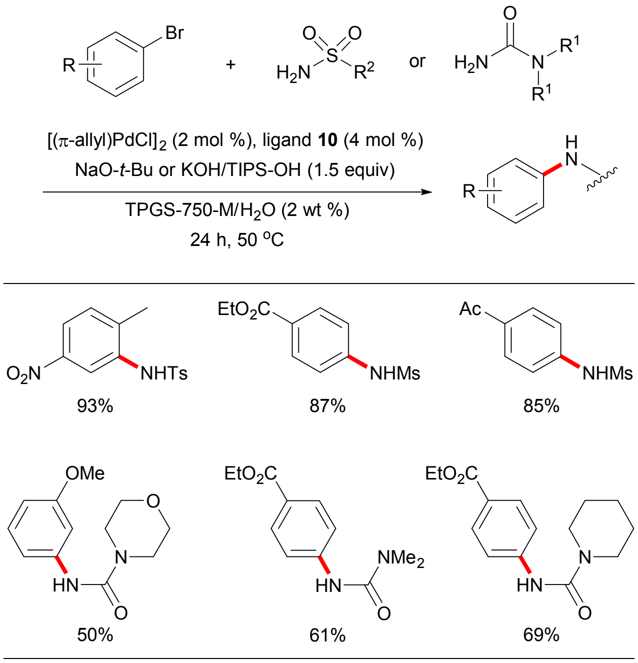
The introduction of an amine substituent onto an aromatic ring is a highly valued process, especially in the pharmaceutical and agricultural arenas. One subset of this general class (*i.e.,* aminations) is the primary amine function, $-NH_2$, which is of particular current interest.[51] Use of analogs, *e.g.,* - NH-Boc, affords the protected amine directly. Most approaches to this latter C-N bond construction involve Pd-catalysis and rely on traditional organic solvents,[52] and usually heat as well.[53] Under micellar catalysis, the NH-R moiety (R = Boc, Cbz, $-CO_2Et$) can be introduced *via* substitution of aryl bromides to form the targeted carbamate appendage (Scheme 14).[54] Most couplings of this type can be effected at ambient temperatures using ligand **10**, although on occasion mild heating to 50 °C can help drive the reaction to full conversion.

Scheme 14 Scope of amidations of aryl bromides with carbamates



Literature methods for inserting the sulfonamide group as an $-NH_2$ equivalent tend to rely not only on traditional organic solvents, but also on conditions that are considerably different from those that lead to carbamates.[55] Such is not the case using micellar catalysis, where the same conditions apply to both functionalities. In fact, this technology applies even beyond carbamates and sulfonamindes: ureas, likewise, can be introduced under otherwise identical conditions. Thus, in nanomicelles composed of TPGS-750-M, and with the same palladium catalyst, ligand, and base, it is now possible to install a carbamate, sulfonamide, or urea as a primary amine surrogate in water at temperatures between 22 and 50 °C (Scheme 15).

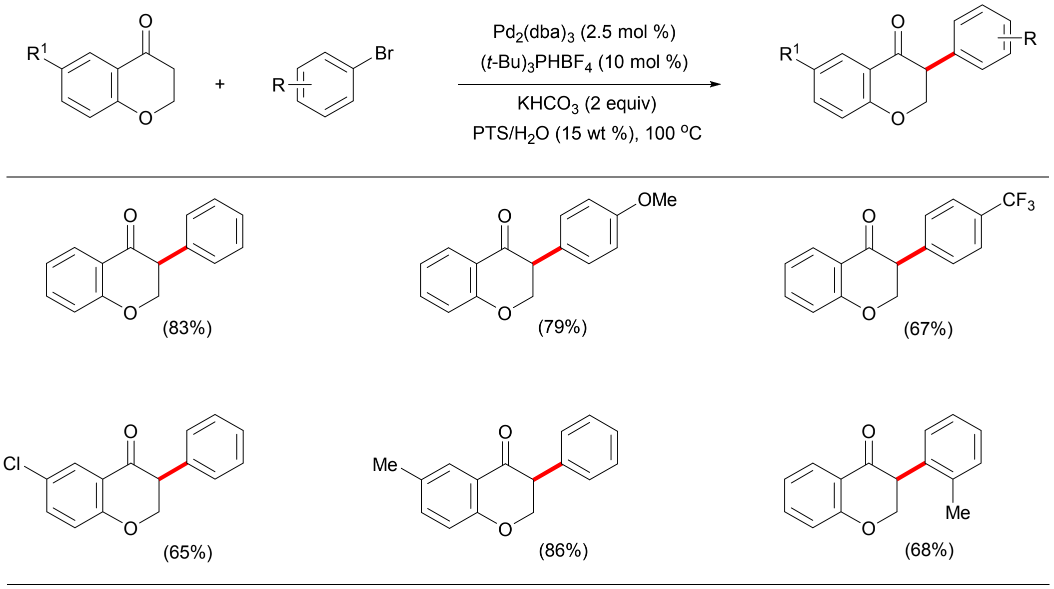
Scheme 15 Sulfonamides and ureas used as coupling partners with aryl bromides



3.7 α-Arylation of 4-chromanones

Exposure of 4-chromanones to Pd-catalyzed α-arylations under basic conditions in a mixture of aqueous dioxane has been observed to afford typically modest yields of the desired substituted products, isoflavanones.[56] A study of these couplings in pure water, however, under the influence of various surfactants, including PTS, Tween 80, CTAB, and SDS, indicated that the preferred conditions in terms of isolated yields consisted of 15 weight percent PTS in refluxing water for 2-4 hours (Scheme 16).[57] Selective monoarylation was observed when the ratio of chromanone to aryl bromide was 2:1 (diarylated product was <5%). The nature of the coupling partner halide seemed not to matter, as both electron-rich and electron-poor educts readily reacted. Likewise, the position of the substituent on the aryl ring, whether *ortho*- or *para*-, did not impact the arylation.

