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Effects of Co-solvents on Reactions Run under Micellar Catalysis Conditions

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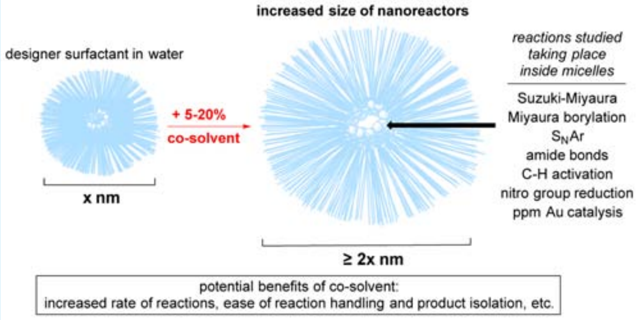
Supporting Information

ABSTRACT: The impact of varying percentages of an organic solvent added to reactions run in aqueous nanomicelles as the reaction medium has been investigated. Issues such as rates of reaction, percent conversion, and yield, as well as various practical aspects (e.g., effect on stirring, etc.), are discussed, leading to an operationally simple method for the general improvement of potentially problematic systems across a broad range of reaction types, in particular for reactions run at scale.



The expanding list of applications of designer surfactants such as TPGS-750-M (**1**, Figure 1) and their in situ derived nanomicelles as an alternative reaction medium to organic solvents in which numerous synthetic transformations can be carried out is now quite extensive.[1] While several types of transition metal-catalyzed processes are especially well-suited to these conditions (e.g., Pd- and Ni-catalyzed cross-couplings,[1b,2] Au-catalyzed processes,[3] etc.), many other reaction types not only are amenable but also offer unique opportunities to benefit from the presence of the surrounding water (e.g., olefin metathesis in the presence of CuI[4] or at reduced pH[5]), along with elimination of egregious dipolar aprotic and water-miscible organic solvents (e.g., in S_NAr reactions[6]). The broad generality of this reaction medium allows for tandem processes to be developed, where sequences of reactions that no longer require differing reaction solvents can be run in a single pot, maximizing efficiency and minimizing waste.[6−13] While the notion of "getting organic solvents out of organic reactions" remains our goal, we have developed an appreciation for the vagaries associated with the solubility properties of starting materials, most notably highly crystalline solids that can be quite slow to gain entry into the hydrophobic micellar core, making use of this technology impractical. Flocculent solids can be tough to fully consume, and in some cases, educts viewed as "brick dust" that are only soluble in highly polar media may be outside the scope of this green chemistry.

Initial solubility, however, is but one of the potential problems that may arise, especially with reactions run at scale.[14] Starting materials, and/or the desired product(s), may present unpredictable practical issues during or post-reaction at the workup stage. For example, materials at any stage may adhere to the stirrer and form an intractable gum, preventing continued stirring and/or full conversion. Extraction of the product from such intractable solids can be time-consuming and may require extensive handling, including solubilization in copious amounts of undesirable organic solvents.

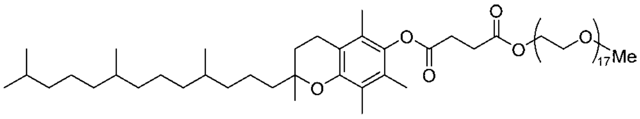


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Figure 1. Structure of TPGS-750-M.

Fortunately, a straightforward modification to existing, otherwise optimized conditions that serves to further generalize this aqueous technology and overcome these limitations has been found. In this report, therefore, we describe the influential role that selected organic co-solvents can play in facilitating many types of reactions run in water, and under very mild conditions.

In screening an array of organic solvents,[3a,9,10,15] added in the range of 5−20% by volume, the most effective have been found to be THF, acetone, and PEG-200.

Each of these is water-miscible, which has implications for workup and recycling of the aqueous reaction mixtures (vide infra). On occasion, toluene has also been found to be quite useful. Several types of reactions were investigated to determine

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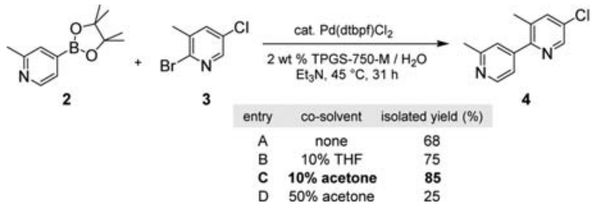
co-solvent effects on kinetics, yields, and physical properties of reaction mixtures.

