

# Surfactant-Dependent Partitioning of Organics in Aqueous–Organic Reaction Systems

Yiqing Zhang and Suzanne A. Blum<sup>\*[a]</sup>

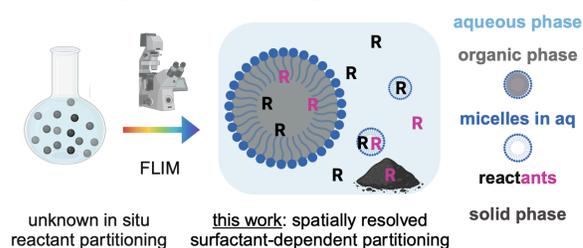
[a] Y. Zhang and Prof. S. A. Blum  
Chemistry Department  
University of California, Irvine  
Irvine, CA 92697-2025 (USA)  
E-mail: blums@uci.edu

Supporting Information Placeholder

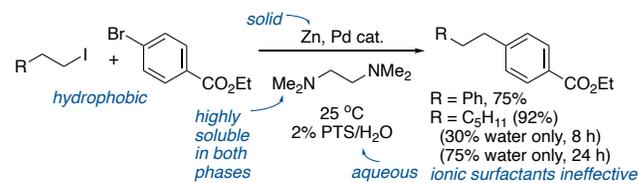
**ABSTRACT:** Performing organic reactions in water provides environmental and toxicity advantages compared to in organic solvents, but such strategies are still evolving, limited by current understanding of these multiphasic systems. Here, a fluorescence lifetime imaging microscopy (FLIM) technique characterizes surfactant-dependent partitioning of organics in a system that mimics the early, zinc-related steps of a Negishi-like cross-coupling reaction in water, under synthetically relevant high concentrations of substrate (0.18 M), where large emulsion droplets (5–20  $\mu\text{m}$ ) form an organic phase. Brij-30 resulted in the highest degree of partitioning of organics in the aqueous phase, which was not predictable from simple hydrophilic–lipophilic balances (HLB). The ionic surfactant CTAC suppressed reactivity of the metallic zinc surface with both neutral (TMEDA) and anionic (carboxylate) reactants, presumably through competitive chloride binding and concurrent cetrimonium coating, a finding that may contribute to the reduced performance of ionic surfactants in the bench-scale coupling reaction.

In order to react, reactants must be colocalized. Thus, the understanding of partitioning in multiphasic reaction systems underpins targeted reaction progress. Water–surfactant emulsions provide a promising and sustainable medium for performing organic chemistry, while avoiding the toxicity associated with organic solvents<sup>1–3</sup> and have been applied in highly impactful applications from academic to agrochemical to pharmaceutical synthesis.<sup>4–15</sup> Unpredictable or irreproducible behavior, however, is currently limiting progress.<sup>16,17</sup> The complexity of these systems has so far restricted understanding of partitioning and thus of valuable mechanistic insight that may arise to overcome irreproducibility challenges and aid in the development of broader applications (Figure 1a).

a. Sustainable organic chemistry in water generates complicated emulsions



b. Inspiration: Multiphasic Negishi-like cross-couplings in water (Lipshutz 2009)



**Figure 1. a.** Knowledge gap bridged through analytical method development. **b.** Negishi-like cross-coupling reaction in water.

With the high concentrations of substrates (0.1–1 M) and surfactants (1–3 wt%) employed under synthetic conditions, phase separation occurs:<sup>14,18,19</sup> Larger emulsion droplets (organic phase) contain high concentrations of organic substrates and surfactant, and likely some water;<sup>18,19</sup> simultaneously, the aqueous phase may contain dispersed, individual micelles with organic substrates and interior water,<sup>20,21</sup> or free organics. The mixed composition of both phases makes the concept of phase distinction more complex. Both discrete micelles and emulsion droplets have been previously imaged in situ in systems containing representative reaction components, providing support for these species under reaction conditions.<sup>22,23</sup> Reactions can plausibly occur in both phases;<sup>24</sup> thus, in any given system, it remains mechanistically unclear which reaction steps occur where. While higher

concentrations of reagents in a given phase (thermodynamics) does not dictate that the reaction occurs in that phase (kinetics), partitioning data provides a robust starting point for improving reaction models.