Scheme 16 α-Arylation of 4-chromanones with aryl bromides in water



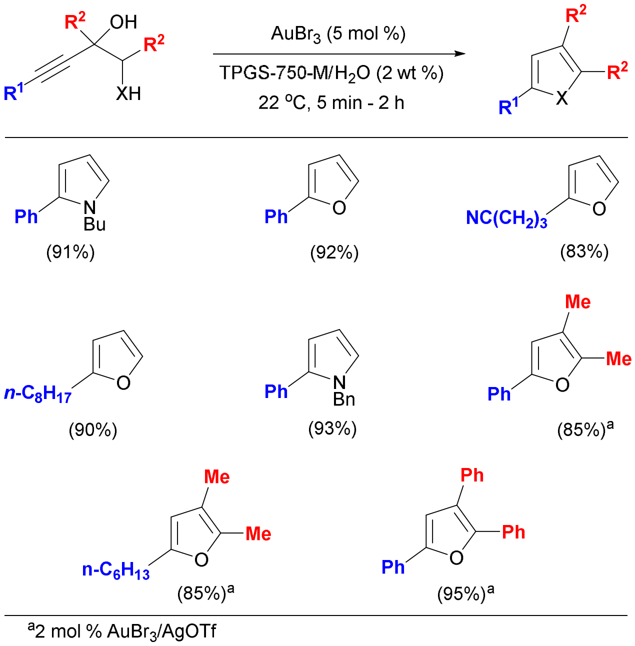
General procedure for the α-arylation of 4-chromanones in water.[57]

$Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), (t-Bu)$_3$PHBF$_4$ (29.0 mg, 0.1 mmol), and $KHCO_3$ (200 mg, 2.0 mmol) were placed in a reaction vessel containing a magnetic stir bar under an argon atmosphere. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated thrice. A degassed solution of 15 wt % PTS in H_2O (5 mL), a 4-chromanone derivatives (2.0 mmol), and an aryl bromide (1.0 mmol) were then sequentially added under argon. The reaction vessel was placed in an oil bath heated to 100 °C and after a few minutes at this temperature the color of the reaction mixture changed from dark brown to pale green. The mixture was then maintained at 100 °C for 2-4 h and periodically monitored by GC, GCMS, and TLC analyses of its samples extracted with EtOAc. It was then allowed to cool to rt and diluted with EtOAc (25 mL). The reaction mixtures were filtered over silica gel, concentrated under reduced pressure, and the resulting residues were purified by flash chromatography on silica gel.

3.8 Au-Catalyzed cyclodehydrations…in water

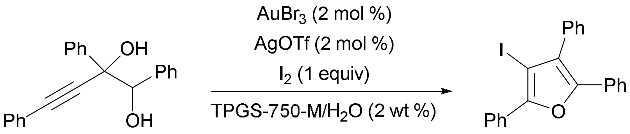
Although the notion of a dehydration reaction done in a medium of water seems at first counterintuitive, the interior of nanomicelles in which a substrate resides is strictly hydrophobic. Hence, water formed *via* cyclodehydration in this environment will be quickly extruded into the surrounding medium, thereby driving the process towards the desired product.[58] Vicinal diols containing an appropriately positioned alkynyl residue (Scheme 17) are highly prone to gold-catalyzed ring closure/dehydration, affording substituted furans in excellent yields.[59] Likewise, the amino alcohol analog undergoes the related cyclodehydration to the corresponding pyrrole. These reactions require only a few hours at global concentrations of *ca*. 0.5 M. Use of NaCl in the aqueous medium, as noted previously,[8,9] works to great advantage in terms of reaction rates while

Scheme 17 Gold catalyzed dehydrative cyclization of diols and amino alcohols



maintaining high overall yields. The presence of a trapping agent in the pot, *e.g.,* I_2, led to 3-iodofuran derivative **11**, a product well suited to further cross-coupling chemistry (Scheme 18).

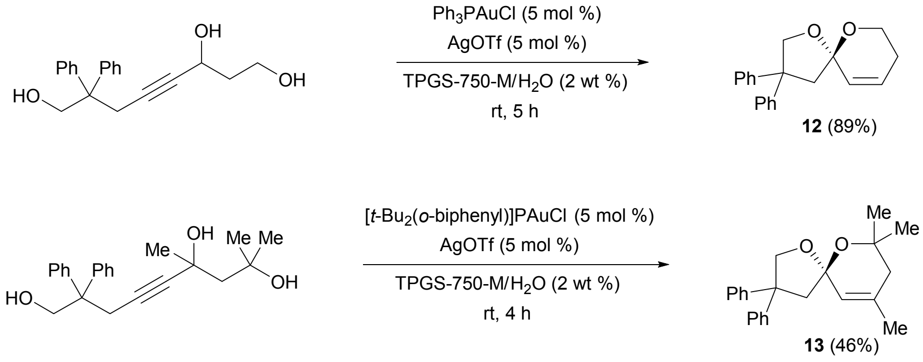
Scheme 18 Gold-catalyzed cyclization/iodination



11 (93%)

Acetylenic triols have also been exposed to micellar conditions, in these cases arriving at spirocyclic products. The efficiency of these ring closures appear to be a function of the substitution pattern in the educts. As illustrated in the example below (Scheme 19), spirocycle **12** is formed in high yield. However, when a tertiary alcohol is the nucleophile the closure is far slower. Changing the catalyst from $(Ph_3P)AuCl$ to [*c*-Hex$_2$(*o*-biphenyl)]PAuCl or [*t*-Bu$_2$(*o*-biphenyl)]PAuCl, in the presence of AgOTf, increased the conversion, although the yield of **13** still remained modest.

