Taming Troublesome Suzuki–Miyaura Reactions in Water Solution of Surfactants by the Use of Lecithin: A Step beyond the Micellar Model

Chiara Ceriani, Erika Ghiglietti, Mauro Sassi, Sara Mattiello,* and Luca Beverina*

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ABSTRACT: The use of water solutions of industrial and designer surfactants enables performing a wide variety of chemical transformations on hydrophobic precursors. Most reactions are clean, fast, and efficient with vast benefits for overall sustainability. The widespread adoption of such methods is somewhat hampered by a lack of generality in the case of troublesome substrates and scaling up. The common literature solution for such issues is the use of small amounts of organic solvents. We here show that the use of a mixture of L-α-lecithin and Tween 80 is a preferable solution enabling the taming of particularly troublesome reactions where even the cosolvent approach fails. The strong reduction of all interface tensions characterizing such complex multiphase systems is key to the results achieved. The protocol is general and scalable.

INTRODUCTION

The development of improved synthetic methods offering selectivity, high yield, and short reaction times while providing moderate or no heating is a cornerstone of modern sustainable chemistry.[1,2] Unfortunately, the need for organic solvents remains the elephant in the room.[3,4] Despite the obvious benefits, their replacement with water in homogeneous phase reactions is troublesome as the vast majority of fine chemicals and/or precursors are water insoluble. The literature shows that the addition of surfactants to water can drastically change such a scenario.[5−9] Several different chemical processes can be profitably performed in water with high yield, irrespective to the solubility of reagents and products.[10−14] Gathered under the banner of "micellar catalysis" (MC), such methods witnessed an enormous boost in scope, generality, and synthetic usefulness in the last 10 years, even at the industrial scale.[15−18]

Strictly speaking, MC refers to the catalytic effect on reactions performed in a homogeneous single-phase nano-dispersed medium obtained in the presence of a water-based surfactant solution above the critical micellar concentration (CMC).[19] Under such conditions, surfactant molecules assemble into micelles, thermodynamically stable association colloids having a hierarchical structure consisting in a lipophilic core, and a hydrophilic periphery. Micelles formation is accompanied by a steep increase in solubility of lipophilic reagents/catalysts, mostly localizing in the micelle core. Higher reagent concentration, co-localization and hydrophobic effects play a central role in the observed catalysis.[19,20]

However, such a prototypical micellar system is limited to low reagent loading. Concentrations lower than 10^{-4} M, far below the saturation concentration, which maintains a single isotropic solution (maximum additive concentration, MAC), are typical of earlier kinetic studies.[21,22] The scope of surfactant-enhanced reactions was later extended toward

synthetically useful applications. Such shift was accompanied by substantial deviations from the aforedescribed micellar model. Formal concentrations of reactants were substantially increased exceeding MAC and thus leading to complex multi-phase systems. As an example, typical experimental conditions involve the use of a 1 to 3 wt % water solution of the surfactant and 0.5 to 1 M formal concentrations of poorly water-soluble reagents resulting in inhomogeneous mixtures as those depicted in Figure 1.

