

# Transition-Metal-Catalyzed Cross-Couplings Going Green: in *Water* at Room Temperature



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## 1. Introduction

It has now been 15 years since Sheldon introduced the environmental factor, or “E Factor”, as a numerical measure of the amount of waste produced in manufacturing processes of oil, bulk or fine chemicals, and pharmaceuticals (expressed in kg waste/kg product).<sup>1</sup> This focus on “atom utilization” takes into account not only Trost’s “atom economy”,<sup>2</sup> but also the associated environmental impact of salt formation and organic byproducts. Today, the E Factor is “a way of life” for the industrial chemical enterprise. Academic labs are also faced with increasing external scrutiny of solvent usage and waste disposal practices, and expanding environmental safeguard requirements. Efforts to influence the extent of chemical insults to the environment at large are manifested throughout the field: journals devoted solely to this cause (e.g., *Green Chemistry*); books in their entirety on, or related to, the subject;<sup>3a–c</sup> and conferences dedicated solely to green chemistry.<sup>3d</sup> New technologies are being engineered to mitigate waste production, with advances in organometallic, organic, and bioorganic catalysis. Alternative reaction media such as fluoruous, aqueous, as well as those involving supercritical CO<sub>2</sub> and ionic liquids, are thriving.<sup>4</sup> Regardless of whether these advances are driven by truly environmental issues focused on “sustainability”, improved economics, public relations, and/or other factors, the trend going forward is clear.

Interestingly, the E Factor does not take water into account. The reason given is that its inclusion skews the numbers significantly upward and reduces differences between processes, rendering them more difficult to interpret and, hence, less meaningful.<sup>1</sup> The

unstated implication is that the quantities of water involved in workups and the resulting waste streams are huge, and that accurate data are tough to get. Water as a reaction solvent, however, is an important alternative medium. Nonetheless, today’s enthusiasm for the inclusion of water in one’s choice of conditions has been criticized,<sup>5</sup> in part due to the confusion in the literature regarding terminologies, such as “in water”, “with water”, and “on water”.<sup>3c,6</sup> While the use of this solvent alone has fundamental merit in that water is inexpensive, nontoxic, and safe with respect to handling, the counterargument usually focuses on downstream items: the amounts of organic solvent(s) still needed for workup, issues of product isolation, and losses of catalysts involved. Indeed, while homogeneous catalysis in organic media already plays a prominent role in green chemistry, Sheldon further notes, “Preferably, the catalyst solution remains in the reactor and is re-used”.<sup>1</sup> Thus, the concept of catalyst recycle and, hence, minimization of organic solvent(s) invested, are also worthy practical goals.

One approach towards increasing the potential for water to compete with organic solvents highlights a reaction variable relatively underdeveloped in the synthetic community, in particular in transition-metal-based cross-couplings: micellar catalysis.<sup>7</sup> Micelles, in general, are formed at low concentrations (CMCs, or critical micelle concentrations, are typically 10<sup>−3</sup>–10<sup>−4</sup> M) in pure water.<sup>8</sup> They are characterized as amphiphilic aggregates that combine lipophilic interiors with hydrophilic exteriors, and come in three “flavors”: cationic, anionic, and nonionic. A wealth of information (mostly physical chemistry) on micelles is available,<sup>9</sup> but a surprising dearth of applications to organometallic cross-couplings currently exists. Why? Could it be that to many synthetic organic chemists, all surfactants (a contraction of “surface active agents”) are more or less the same, that “soap is soap”? This may seem like an oversimplification, but there is extensive evidence to document this state of affairs. For example, consider some of the most common name reactions in transition-metal-mediated organic synthesis, the Heck and Suzuki couplings, and Nobel Prize winning olefin cross-metathesis chemistry. Are there examples of such reactions run in pure water, at room temperature, and involving water-insoluble substrates? In some cases there are, but these are few in number (vide infra). In the recent monograph *Organic Reactions in Water*,<sup>3c</sup> there are several outstanding chapters on all

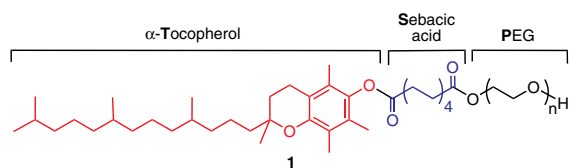
aspects of chemistry in water, including reviews by those who have contributed to organometallic chemistry in this medium.<sup>10a</sup> The most relevant review to transition-metal-based cross-couplings is by Chao-Jun Li on “Metal-Mediated C–C Bond Formations in Aqueous Media”.<sup>10b</sup> From this extensive summary, and earlier work and reviews by Li’s group,<sup>10b,c</sup> it appears that micellar catalysis has not been *commonly* applied to key cross-coupling reactions, including those catalyzed by Pd. And for reactions that do include surfactants, the choices are usually limited to those introduced decades ago when the impetus was to provide an inexpensive approach to enhancing the water solubility of compounds associated with, e.g., the petroleum, food, textile, and cosmetics industries prior to the arrival of modern organometallic cross-coupling chemistry. This is not to say that surfactant technology today is a dormant area of research; in fact, entire books are available on this field alone.<sup>9b</sup> But just as ligands in organometallic chemistry have evolved exponentially to meet the increasing demands of evermore-complex synthetic problems, so is there room for amphiphiles to be tailored to enhance opportunities not only in synthesis, but in green chemistry. Few uses of micelles appear in popular monographs or reference works dedicated to organometallics, such as Schlosser’s *Organometallics in Synthesis: A Manual*,<sup>11a</sup> or Beletskaya’s chapter in Negishi’s *Handbook of Organopalladium Chemistry for Organic Synthesis*.<sup>11b</sup> Where is palladium, copper, or ruthenium in the cover artwork of the issue of *Angewandte Chemie* featuring the Oehme review on micellar catalysis in 2005?<sup>7a</sup> Shaughnessy’s paper on Pd-catalyzed couplings in aqueous media includes a discussion, in part, on the uses of ionic surfactants (phase-transfer reagents), although product isolation is noted as potentially problematic. Nonetheless, the “trick” of solubilizing organic substrates by employing micelle-forming amphiphiles derives from the exclusive presence of water as solvent. In fact, an organic co-solvent would likely reduce the prospects for catalysis by competing with the substrate(s) for occupancy within the lipophilic core of the micelle. This may seem counterintuitive; i.e., that more “greasy” materials

should, in principle, make for better substrates in water, and that any “assistance” by organic co-solvents might actually decrease reaction rates. Perhaps these observations explain, in part, the paucity of attention paid to nonionic surfactants in transition-metal-catalyzed organic synthesis. The question, however, remains as to whether all such amphiphiles are “created equal”; that is, are there significant benefits when a particular surfactant is “matched” to a particular metal-catalyzed cross-coupling? An analogous query years ago might have been: are all ligands in metal-catalyzed cross-couplings the same? Intuitively, the answer may already be obvious; in fact, there are already hints to such distinctions between amphiphiles.<sup>12</sup>

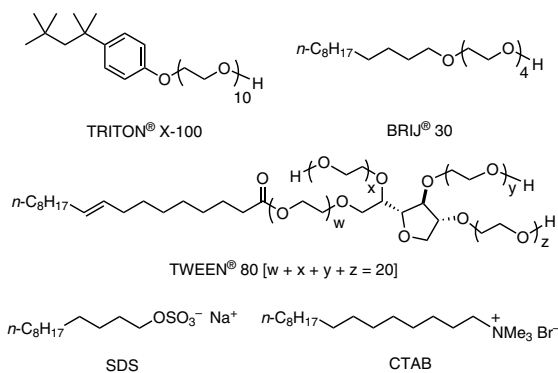
The benefits that “tailor-made” amphiphiles might offer catalysis: e.g., chemistry in water, rate accelerations, etc., could be substantial. However, in order for these to be realized, well-defined structure–function relationships associated with surfactants in *organic synthesis* are needed. In brief, what are the rules for micellar catalysis here? The short answer is: no one knows. But there are analytical tools—e.g., Dynamic Light Scattering (DLS) to study average particle size,<sup>13</sup> and Transmission Electron Microscopy (TEM)<sup>14</sup> to view the size, shapes, and distribution of micelles in water—that can aid greatly in our understanding; techniques that are otherwise infrequently employed by synthetic organic chemists. Thus, in this review, an early spotlight is placed on a few very common name reactions,<sup>15</sup> carried out at ambient temperatures and in water alone, both insofar as prior art is concerned, as well as with a focus on very recent advances with the aid of the amphiphile PTS (polyoxyethanyl  $\alpha$ -tocopheryl sebacate) (**1**; **Figure 1**).<sup>16</sup> Perhaps as a library of information is accumulated as to which amphiphile(s) work best in various situations, an understanding of the structure–reactivity relationships between amphiphile, substrates, and catalysts will emerge.

