Title

Avoid Relying on Hazardous Organic Solvents for your Organic Reactions: Water as the Reaction Medium

Author

Cao, Yilin

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Reflective Essay

The first time I witnessed a reaction in water as a freshman, I was totally amazed. My research group at UCSB is trying to replace the hazardous and traditional organic solvents with water, enabled by designer surfactants, in order to mimic organic solvents and reduce the amount of organic waste. Over the years, I have become increasingly interested in how to make the study of chemistry and its advancements less toxic to the planet. This is exciting and world-changing work, and as I become a more competent researcher and writer, I am interested in making scientific discovery and hypothesis more accessible. When I took the technical writing class last quarter, I jumped at the opportunity to share this area of research with a general audience for a white paper assignment. In this undertaking, the UCSB's Library was my greatest tool.

Data collections and analysis are essential for this research process. When I studied the examples of reactions in water, e.g., Suzuki reaction in water, I typed the keywords "Suzuki Reaction; water" on the Library's discovery tools and evaluated the sources by clicking the "peer-reviewed Journals" button to brainstorm. After I decided to focus on the "ppm level palladium-catalyzed reactions in water,", I utilized "ppm level palladium-catalyzed; water" as the keyword to narrow down the searching area. In addition, I used the databases of American Chemical Society Journals, Reaxys, and SciFinder on the Article Indexes & Research if I want to check a specific journal article or chemical structure. I also read the references of papers of interest to find related articles they cited or cited by other scholars. When I could not directly access the sources online, Interlibrary Loan always gave me a hand, allowing me to get the resources in a timely manner. Once I found a useful article, I downloaded citations by using the library's catalog and exported the "RIS" file into Zotero to compile my bibliographic citations. This would not only help me to keep track of my sources but also cited them automatically in a desired style, e.g., IEEE, if it did not appear as a default format on the library research's citation page.

In addition to the research process, I also attended many academic workshops from the UCSB Library, which helped me to develop not just my academic writing but also my other skills, such as R programming. I frequently found myself browsing Dr. Huber's Chemical Literature website, which taught me a lot about data collection and exploring specific chemical structures.

When I look back on my undergraduate research journey, I learned the process of searching credible primary sources, analyzing previous works, understanding the significance of a certain experiment, and applying the knowledge to propose my own independent research project. Thanks to the help of UCSB Library, I can more easily and efficiently make progress in the research process. Especially during the online studying environment this year, the off-campus access of UCSB Library assisted me tremendously in accessing online resources and databases. There are still a lot of things for me to explore in my research career, and I believe that the UCSB library will always be a "mentor" that stands behind me and helps me explore this abstruse and beautiful scientific world.

Avoid Relying on Hazardous Organic Solvents for Your Organic Reactions:

Water as the Reaction Medium

Yilin Cao

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Chemical Wastes (Clean Management Environmental Group, Inc.)

Executive Summary

The organic waste generated from the organic reactions is a long-term global problem for both academics and industries. As the development the society, chemists pay more attention on reduce those organic wastes. In organic chemistry, solvents are always necessary for conducting a reaction. Solvents play an important role in dissolving substances, stabilizing ions, and controlling reaction rates. Not surprisingly, more than 90 percent of chemists only use organic solutions as the reaction solvent, and disposal of these wastes is increasingly problematic for the health of the Earth.

Top-left: green barrels (Katusa Research); bottom-left: water (Kalayni, Prnewsprime); right: green chemistry (Om,Nykdaily)

Water is a solvent that has been selected from Nature. Using recyclable alternative solvents to replace those hazardous organic solvents is an ideal solution to this challenge. In this white paper, I specify the problems caused by the hazardous organic solvents. Second, I demonstrate the importance of green chemistry and its 12 principles. Last, I discuss the challenges and the benefits of water as the reaction medium.

Problem: Organic Waste

A majority of traditional organic chemistry reactions rely on hazardous organic solvents, especially polar solvents that have no acidic hydrogen when conducting chemical reactions, e.g., N, N-dimethylformamide (DMF), or dimethyl sulfoxide (DMSO). Work-up refers to a series of steps to isolate or purify the product of a chemical reaction, and is required for most of reactions [1]. Not surprisingly, many work-up steps, including extractions, purifications, and cleaning processes also used a large quantity of organic solvents.