Despite the fact that the extensive literature from the group of prof. Lipshutz and prof. Handa amongst others[23] clearly demonstrated that dealing with a complex multiphase system does not preclude effective surfactant enhanced catalysis, unpredictable behavior is often encountered.[25] These limits often manifest themselves as lack of reproducibility when changing the experimental setup, particularly regarding to the mixing method.[11,23] The use of limited amounts of organic solvents along with mild heating mitigates the problem but does not represent a completely satisfactory solution: processes still rely on organic solvent and no insight on the underlying mechanism is given.[16,17,23,26] In such complex multiphase systems, the surfactant can still form micelles or other aggregates but also lies at the phase boundary, lowering the interfacial tension and allowing the formation of very small, kinetically stable, droplets/particles.[27] Alongside with the bona fide micellar catalysis, other surfactant-mediated processes are also at work. Boyer et al. showed that under biphasic conditions, the catalytic effect of the surfactant can result
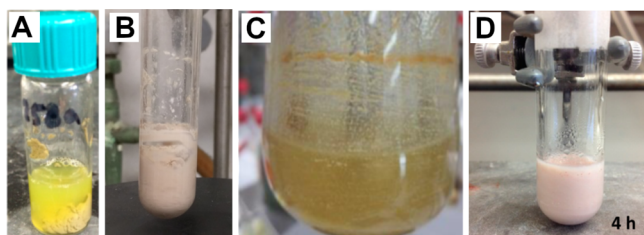
Figure 1. Pictures of relevant micellar reactions reported in the literature. (A) Direct arylation between N-(m-hydroxyphenyl)-N′,N′-dimethylurea, and 4-iodoanisole. Reprinted with permission from ref 16. Copyright 2017 American Chemical Society. (B) Suzuki-Miyaura coupling between BTBT-Br and phenylboronic acid. Reprinted with permission from ref 14. Copyright 2019 Royal Society of Chemistry. (C) Amide bond formation between (S)-N-(benzyloxycarbonyl)-valine and tert-butyl (3R,4S,5S)-3-methoxy-4-(N-methylamino)-5-methylheptanoate hydrochloride. Reprinted with permission from ref 23. Copyright 2016 American Chemical Society. (D) Cross-metathesis reaction between 1-tert-butyldimethylsilyloxy-2-(2-propenyl)benzene and methylvinylketone. Reprinted with permission from ref 24. Copyright 2014 American Chemical Society.

from a combination of interfacial catalysis (IC) and a hybrid inverse phase transfer catalysis (IPTC).[28−30] The latter involves a dual role played by the surfactant: enhancing mass transport of reagents to the water phase and therein promoting the micellar catalysis of the chemical step (Figure 2). This
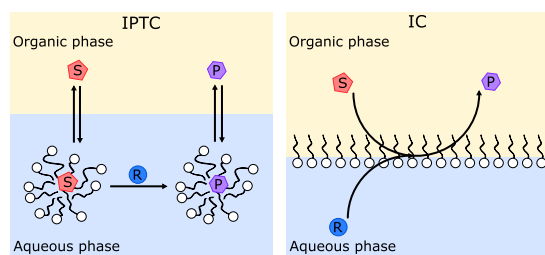

Figure 2. Principles of an inverse phase transfer catalysis (IPTC) and interfacial catalysis (IC) with a surfactant as catalyst (S, substrate; R, reactant; P, product) as described by Boyer et al.[29]

observation highlights the fact that in complex multiphase systems, normal and inverse phase transfer catalysis (PTC, IPTC), micellar catalysis (MC), and interface catalysis (IC) become intertwined phenomena. So far, the capability to form micelles of a certain dimension and aspect ratio guided the selection of the most suitable surfactant for reactions in a water environment. Such features are critical but insufficient: the capability to maintain efficient mass transfer through different phases during the whole chemical process is at least as important.

We here describe a different approach capable of taming capricious reactions without the use of any organic solvent and/or heating. For this purpose, we sampled some particular examples of troublesome coupling reactions carried out on liquid reagents having issues of reproducibility when performed in aqueous surfactant solutions. Once recognized that the true nature of reactions carried out with liquid reagents and a limited amount of surfactant is that of an emulsion, we selected a surfactant mixture specifically devised to better counterbalance the surface tension. In particular, we selected a mixture of two commercially available, food-grade amphiphiles, Tween 80 and L-α-lecithin, known as efficient

emulsifiers for oil spills. Under such conditions, we demonstrate that it is possible to successfully address all reproducibility issues in terms of mixing method in a Suzuki−Miyaura (SM) coupling so tenaciously irreproducible that not even the cosolvent method afforded satisfactory results. We also show that such approach is general, providing excellent results for other reagents featuring similar behavior.