## 2. Amphiphiles, Surfactants, Emulsifiers, Soaps, ...

For all intents and purposes in the discussion below relating to organometallics in organic synthesis, these terms will be used interchangeably regardless of the technical definition of each. Virtually all that appear in journals that cater to organic chemistry are composed of two components: a nonpolar, usually hydrocarbon tail, and a polar, either charged or neutral head group that represents the hydrophilic (or “water-loving”) segment (**Figure 2**). Examples of nonionic surfactants include TRITON® X-100,<sup>17</sup> BRIJ® 30,<sup>18</sup> and polysorbates<sup>19</sup> (e.g., TWEEN® 80). Perhaps the most commonly used anionic surfactant is sodium dodecyl sulfate (SDS; technically a detergent),<sup>20</sup> while cationic surfactant cetyltrimethylammonium bromide (CTAB) is also a frequently employed, off-the-shelf reagent. Unlike these combinations of a lipophile attached to a water-solubilizing moiety such as polyethylene glycol (PEG), PTS (**1**) is an unsymmetrical diester and, therefore, contains *three* components: a dicarboxylic acid (Sebacic acid in this case), a lipophilic portion in vitamin E (or  $\alpha$ -Tocopherol), and a hydrophilic subsection based on PEG-600 (which consists of a distribution of oxyethanyl units centered at 13 in number). Very closely related to PTS is PSS (**Figure 3**).<sup>16</sup> In this amphiphile (PSS), the hydrocarbon portion of PTS containing a *linear* side chain 13 carbons in length as part of vitamin E is replaced by a *polycyclic* hydrocarbon characteristic of the cholesterol mimic,  $\beta$ -Sitosterol. Note that while PSS is otherwise identical to PTS insofar as the 10-carbon spacer acid and the length of PEG are concerned, the well-known emulsifier TPGS<sup>21</sup> varies in the nature of the dicarboxylic acid between the lipophilic vitamin E and hydrophilic PEG moieties. That is, in TPGS, the parent chain is the 4-carbon-containing succinic



**Figure 1.** Structure of the Nonionic Amphiphile PTS (**1**,  $n = \text{ca. } 13$ ).



**Figure 2.** Commonly Used Nonionic and Ionic Surfactants.

(Ref. 17–20)

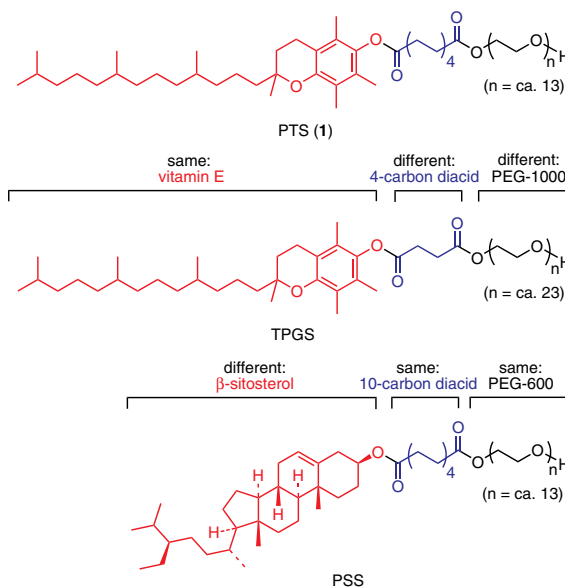
acid. Moreover, the PEG portion in TPGS is PEG-1000, which substantially shifts the ratio of water-soluble (hydrophilic PEG) to water-insoluble (lipophilic vitamin E + sebacic acid) components, usually referred to as the Hydrophilic–Lipophilic Balance (HLB).<sup>22</sup> At first glance, these might seem like very subtle distinctions between “soaps.” However, these three molecules are quite distinct from each other: neither TPGS nor PSS functions as well as PTS as a reaction medium in C–C-bond-forming reactions in water that have been studied to date (vide infra). Perhaps even more crucial here for developing a fuller appreciation of the micellar array is recognition that the hydrocarbon interior (vitamin E in the case of PTS) *functions as the reaction solvent*. Hence, just as solvent effects can play a defining role in many organic reactions, so might the makeup of an amphiphile that is providing, in a “like-dissolves-like” way, the organic environment...albeit in water.

### 3. PTS: Brief History and Background

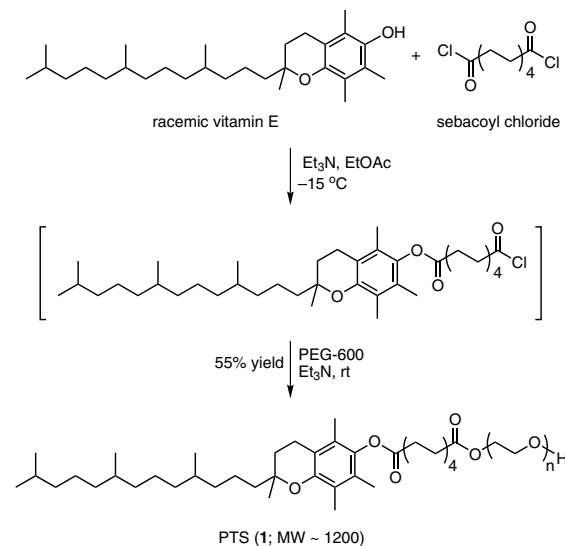
At the National Research Council (NRC) in Ottawa, scientists led by Dr. Henryk Borowy-Borowski first prepared PTS as described in U.S. Patent 6,045,826.<sup>16</sup> Starting with sebacoyl chloride, initial esterification with  $\alpha$ -tocopherol led to a monoester (Scheme 1). Second-stage introduction of PEG-600 gave PTS (1) as the major product, albeit in modest yield (ca. 55%). Purification involving a variety of non-chromatographic manipulations improves the quality of the material, but given the variation in the number of oxyethanyl units [i.e.,  $(-\text{OCH}_2\text{CH}_2)_n$ ] in most of the commonly used PEGs (in this case,  $n = \text{ca.}13$ ), along with small amounts of various diesters formed as side-products, it is technically inaccurate, as well as economically unrealistic, to claim that PTS is a “pure” compound. Identical phenomena can be found for other commonly PEGylated materials, not only among surfactants but also in the pharmaceutical arena (e.g., PEGylated peptides,<sup>23</sup> etc.).

The NRC’s goal was to leverage PTS as a carrier for the expressed purpose of solubilizing a yellow-orange and highly lipophilic solid, the dietary supplement coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>, MW 863; Figure 4A), in water. Dr. Marianna Sikorska and co-workers conducted extensive biochemical studies at this national lab, relying on PTS-derived aqueous solutions of CoQ<sub>10</sub>. Her team examined CoQ<sub>10</sub>–PTS in both cells and animals (in vitro and in vivo) with regard to safety and efficacy in specific disease models.<sup>24</sup> They were particularly interested in neurodegenerative disorders and ischemic brain damage, and demonstrated the neuroprotective effect of water-soluble CoQ<sub>10</sub>. The properties of PTS (vide infra) allow for the generation of translucent solutions of CoQ<sub>10</sub> in pure water even at concentrations of >50 mg/mL (Figure 4B)!

PTS itself is a viscous, pale-yellow, honey-like substance (Figure 4C). In water above its critical micelle concentration (0.28 mg/mL, or  $2.31 \times 10^{-4}$  M), it forms essentially colorless solutions—with micelles *averaging* 22–25 nm in diameter as indicated by light-scattering data.<sup>25</sup> On the other hand, cryo-TEM measurements<sup>26</sup> show a mixture of smaller spherical (ca. 8 nm) and worm-like (ca. 50 nm) particles (Figure 5).<sup>25,26</sup> Interestingly, dissolution of CoQ<sub>10</sub> within these nanometer-size micelles does not alter, on average, their size. This “trend” is corroborated by similar observations involving other “actives” such as  $\omega$ -3 fatty acids (i.e., fish oil containing DHA and EPA can be solubilized in water at a remarkable 100 mg/mL),<sup>27</sup> as well as the practically water-insoluble antitumor agent paclitaxel which forms a clear, water-white solution even at 10 mg/mL (Figure 4D).<sup>28a</sup> Thus, as a solubilizing agent, where ratios of PTS to active will vary (e.g., PTS:CoQ<sub>10</sub> = 3:1 by weight,<sup>16</sup> PTS:paclitaxel = 10–20:1 by weight),<sup>28a</sup> PTS in micelle form is capable of accommodating compounds that are essentially insoluble in water. It was the recognition of these properties of