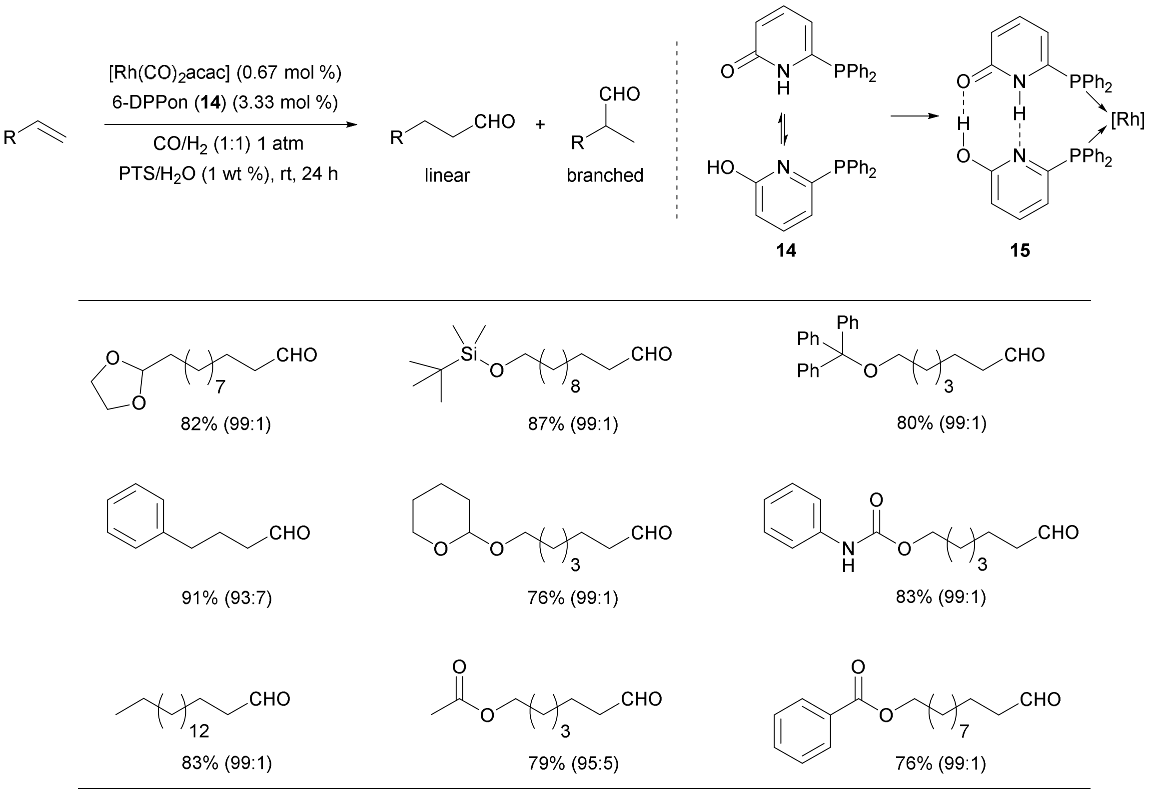
Scheme 19 Gold-catalyzed spirocyclization in water at rt



3.9 Hydroformylation

Nanoreactors composed of PTS in water have been found to enable Rh-catalyzed, regio-controlled hydroformylation of terminal olefins to the corresponding aldehydes, notably at ambient temperatures *and* pressures.[60] Pyridyl system **14** (DPPon), tailor made to maximize hydrogen binding and act as a bidentate ligand for rhodium (as in **15**), shows both high reactivity along with selectivity, affording aldehydic products with typically high (99:1) linear-to-branch ratios (Scheme 20). Other surfactants, such as SDS and Triton X-100, were also studied, and while the latter afforded excellent results in terms of chemoselectivity (93:7) and regioselectivity (99%), a relatively high loading (6%) was required. PTS, on the other hand, could be used at the one weight percent level with comparable results. The corresponding "on water" experiment yielded no product. Surprisingly, the regioselectivities observed for some cases studied were determined to be better than those previously found from reactions in THF, observations ascribed to the hydrophobic effect (*i.e.,* the unusually high concentrations found within micellar arrays).[61]

Scheme 20 Hydroformylation of terminal olefins in water at room temperature

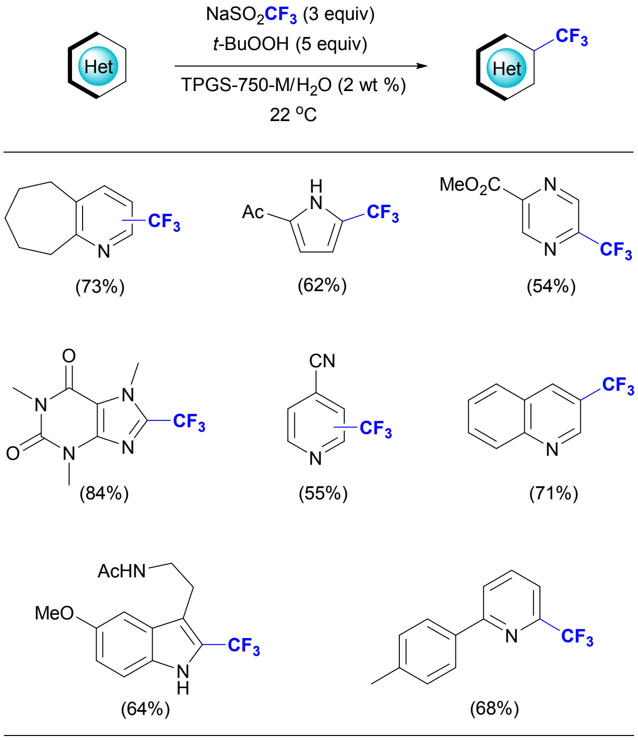


General procedure for the hydroformylation of alkenes in water.[60]
A flat-bottom Schlenk tube equiped with a cross magnetic stirring bar was, under an argon atmosphere, charged with substrate (1.00 mmol, 1.0 equiv), [Rh(CO)$_2$acac] (1.73 mg, 6.70 μmol 0.67 mol %) and 6-DPPon (**14**) (9.30 mg, 33.3 μmol, 3.33 mol %). After that a PTS/H_2O mixture (1.0 wt %, 3.0 mL) was added and the argon atmosphere replaced with CO/H_2 (1:1, 1 atm) by 3 cycles of vacuum/synthesis gas. The reaction mixture was then stirred vigorously at rt and under 1 atm of CO/H_2 (1:1) for 24 h. Afterwards the mixture was diluted with Et_2O (5 mL), filtered through a short column of silica gel and the silica gel washed with Et_2O (200 mL). The combined filtrates where evaporated under reduced pressure and the NMR-yield determined with 1,3,5-trimethoxybenzene (16.8 mg, 0.100 mmol, 0.1 equiv.) as internal standard. Pure compounds where obtained after column chromatography on silica gel.