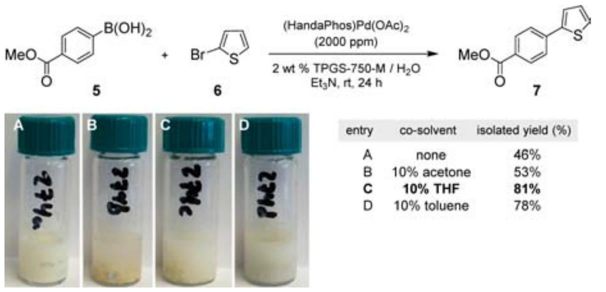
Suzuki–Miyaura (SM) Cross-Couplings.[1a] Figure 2 shows the results of an SM reaction involving solids **2** and **3**, in 2 wt % TPGS-750-M/H_2O. For this case, it was found that while the use of a co-solvent had essentially no effect on the physical appearance of the reaction mixture run at 45 °C, the presence of 10% acetone (by volume) increased the isolated yield from 68% to 85%. Further increases in the acetone content (e.g., to 50%) led to a dramatic decrease in isolated product (25%).



entry	co-solvent	isolated yield (%)
A	none	68
B	10% THF	75
C	**10% acetone**	**85**
D	50% acetone	25

Figure 2. Effects of THF and acetone on a SM coupling.

Earlier this year our group released a communication introducing HandaPhos, a highly active ligand for SM couplings enabled by only ppm levels of its 1:1 complex with palladium.[7] Examination of THF, acetone, and toluene as co-solvents at the 10% level identified both THF and acetone as effective additives, thereby enhancing the rate of the coupling between solid **5** and liquid **6**, shown in Figure 3. In comparison to the control system, higher isolated yields were produced using 10% co-solvent. And while the highest yield of **7** was achieved by utilizing THF (81%), 10% toluene showed a more uniform and stable suspension without precipitation.

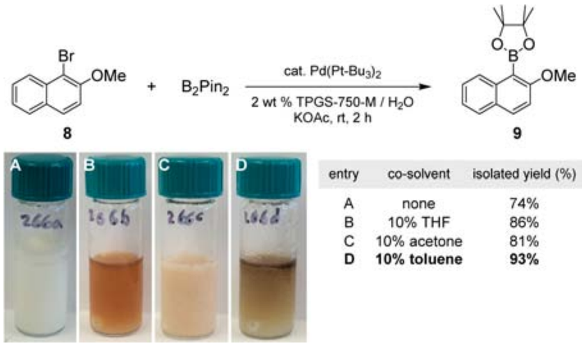


entry	co-solvent	isolated yield (%)
A	none	46%
B	10% acetone	53%
C	**10% THF**	**81%**
D	10% toluene	78%

Figure 3. Impact of co-solvent on SM cross-coupling.

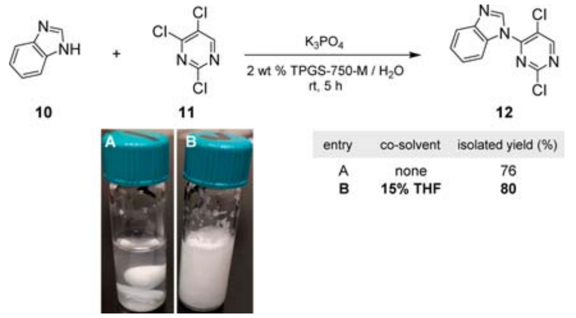
Miyaura Borylation.[16] C-BPin bond-forming reactions may also benefit by the addition of a co-solvent, due mainly to the flocculent/crystalline nature of B_2Pin_2. This reagent has the tendency to float upon the surface of the aqueous reaction mixture, which may lead to increased reaction times and undesirable behavior at scale. Use of either 10% THF or acetone, where the B_2Pin_2 could be added as a predissolved solution to solid educt **8**, completely eliminated this phenomenon affording product **9** (Figure 4).

S_NAr Reactions.[6] When performing these substitution reactions involving equimolar amounts of solid benzimidazole **10** and liquid 2,4,5-trichloropyrimidine, **11**, use of co-solvent led to a distinct difference in reaction appearance compared with that seen in water alone (Figure 5). Under standard S_NAr conditions, aggregation of the product was observed, and while only a modest improvement in reaction yield was achieved by the use of 15% THF, the mixture was transformed into a stable suspension, an important consideration when run at scale.



entry	co-solvent	isolated yield (%)
A	none	74%
B	10% THF	86%
C	10% acetone	81%
D	**10% toluene**	**93%**

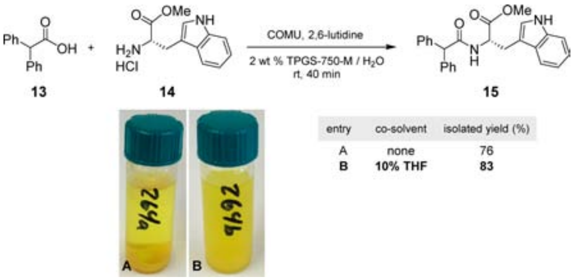
Figure 4. Miyaura borylations with co-solvents.



entry	co-solvent	isolated yield (%)
A	none	76
B	**15% THF**	**80**

Figure 5. Representative S_NAr reaction.