**Figure 3.** Structural Comparisons between PTS, TPGS, and PSS. (Ref. 16,21)



**Scheme 1.** Preparation of the Unsymmetrical Diester PTS.

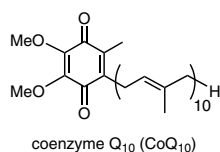
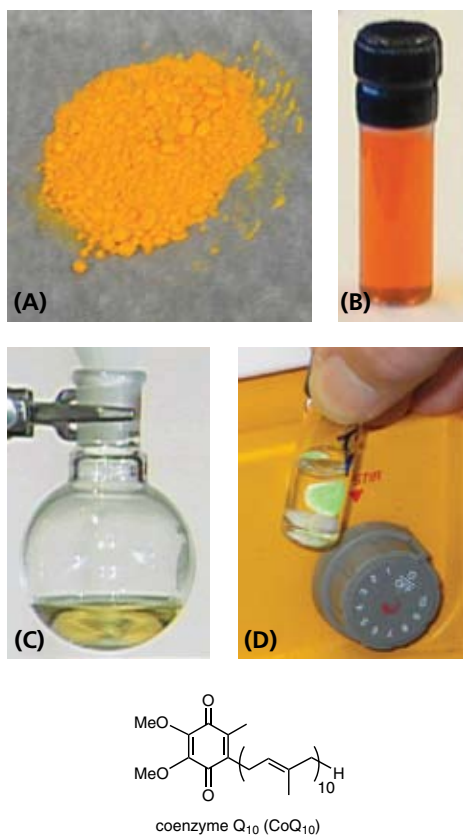
(Ref. 16)

PTS that triggered the question: Why not apply the benefits of water-solubilization with PTS to lipophilic substrates, additives, catalysts, etc. by putting these species into micelles? Surely, such occupants would react ... and they do.

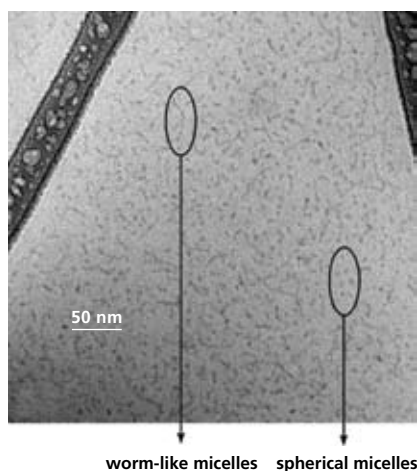
## 4. Synthetic Chemistry in PTS–H<sub>2</sub>O

### 4.1. Heck Coupling

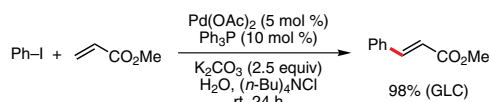
With so much fundamental literature on the Heck reaction dating back to the early 1970s,<sup>11,29</sup> how could we make a contribution of consequence today in this area? Although recent and highly effective methodologies exist for Pd-catalyzed Heck olefinations at room temperature in organic solvents,<sup>30</sup> and in water with heating,<sup>31</sup> to the best of our knowledge the overlap of these two



**Figure 4.** (A) Pure, Water-Insoluble Coenzyme Q<sub>10</sub>. (B) Solution of 50 mg/mL CoQ<sub>10</sub> in PTS-H<sub>2</sub>O. (C) Neat PTS. (D) Solution of TAXOL® in PTS-H<sub>2</sub>O (10 mg/mL). (Photos © B. H. Lipshutz.)



**Figure 5.** Cryo-TEM Image of PTS-H<sub>2</sub>O. (Photo © B. H. Lipshutz.) (Ref. 25,26)



**eq 1** (Ref. 32)

highly desirable features had not been accomplished in any general way; that is, Heck couplings with especially lipophilic aryl halides in water as the only solvent at ambient temperatures. Independent of halide (or pseudohalide), the problem of substrate and ligand solubility, in addition to substrate reactivity as well as catalyst stability, weigh heavily on the prognosis for success given these stringent requirements. As early as 1994, Jeffery's paper entitled "Heck-type Reactions in Water" suggested that the combination of an alkali metal carbonate as base and a tetraalkylammonium salt as phase-transfer agent (PTA), along with catalytic Pd(OAc)<sub>2</sub>-Ph<sub>3</sub>P, could be used in neat water to couple iodobenzene and methyl acrylate (**eq 1**).<sup>32</sup> The PTA is presumably providing the organic phase in which the coupling takes place. In the absence of a PTA, very low conversion was observed (5%) even at 50 °C. The following year, Bumagin et al. reported<sup>33</sup> the first Heck coupling of water-insoluble substrates with either styrene or acrylic acid in pure water without recourse to a PTA (such as *n*-Bu<sub>4</sub>NBr, which is also effective as an additive in heated water<sup>34</sup>). Both aryl iodides and bromides gave cross-coupled products in the presence of Na<sub>2</sub>CO<sub>3</sub> as base at 100 °C; most reaction times were on the order of 2–7 hours. Notably, simple palladium salts (PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>) served as catalyst precursors, and Ph<sub>3</sub>P was only required in reactions of bromides (**eq 2**). A decade later, a ligand-free, nanometric form of colloidal palladium was described by Bhattacharya, Srivastava, and Sengupta that mediates Heck (and Suzuki) couplings in water at 80–100 °C (**eq 3**).<sup>35</sup> The key to their success was inclusion of one half to one full equivalent of the cationic surfactant CTAB (see Figure 2), which was needed to stabilize the newly formed palladium nanoclusters. Particles of these nanoclusters on average were shown by TEM to have a diameter of 5 nm. Such reactions in water are considered "non-conventional methodologies", a topic covered in detail by Alonso, Beletskaya, and Yus in their review on Heck reactions in *Tetrahedron* in 2005.<sup>36</sup>

Might nanoparticles of PTS in water supply the "solution" by simultaneously emulsifying the aryl iodide, olefin, and ligated palladium catalyst such that coupling would occur *without* heating above room temperature? Considering that vitamin E represents only ca. one-third the weight of PTS (MW ~1200), the effective concentration inside the micelle could be quite high, thus potentially dropping the reaction temperature due to this well-known effect in micellar catalysis.<sup>37</sup> Also, advantage would certainly be taken of the latest developments in ligand design, although the behavior of ligated Pd complexes in nonionic micelles of PTS had yet to be established. There were four key questions that had to be addressed for PTS to succeed: (1) Can the optimum amount of PTS in water be easily determined, and is it general? (2) Are there significant differences between metal catalysts under micellar conditions? (3) Does PTS compare favorably with other surfactants, or none at all? (4) Is product isolation from PTS *easily* achieved? Fortunately, the answer to all four turned out to be yes.

Insofar as these crucial points are concerned, 15% PTS (by weight) in water appeared to be more effective than were lower concentrations. Admittedly, this level of amphiphile seemed high (although it corresponds to only 0.124 M), but it *was* the experimentally determined amount that led to the fastest Heck reactions and highest conversions. That is, under a given set of conditions, in particular using catalyst **2a** (**Figure 6**), 2, 5, and 10 wt % levels of PTS were not nearly as effective. Only in hindsight is it now clear that this determination was due to issues specific to these conditions; i.e., precipitation of in situ generated PdI<sub>2</sub> and the resulting net instability of this catalyst system, both translating into a need for more PTS to maintain the catalyst in solution. Very recently, in fact, it has been found that far less PTS can be used

with a change in ligand on Pd (vide infra). Hence, again with the benefit of hindsight, it is not surprising that 15% is *not* the ideal amount of PTS for any of the other name reactions discussed herein; indeed, no more than 5 wt %, and more often 2.5 wt %, in water is recommended. As originally reported, using 2 mol % of palladium catalyst **2a**<sup>38a</sup> and Et<sub>3</sub>N as base led to Heck couplings between aryl iodides and either acrylates or styrenes at room temperature at an arbitrarily chosen 0.5 M substrate concentration in pure water (eq 4, 5).<sup>25</sup> Of the three common commercially available acrylate esters tested, the *least* effective was the more water soluble: methyl acrylate. The more lipophilic *t*-butyl and 2-ethylhexyl acrylates performed better in micelle-forming PTS–water. Ratios of olefin to iodide are in the 1.5–2:1 range. Depending on substrate, the ratios of *E* and *Z* products can vary, although the expected *E* isomer is strongly favored in all cases. Each of the coupling partners involved is water-insoluble. Other surfactants were also screened in a model system, including TRITON<sup>®</sup> X-100, BRIJ<sup>®</sup> 30, TPGS, PEG-400, and SDS (see Figure 2). Differences between these and PTS were substantial, with the exception of TRITON<sup>®</sup> X-100, which occasionally afforded similar results.