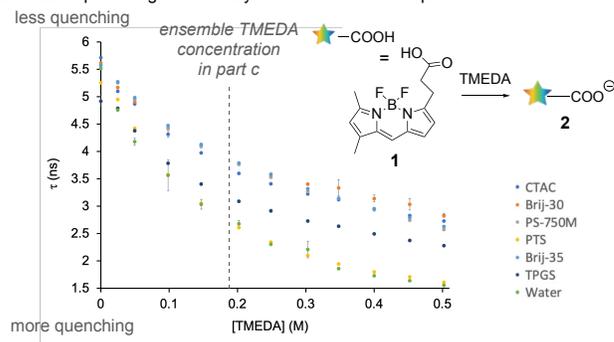
Traditional analytical methods (e.g., NMR, UV-vis spectroscopy) fail at measuring partitioning of reagents due to ensemble averaging, lack of spatial resolution, and/or insufficient measurement ability under the highly concentrated conditions of synthetic reactions, which produce phase-separated, frothy, opaque emulsions.<sup>25–28</sup> Calculation-based models<sup>18,29</sup> are similarly restricted because they lack robust experimental data to employ as starting points.

We became interested in exploring if fluorescence lifetime imaging microscopy (FLIM)<sup>22,23</sup> could address this gap in partitioning/localization knowledge by offering: 1) spatial resolution to differentiate emulsion droplets, from aqueous phases, from solids, 2) production of a signal indicating composition, 3) operation close to native synthetic conditions (including not requiring synthesis of labeled versions of reactants or surfactants, and high concentrations), and 4) time resolution suitable for in situ monitoring of system evolution. It is important to note that the technique does not distinguish location between organics dissolved in the aqueous phase inside of micelles and dissolved in the aqueous phase outside of micelles, but rather distinguishes partitioning between the bulk organic phase (emulsion droplets) and aqueous phase.

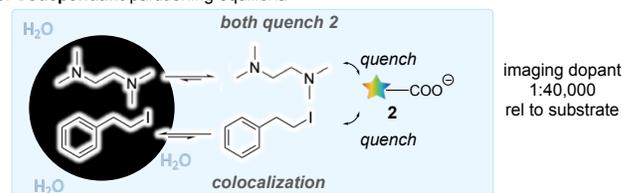
A Negishi-type cross-coupling reaction in water developed by Lipshutz served as inspiration for initial studies (Figure 1b).<sup>5,30</sup> This reaction contained three phases: an organic phase, an aqueous phase, and solid metallic zinc powder. The initial report identified PTS and other nonionic surfactants as viable, and noted that reactions also proceeded in pure water in the absence of surfactant, albeit more slowly (reaching full consumption of substrate only after 24 h rather than 8 h).<sup>5</sup> The reasons for surfactant-dependent outcomes remained, however, poorly understood. These reactions progress through organozinc intermediates, which are typically hydrolytically unstable; the stability was attributed in part to the chelation of the tetramethyl ethylene diamine (TMEDA) to the presumptive organozinc intermediate.<sup>5,31,32</sup> Thus, the surfactant's impact on colocalization of TMEDA, organoiodide, and zinc, are relevant factors.

The FLIM strategy employed BODIPY imaging agent **1**, harnessing its quenching, and thus change in fluorescence lifetime ( $\tau$ ), in the presence of TMEDA and/or 2-iodoethylbenzene (Stern–Volmer constants: TMEDA = 6.8, 2-iodoethylbenzene = 4.3). Six surfactants commonly employed in synthetic reactions (PS-750M, Brij-35, CTAC, Brij-30, TPGS, PTS) at 1.8 wt% in water, and pure water were evaluated, at concentrations akin to those reported by Lipshutz.<sup>5,30</sup>

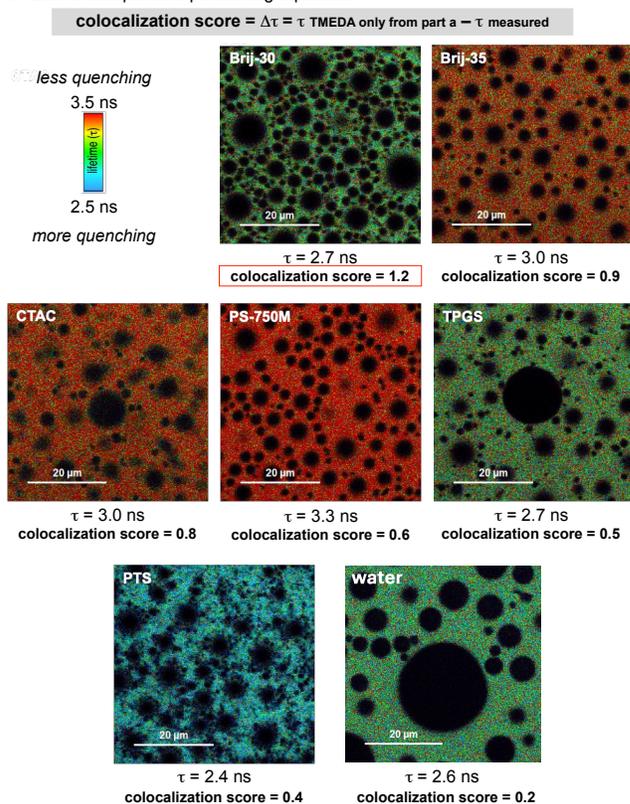
**a. TMEDA quenching of 1 and 2 yields concentration-dependent  $\tau$**