3.10 Trifluoromethylation of heterocycles

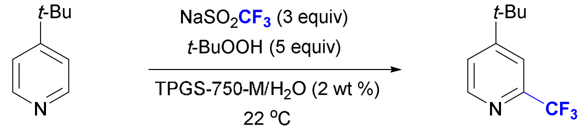
Fluorination of organic molecules is today among the hottest of areas in organic synthesis. The virtues of replacing hydrogen with fluorine are well established from the medicinal perspective.[62] Trifluoromethylation of heterocycles is of particular interest, with numerous processes of late providing solutions to this valued approach to drug development. While most of these processes are organometallic in nature,[63] those that are even metal-free[64] have paid little consideration to their environmental impact. In one highly regarded contribution, Langlois' reagent ($NaSO_2CF_3$; **16**) was identified as an excellent and inexpensive source of CF_3 radicals that react with many heterocycles to give trifluoromethylated products.[65] While the literature conditions rely on a chlorinated solvent in a mixed aqueous/organic medium, nanomicelles in water have been demonstrated to function equally effectively.[66] That is, yields of isolated products are as good or better than those reported on identical educts, and as a bonus, the amounts of both Langlois' reagent (**16**) and *t*-BuOOH (as oxidizing agent) could in several cases be reduced by 50% (Scheme 21).

Scheme 21 Trifluoromethylation of heterocycles in water at room temperature.



The regioselectivity is variable as a function of the substrate. E Factors associated with this technology are on the order of only 5-6. Moreover, the aqueous medium could be recycled, adding to the potential of this green technology (Scheme 22).

Scheme 22 Recycling of the aqueous reaction mixture and E Factor associated with trifluoromethylation



E Factors

based on	with recycling
total organic solvent	6.1
aqueous media included	8.9

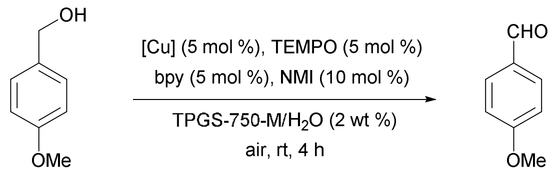
cycle	yield (%)
1	78
2	79
3	73
4	68
5	62

General procedure for trifluoromethylation of heterocycles in water.[66]
To a 5 mL round bottom flask with a PTFE stir bar and a septum was added 2 wt % TPGS-750-M (2.0 mL, 0.5 M), the heterocycle (1.00 mmol), and sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and the mixture was then cooled to ~5 °C and stirred for 2-3 min. TBHP was then added (70 wt. %, 5.00 mmol, 690 uL) dropwise, and the mixture allowed to stir vigorously at rt (~23 °C) until complete as judged by TLC. The reaction was then quenched with saturated $NaHCO_3$ (2 mL), extracted with EtOAc (3 mL), and concentrated under reduced pressure. Flash chromatography eluting with 20% EtOAc/hexanes provided the desired trifluoromethylated analog.

3.11 Oxidations of alcohols

Due to the many challenges associated with Pd-catalyzed aerobic oxidations of alcohols (*e.g.,* formation of Pd black, low turnover numbers, susceptibility to deactivating ligands, etc.),[67] catalysis using copper,[68] and in particular, Cu(I)/TEMPO is a viable, practical alternative.[69] Procedures that effect such routine oxidations for a variety of alcohols, including alkanols and both allylic and benzylic arrays, have been well developed using copper(I) (5%) in the form of $Cu(CH_3CN)_4OTf$, together with TEMPO (5%) and *N*-methylimidazole, run in acetonitrile at room

Scheme 23 Impact of the copper salt on the extent of oxidation



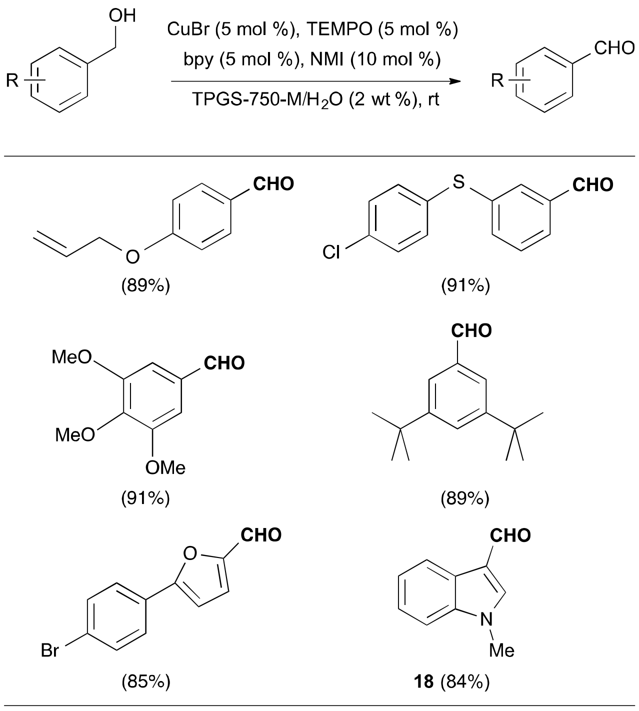
17

Cu source	conv. (%)[a]
$[Cu(CH_3CN)_4]OTf$	64
$Cu(OTf)_2PhMe$	58
CuCl	63
Cu powder	35
$CuBr_2$	97
CuBr	100 (98)[b]

[a]Determined by GC. [b]Isolated yield.

temperature.[70] Air is attractively used as the stoichiometric oxidant. A "greener" variant has been developed, in part, where the same types of ingredients have been utilized for allylic and benzylic systems, albeit the organic solvent has been replaced by water in which nanoparticles composed of TPGS-750-M are present.[71] The source of copper was also changed to the far less expensive CuBr, driven by the fact that $Cu(CH_3CN)_4OTf$ under these conditions did not afford synthetically useful levels of conversion in reasonable reaction times at 0.5 M. The Cu(II) analog, $Cu(OTf)_2$•PhMe led to somewhat lower levels of product formation using model benzyl alcohol **17** (Scheme 23). Representative examples of this oxidation in water at room temperature are illustrated in Scheme 24. E Factors based on organic solvent usage are very low, typically only 1-1.2. When the water for the reaction is included, an initial value of ca. 6 was obtained, although upon recycling the ratio, including water, was only 2.2.