Dynamic Light Scattering (DLS) data on TPGS in water reveal a very narrow range of particles (12.5–12.8 nm), or about half the average size of PTS (Table 1).<sup>38b</sup> Switching from PEG-600 to PEG-1000 in the synthesis of PTS (see Scheme 1) results in TPGS and PTS now differing only in the diacid (4 vs 10 carbons) that links  $\alpha$ -tocopherol to PEG-1000. DLS on the more hydrophilic PTS-1000 shows an average micelle diameter of only 7 nm! Remarkably, the BRIJ<sup>®</sup> 30 micelle diameter is, on average, ten times that of a TRITON<sup>®</sup> X-100 micelle. Such changes in size potentially translate into *significant* variations in lipophilic core (i.e., “solvent”) volume (*V*), since *V* is proportional to *r*<sup>3</sup> (*r* = radius of micelle particle).

A few other sources of palladium were examined (e.g., Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>, and Pd(dba)<sub>2</sub>), but none led to any identifiable benefit (in rate, yield, etc.). Importantly, **product isolation** is facile (at least on a research scale), using either a rough filtration of the reaction mixture through silica to remove both PTS and water, or by standard extractive workup. With solvents such as petroleum ether, diethyl ether, dichloromethane, and ethyl acetate, PTS is fully retained atop the silica adsorbent. The formation of *tert*-butyl (*E*)-5-(3-*tert*-butoxy-3-oxopropen-1-yl)-1*H*-indole-1-carboxylate is a representative reaction (eq 6).<sup>25</sup> Well worth noting in the conditions associated with such reactions are the items *missing*: there is no need for solvent degassing, no weighing of substrates or catalyst in a glove box or other inert atmosphere conditions (although this is catalyst-dependent), and obviously no concern about drying any materials involved (including glassware). Given the phosphine ligand present in the catalyst, however, and the time for reactions (hours), a blanket of argon is routinely maintained. Good stirring is also important, although here again, standard laboratory equipment suffices. PTS–H<sub>2</sub>O is stable in a (preferably brown) bottle on the shelf for years.

In an effort to significantly reduce the originally prescribed 15 wt % PTS, a search for another ligand system was undertaken. The key observation focused on providing a catalyst already in the active Pd(0) state, thereby avoiding reduction of a Pd(II) precursor salt, as is required with **2a**. Thus, switching to preformed catalyst [(*t*-Bu<sub>3</sub>P)<sub>2</sub>Pd] (**2b**), the Heck coupling of 4-iodoanisole with *t*-butyl acrylate, now using only 5 wt % PTS under otherwise identical conditions, gave the anticipated cinnamate in very high isolated yield (eq 7).<sup>28a</sup>

While these intermolecular Heck reactions appear well suited to the aqueous conditions developed, they involve iodides as coupling partners. Recent preliminary efforts have identified a protocol

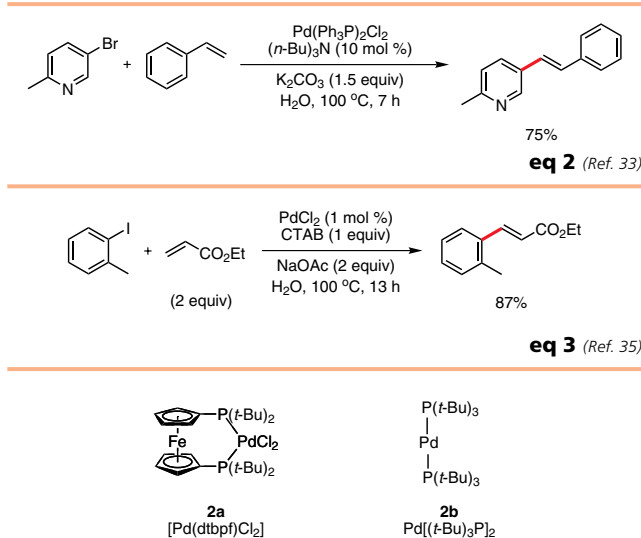


Figure 6. Catalysts for Heck Coupling in PTS–H<sub>2</sub>O. (Ref. 38a)

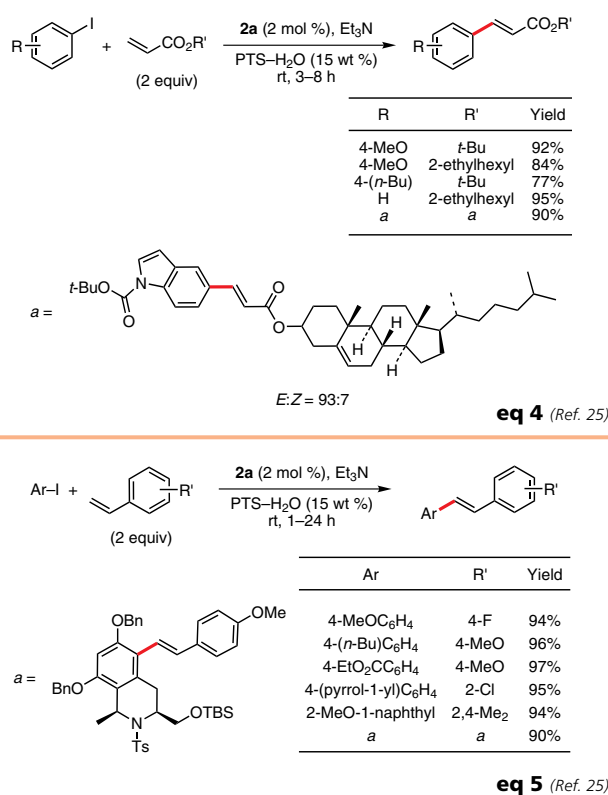
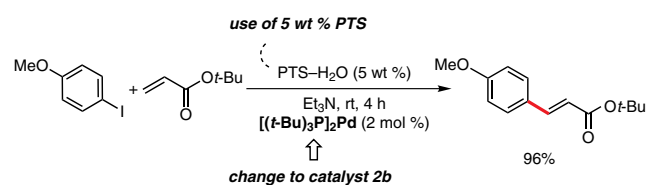
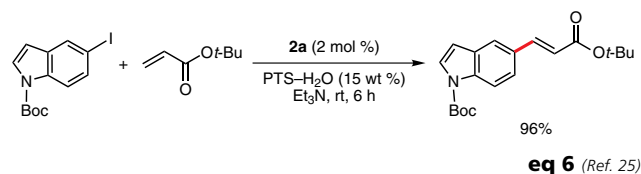


Table 1. Average Diameter of Selected Surfactants in Water (by Dynamic Light Scattering; DLS) (Ref. 38b)

Amphiphile	Diameter	Comparisons
PTS with PEG-600 ( <b>1</b> )	24 nm	increased length of PEG: smaller particles
PTS with PEG-1000	7 nm	
TPGS	13 nm	only difference: 4- vs 10-carbon acid linker
PSS	20 nm	
TRITON <sup>®</sup> X-100	10 nm	more hydrophilic PEG, much smaller particles
BRIJ <sup>®</sup> 30	110 nm	

*linear vs cyclic grease: give different results*

involving aryl bromides, but not quite yet at room temperature; very gentle heating to 38–50 °C is still necessary (**Scheme 2**).<sup>39</sup> As alluded to earlier, the change from iodide to bromide avoids potential precipitation of palladium halide salts; hence, 5 wt % PTS along with the Pd(0) catalyst **2b** also work well together here. These conditions approach the mildest of those known to date... even in organic solvents.<sup>30</sup> Given the usual dramatic influence of the environment surrounding the metal, prospects for finding a ligand that further lowers the reaction temperature also seem reasonable.



**Heck coupling using 5 wt % PTS–H<sub>2</sub>O.**<sup>28a</sup> The catalyst {Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub>, 5.1 mg, 0.01 mmol} and 4-iodoanisole (117 mg, 0.50 mmol) were introduced under argon into a 5.0-mL microwave vial equipped with a stir bar and a TEFLO<sup>®</sup>-lined septum. The PTS–H<sub>2</sub>O solution (1.0 mL, 5 wt % PTS), triethylamine (208 μL, 1.50 mmol), and *tert*-butyl acrylate (145 μL, 1.0 mmol) were then added by syringe. The heterogeneous mixture was stirred vigorously at room temperature, becoming almost homogeneous after 10–30 min, and its progress was monitored by TLC (10 vol % EtOAc–hexane). Upon consumption of 4-iodoanisole (4 h), the dark-purple mixture was diluted with EtOAc (~1.5 mL), filtered through a pad of silica gel to remove PTS–H<sub>2</sub>O, and the pad was rinsed with additional EtOAc (2 × 5 mL). The ethyl acetate filtrates were combined and the volatiles were removed in vacuo. The resulting crude product was purified by silica gel chromatography (5 vol % EtOAc–hexane) to yield 112 mg (96%) of *tert*-butyl (*E*)-3-(4-methoxyphenyl)propenoate as a colorless liquid. The <sup>1</sup>H NMR data of this product matched those previously reported.<sup>28b</sup>

than an acrylate or styrene. Of course, details had to be addressed such as (a) the amount of PTS, (b) which aryl halide(s) react(s) at room temperature, and (c) the “scope and limitations” with substitution patterns associated with each educt. However, catalyst **2a** (see Figure 6) and base (Et<sub>3</sub>N) were both carried forward from our experience with Heck reactions.