RESULTS AND DISCUSSION

We identified several SM coupling reactions showing reproducibility issues; some of which are shown in Scheme 1 (additional examples and reactions details are listed in Table S1 of the Supporting Information). Differences in the reaction outcome were observed upon modifications in: vessel, stirrer/mixing apparatus, and stirring speed. Among them, the SM coupling of (4-bromophenyl)methyl acetate (1) with 2-thienylboronic acid (shown in heading of Table 1) displays a particularly erratic behavior. Data in the first part of Table 1 (entries 1−8) summarize the results obtained upon systematically varying the mixing setup using either a 2 wt % solution of Kolliphor EL (K-EL) or a 2 wt % solution of the state-of-the-art designer surfactant TPGS-750-M in water as the reaction medium. The choice of such surfactants was dictated by their literature established performance for micellar coupling reactions.[31−33] Comparison among entries 1 to 5 clearly shows that conversion is strikingly influenced by the chosen mixing setup, going from 15 to 80%. However, when the reaction was performed twice using the same setup and stirring speed, consistent results were obtained (entries 4−5). In all of the cases, leaving reactions stirring for more than 3 h did not improve conversions. Not even performing the reaction using the well-known TPGS-750-M surfactant allowed to obtain reproducible results (entries 6−7). Such a dependency of conversions from the mixing method suggests that interphase mass transfer may become rate limiting once massive phase separation occurs during the evolution of reagents into products. This phenomenon appears as the ultimate result of the kinetic instability of the emulsion toward flocculation, coalescence, and creaming.[34] In support of this hypothesis, when we carried out the coupling using an Ultra-Turrax homogenizer that guaranteed thorough mixing, we consistently observed essentially quantitative conversion (entry 8).

As already mentioned, the literature acknowledges that the use of a moderate amount of a cosolvent might be an efficient strategy to tackle such mixing issues in micellar catalysis.[23,26,35,36] Acetone and THF in particular are recognized as efficient cosolvents for the SM coupling.[16] However, such an approach, which remains a valid and resourceful protocol to clear away most of the toxic organic solvents, in our case improved only modestly the behavior of the reaction (entries 9−12) and, at the same time, does not fully honor the commitment to clear away organic solvents.

Once recognized that the reproducibility was dependent on the kinetic stability of the obtained emulsion, we decided to approach the problem using an improved surfactant mixture able to tackle this issue. In particular, taking inspiration from the literature pertaining self-emulsifying systems (i.e., systems requiring very little energy to form fine emulsions),[37,38] we chose to test the Tween 80/L-α-lecithin surfactant mixture. Thanks to their synergistic action, this food-grade amphiphile combination already proved to be an effective and safer alternative to toxic solvent-based dispersants for marine oil spills[39−41] and also found application in drug delivery.[42] We