Scheme 24 Oxidation of activated alcohols in water at room temperature



Representative oxidation of alcohols in water. Preparation of 1-methyl-1*H*-indole-2-carbaldehyde (18).[71]

To a microwave vial equipped with a stir bar was added (1-methyl-1*H*-indol-2-yl)methanol (80.6 mg, 0.5 mmol), copper bromide (3.6 mg, 0.025 mmol), 2,2'-bipyridine (3.9 mg, 0.025 mmol), TEMPO (3.9 mg, 0.025 mmol), *N*-methylimidazole (4 μL, 0.050 mmol), and 2 wt % TPGS-750-M solution in water (1.0 mL). The reaction was stirred vigorously until the starting material was consumed (TLC). The reaction mixture was then diluted with EtOAc, poured over a plug of silica gel and filtered *in vacuo*, using additional EtOAc as eluent. The extracts were then concentrated *in vacuo* to afford the crude product which was purified by flash column chromatography using 10% EtOAc/hexanes to provide the desired compound **18** as a pale yellow solid (66.5 mg, 84%).

4. “Nok.” A Third Generation Designer Surfactant

While there have been many successes in cross-coupling and related chemistry to date with aqueous solutions of the engineered surfactant TPGS-750-M,[6b] its make up is dependent upon a commodity chemical, vitamin E, the availability of which can be quite variable, as can its price. To both avoid such a dependency, and to drive the cost of micellar catalysis down while maintaining strict adherence to the principles of “benign by design”,[10] a new amphiphile was envisioned based on readily available and inexpensive phytosterols. In particular, β-sitosterol was chosen, as it is an established cholesterol mimic commonly found in a variety of food products.[72] Using a commercially available mixture of plant extracts rich in β-sitosterol (70%),[73] the construction of amphiphile followed the same approach used previously to prepare TPGS-750-M (Figure 2).[8] In this case, however, it was found empirically that better results were obtained when the surfactant incorporated MPEG-550, rather than MPEG-750. This new micelle-forming compound, which according to the common nomenclature would be “SPGS-550-M” (SPGS = **S**itosteryl **P**olyoxy**G**lyceryl **S**uccinate), has been named “Nok”, the nickname of the graduate student (Ms. Piyatida Klumphu) from Thailand, who first synthesized it.[14]

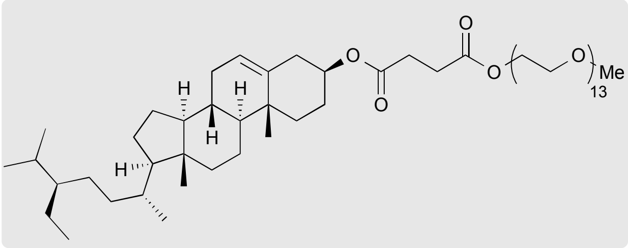
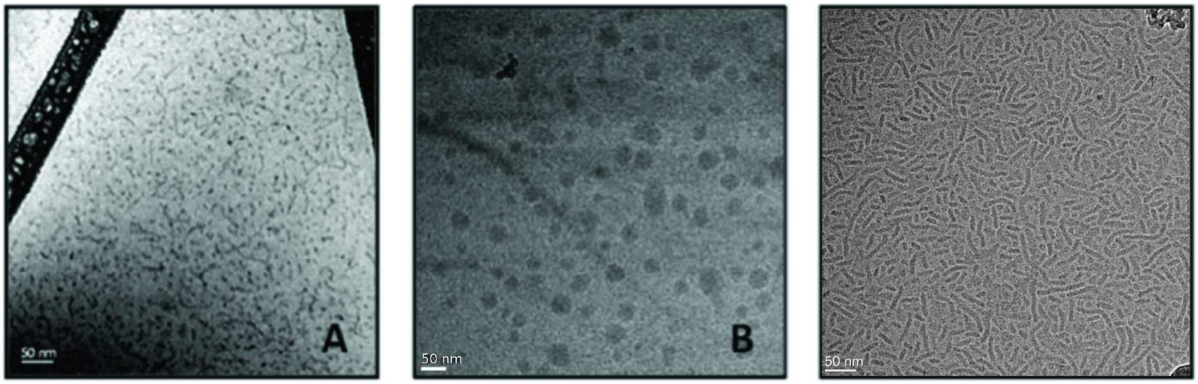


Figure 2 Structure of the 3rd generation surfactant “Nok” (SPGS-550-M).

Although Nok has been shown by Dynamic Light Scattering (DLS) to contain nanoparticles that are on average *ca.* 45-50 nm in size, remarkably and unlike either PTS or TPGS-750-M, these are not spherical in nature. Rather, cryo-TEM[74] measurements clearly show that Nok forms an intricate array of worm-like particles, apparently to the complete exclusion of spherical micelles (Figure 3).