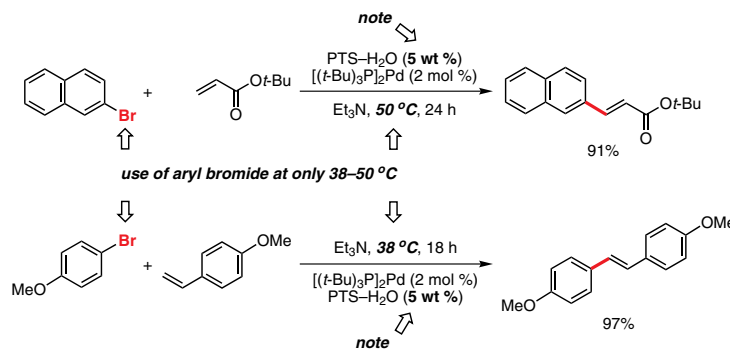
That only 1–2 wt % PTS in water is needed was established early on, using an aryl iodide and arylboronic acid.<sup>40</sup> Lesser amounts of PTS gave higher levels of conversion more rapidly than did solutions containing 5, 10, or 15 wt % in H<sub>2</sub>O. Relatively little effort was directed towards couplings with (water-insoluble) iodides, as they reacted quickly as expected. Bromides were also excellent partners, both of the electron-rich and electron-poor varieties (**eq 8**). Products were easily isolated from PTS upon workup; there are no issues of frothing or stickiness. Other surfactants (e.g., TRITON<sup>®</sup> X-100, TPGS, and BRIJ<sup>®</sup> 30) served in a similar capacity to varying extents, as was observed with Heck couplings.<sup>25</sup> In general, however, PTS was the carrier of choice for a wide range of aryl bromides and boronic acids. Nonetheless, there are several alternatives for effecting Suzuki–Miyaura couplings of aryl bromides in water at room temperature. Again, a 2008 critical overview of “non-conventional methodologies” is available from the team composed of Alonso, Beletskaya, and Yus.<sup>41</sup> A number of advances of late are noteworthy, including Shaughnessy’s development of trialkylphosphino ligands, in particular *t*-Bu-Amphos (**3**), which is best used with unhindered systems (**eq 9**).<sup>42</sup> In the presence of palladacycle **4** or **5** (**Figure 7**), more sterically demanding cases couple at 80 °C. Recycling the catalyst system based on **5** is also possible.<sup>43</sup> Related complex **6** and palladacycle **7**, described by Sudalai and co-workers,<sup>44</sup> likewise, effect couplings in water at 25 °C in the presence of KOH (2 equiv).

Lee and co-workers generated spherical micellar aggregates of ca. 10–15 nm in diameter associated with amphiphilic rod–coil molecules (**eq 10**).<sup>45</sup> In this system, hydrophobic disk-like rod bundles function as a reaction medium, surrounded by hydrophilic PEG chains. Interactions between aromatic moieties within the host micelle and the substrates (aryl halides and boronic acids) account for the enhanced rates of C–C-bond formation in water at room temperature.

The lingering question regarding participation by aryl chlorides has also been asked and answered insofar as PTS is concerned, but not to the same level of satisfaction as with bromides—at least initially. That is, some aryl chlorides did, in fact, react at room temperature, while others that would be expected to form biaryls

#### 4.2. Suzuki–Miyaura Coupling

With the groundwork laid for the use of PTS–water in Heck reactions, the only potential major difference between the Heck and Suzuki–Miyaura couplings was the partner: a boronic acid rather



**Scheme 2.** The Heck Reaction with Aryl Bromides in 5 wt % PTS–H<sub>2</sub>O. (Ref. 39)

reacted sluggishly. The problem in these cases could be oftentimes “fixed” by applying mild heat: no more than 50 °C was usually enough to drive the reactions essentially to completion. However, how does one achieve a more general room-temperature Suzuki–Miyaura coupling with aryl chlorides in PTS–water? The answer: change the ligand.

Although the Pd–dppf complex **2a**, and more recently catalyst **2b** (see Figure 6), function extremely well in most Heck<sup>25</sup> and Suzuki–Miyaura couplings<sup>40</sup> in water, the N-heterocyclic carbene containing complex **8** (Figure 8) leads best to biaryl couplings with aryl chlorides (eq 11).<sup>40</sup> Thus, under otherwise identical conditions (1–2 wt % PTS–water, room temperature, Et<sub>3</sub>N) catalyst **8** gave cross-coupled products in high isolated yields. Worthy of mention is the case of tri-ortho-substituted biaryls (e.g., **10d**), which appear to represent the steric limit of this technology to date. A more extensive study of catalysts, however, has not been made as yet. Lowering the amount of PTS 10-fold (i.e., to 0.1% by weight; eq 12) may provide enough surfactant given the appropriate catalyst. By way of comparison with the “on water” experiment, coupling to make terphenyl **11** in the complete absence of PTS, under otherwise identical conditions, gave significantly lower results: 99% vs 73% conversion; 93% vs 57% isolated yield (eq 13).

Other technologies that result in biaryl couplings using aryl chlorides in water also exist, although reaction temperatures tend to be in excess of 80 °C. There is a hint that room-temperature couplings may be possible, using capillary microreactors.<sup>46</sup> Otherwise, known processes rely on ligands carefully crafted for such Pd-catalyzed purposes, such as sulfonated biarylmonophosphine **12**<sup>47</sup> and *t*-Bu-Amphos (**3**),<sup>42</sup> usually aided by heat and/or some degree of substrate water solubility (eq 14).

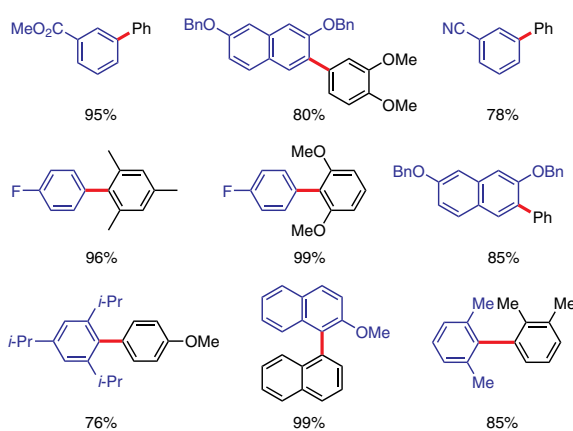
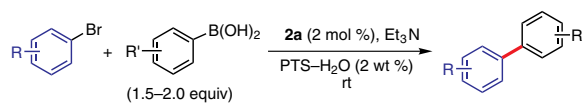
Phase-transfer agents, including Bu<sub>4</sub>NBr<sup>48</sup> and, more recently, CTAB as part of the unusual combination with heterogeneous Pd/C in water, provide access to unsymmetrical biaryls from activated chloroarenes (eq 15).<sup>49</sup>

Phenol-based leaving groups represent another opportunity in PTS-assisted Suzuki–Miyaura couplings. While triflate (CF<sub>3</sub>SO<sub>2</sub><sup>-</sup>) and nonaflate (C<sub>4</sub>F<sub>9</sub>SO<sub>2</sub><sup>-</sup>) derivatives smoothly react, less common by far is the use of the perfluorooctanesulfonate moiety, C<sub>8</sub>F<sub>17</sub>SO<sub>2</sub><sup>-</sup>, as a leaving group (eq 16).<sup>50</sup> The additional fluorinated carbon increases lipophilicity and, hence, the presumed solubility in the vitamin E core of PTS micelles.<sup>40</sup> In terms of cost, it is the least expensive of these three leaving groups.

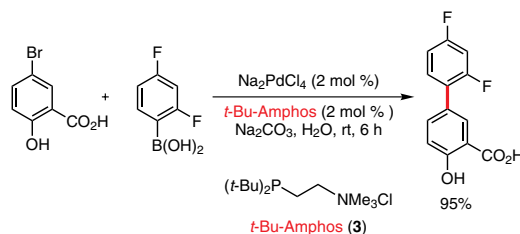
Currently under study are Suzuki–Miyaura couplings involving heteroaromatic halides, heteroaromatic boronic acids, or combinations of both. Judging from the early returns (e.g., eq 17),<sup>51</sup> the breadth of potential applications looks encouraging, although it is unrealistic to attempt to examine all the combinations from just commercially available partners.