In the area of fine chemistry and pharmaceutical production, appropriately 20 million metric tons of organic solvents were needed in 2012 [2]. This number was even increasing 28.5 million metric tons in 2020 [3] due to the growing demand for complex molecule drugs and the development of pharmaceuticals.

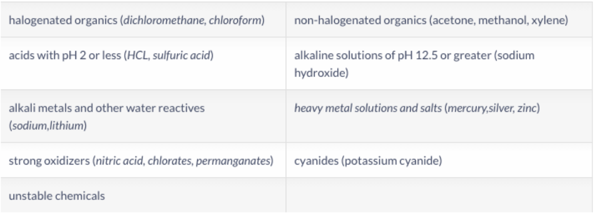
Unfortunately, those organic solvents are composed of a large percentage of organic wastes for both academics and industries. As estimated by GlaxoSmithKline [4] in 2002, solvents that account for 85% of the total mass of chemicals, produce 80-85% of organic wastes with typically 50%-80% recovery efficiency [5]–[6].

Laboratory Glasswares (Laboratory News)

Organic Solvent Waste: Disposal and Treatment

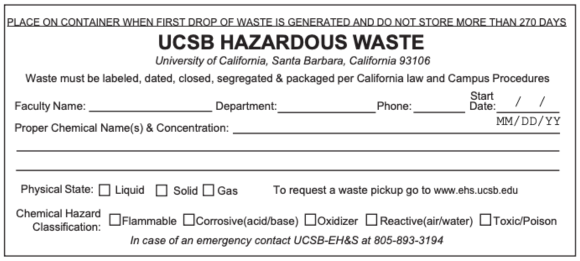
Disposal

Each university lab has detailed and strict regulations to dispose of those waste solvents. The wastes must storage in a designable area with correct labeling and identification. For the wastes sheet, the name of the wastes & concentration (must write in proper chemical name and abbreviations or chemical structures are not acceptable), the physical states, and chemical hazard classification must be filled clearly. Here are the University of California, Santa Barbara (UCSB) categories of group waste (Figure 1) and the Hazardous Waste Label (Figure 2).



halogenated organics (*dichloromethane, chloroform*)	non-halogenated organics (acetone, methanol, xylene)
acids with pH 2 or less (*HCL, sulfuric acid*)	alkaline solutions of pH 12.5 or greater (sodium hydroxide)
alkali metals and other water reactives (*sodium,lithium*)	*heavy metal solutions and salts* (*mercury,silver, zinc*)
strong oxidizers (*nitric acid, chlorates, permanganates*)	cyanides (potassium cyanide)
unstable chemicals	

Figure 1. UCSB categories of group table waste



PLACE ON CONTAINER WHEN FIRST DROP OF WASTE IS GENERATED AND DO NOT STORE MORE THAN 270 DAYS

UCSB HAZARDOUS WASTE

University of California, Santa Barbara, California 93106

Waste must be labeled, dated, closed, segregated & packaged per California law and Campus Procedures

Faculty Name: ____________ Department: ____________ Phone: ________ Start Date: __/__/__ MM/DD/YY

Proper Chemical Name(s) & Concentration: ____________

Physical State: ☐ Liquid ☐ Solid ☐ Gas

To request a waste pickup go to www.ehs.ucsb.edu

Chemical Hazard Classification: ☐Flammable ☐Corrosive(acid/base) ☐Oxidizer ☐Reactive(air/water) ☐Toxic/Poison

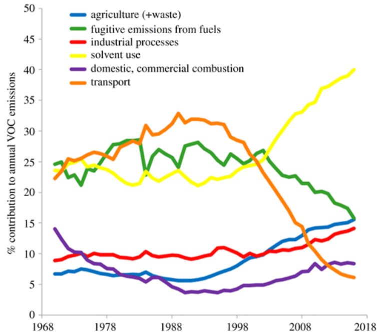
In case of an emergency contact UCSB-EH&S at 805-893-3194

Figure 2. UCSB hazardous easte label

Treatment

Incineration is the most common method to handle those collected organic solvents wastes. The collected liquid organic wastes are usually transported to a central waste-handling location. Then, with carefully examined, those labeled and identified solvent wastes are placed in the drums and trucked to an incinerator site, a kiln that destroys them with 980 °C [7]. However, waste incineration is always related to air pollution when they emission into the atmosphere. For example, burning a tonne of acetone (a widely used organic solvent) generates 2000 kg of CO_2 [8]. Burning solvent wastes not only generate carbon contained greenhouse gases, such as CO_2 or CH_4, but also other pollutants, including CO, HCl, SO_2, NO_x, and heavy metals [9].