Amide Bond Formation.[17] As a representative case, coupling of solid diphenylacetic acid, **13**, with solid L-tryptophan methyl ester, **14**, under standard (co-solvent-free) conditions led to conversion to amide **15**. However, precipitation of the accumulated product onto the stir bar halted stirring of the reaction mixture after only 30 min (Figure 6). This type of precipitation can grossly effect the extent of conversion, rendering these conditions unsuitable for scale-up. On the other hand, use of 10% THF leads to a stable suspension, thus allowing the reaction to stir freely and proceed to a higher degree of conversion. Previous studies on amide couplings in aqueous TPGS-750-M have also been shown to benefit from the presence of PEG as co-solvent.[15]



entry	co-solvent	isolated yield (%)
A	none	76
B	**10% THF**	**83**

Figure 6. COMU-mediated amide bond formation.

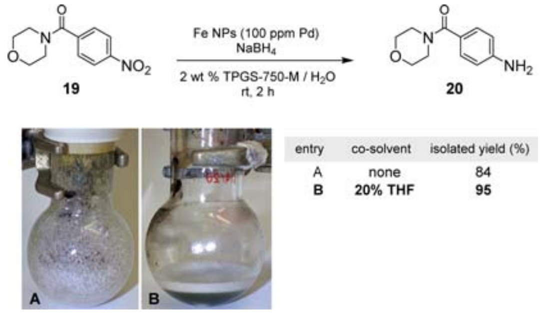
C–H Activation.[18] Palladium-catalyzed C–H activation of aryl urea solid **16**, followed by coupling with solid 4-iodoanisole, **17**, afforded a higher yield in the absence of a co-solvent (Figure 7). Nonetheless, utilizing 10% THF or acetone led to freely flowing material in the reaction mixture, which also produced heavy precipitation of the product and silver salt.

Reductions of Nitroaromatics.[9] Aromatic/heteroaromatic nitro compounds are often challenging substrates in general

entry	co-solvent	isolated yield (%)
A	**none**	**72**
B	10% THF	59
C	10% acetone	65

Figure 7. Pd-catalyzed C−H activation.

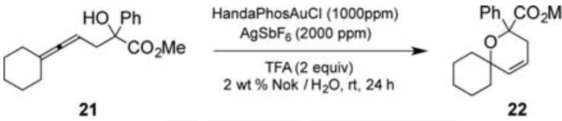
due to their limited solubility in aqueous nanomicelles, a result of their highly crystalline nature and relatively high melting points. Recently, we have disclosed a new method for efficient Fe/ppm Pd-catalyzed/NaBH$_4$ nitro group reductions in water that utilizes a co-solvent to assist with highly crystalline, sparingly soluble substrates.[9] For this system, the co-solvent not only enhances solubilization of the starting material and intermediates within the micellar core but also shows a pronounced effect on the amount of foaming resulting from the evolution of H$_2$. An excellent example of this is the reduction of (solid) nitroaromatic **19** to amine **20**, where the absence of co-solvent increases nucleation sites for gas evolution leading to foaming, which can grow to occupy the entire volume of the flask (Figure 8A). When carried out with 20% THF, foaming is negligible due to the decrease in surface tension of the solvent, leading to rapid reduction of any foam, along with greatly improved stirring (Figure 8B). Furthermore, solid precipitation is not observed throughout the course of the reaction, which in the composite affords a significant increase in yield from 84% to 95%.



entry	co-solvent	isolated yield (%)
A	none	84
B	**20% THF**	**95**

Figure 8. Fe/ppm-Pd NP-catalyzed reduction.

Cyclizations of Allenic Alcohols. As part of a more general study on HandaPhos technology applied to ppm level Au-catalyzed reactions run under these micellar catalysis conditions, cyclization of liquid allenic alcohol **21** was effected using (HandaPhos)Au (1000 ppm, or 0.10 mol %) to produce cyclic ether **22** in good yield (Figure 9). In the same manner as ppm Pd-catalyzed SM couplings with HandaPhos, a low catalyst loading results from precomplexation in organic solvent, which is then used as a means of transferring the catalyst to the aqueous reaction mixture. For this transformation, a distinct relationship between co-solvent selection and yield was revealed. That is, the addition of 10% toluene (but not acetone or THF) was found to increase the yield from 33% to 91%, further exemplifying the potential impact of co-solvent screening in these systems.



entry	co-solvent	isolated yield (%)
1	none	33
2	**10% toluene**	**91**

Figure 9. ppm (HandaPhos)Au(I)-catalyzed ether formation.