**b. Codependant partitioning equilibria**



**c. FLIM of codependant partitioning equilibria.**



**Figure 2.** **a.** TMEDA-only quenching of **1** and **2**. **b.** TMEDA increases solubility of 2-iodoethylbenzene in water, leading to codependant partitioning. **c.** FLIM images with ensemble concentrations 0.18 M TMEDA, 0.42 M 2-iodoethylbenzene,  $0.96 \times 10^{-6}$  M **1**.

Fluorescence lifetimes of BODIPY fluorophore **1**, and of its water-soluble TMEDA-deprotonated analog **2**, quantitatively correlated with TMEDA concentration, as

determined by FLIM (Figure 2a). The degree of quenching was found to be surfactant-dependent even at 0 M TMEDA, a finding attributed to differing microenvironments caused by the surfactants, but accounted for within each calibration curve. Calibration data were fit, allowing interpolation of  $\tau$  for TMEDA concentrations between measured data points. Under these substrate-free conditions, no emulsion droplets were observed during imaging, presumably due to the alternative presence of only (smaller) micelles in the aqueous phase.

Next, a successful substrate from Negishi-like cross-couplings, 2-iodoethylbenzene, was added, reaching ensemble concentrations of 0.18 M TMEDA, 0.42 M 2-iodoethylbenzene, and  $0.96 \times 10^{-6}$  M **1** (Figure 2b). At this low doping of  $\sim$ 1:40,000 imaging agent–substrate, **1** is not expected to significantly alter the system, but rather serve as a spectator that informs on the partitioning of other components through its variable fluorescence lifetime. As shown in Figure 2c, these conditions produced large, dark emulsion droplets (“the bulk organic phase”), with fluorescent BODIPY carboxylate **2** preferentially partitioned in the aqueous phase, as demonstrated by the bright region outside of the droplets.

Now, the fluorescence lifetime of the aqueous phase was a combined result of the TMEDA partitioning (previously measured as a standalone in Figure 2a) plus the 2-iodoethylbenzene partitioning (nonpolar and nonhydrogen bonding, and thus expected to strongly partition into the emulsion droplets in the absence of codependent effects of additional reagents and surfactant on aqueous phase properties).

A “colocalization score” was defined as the difference in  $\tau$  (caused by increased quenching) that occurred when both 2-iodoethylbenzene and TMEDA were present, compared to that with TMEDA alone (i.e., colocalization score =  $\Delta\tau = \tau_{\text{TMEDA only}} - \tau_{\text{measured TMEDA and 2-iodoethylbenzene}}$ ).