Scheme 1. Examples of Variable Results Obtained for SM Coupling Reactions of 1, 2, and 3 with 2-Thienylboronic Acid[a]
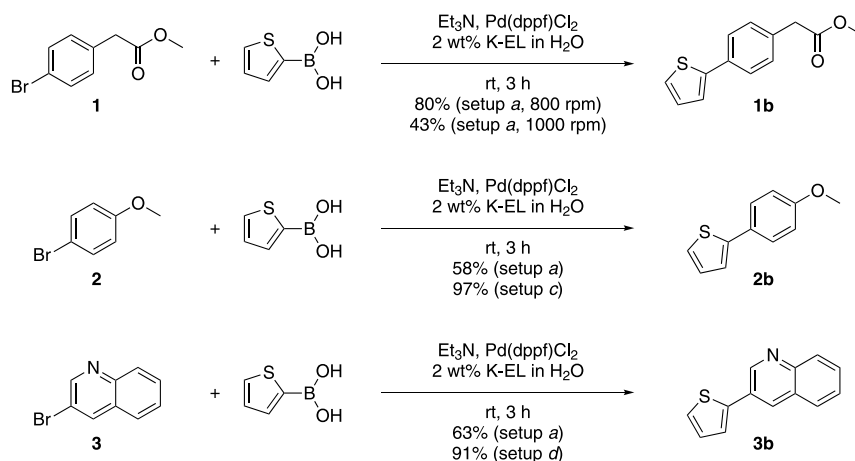
[a]Reaction conditions: 1 M of bromide, 1 M of boronic acid, 1.5 M of Et₃N, 0.02 M of Pd(dppf)Cl₂ in 2 wt % aqueous solution of Kolliphor EL, room temperature, 3 h. Couplings are performed on 2 mmol of bromide, and scale is unvaried in all reactions. Setup a: 10 mL roundbottom test tube (inner diameter: 1.2 cm, height: 9 cm), cylindrical stirrer (2.5 cm length), see Figure S1A. Setup c: 4 mL vial (inner diameter: 1.3 cm, height: 4.4 cm), two piled round stirrers (diameter: 1.0 cm, height: 0.8 cm), see Figure S1C. Setup d: 4 mL vial (inner diameter: 1.3 cm, height: 4.4 cm). Reaction was first homogenized using an Ultra-Turrax high-shear mixer for 10 min at 5000 rpm (see Figure S1D) and subsequently mixed using two piled round stirrers (diameter: 1.0 cm, height: 0.8 cm).

Table 1. SM Coupling of 1 with 2-Thienylboronic Acid Performed with Different Setups and Aqueous Media (Reaction Conditions: 1.0 M of Bromide, 1.0 M of Boronic Acid, 1.5 M of Et₃N, 0.02 M of Pd(dppf)Cl₂, Room Temperature, 3 h)[a]
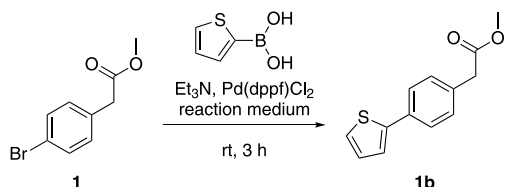
entry	setup	stir. speed (rpm)	reaction medium	conv.
1	a	800	2 wt % K-EL in H₂O	80%
2	a	1000	2 wt % K-EL in H₂O	43%
3	b	800	2 wt % K-EL in H₂O	15%
4	c	1000	2 wt % K-EL in H₂O	65%
5	c	1000	2 wt % K-EL in H₂O	68%
6*	a	800	2 wt % TPGS-750-M in H₂O	50%
7*	a	1000	2 wt % TPGS-750-M in H₂O	67%
8	d	1000	2 wt % K-EL in H₂O	94%
9	a	800	(2 wt % K-EL in H₂O)/THF 9:1	25%
10	a	1000	(2 wt % K-EL in H₂O)/THF 9:1	72%
11	a	800	(2 wt % K-EL in H₂O)/acetone 9:1	70%
12	a	1000	(2 wt % K-EL in H₂O)/acetone 9:1	61%

[a]Setups a, c, and d are described in the caption of Scheme 1. Setup b: 100 mL round bottom test tube (inner diameter: 2.7 cm, height: 20 cm), cylindrical stirrer (2 cm length), see Figure S1B. *, reaction was performed under a N₂ atmosphere.

thus decided to test an aqueous 2 wt % Tween 80/lecithin 8:2 mixture (TL82), suitable to obtain oil-in-water emulsions, as the medium for our troublesome SM coupling. This particular ratio was selected in order to obtain an HLB (hydrophilic lipophilic balance) value similar to that of both Kolliphor EL (with which we already had a vast experience) and TPGS-750-M, the standard in micellar catalysis. Also, lecithin is not water soluble and using mixtures at a higher lecithin content would have led to poor dispersibility in water.