Figure 3. Trends in sectoral contributions to national emissions of volatile organic compounds (VOCs), as a percentage of the overall annual national total, 1970 to 2017 [9].



Green Chemistry

Aiming

In response to the toxic and hazardous chemicals produced by traditional chemistry, scientists began to work toward “green” or “sustainable chemistry”, working to design chemical products and processes that reduce or mimic the hazards of chemical feedstock, reagents, solvents, and products [10].

12 Principles of Green Chemistry [10]

12 Principles of Green Chemistry (Kenneth buddha Jeans)

In 1998, Paul Anastas and John Warner proposed the *12 Principles of Green Chemistry,* which was one of the most important documents in green chemistry.

Two of the principles deal with organic wastes.

Principle one: prevention wastes. It is better to prevent waste than to treat or clean up waste after it has been created. The often-measure of waste is the E-factor, which will explain explicitly in the next session.

Principle five: safer solvents and auxiliaries, which to choose solvents that make sense chemically, reduce the energy requirements, have the least toxicity, have the fewest life cycle environmental impacts, and don't have major safety impacts.

Green Chemistry// CONTINUED

E factor

To simplify a metric of green chemistry, the environmental factor (E factor) was introduced by Sheldon in 1992 to measure how environmentally friendly, or harmful, a chemical process is.

$$\text{E factor} = \frac{\text{mass of total waste}}{\text{mass of product}}$$

The lower the E factor, the more environmentally friendly the reaction [11]. A higher E factor indicates more waste and negative environmental impact. The ideal E factor is zero [12].

Figure 4 shows some different E factors in the different chemical industries [11]. One reason that the E factor increases in the pharmaceutical industry is due to the multi-step syntheses and, indeed, wastes are accumulated after each step. In addition, the fine chemical industry and the pharmaceutical industry widely use classical reagents that have proven to work well for decades, rather than novel designed catalysts or greener solvents [12].

Industry sector	Volume/tonnes year^{-1}	E factor
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals industry	10^2–10^4	5–>50
Pharmaceutical industry	10–10^3	25–>100

Figure 4. E factors in different chemical industry [11]

Solution: Water as the Alternative Solvent

Under the fifth principle of *12 Principles of Green Chemistry*, chemists began to develop alternative solvents to replace traditional organic solvents to reduce organic solvent wastes. So far, the developed alternative solvents include 2-methyltetrahydrofuran (2-MeTHF), cyclopentyl methyl ether (CPME), ionic liquids, supercritical fluids, and very importantly, water [13].

Challenge

Water, which Nature has selected as its preferred solvent, is considered the "greenest" of all the solvents. The E factor of water equals zero, meaning it is not considered as a chemical waste in the synthesis process [14]. Unfortunately, through the development of the evolution of solvents in organic chemistry, due to its poor solubility of organic materials, water has been less commonly used as the optimal solvents.