### 4.3. Olefin Metathesis

Included within the broad area of olefin metathesis are subcategories such as cross-metathesis (CM) and ring-closing metathesis (RCM). Both have been warmly embraced by the synthetic community,<sup>52</sup> as they offer astounding functional group tolerance, efficiency, and potential for fine-tuning via ligand modification on a ruthenium-based catalyst (Figure 9).<sup>53–59</sup> Distinctly missing in the arsenal of metathesis weapons is a process for conducting CM in water at room temperature. Up until very recently, such olefin exchanges were performed exclusively in organic media, typically in (refluxing) CH<sub>2</sub>Cl<sub>2</sub>. Advances in ligand design have altered not only the reactivity profile of Grubbs and Grubbs–Hoveyda catalysts, but also produced water-soluble variants (Figure 10).<sup>60–64</sup> Nonetheless, accommodation of water-insoluble substrates has



eq 8 (Ref. 40)



eq 9 (Ref. 42)

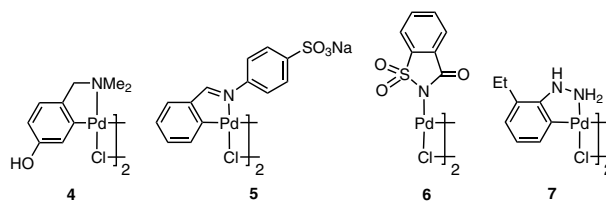
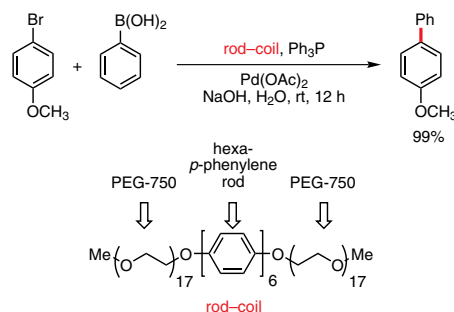
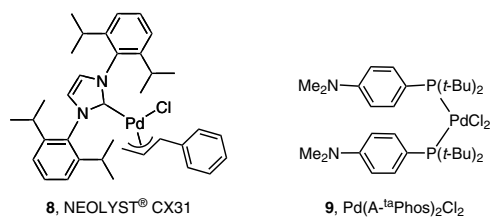


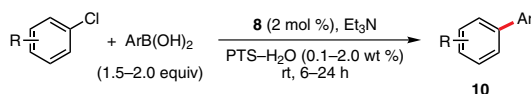
Figure 7. Palladacycle and Related Catalysts for the Suzuki–Miyaura Coupling. (Ref. 42,44)



eq 10 (Ref. 45)

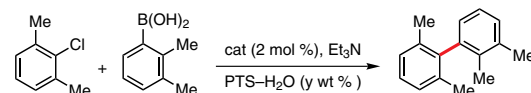


**Figure 8.** Catalysts Used in Suzuki–Miyaura Cross-Couplings of Aryl Chlorides in PTS–H<sub>2</sub>O. (Ref. 40)



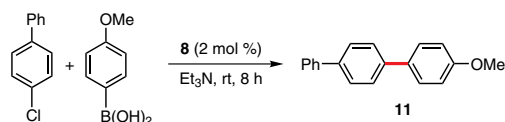
<b>10</b>	R	Ar	Yield
<b>a</b>	2-MeO	Ph	100%
<b>b</b>	2,6-Me <sub>2</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	99%
<b>c</b>	4-NC	2,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	96%
<b>d</b>	2,6-Me <sub>2</sub>	1-Np	100%

**eq 11** (Ref. 40)



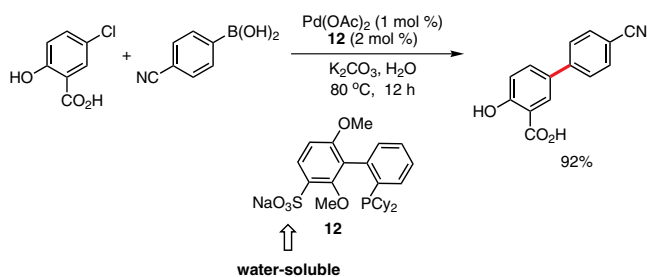
Cat.	y	T, °C	t, h	Yield
<b>2a</b>	1	50	24	28%
<b>8</b>	1	23	4	98%
<b>8</b>	0.1	23	24	97%

**eq 12** (Ref. 40)

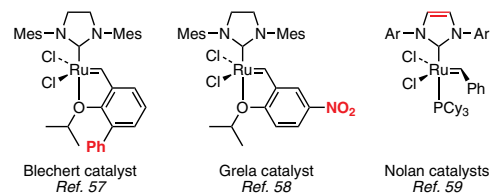
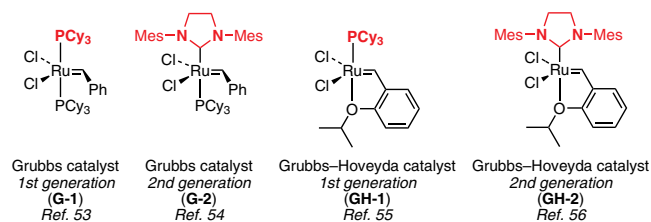
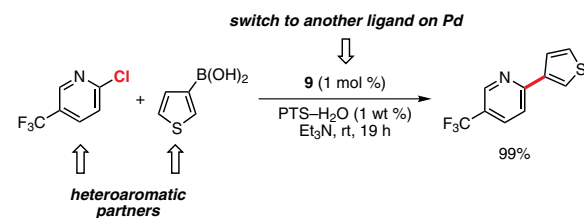
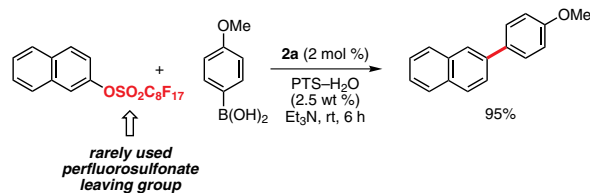
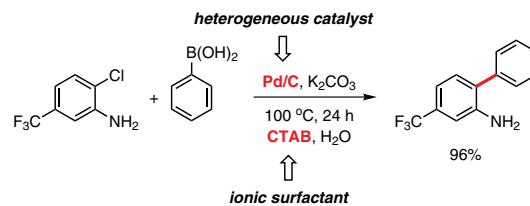


Medium	Conv.	Yield
PTS–H <sub>2</sub> O (1 wt %)	99%	93%
No PTS ("on water")	73%	57%

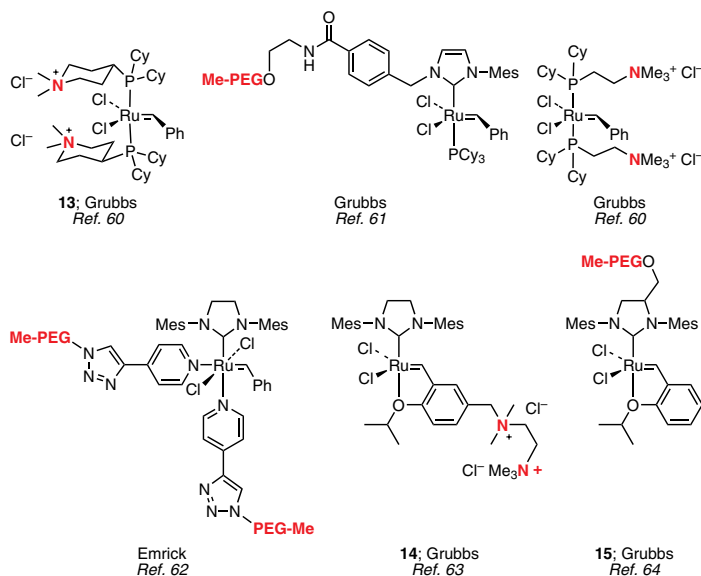
**eq 13** (Ref. 40)



**eq 14** (Ref. 47)



**Figure 9.** Representative, Water-Insoluble Metathesis Catalysts.

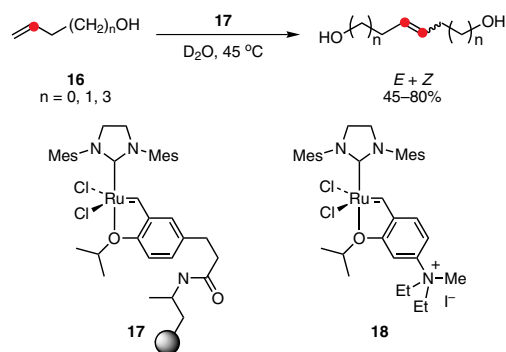


**Figure 10.** Representative Water-Soluble Catalysts for Metathesis.

remained of paramount concern, oftentimes forcing employment of low-molecular-weight (and hence, somewhat water-soluble) educts (e.g., **16**), or charged species that have innate solubility in aqueous media. For example, Blechert, Connon, and co-workers prepared a PEGA-NH<sub>2</sub>-derived catalyst, **17** (eq **18**),<sup>65,66</sup> which was used in homocouplings of hydroxyl-functionalized olefins, **16**, in heavy water at 45 °C. Levels of conversion, however, were variable. Related cross-metatheses, specifically on allyl alcohol (**16**, *n* = 0), were achieved in high yields (99%) by Grela and Mauduit employing catalyst **18**, although the best results with species **18** were obtained for the related analogous RCM reactions in CH<sub>2</sub>Cl<sub>2</sub>.<sup>67,68</sup> PTS represents one remarkably enabling technology that goes a long way towards eliminating concerns regarding the solubility characteristics of both catalysts and substrates. What organic chemists oftentimes refer to as “dump and stir” procedures are now in hand for both olefin CM and RCM, conducted at ambient temperatures; just add water.