The first striking difference with prior experiments was observed during sample preparation: a simple visual comparison, Figure 3, highlights the superior stability of the emulsion
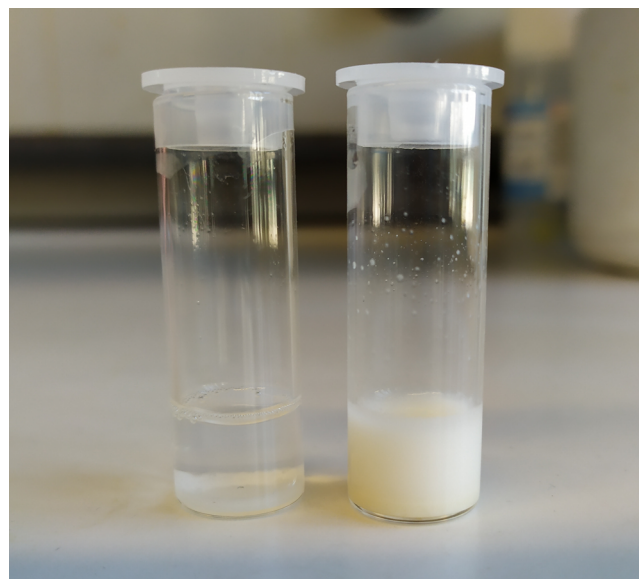

Figure 3. Coalescence of the emulsions of **1** (1 mmol) prepared in 1 mL of a 2 wt % aqueous solution of K-EL (left) and TL82 (right).

of **1** in TL82 versus that obtained in K-EL. While both mixtures were prepared identically and thoroughly mixed with the aid of an ultrasound bath, in the case of K-EL, rapid coalescence occurs and two layers separate. Conversely, a fine and stabler emulsion forms when using TL82, meaning that the surface tension of this system is lower and droplets of organic phase are stabilized more effectively.

Table 2 summarizes results obtained performing the coupling reaction in both aqueous K-EL and TL82 surfactant mixture with two different setups.

Table 2. Conversions for the SM Coupling Shown in Scheme 1 Performed in 2 wt % Aqueous Solution of K-EL or TL82[a]

entry	surfactant	atm	stirring speed (rpm)	conversion (Time)
1	K-EL	air	800	80% (3 h)
2	K-EL	air	1000	43% (3 h)
3	TL82	air	800	90% (1 h)
4	TL82	air	1000	92% (1 h)
5	TL82	N$_2$	800	97% (1 h)

[a]The stirring setup (10 mL round bottom test tube equipped with a cylindrical stirring bar) is unvaried in all reactions.

Reactions performed in TL82 do not show the reproducibility issues previously observed with K-EL and TPGS-750-M, with the conversion rising to 90% in 1 h when working under air unregarding to the mixing setup used to perform the reaction (entries 3−4). Employing such a self-emulsifying system allows obtaining an emulsion whose features are essentially independent from the mixing method due to the reduced surface tension. The observed higher catalytic activity is also believed to be a consequence of the formation of a finer and stable emulsion and unhindered interphase mass transport.

Performing the reaction under an inert atmosphere allowed reaching an even higher 97% conversion (entry 5). This last result was expected, as environmental oxygen is a known poisoning agent for the Pd(0) catalyst involved in the reaction.

To exclude an effect of ionic interactions between 2-thienyl boronate and lecithin (due to its zwitterionic nature) in the observed reaction behavior, we also performed the coupling using a K-EL/lecithin 8:2 mixture, which does not have self-emulsifying capabilities. With this surfactant mixture, the

reaction gave again unreliable results (see Table S2 in the Supporting Information).

As the emulsifying capabilities of the TL82 mixture proved suitable to both overcome the reproducibility issues of the chosen test coupling and to improve the reaction conversion, we decided to test its performance on other substrates featuring a similar behavior. We therefore performed the coupling reaction of 2-thienylboronic acid with other aryl bromides: 4-bromoanisole (**2**), 3-bromoquinoline (**3**), and 3-bromothiophene (**4**). Scheme 2 summarizes the obtained results.