Notwithstanding the observed benefits associated with co-solvent usage, the question remains as to whether nanomicelles still exist in the presence of organic solvent. Insight was obtained using dynamic light scattering data acquired for samples containing TPGS-750-M in the presence of 5%, 10%, and 15% THF (Table 1). As the data illustrate, particles of initially 57 nm increase in size to ca. 100 nm, with populations becoming more diverse when compared to the control sample measured in water only. The expansion of micelles in the presence of organic solvent is expected, as solvent molecules can organize themselves within the micellar framework, causing particle growth until saturation, at which point no additional swelling is observed.[19] These observations are in agreement with the DLS data collected (Figure 10). Likewise, particles of this surfactant also increased in size upon introduction of 15% acetone (Table 1, entry 5).

Table 1. Average Particle Size of Micelles + Co-solvent

entry	co-solvent (% v/v)	ave particle size (nm)
1	none (control)	57
	THF	
2	5	104
3	10	129
4	15	101
	acetone	
5	15	113

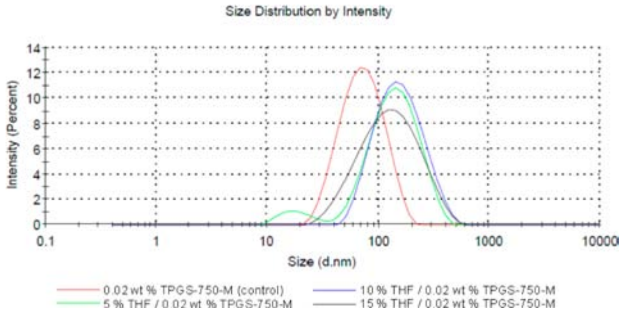
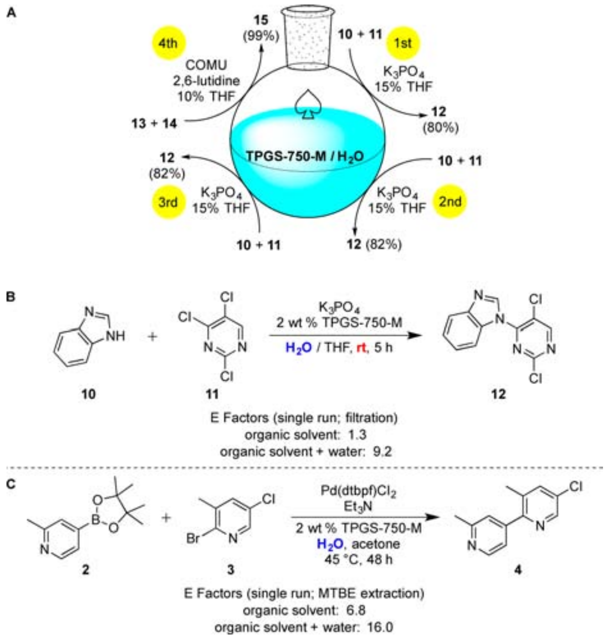


Figure 10. DLS data (particle size): TPGS-750-M/H$_2$O + THF.

As previously reported, the use of TPGS-750-M for micellar catalysis lends itself for the opportunity to recycle the reaction medium by simply removing organic components from the reaction via extraction with minimal EtOAc. As Scheme 1A highlights, the aqueous medium used for the S$_N$Ar reaction to produce **12** can be recycled two additional times for the same reaction without effecting yield. Upon neutralization of the remaining aqueous medium, a nearly quantitative yield of **15** from **13** and **14** under COMU-mediated peptide coupling

Scheme 1. Recycling and E Factor Studies



conditions was obtained. And although this modification requires the addition of organic solvent to the reaction mixture, the amount of organic waste generated is still quite low when calculating Sheldon's E Factor.[13,20] By means of a simple filtration, **12** was isolated in 80% yield resulting in an exceptionally low E Factor of 1.25. The low E Factor of 6.8 was achieved by extraction with minimal MTBE to afford **4**.

In summary, use of a co-solvent as an additive to aqueous solutions containing nanomicelles derived from TPGS-750-M adds yet another dimension to micellar catalysis as an attractive alternative approach to traditional organic solvents alone as reaction media. The preferred co-solvents are THF, acetone, and PEG-200, although toluene is occasionally advantageous. These observations can help address those occasions where substrate and/or catalyst solubility may be an issue, and when various practical aspects, especially at scale,[21] can otherwise be problematic. Such aqueous solutions are amenable to recycling, while DLS measurements have shown that added co-solvent enlarges the size of the nanoreactors in which the chemistry is taking place.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03468.

> Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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