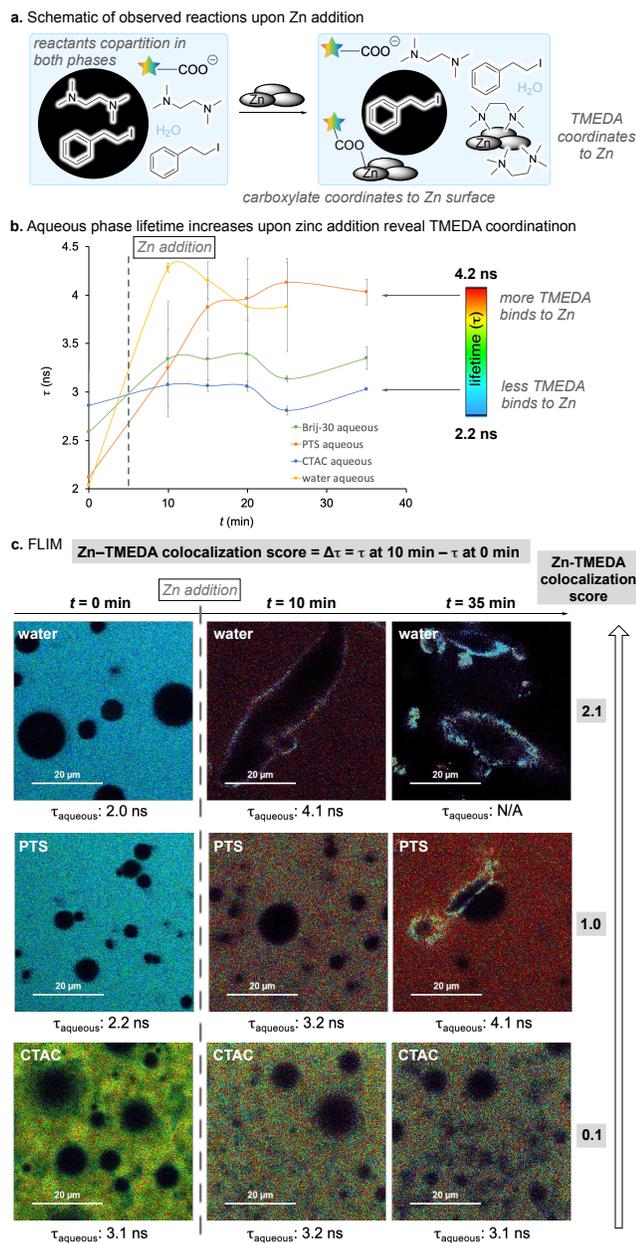
With this definition, a higher colocalization score corresponded to more 2-iodoethylbenzene in the aqueous phase and thus more colocalization with TMEDA, and by mass balance, to less 2-iodoethylbenzene in the bulk organic phase/droplet interiors. In contrast, a lower colocalization score corresponded to the less colocalization of TMEDA and 2-iodoethylbenzene in the aqueous phase and more 2-iodoethylbenzene in the organic phase. Data in Figure 2c show that all aqueous phases exhibited more quenching than with TMEDA alone, as demonstrated by positive colocalization scores (0.2–1.2), characterizing solubility of 2-iodoethylbenzene. Limitations of the FLIM approach included that  $\tau$  provided a composite effect from all possible quenching reactants rather than enabling teasing out quantitative contributions from each.

A significance of this data is that surfactants do not just stabilize the emulsion droplets, but also substantially impact phase composition through partitioning adjustments. The trend of decreasing colocalization scores of Brij-35, PS-750 M, TPGS, and PTS (0.9-to-0.4) indicated

increasing amounts of 2-iodoethylbenzene partitioned out of the aqueous phase and in the organic phase, which generally matched the increasing lipophilicity of the surfactants as estimated by their respective hydrophilic–lipophilic balances (HLB).<sup>33</sup> Brij-30, with the smallest HLB and the most lipophilic affinity, however, was an exception to this trend and instead exhibited the highest colocalization score, corresponding to the least 2-iodoethylbenzene partitioning in the organic phase. This exception, and the lack of HLB analysis to account for backbone polarity,<sup>2,34,35</sup> underscore the importance of a measurement technique rather than a simple HLB theoretical approach.

Notably, the colocalization scores for PTS (0.4) and pure water (0.2)—the conditions reported by Lipschutz<sup>5,30</sup>—differed slightly, with pure water exhibiting the lowest colocalization score and less reactants dissolved in the aqueous phase and thus more (co)dissolved in the organic phase, as expected for the medium with the most distinction in hydrophilicity/lipophilicity between its phases. Yet, the overall reaction was reported to be slower in pure water than in PTS. Given this partitioning data, a possible interpretation of the bench-scale reaction outcome is that in pure water, the organics are primarily colocalized in the emulsion droplets, where overall chemical reaction is slower. In PTS, the organics may be distributed between emulsion droplets (slower reaction) and micelles in aqueous phase (faster reaction), resulting in an overall faster chemical reaction. The reasons for such kinetic differences remain unknown and lie outside the scope of the current partitioning study. The extent to which such a model may assist in broader understanding of bench-scale yields with many different surfactants, beyond the reported PTS and water comparison,<sup>5,30</sup> remains to be explored.