In all of the cases, reactions performed using the K-EL surfactant did not exceed 65% conversion after 3 h. Using the TL82 surfactant mixture, we obtained quantitative conversion in the case of substrates **2** and **4** in just 1 h and 94% conversion for substrate **3** in 3 h. As observed for substrate **1**, the use of TL82 allows to obtain higher conversions in a shorter time. Preliminary results show that the TL82 can be successfully applied in the Sonogashira and Heck couplings as well (see Scheme S1 of the Supporting Information). In terms of stability under the reaction conditions required by the various cross couplings we tested, the TL82 mixture appears to be suitably robust (see Section 5 of the Supporting Information). Indeed, lecithin itself is reported to be particularly stable at high pH levels and in the absence of oxygen. Such conditions are very similar to those that we employed in our reactions.[43−45]

Finally, we tested the robustness toward scaling up of our protocol by performing the coupling reaction of **1** with 2-thienylboronic acid on 10 g reagents (a 14-fold increase in the scale) in a round-bottom flask and using a mechanic stirrer under otherwise identical conditions to Table 2, entry 5 test. Upon the addition of Et$_3$N, the initial biphasic mixture turned into a homogeneous emulsion (Figure 4), and the reaction spontaneously warmed up to 35 °C over 10 min. We achieved complete conversion within 1 h and isolated the target

Scheme 2. Conversions Obtained for the Coupling Reaction between 2, 3, and 4 with 2-Thienylboronic Acid (1 M of Bromide, 1 M of Boronic acid, 1.5 M of Et$_3$N, 0.02 M of Pd(dppf)Cl$_2$, Room Temperature) in 2 wt % Surfactant Solution of K-EL or TL82[a]
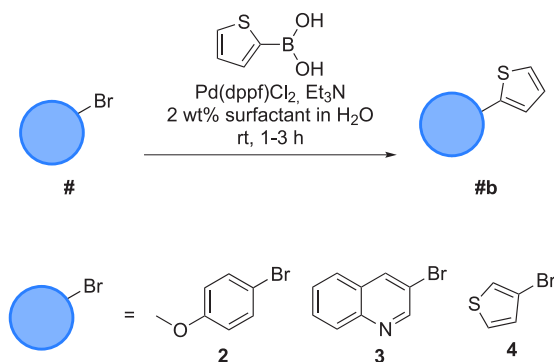
Entry	Product	Surfactant	Conversion (Time)
1	**2b**	K-EL	58% (3 h)
2	**2b**	TL82	100% (1 h)
3	**3b**	K-EL	63% (3 h)
4	**3b**	TL82	94% (3 h)
5	**4b**	K-EL	60% (3 h)
6	**4b**	TL82	100% (1 h)

[a]Reactions performed with TL82 surfactant were run under a N$_2$ atmosphere. The stirring setup (10 mL roundbottom test-tube equipped with a cylindrical stirring bar, stirring speed of 800 rpm) is unvaried in all reactions.
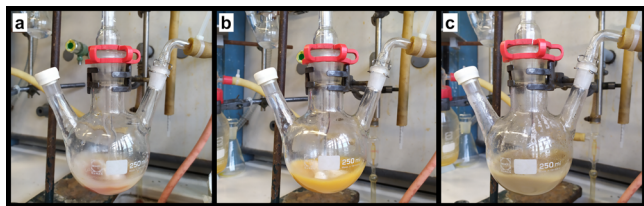
Figure 4. SM coupling of **1** with 2-thienylboronic on a 10 g scale. (a) Reaction mixture appearance before the addition of Et_3N. (b) Reaction mixture appearance 1 min after the addition of NEt_3. (c) Reaction mixture appearance 1 h after the addition of Et_3N.

compound in 97% yield. Lowering the catalyst amount to 1.5 and 1 mol % of $Pd(dppf)Cl_2$ gave 83 and 78% conversion, respectively, after 3 h. The literature reports examples of catalysts that are far more effective than the commercially available one we selected. In particular, Liphshutz et al. and Handa et al. demonstrated the possibility to carry out SM and Sonogashira reactions at ppm levels of Pd.[46,47] Such a solution also represents the ideal strategy to reduce possible palladium contamination in the product, a problem we intentionally did not address in this paper. We here focus only on demonstrating that the TL82 mixture enables running efficient SM coupling on otherwise troublesome substrates even in the large scale.