PTS
10 nm spheres
&
variable sized worms

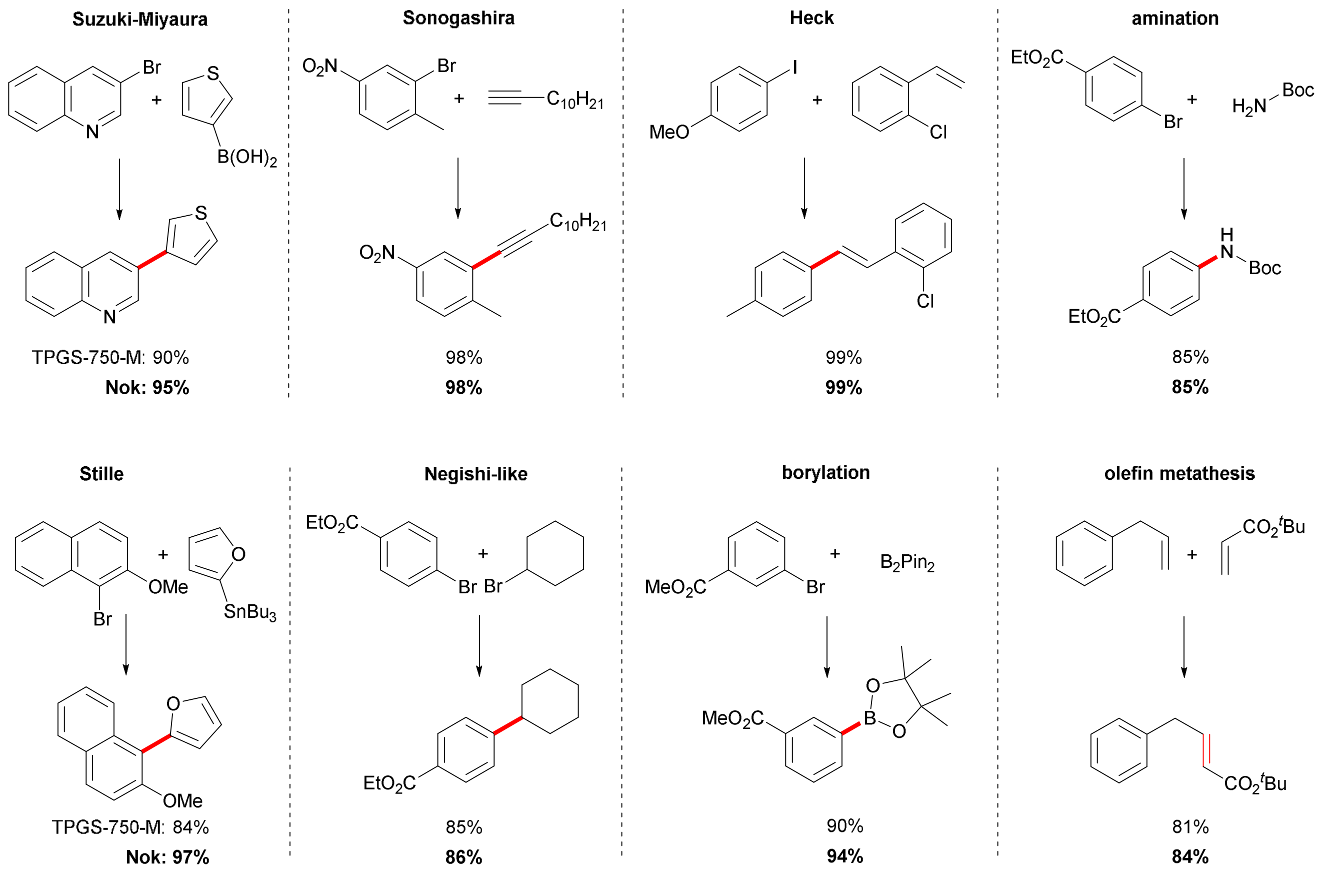
TPGS-750-M
60 nm spheres

Nok
average 46 nm particles
of
variable sized worms

Figure 3 Cryo-TEM image of (**A**) PTS; (**B**) TPGS-750-M; (**C**) Nok.

While these physical differences are quite dramatic, the most important aspect to Nok is its ability to enable the same types of transition metal-catalyzed couplings with efficiencies that are typically comparable to or better than those seen using TPGS-750-M. Many types of reactions have been studied for comparison purposes, including olefin metathesis, Suzuki-Miyaura, Sonogashira, Heck, Stille, and Negishi couplings, among others (*e.g.,* aminations and borylations); representative cases of each are illustrated below (Scheme 25).

Scheme 25 Cross-couplings in TPGS-750-M/H_2O *vs.* Nok/H_2O.



5. What's all this worth? An evaluation based on E Factors

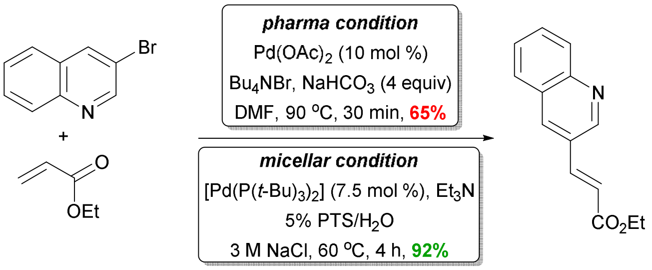
Although several metrics have been devised over the past few decades as a measure of the extent of greenness associated with a given transformation[3,75] the introduction of E Factors by Sheldon in 1992 remains as one of the most easily applied and yet meaningful tools for the numerical evaluation of the extent to which any given process is environmentally offensive.[2] These numbers are meant to illustrate how much waste is being created for a given reaction, as measured in kilograms, for every kilo of desired product formed. In other words, unlike, *e.g.,* process mass intensity (PMI),[3] where the mass of all materials inputted is taken into consideration *up front* in a process, E Factors look at the back end. As originally scribed, E Factors do not include water in the calculation, since industrial workups tend to include such huge volumes that these would render the overall numbers too large and less meaningful insofar as the other (non-aqueous) components involved are concerned.[76] But times have changed, and process chemists have continuously argued that waste water is still "waste." After all, many organic solvents are to varying degrees water-miscible, in which case the water used becomes, in essence, organic waste as well. This may have been part of the thinking that led the American Chemical Society Pharmaceutical Roundtable members, within the Green Chemistry Institute, to favor the PMI yardstick that takes water into account.[3] But calculation of an E Factor that reflects both the organic solvent and water workup is equally descriptive, and hence, a valid assessment, although slightly redefined. Moreover, it is perhaps not surprising that among the variables involved in a PMI calculation, most of the inputted mass (88%) is typically attributable to organic solvents (56%) and water (32%).[3] And insofar as E Factors are concerned, at least as originally conceived, it is today well established that 80-90% of organic waste is organic solvents.[4] Thus, both approaches consider the same two reaction parameters, whether early on, or at the end: organic solvent(s) and water.