Next, the partitioning at the zinc solid–solution interface was examined (Figure 3a). Under oxygen-free conditions, TMEDA, 2-iodoethylbenzene, and imaging agent **1** were added to four systems: two nonionic surfactants (Brij-30 and PTS), ionic CTAC, or pure water. The reactions were stirred to mix, and imaged by FLIM ( $t = 0$ ). Then, zinc powder was added at  $t = 5$  min, the reactions were stirred, and then monitored with time in the absence of further stirring. Figure 3b shows FLIM images from select timepoints for three of four systems; standard deviations derive from duplicate experiments, showing reproducibility of trends.



**Figure 3.** a. Schematic of reactions after the addition of zinc. b. Zinc scavenging of TMEDA is time- and surfactant-dependent. c. FLIM images.

An immediate increase in fluorescence lifetime (red shift) in the aqueous phases of PTS, Brij-30, and in water occurred upon zinc addition, attributed to unexpected substantial scavenging of the TMEDA from the aqueous phase and its coordination onto the zinc solids (Figure 3c). In contrast, the ionic surfactant CTAC appeared to inhibit TMEDA coordination, plausibly through competitive chloride coordination to zinc with concurrent cetyltrimonium surface coating, as visible by the consistent green color of the FLIM images at all timepoints. Consistent with the idea that cetyltrimonium coating plays a role in this surface passivation, a comparison experiment in

which NaCl was added to PTS did not result surface passivation, but addition of Bu<sub>4</sub>NCl did result in passivation.

To compare the surfactant-dependent degree of TMEDA scavenging by zinc, a zinc-TMEDA colocalization score was defined as  $\Delta\tau = \tau_{10 \text{ min}} - \tau_{0 \text{ min}}$  no zinc. Comparison of PTS and pure water showed that water had a higher Zn-TMEDA colocalization score (2.1 vs 1.0), indicating that TMEDA was scavenged at a somewhat faster rate in water, whereas CTAC remained near unchanged (0.1), indicative of its lack of scavenging.

A series of control experiments under otherwise similar conditions with zinc but in the absence of the 2-iodoethylbenzene showed similar FLIM changes (or lack of changes), demonstrating that the lifetime effects were not caused by reaction between 2-iodoethylbenzene and zinc. An additional control series, but to which zinc was not added, remained at constant  $\tau$ .

Finally, at  $t = 35 \text{ min}$ , coordination of **2** was substantial on the surfaces of zinc in pure water and PTS, as observed by the bright blue/green outlines of zinc particles. Consistent with the conclusion that CTAC passivates the zinc surface against additional coordination, coordination of **2** with time did not occur in the CTAC system: the outlines of the zinc particles remain unobservable.

The dramatic difference in reactions of the zinc surface in the presence of the ionic surfactant CTAC may contribute to the inefficiency of bulk reaction outcomes with ionic surfactants as previously reported by Lipschutz,<sup>5,6</sup> but alternative causes cannot currently be ruled out.

In conclusion, colocalization of reactants is strongly impacted by surfactant selection and co-reactant presence and is characterizable by FLIM. Water-soluble organic cosolvents (e.g., acetone, THF, or acetonitrile) commonly added to synthetic systems may behave similarly to TMEDA by increasing solubility of organic substrates into the aqueous phase,<sup>17</sup> setting up additional opportunities for competing reactions both inside emulsion droplets and inside micelles<sup>18</sup> that may ultimately occur with different rates and selectivities; reaction reproducibility<sup>15</sup> may thus depend on the relative stability and homogeneity of these micellar (aqueous phase) and droplet (organic phase) species. Brij-30 resulted in the highest colocalization of organics in the aqueous phase, in contrast to that predicted from a simple HLB analysis, highlighting the importance of an experimental—rather than strictly theoretical—approach. The passivation of the zinc surface by CTAC toward both TMEDA and **2** may reflect broader passivation against reactants and thus underpin the reported failure of ionic surfactants in the bench-scale cross-coupling.<sup>5</sup> These findings contribute mechanistic understanding to surfactant selection in sustainable reaction systems in water.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge.

Detailed experimental procedures and replicate fluorescence microscopy data (PDF)

## AUTHOR INFORMATION

### Corresponding Author

**Suzanne A. Blum** – Department of Chemistry, University of California, Irvine, Irvine, California 92697-2025, United States; orcid.org/0000-0002-8055-1405; Email: [blums@uci.edu](mailto:blums@uci.edu)

### Author

**Yiqing Zhang** – Department of Chemistry, University of California, Irvine, Irvine, California 92697-2025, United States; orcid.org/0000-0002-5404-4629.