Concerned about the possible hazards connected with the exothermic behavior we observed, we repeated the reaction three more times on the same scale, with the same setup and at 2 mol % catalyst loading. The first repetition was performed working identically but with a thermometer inserted in the reaction mixture (previously, we monitored the temperature of the reactor's walls by means of an IR scanner). The maximum temperature reached was 50 °C, and conversion was again quantitative after 1 h. In the second repetition, we added the base dropwise over a period of 10 min while keeping the reactor immersed in a water bath. In this case, we did not measure any appreciable raise in the temperature, yet we noted that such a slow addition is not helpful for the homogeneity of the reaction mixture. Lumps of sticky material formed, which were difficult to redisperse. The conversion was 72%, and the isolated yield was 68%. In the third repetition, we studied the effect of the slow addition of the catalyst. While setting up the reaction, we added the base all at once to the emulsion of bromide and boronic acid. We noticed that just after the addition of the base and prior to the introduction of any catalyst, the reaction warmed up to almost 40 °C, meaning that most of the exothermic effect is connected with the acid–base reaction of the boronic acid with the base. This observation reduces the concerns for possible decompositions reactions leading to runaway thermal effects. Once back at room temperature, we added the catalyst over a period of 10 min. Again, we observed some demixing while doing so. The conversion was 84%, and the isolated yield was 82%. Puzzled by the partial demixing effect observed in both cases, we heated samples taken from the second and third repetitions at 50 °C by external heating, thereby restoring a homogeneous, freely stirring emulsion. Our observations suggest that reaching a temperature around 50 °C in the early stage of the reaction is helpful in maintaining a homogeneous emulsion (well in agreement with the fact that emulsions are easier to form at high temperatures).

CONCLUSIONS

Micellar reactions carried out at formal concentrations vastly exceeding MAC are strongly impacting the sustainability of a vast number of chemical transformations including cross-couplings. We have faced the known issue of lack of reproducibly, particularly when changing the experimental setup and reaction scale, from a different perspective with respect to the existing literature. Whereas the general consensus to tame problematic micellar reactions requires the use of an organic cosolvent, we focused our attention on the details of the formulation state of the reaction mixture and carefully tuned the tenside cocktail accordingly. Above MAC, micellar reactions are complex heterogeneous mixtures where micellar catalysis coexists with other catalytic mechanisms like IC and IPTC. The mass transfer between emulsion droplets, dispersed particles, and micelles dominates the reaction behavior to the point that the capability of a given surfactant to assemble into micelles of a certain shape and/or volume has only a limited impact on the overall conversion. On the other hand, the capability of the tensides to efficiently and rapidly emulsify the oil phase maximizing the contact area of all interphases becomes the limiting step. Indeed, we show that the use of a Tween 80/L-α-lecithin surfactants mixture, a system well-known to readily provide finely dispersed emulsion of the most hostile hydrophobes, leads to satisfactory results in a number of S–M couplings where other commercial and designer surfactants failed, even in the presence of cosolvents. Even more importantly, all reactions proved to be insensible to setup parameters like the stirring speed and reaction scale, generally heavily impacting on standard micellar protocols. Our findings clearly show that the capability of a given surfactant to self-assemble into micelles with given characteristics does not necessarily grant success in all reactions. Above MAC, the true nature of the reactive formulation at hand requires balancing of interface tension between complex pseudo phases, thus favoring the selection of high surface pressure tensides. Our approach is general, do not require the use of any organic solvent and is based on industrially scaled, food grade surfactants.