For cross-metathesis, introduction of a Type I and Type II olefin<sup>69</sup> combination to a mixture of 2.5 wt % PTS–water containing the Grubbs 2nd-generation<sup>54</sup> catalyst leads to product olefins **19** in good isolated yields (eq **19**).<sup>70</sup> The reagents (simple acrylates and enones, and Ru catalysts) and the reaction medium (PTS–H<sub>2</sub>O) are readily available items of commerce. No special precautions are needed with respect to either solvent degassing or protection of reactions from air. Purification follows from established protocols (vide supra) usually involving simple filtration of reaction mixtures through a silica gel plug, followed by a standard extractive workup. Other functional groups that withstand these mild aqueous metathesis conditions include epoxides, allylic silanes, and nonracemic N-protected amino acid derivatives. Most reactions, run at overall concentrations of 0.5 M in PTS–water, usually take ≤12 hours to reach completion, and afford mainly, if not exclusively, *E* enones or enoates.

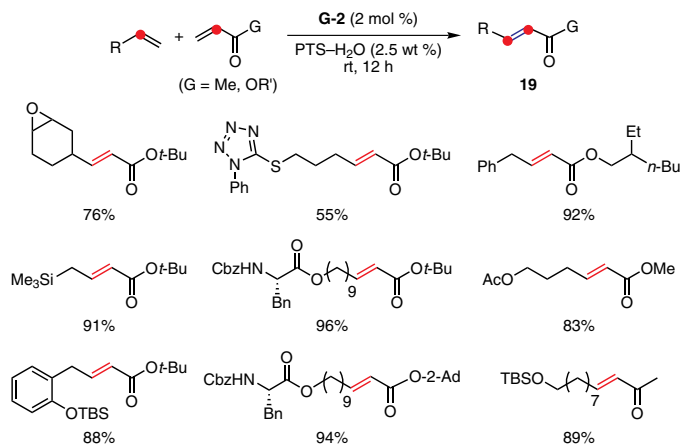
Ring-closing-metathesis (RCM) reactions in water have been of interest for over a decade.<sup>52,71</sup> Most approaches rely on ruthenium complexes that bear ligands modified to ensure water solubility (see Figure 10). An amphiphilic catalyst consisting of a block co-polymer based on poly(2-oxazoline) also shows promise



**eq 18** (Ref. 65,67)

in water, with good prospects as well for ease of separation and recycling.<sup>72</sup> With water-soluble substrates, good conversions to cyclic products were achieved. A summary of the current state of ring-closing metathesis in water can be found in **Table 2**.<sup>60b,63,64,72–76</sup> Just earlier this year, ultrasonication was shown by Grela to afford carbo- and heterocyclic rings in excellent yields without recourse to surfactants.<sup>74,75</sup> Presumably, RCM occurs under acoustic emulsification within the droplets of each diene, which are otherwise water-insoluble. In the absence of water, oligomerization is a competing pathway (eq **20**).<sup>74</sup>

The ionic surfactant SDS had been examined in 2002 by Davis and Sinou in related RCM reactions in water,<sup>76</sup> although in this early study use of the less reactive Grubbs 1st-generation catalyst precluded formation of tri- and tetrasubstituted olefinic products. Relatively high percentages (ca. 5 wt %) of amphiphile were also part of this recipe. The conclusion from this study was that a surfactant may not be essential for RCM reactions in water. Use of PTS in this context relies on less surfactant (1.5–2.5% by weight) than that used in CM reactions (i.e., 2.5 wt %), and

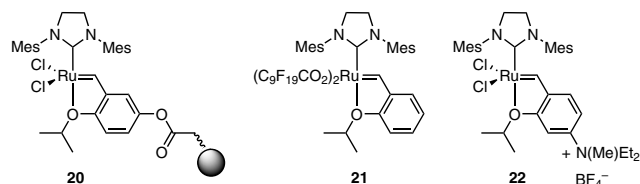


eq 19 (Ref. 70)

Table 2. Literature Reports on RCM Reactions in Water

Year	Catalyst	Additive	Examples	Comments	Senior Author	Ref.
1998	13	-	2	5–60% conversions, 5–10 mol % catalyst, degassed H <sub>2</sub> O, 45 °C under argon, ring size: 5	Grubbs	60b
2002	Grubbs 1st Gen	SDS <sup>a</sup>	8	23–100% conversions, 5 mol % catalyst, degassed H <sub>2</sub> O, 25 °C under N <sub>2</sub> , 0.5 h, 0.05 M SDS, ring sizes: 5 and 6	Sinou	76
2004	20	-	1	90% conversion, 1 mol % catalyst, degassed H <sub>2</sub> O, 25 °C under N <sub>2</sub> , 1 h, ring size: 5	Weberskirch	72
2006	15	-	5	5–95% conversions, 5 mol % catalyst, degassed H <sub>2</sub> O, 25 °C under argon, 12–36 h, ring sizes: 5 and 6	Grubbs	64
2007	21	DTAC <sup>b</sup>	1	91% conversion, 25 °C, 3.5 h, 0.048 M DTAC, ring size: 5	Mingotaud	73
2007	14	-	5	5–95% conversions, 5 mol % catalyst, degassed H <sub>2</sub> O, 30–45 °C, under argon, 24 h, ring sizes: 5 and 6	Grubbs	63
2008	Grubbs 2nd Gen	-	5	65–99% yields, 5 mol % catalyst, 40 °C ultrasonication, 5 h, ring sizes: 5 and 6	Grela	74
2008	22	-	4	95–99% conversions, 5 mol % catalyst, 25 °C, 5–24 h, ring size: 5	Grela	75

<sup>a</sup> SDS = sodium dodecyl sulfate. <sup>b</sup> DTAC = dodecyltrimethylammonium chloride.



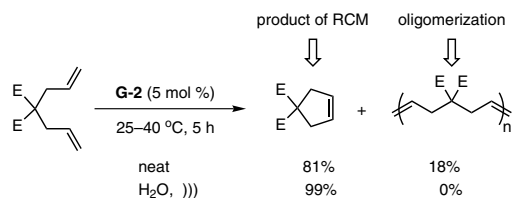
leads to *consistently* high conversions and hence, isolated yields.<sup>77</sup> RCM reactions in neutral PTS micelles take high place fairly quickly (1–3 hours), including the formation of seven-membered rings and trisubstituted arrays, mediated by the Grubbs 2nd-generation or Grubbs–Hoveyda 2nd-generation catalyst without high dilution (0.10 M) (eq 21).<sup>77</sup> Although most examples to date have been carried out under these conditions, increasing the total concentration of substrate to 0.30 M did not significantly alter the reaction rate, or the extent of conversion or homocoupling.

Applications of cross-metathesis to tandem processes can easily be envisioned. One recent example of dienoate formation calls for the coupling of an acrylate with a simple phenolic derivative of homoallyl alcohol (23; formed via *O*-alkylation of *p*-nitrophenol).<sup>78</sup> The resulting initial product readily undergoes elimination to generate the corresponding doubly unsaturated ester 24 (Scheme 3). Although most examples were studied in organic media, results in PTS–H<sub>2</sub>O were essentially identical.

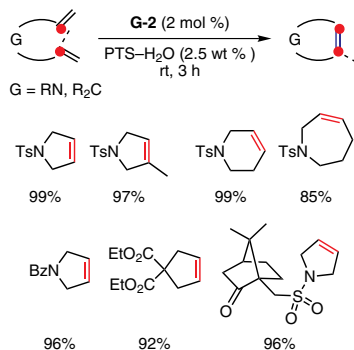
So, what about “seawater”, rather than water out of the bottle, as the solvent for these cross-couplings using PTS? The answer is “yes”; at least insofar as CM and RCM reactions go, they work equally well in this medium (Scheme 4).<sup>79</sup> Of course, we can only make this claim for water taken from the shores of the Pacific Ocean in Southern California! Interestingly, DLS indicates that such PTS–seawater contains 75-nm particles; thus, the presence of Na<sup>+</sup> (and likely other cations as well) increases the size of these nanoreactors (from 24 nm, in sweet water), presumably due to elongation of PEG as a result of greater ionic strength of the water.