## ACKNOWLEDGMENT

The authors thank the National Institutes of Health (R01GM131147) and the University of California, Irvine (UCI) for funding. Figures were created with BioRender.

## REFERENCES

- Buono, F.; Nguyen, T.; Qu, B.; Wu, H.; Haddad, N. Recent Advances in Nonprecious Metal Catalysis. *Org. Process Res. Dev.* **2021**, *25* (7), 1471–1495. <https://doi.org/10.1021/acs.oprd.1c00053>.
- Kincaid, J. R. A.; Wong, M. J.; Akporji, N.; Gallou, F.; Fialho, D. M.; Lipshutz, B. H. Introducing Savie: A Biodegradable Surfactant Enabling Chemo- and Biocatalysis and Related Reactions in Recyclable Water. *J. Am. Chem. Soc.* **2023**, *jacs.2c13444*. <https://doi.org/10.1021/jacs.2c13444>.
- Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. Catalytic Organic Reactions in Water toward Sustainable Society. *Chem. Rev.* **2018**, *118* (2), 679–746. <https://doi.org/10.1021/acs.chemrev.7b00417>.
- Pang, H.; Hu, Y.; Yu, J.; Gallou, F.; Lipshutz, B. H. Water-Sculpting of a Heterogeneous Nanoparticle Precatalyst for Mizoroki–Heck Couplings under Aqueous Micellar Catalysis Conditions. *J. Am. Chem. Soc.* **2021**, *143* (9), 3373–3382. <https://doi.org/10.1021/jacs.0c11484>.
- Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. Zn-Mediated, Pd-Catalyzed Cross-Couplings in Water at Room Temperature Without Prior Formation of Organozinc Reagents. *J. Am. Chem. Soc.* **2009**, *131* (43), 15592–15593. <https://doi.org/10.1021/ja906803t>.
- Duplais, C.; Krasovskiy, A.; Lipshutz, B. H. Organozinc Chemistry Enabled by Micellar Catalysis. Palladium-Catalyzed Cross-Couplings between Alkyl and Aryl Bromides in Water at Room Temperature. *Organometallics* **2011**, *30* (22), 6090–6097. <https://doi.org/10.1021/om200846h>.
- Ceriani, C.; Pallini, F.; Mezzomo, L.; Sassi, M.; Mattiello, S.; Beverina, L. Micellar Catalysis beyond the Hydrophobic Effect: Efficient Palladium Catalyzed Suzuki–Miyaura Coupling of Water and Organic Solvent Insoluble Pigments with Food Grade Surfactants. *Journal of Organometallic Chemistry* **2022**, *962*, 122267. <https://doi.org/10.1016/j.jorganchem.2022.122267>.
- Handa, S.; Wang, Y.; Gallou, F.; Lipshutz, B. H. Sustainable Fe–Ppm Pd Nanoparticle Catalysis of Suzuki–Miyaura Cross-Couplings in Water. *Science* **2015**, *349* (6252), 1087–1091. <https://doi.org/10.1126/science.aac6936>.
- Handa, S.; Smith, J. D.; Hageman, M. S.; Gonzalez, M.; Lipshutz, B. H. Synergistic and Selective Copper/Ppm Pd-Catalyzed Suzuki–Miyaura Couplings: In Water, Mild Conditions, with Recycling. *ACS Catal.* **2016**, *6* (12), 8179–8183. <https://doi.org/10.1021/acscatal.6b02809>.
- Sanzone, A.; Mattiello, S.; Garavaglia, G. M.; Calascibetta, A. M.; Ceriani, C.; Sassi, M.; Beverina, L. Efficient Synthesis of Organic Semiconductors by Suzuki–Miyaura Coupling in an Aromatic Micellar Medium. *Green Chem.* **2019**, *21* (16), 4400–4405. <https://doi.org/10.1039/C9GC01071H>.