In focusing on E Factors, therefore, an argument can be made that there are two values that should be calculated for each reaction to assess levels of waste being created: one based on just organic solvents, and the second, in line with the times, a reflection of both solvent(s) and water used. Historically, E Factors based on solvents alone have not been kind to the fine chemicals and pharmaceutical industries, with values ranging between 5-25 for the former, 25-100 for the latter.[76] Had water been part of these equations, clearly the numbers would jump substantially. However, as chemistry continues to mature, and chemists are confronted with rules and regulations mandating that environmental considerations become part of the planning process,[77] E Factors are dropping. Companies are now vying for recognition of their achievements on this front, competing for such prizes as Presidential Green Chemistry Challenge Awards. But from a general perspective, there remains much to be done to convince researchers that going green offers not only an opportunity to minimize a process' impact on the environment, or to receive earned recognition, but that the economic benefits of greener process are there to be reaped as well. In fact, in side-by-side comparisons between processes that are traditional versus those that are green, green wins.[78]

Since many of the processes currently employed by pharma companies rely on transition metal-catalysis, a study has been reported in which several published procedures (*e.g.,* Heck, Suzuki-Miyaura, and Sonogashira couplings) from large pharmaceutical companies were identified and their corresponding E Factors calculated.[79] Both values were easily ascertained; one based on the amounts of organic solvent(s) involved, the other derived from their combined usage of solvent(s) and water. These identical reactions were then performed under far greener conditions, using nanoreactors *in water*, composed of an environmentally benign "designer" surfactant (TPGS-750-M, or PTS). Each product was isolated by an "in-flask" extraction with the minimum volume of a single green and recyclable organic solvent (*e.g.,* EtOAc); *i.e.,* the reaction mixture never left the reaction vessel. Once extracted, each product could be purified accordingly, but more importantly, the aqueous medium that retained the surfactant could be recycled within the same reaction flask. *E Factors in all cases dropped dramatically, usually by an order of magnitude.* Additional features worthy of mention include the associated higher yields, high reaction concentrations that minimize the amount of water invested, oftentimes less catalyst, and in most cases, use of ambient temperatures. Representative examples are shown below, as is one case involving recycling of the aqueous reaction mixture (Scheme 26).

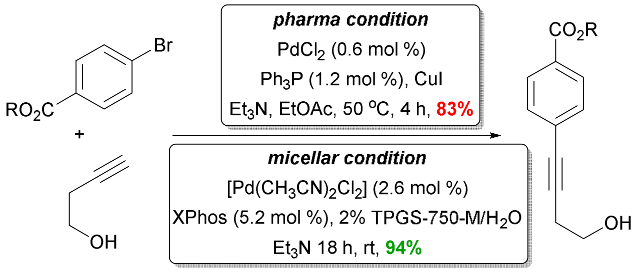
Scheme 26 Representative comparison of E Factors in cross-coupling reactions.

Heck Coupling



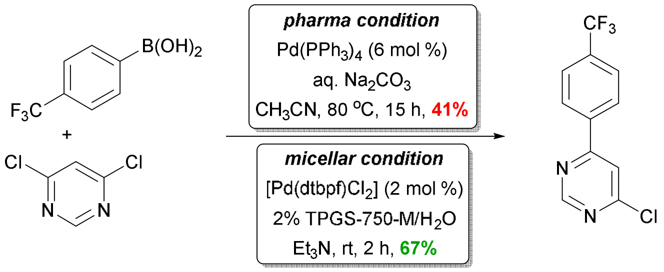
	based on	pharma	micellar
E Factors	total organic solvent	40.3	2.2
	aq. workup included	137	7.6

Sonogashira Coupling



	based on	pharma	micellar
E Factors	total organic solvent	31.1	3.7
	aq. workup included	37.9	7.0

Suzuki-Miyaura Coupling



	based on	pharma	micellar	with recycle
E Factors	total organic solvent	22.0	1.9	1.9
	aq. workup included	50.0	7.6	1.9

Beyond the obvious decrease in waste created by these heavily utilized cross-couplings that are now amenable to micellar catalysis come attendant "bonuses" that should not be overlooked. For example, use of room temperature conditions usually translate into cleaner reactions. In other words, in the absence of heating, the impurity profile associated with a given process is likely to improve significantly. This could simplify product isolation and purification, and thus, lead to a cost savings. Secondly, reactions run at room temperature may offer opportunities for greatly increased throughput. That is, rather than a large reaction vessel taking time to heat, ambient temperature reactions have no such time investment. Moreover, ambient temperature reactions can be easily manipulated (*e.g.,* to monitor reaction progress), and the vessel and its aqueous contents can be re-used far more quickly than for traditional heated reactions in organic media that require cooling and a water workup. Lastly, opportunities for applications using micro-flow conditions might improve E Factors even further.

6. Practical considerations: techniques for product isolation

Many tend to ask, after reading or hearing about this chemistry: how easy is it to get the product out of these reaction mixtures? This was the very first item on our agenda when developing such micellar catalysis, since reaction mixtures that foam or create intractable emulsions, regardless of the payoff downstream, are usually undesirable. Fortunately, the properties of these designer surfactants are such that their use and handling are trivial; indeed, they are ideal for not only research purposes, but can also be applied to undergraduate lab experiments with ease,[80] and are even amenable to high school classrooms where the equipment available may be minimal.

There are several alternatives for “workup”:

(1) *in-flask extraction*. In this procedure, a minimum amount of a single, less dense than water organic solvent (*e.g.,* an ether, EtOAc, a hydrocarbon, etc.) is added to the reaction vessel. After ***gentle*** stirring for a few minutes, the organic solvent is removed and the process repeated 1-2 times. Since only one solvent is used in these extractions, it can be recovered and recycled. The reaction mixture that remains in the flask containing the surfactant can then be exposed briefly to a high vacuum to remove residual organic solvent, and then re-used in another reaction.