EXPERIMENTAL DETAILS

General Information. All reagents, $Pd(dppf)Cl_2$, and $Pd(dtbpf)Cl_2$ catalysts were bought from Fluorochem. [Pd-(cinnamyl)Cl]$_2$, surfactants, and solvents were bought from Sigma-Aldrich. L-α-Lecithin (95%) was bought from Nutritional Biochemical Corporation. For reactions performed under anaerobic environment, water was carefully deoxygenated before use by bubbling N_2 under reflux for 3 h, and Et_3N was carefully deoxygenated by freeze–pump–thaw degassing.

Reaction conversions were quantified by gas chromatography–mass spectroscopy (GC–MS) or ^1H NMR. For reactions performed on substrates **1**, **2**, and **3**, composition of reaction mixtures was quantified by quantitative GC–MS through peak integration based on the response factor method (see the Supporting Information for details). For reactions performed on other substrates, composition of reaction mixtures was quantified by ^1H NMR.

General Procedure for Small-Scale Reactions. Unless when otherwise stated, reactions were performed in a round bottom test tube (10 mL volume, available from CEM Corporation) equipped with a cylindrical stirring bar and under a standard laboratory atmosphere (setup a shown in

Figure S1A of the Supporting Information). In a typical procedure, bromide (2 mmol), boronic acid (2 mmol), and Pd(dppf)Cl$_2$ (0.04 mmol) were weighted in the vessel and 2 mL of the chosen surfactants solution was added under stirring. After 5 min, Et$_3$N (3 mmol) was added. The reaction mixture was stirred for 3 h and subsequently diluted with CH$_2$Cl$_2$, filtered through a pad of silica and submitted to GC−MS characterization.

Scaled-up Synthesis of 1b. The reaction was performed in a 250 mL three-necked round bottom flask equipped with a mechanical stirrer and a thermometer. 2-Thienyl boronic acid (3.583 g, 28.00 mmol) and Pd(dppf)Cl$_2$ (410 mg, 0.560 mmol) were weighted in the flask, which was subsequently put under a N$_2$ atmosphere. Methyl-4-bromophenylacetate (6.414 g, 28.00 mmol) and degassed TL82 surfactant mixture (28 mL) were subsequently added. The mixture was stirred at 300 rpm for 5 min before the addition of degassed Et$_3$N (5.9 mL, 42 mmol). The reaction spontaneously warmed up to 50 °C over 10 min. The reaction was stirred for 1 h. Excess bromide was steam distilled from the reaction mixture by means of a Claisen distillation apparatus. During the distillation, the volume of the reservoir was kept constant at 100 mL by constant addition of water. The composition of both the distillate and the mixture was monitored constantly by GC−MS. When no bromide was left in the reservoir, the mixture was cooled at 4 °C and the precipitate thus formed was isolated by suction filtration, washed thoroughly on the filter with water and dried till constant weight: 6.302 g, 27.1 mmol, 96.9% (m.p. 50−51 °C). The raw material was submitted to NMR characterization. Further purification was performed by evaporative distillation (water bath, 90 °C, 0.02 mbar) using a standard sublimation apparatus (m.p. 54−55 °C). The NMR spectra of the raw and sublimed materials (Figure S2) are nearly identical. ^{1}H NMR (400 MHz, CDCl$_3$): δ [ppm] 7.57 (d, J = 8.3 Hz, 2H), 7.30−7.26 (m, 4H), 7.07 (dd, J = 5.1, 3.6 Hz, 1H), 3.71 (s, 3H), 3.64 (s, 2H).

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00285.

Pictures of mixing setups, additional reactions, E factor of the scaled-up synthesis of **1b**, assessment of TL82 stability under working conditions, micrographs of the emulsion of **1** in aqueous TL82 (PDF)

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Notes

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