- Mattiello, S.; Rooney, M.; Sanzone, A.; Brazzo, P.; Sassi, M.; Beverina, L. Suzuki–Miyaura Micellar Cross-Coupling in Water, at Room Temperature, and under Aerobic Atmosphere. *Org. Lett.* **2017**, *19* (3), 654–657. <https://doi.org/10.1021/acs.orglett.6b03817>.
- Fleck, N.; Thomas, R. M.; Müller, M.; Grimme, S.; Lipshutz, B. H. An Environmentally Responsible Route to Tezacaftor, a Drug for Treatment of Cystic Fibrosis Prepared in Water via Ppm Au Catalysis as Entry to 2-Substituted Indoles. *Green Chem.* **2022**, *24* (17), 6517–6523. <https://doi.org/10.1039/D2GC01828D>.
- Takale, B. S.; Thakore, R. R.; Irvine, N. M.; Schuitman, A. D.; Li, X.; Lipshutz, B. H. Sustainable and Cost-Effective Suzuki–Miyaura Couplings toward the Key Biaryl Subunits of Arylex and Rinskor Active. *Org. Lett.* **2020**, *22* (12), 4823–4827. <https://doi.org/10.1021/acs.orglett.0c01625>.
- Adamik, R.; Buchholz, B.; Darvas, F.; Sipos, G.; Novák, Z. The Potential of Micellar Media in the Synthesis of DNA-Encoded Libraries. *Chemistry A European J* **2022**, *28* (20), e202103967. <https://doi.org/10.1002/chem.202103967>.
- Yu, T.; Pang, H.; Cao, Y.; Gallou, F.; Lipshutz, B. H. Safe, Scalable, Inexpensive, and Mild Nickel-Catalyzed Migita-Like C–S Cross-Couplings in Recyclable Water. *Angew Chem Int Ed* **2021**, *60* (7), 3708–3713. <https://doi.org/10.1002/anie.202013017>.
- Ceriani, C.; Ghiglietti, E.; Sassi, M.; Mattiello, S.; Beverina, L. Taming Troublesome Suzuki–Miyaura Reactions in Water Solution of Surfactants by the Use of Lecithin: A Step beyond the Micellar Model. *Org. Process Res. Dev.* **2020**, *24* (11), 2604–2610. <https://doi.org/10.1021/acs.oprd.0c00285>.
- Fox, R.; Bailey, D.; Obligation, J.; Borlinghaus, N.; Braje, W.; Li, X.; Mukherjee, S.; Schoen, A.; Towne, T.; Vukelic, S. *A Chemistry in Water Reproducibility Study: Learnings from a Pre-Competitive, Multi-Company Collaboration*; preprint; Chemistry, 2023. <https://doi.org/10.26434/chemrxiv-2023-mgww0>.
- Andersson, M. P.; Gallou, F.; Klumphu, P.; Takale, B. S.; Lipshutz, B. H. Structure of Nanoparticles Derived from Designer Surfactant TPGS-750-M in Water, As Used in Organic Synthesis. *Chemistry A European J* **2018**, *24* (26), 6778–6786. <https://doi.org/10.1002/chem.201705524>.
- Long, J. A.; Rankin, B. M.; Ben-Amotz, D. Micelle Structure and Hydrophobic Hydration. *J. Am. Chem. Soc.* **2015**, *137* (33), 10809–10815. <https://doi.org/10.1021/jacs.5b06655>.
- Boyer, B.; Hambarzumian, A.; Roque, J.-P.; Beylerian, N. Reaction in Biphasic Water/Organic Solvent System in the Presence of Surfactant: Inverse Phase Transfer Catalysis versus Interfacial Catalysis. *Tetrahedron* **2000**, *56* (2), 303–307. [https://doi.org/10.1016/S0040-4020\(99\)00994-1](https://doi.org/10.1016/S0040-4020(99)00994-1).
- Boyer, B.; Hambarzumian, A.; Roque, J.-P.; Beylerian, N. Inverse Phase Transfer Catalysis versus Interfacial Catalysis. Effect of Medium Stirring in the Epoxidation Reaction of Chalcone by Hydrogen Peroxide. *J. Chem. Soc., Perkin Trans. 2* **2002**, No. 10, 1689–1691. <https://doi.org/10.1039/b204953h>.