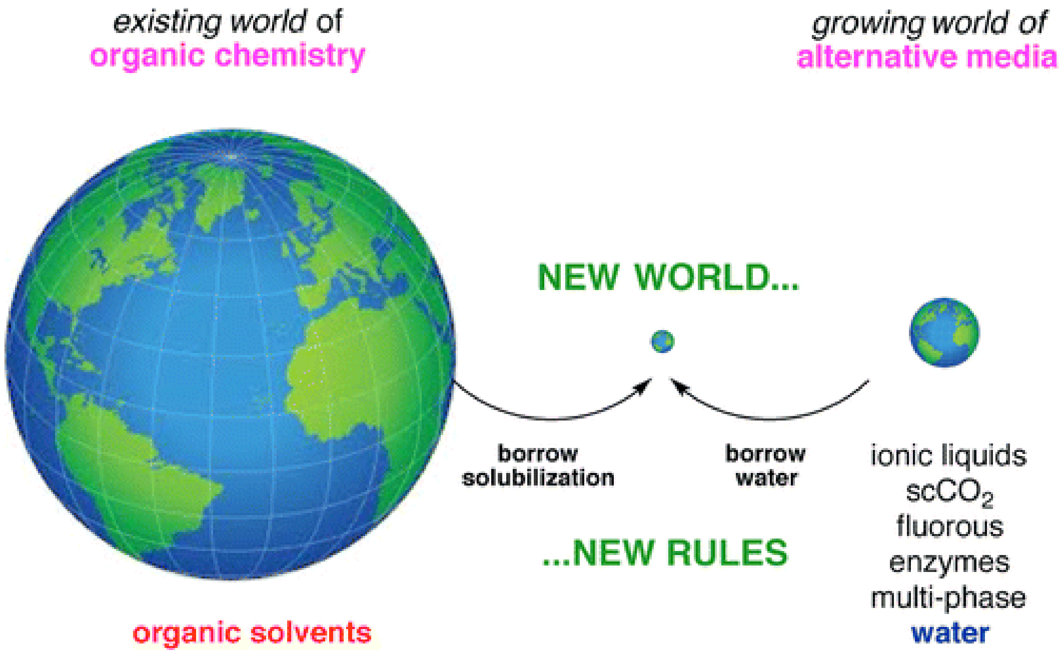
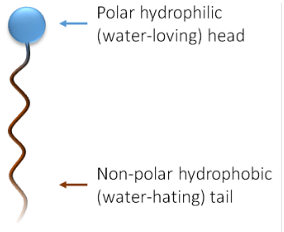


Figure 5. New world of chemistry within aqueous nanomicelles [18].

Surfactants and Micelles

Surface-active agents, or "surfactants," considers as one of the easiest ways to conduct chemical reactions in water. Surfactants (Figure 6a) are amphiphilic molecules that contain a hydrophilic (water-loving) head and a hydrophobic (water-hating) tail, making them able to present between water and immiscible organic species [14]. In other words, one end of the surfactant is water-soluble, and another end is water-insoluble. When the concentration of surfactants achieves a certain level, they will aggregate together and form spheres called micelles (Figure 6b). The external part (surface) of the micelle is water-loving and the internal is water-hating. The reactions take place in the core of the micelles. In daily life, soap is the most common application of surfactants, where the oil reacts and stays with the hydrophobic part in the core of the micelles and the outside of the micelle loves water. When you wash your hands with water, the micelle floats away leaving a clean surface.

(6a) Surfactant (University of Bristol Surfactant Catalog 2013)



(6b) Micelle (Lipshutz group)

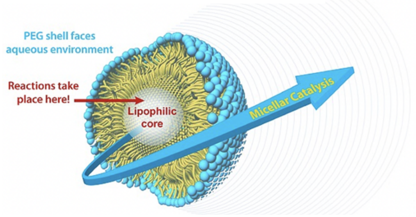


Figure 6. Structures of surfactant and micelle

Micellar Catalysis

In academics, the process of using surfactants to form micelles within reactions is called "micellar catalysis." Nowadays, many laboratories have designed surfactants that show excellent yields (above 90%) of organic reactions in water. Dr. Bruce H. Lipshutz at University of California, Santa Barbara, is a pioneer of green chemistry in water. Some notable representatives of designer surfactants in his lab are TPGS-750-M [15], PTS [16], and NOK [17], and their structures are shown in Figure 7 [18].

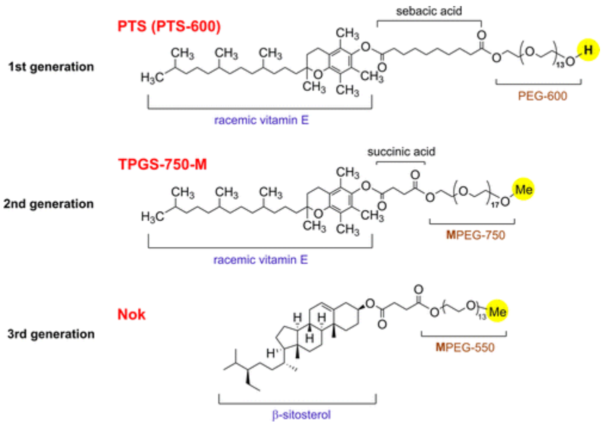


Figure 7. Structures of designer surfactants [18]

Notably, a typical E factor (the calculation is mentioned on Page 7) is low to a range of 5 to 15 when using water as the reaction media, indicating the total wastes of reactions are really small.