## 5. Summary and Outlook

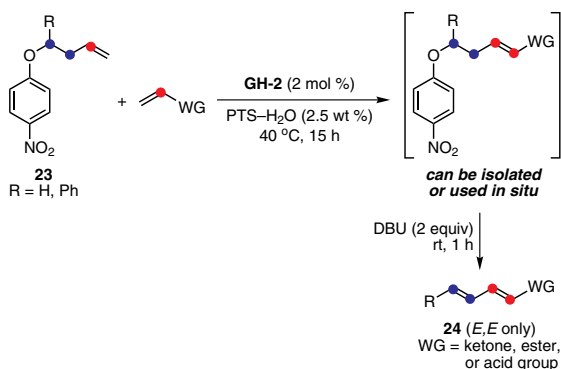
Studies to date on Heck and Suzuki–Miyaura couplings, as well as olefin metathesis reactions, in pure water at room temperature have been very encouraging. The presence of the nanometer-micelle-forming amphiphile PTS may provide the foundation for these aqueous conditions, but the catalysis is still metal-dependent, and the quality of the resulting coupling is highly ligand-driven. In other words, PTS offers an aqueous advantage, and while the metal counts, *the ligand rules*. It is also somewhat premature to assume that many of the remaining important cross-coupling reactions in transition-metal-catalyzed organic synthesis are amenable and will simply follow suit. Nonetheless, based on additional preliminary data in



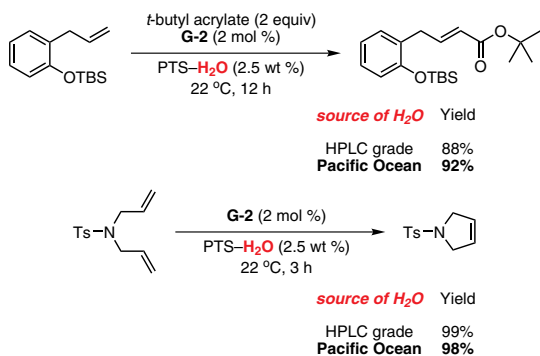
eq 20 (Ref. 74)



eq 21 (Ref. 77)



Scheme 3. Tandem Cross-Metathesis–Elimination to Form Polyenes. (Ref. 78)



Scheme 4. Metathesis Reactions in PTS–Seawater. (Ref. 79)

hand, there is good reason to suspect that related methodologies will be forthcoming. For example, Sonogashira couplings in PTS–H<sub>2</sub>O suggest that aromatic acetylenes can be fashioned from aryl bromides in the absence of copper at 25 °C (eq 22).<sup>80a</sup>

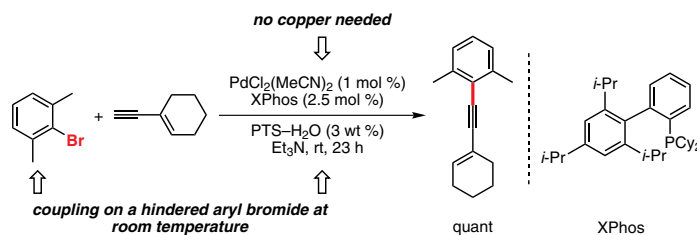
Initial attempts at asymmetric hydrosilylation of a challenging case such as isophorone with catalytic CuH, ligated by Takasago's nonracemic bisphosphine DTBM-SEGPHOS® (25)<sup>81</sup> in PTS–H<sub>2</sub>O, also look promising (eq 23).<sup>82</sup> Thus, PTS is part of the puzzle; one member of a class of “designer” surfactants. That such tailor-made materials in pure water could be viewed simply as supplying “solvents” for several fundamental processes done in pure water intuitively has appeal. Creating new enabling technologies for transition-metal-catalyzed reactions based on micellar catalysis in water may constitute only one approach among many under the umbrella of green chemistry, but it has the potential for considerable impact; getting organic solvents out of organic reactions just makes good sense, and the numbers support this notion. Estimates suggest that, on a yearly basis, 3.2 million MT of solvents are used in chemical manufacturing; a shift of only 1% based on (readily hydrolyzed, safe,<sup>83</sup> and non-polluting) levels of PTS in water would amount to a savings of 32,000 MT of organic solvents (1 MT = 1,000 kg). Thus, it is not hard to see why along “The Road to Sustainability”, as conveyed by Sheldon, Arends, and Hanefeld in their recent monograph *Green Chemistry and Catalysis*,<sup>3b</sup> “The Medium is the Message.”

## 6. Acknowledgements

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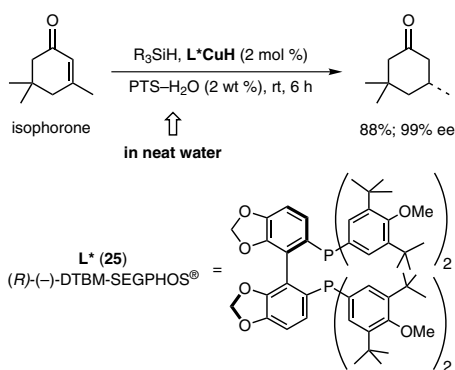
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**Representative Sonogashira coupling in PTS-H<sub>2</sub>O. Preparation of 2-(cyclohexen-1-ylethynyl)-1,3-dimethylbenzene.**<sup>80a</sup> Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> (1.8 mg, 0.007 mmol) and XPhos (6.9 mg, 0.014 mmol) were introduced under argon into a 5-mL, round-bottom flask equipped with a stir bar. The following were then added via syringe under a positive flow of argon in the order shown: degassed PTS solution (1.0 mL, 3 wt %), Et<sub>3</sub>N (150 μL, 1.08 mmol), 2-bromo-*m*-xylene (70 μL, 0.52 mmol), and 1-ethynylcyclohexene (100 μL, 0.85 mmol). A milky, brown mixture developed over 20 min while stirring at rt. The reaction progress was monitored by GC. After 23 h, the mixture was diluted with brine and extracted with EtOAc. The organic extracts were combined and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated by rotary evaporation to give a crude brown oil that was purified by silica gel chromatography (eluting with hexanes) to afford the title compound (110 mg, 100%) as a colorless oil. Its <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectral data matched those previously reported.<sup>80b</sup>

eq 22 (Ref. 80a)



eq 23 (Ref. 82)

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- (83) PTS is FDA GRAS affirmed for use with CoQ<sub>10</sub> in dietary supplements (Notice No. GRN 000202; <http://www.cfsan.fda.gov/~rdb/opa-g202.html>), and has self-affirmed GRAS status for use as a food ingredient (accessed July 2008).

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Squibb Co.), TEFLON® (E. I. du Pont de Nemours and Company, Inc.), TWEEN® (ICI Americas, Inc.).

**Keywords:** cross-couplings; green chemistry; micellar catalysis; designer surfactants; PTS.

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**Bruce Lipshutz** has been at the University of California, Santa Barbara, since joining the faculty in 1979. Much of his career has been focused on developing new reagents and technologies that have broad appeal in the synthetic community, many of which are, or will soon be, commercially available (e.g., SEM-Cl, “Higher Order Cuprates”, “Cuprate-in-a-Bottle”, DCAD, “Copper Hydride-in-a-Bottle”, Ni/C, Cu/C, PTS, etc.). The group’s efforts have now turned in part to “green chemistry”. Thus, an ongoing mix of methods in heterogeneous catalysis, including newly developed mixed-metal-supported cross-coupling reagents and homogeneous catalysis, are being investigated. The latter includes recent contributions in micellar catalysis, with an accent on the development of “designer” surfactants. Also being actively pursued are projects in total or partial synthesis of biaryls that possess axial chirality (e.g., the A–B biaryl section of vancomycin, and the antimalarial korupensamines), and syntheses associated with, or leading to, analogues of coenzyme Q<sub>10</sub> (e.g., total synthesis of piericidin A1).

**Subir Ghorai** was born in 1977 in Panskura, West Bengal, India. After receiving his B.S. and M.S. degrees in chemistry from Jadavpur University, India, he joined the Indian Institute of Chemical Biology (IICB), Jadavpur, in 2000 as a CSIR research fellow. He received his Ph.D. degree in 2005 from IICB, working under the supervision of Dr. Anup Bhattacharjya on the synthesis of chiral dendrimers and heterocycles from carbohydrate precursors. From 2005 to 2006, he worked on isonitrile chemistry as a postdoctoral fellow with Professor Michael C. Pirrung at the University of California, Riverside. Since then, Subir has been a postdoctoral fellow in the research group of Professor Bruce H. Lipshutz at the University of California, Santa Barbara, where he is now working on green chemistry projects involving transition-metal-catalyzed reactions in aqueous media. 