- (22) Peacock, H.; Blum, S. A. Surfactant Micellar and Vesicle Microenvironments and Structures under Synthetic Organic Conditions. *J. Am. Chem. Soc.* **2023**, *jacs.3c01574*. <https://doi.org/10.1021/jacs.3c01574>.
- (23) Peacock, H.; Blum, S. A. Single-Micelle and Single-Zinc-Particle Imaging Provides Insights into the Physical Processes Underpinning Organozinc Reactions in Water. *J. Am. Chem. Soc.* **2022**, *144* (7), 3285–3296. <https://doi.org/10.1021/jacs.2c00421>.
- (24) Serrano-Luginbühl, S.; Ruiz-Mirazo, K.; Ostaszewski, R.; Gallou, F.; Walde, P. Soft and Dispersed Interface-Rich Aqueous Systems That Promote and Guide Chemical Reactions. *Nat Rev Chem* **2018**, *2* (10), 306–327. <https://doi.org/10.1038/s41570-018-0042-6>.
- (25) Schönhoff, M. NMR Studies of Sorption and Adsorption Phenomena in Colloidal Systems. *Current Opinion in Colloid & Interface Science* **2013**, *18* (3), 201–213. <https://doi.org/10.1016/j.cocis.2013.03.004>.
- (26) Smith, J. D.; Ansari, T. N.; Andersson, M. P.; Yadagiri, D.; Ibrahim, F.; Liang, S.; Hammond, G. B.; Gallou, F.; Handa, S. Micelle-Enabled Clean and Selective Sulfonylation of Polyfluoroarenes in Water under Mild Conditions. *Green Chem.* **2018**, *20* (8), 1784–1790. <https://doi.org/10.1039/C7GC03514D>.
- (27) Tomšič, M.; Bešter-Rogač, M.; Jamnik, A.; Kunz, W.; Touraud, D.; Bergmann, A.; Glatter, O. Nonionic Surfactant Brij 35 in Water and in Various Simple Alcohols: Structural Investigations by Small-Angle X-Ray Scattering and Dynamic Light Scattering. *J. Phys. Chem. B* **2004**, *108* (22), 7021–7032. <https://doi.org/10.1021/jp049941e>.
- (28) Shinoda, R.; Uchimura, T. Evaluating the Creaming of an Emulsion via Mass Spectrometry and UV–Vis Spectrophotometry. *ACS Omega* **2018**, *3* (10), 13752–13756. <https://doi.org/10.1021/acsomega.8b02283>.
- (29) Ranaudo, A.; Greco, C.; Moro, G.; Zucchi, A.; Mattiello, S.; Beverina, L.; Cosentino, U. Partition of the Reactive Species of the Suzuki–Miyaura Reaction between Aqueous and Micellar Environments. *J. Phys. Chem. B* **2022**, *126* (45), 9408–9416. <https://doi.org/10.1021/acs.jpcc.2c04591>.
- (30) Krasovskiy, A.; Thomé, I.; Graff, J.; Krasovskaya, V.; Konopelski, P.; Duplais, C.; Lipshutz, B. H. Cross-Couplings of Alkyl Halides with Heteroaromatic Halides, in Water at Room Temperature. *Tetrahedron Letters* **2011**, *52* (17), 2203–2205. <https://doi.org/10.1016/j.tetlet.2010.11.160>.
- (31) Clark, J. H.; Duke, C. V. A.; Miller, J. M.; Brown, S. J. Evidence for the Existence of Cu<sup>+</sup> and Cu(CN)<sub>2</sub><sup>−</sup> In Supported Copper Cyanide Reagents. *J. Chem. Soc., Chem. Commun.* **1986**, No. 11, 877. <https://doi.org/10.1039/c39860000877>.
- (32) Fleckenstein, J.; Koszinowski, K. Microsolvated and Chelated Butylzinc Cations: Formation, Relative Stability, and Unimolecular Gas-Phase Chemistry. *Chem. Eur. J.* **2009**, *15* (46), 12745–12753. <https://doi.org/10.1002/chem.200901963>.
- (33) Schott, H. Hydrophilic-Lipophilic Balance, Solubility Parameter, and Oil-Water Partition Coefficient as Universal Parameters of Nonionic Surfactants. *Journal of Pharmaceutical Sciences* **1995**, *84* (10), 1215–1222. <https://doi.org/10.1002/jps.2600841014>.
- (34) Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A.; Gaston, R. D.; Gadwood, R. C. TPGS-750-M: A Second-Generation Amphiphile for Metal-Catalyzed Cross-Couplings in Water at Room Temperature. *J. Org. Chem.* **2011**, *76* (11), 4379–4391. <https://doi.org/10.1021/jo101974u>.
- (35) Brals, J.; Smith, J. D.; Ibrahim, F.; Gallou, F.; Handa, S. Micelle-Enabled Palladium Catalysis for Convenient Sp<sup>2</sup>–Sp<sup>3</sup> Coupling of Nitroalkanes with Aryl Bromides in Water Under Mild Conditions. *ACS Catal.* **2017**, *7* (10), 7245–7250. <https://doi.org/10.1021/acscatal.7b02663>.