(2) *direct filtration through sodium polyacrylate*. The water-absorbing properties of sodium polyacrylate, conveniently distributed within a baby’s diaper, are remarkable. Thus, by simply taking a section of a disposable diaper and placing it atop a silica gel column offers a very effective means of removing the water associated with such aqueous mixtures (Figure 4). Since most of these micellar reactions are run at global concentrations in the 0.5 – 1.0 M range, the little water present is quickly absorbed, and the polar surfactant remains at the top of the silica gel. Thus, by eluting with a single organic solvent (that can again be recovered), the product is easily isolated in purified form.

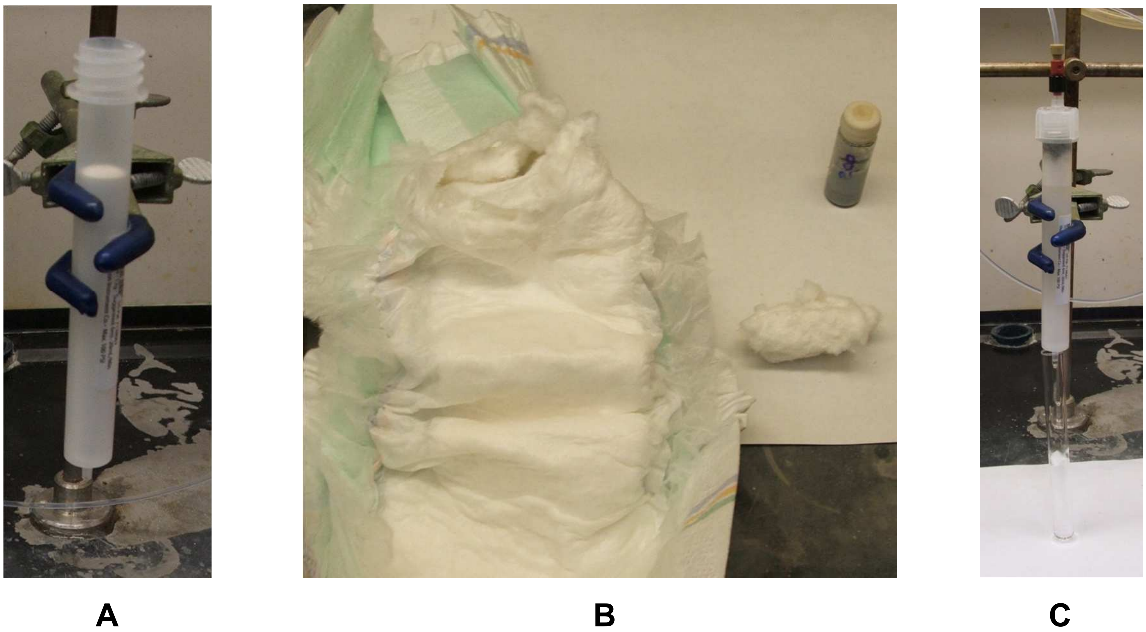


Figure 4 A. A disposable silica gel column with screw top removed; **B**. A section removed from a commercial diaper alongside a reaction mixture in a vial; **C**. A column containing the section of diaper loaded onto the silica, to which the aqueous reaction mixture has been applied, the cap screwed back on, and an organic solvent eluting down the column.

(3) *precipitation of solid products*. Most organic products, as with starting materials, are insoluble in pure water. Thus, as products form inside micelles, and given the facile and dynamic exchange phenomena characteristic of micellar catalysis (*i.e.,* where all components are exchanging through water between micelles),[7] solids form and begin to precipitate. Once the reaction is over, further dilution with water increases precipitation; simple filtration leads to product isolation. The aqueous filtrate, based on its new total volume, can be augmented with neat surfactant to bring the level back to 2 wt. %, in which case the resulting solution is now ready to be reused for another surfactant-enabled reaction.[38]

7. Summary, concluding remarks, and future perspectives

The processes enabled by micellar catalysis that appear in this review cover many areas of synthesis, including several metal-catalyzed C-C, C-O, and C-N bond constructions involving, Pd, Au, Rh, Ru, and Cu, as well as oxidations and non-transition metal-based chemistry highlighting reductions of nitroaromatics and alkyl halides. These, as with those discussed in prior reviews,[6,81] are merely representative of the myriad opportunities that exist for using water as an alternative medium at ambient temperatures. The secret to success is surfactant technology *designed by organic chemists for organic synthesis*, rather than by chemists working in other areas that are mainly concerned with emulsifying oil and water. This approach derives its origins squarely from nature, where hydrophobic pockets are routinely created with biomolecules in the course of doing the chemistry of life. But rather than using such complex systems, although such an approach has not escaped the attention of organic chemists,[82] alternative amphiphilic species can be designed that, likewise, serve as the reaction medium following self-aggregation into nanomicelles. And so, just as nature creates its own selective organic media as needed *in vivo*, organic chemists can devise, construct, and apply tailor-made reactors that are highly effective hosts to organic reactions, notwithstanding the surrounding water. The concept applies equally well even to water-sensitive organometallics such as organozinc reagents, where traditional dogma teaches that the use of highly reactive organometallics in the presence of *any* water, let alone in water only, is generally considered prohibitive. The design features start with adherence to the *12 Principles of Green Chemistry*, in particular that new surfactants should be themselves "benign by design." That creed, as discussed herein, led to the introduction of "Nok', a third generation amphiphile based on a phytosterol, β-sitosterol, a well known cholesterol mimic. In principle, there is no limit to the number of possible lipophilic cores that could serve as reaction solvent, as do α-tocopherol (in PTS and TPGS-750-M) and β-sitosterol (in Nok). Future generations of surfactants that address elements such as increasing reaction rates, cost, stereochemical issues, and even transmission of chirality can be envisioned. Although such goals will translate into new advances in synthesis, they will also come with an awareness of their impact on the environment; they will be, at least, green*er*. And as the hydrophobic effect gains in appreciation as the "rules" under which micellar catalysis is operating become known, many new discoveries will come. These advances, while green in nature, will add to the overall excitement in chemistry, further inspiring practitioners of modern organic synthesis to consider shifting away from use of traditional organic solvents. And with each move, made one chemist at a time, *your* E Factors will come down.

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