Benefit

Once the problem of the poor solubility of water was solved, many reactions can be conducted in water via micellar catalysis. Figure 8 shows some famous "name" reactions that can be achieved in water. Some of them even have higher yields than those in the traditional organic solvents. Many methodologies in water also show a great ability to synthesize the precursor or a drug, indicating the possibilities of using this new technology in the pharmaceutical industry [18]. In addition, using water as an alternative solvent not only reduces the organic wastes but also helps to lower the high-temperature reactions to room or mild (40 - 60 °C), saving more energy.

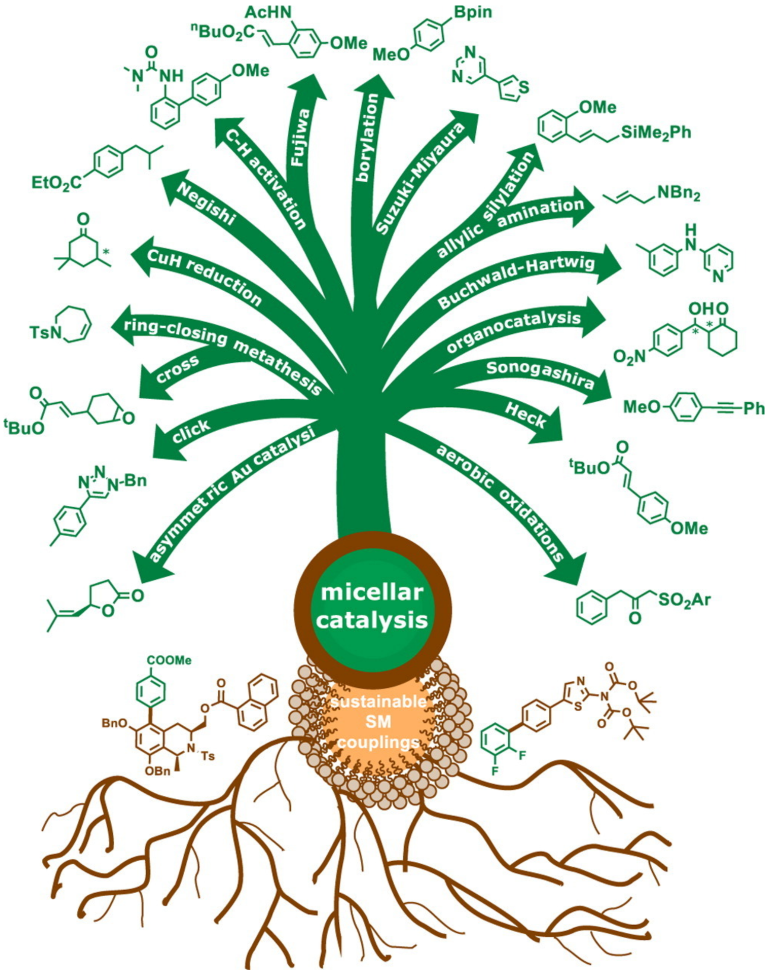


Figure 8. Example reactions [18]

A specific application: ppm level palladium-catalyzed reactions in water

Only using ppm level (< 0.1 mol) palladium to catalyze the reactions is a novel application of micellar catalysis. Due to its high selectivity of product, palladium (Pd), is one of the most commonly used catalysts in synthetic and materials chemistry in both academics and industry. The 2010 Nobel Prize in Chemistry awarded to Heck, Negishi, and Suzuki future promotes the studies and applications in this area [19].

From 2015 to 2020, seven pharmaceutical drugs approved by the United States Food and Drug Administration (the U.S. FDA) were synthesized via palladium-catalyzed reactions. However, Pd is also considered as one of the endangered metals, and thus very expensive (Figure 9). As a result, for the sustainability aspect, using lower loading of Pd catalyst in the reactions is a solution to this problem [20].

Figure 9. Cost of palladium over time [20]

Combining the solvents and the Pd shortage, three issues need to be addressed: (1) replace organic solvents with recyclable water; (2) minimize the energy input, and (3) reduce the loading of Pd catalyst to 0.1 mol% [20]. Notably, ppm level palladium (< 0.1mol% or 1000 ppm) was proven to work well in recyclable water by using different surfactants. Below is one example of one "name" reaction Suzuki-Miyaura (SM) cross-coupling. This reaction was run at the 1000 ppm level of Pd catalyst which in the designer surfactant Nok in water (Figure 10) [21].

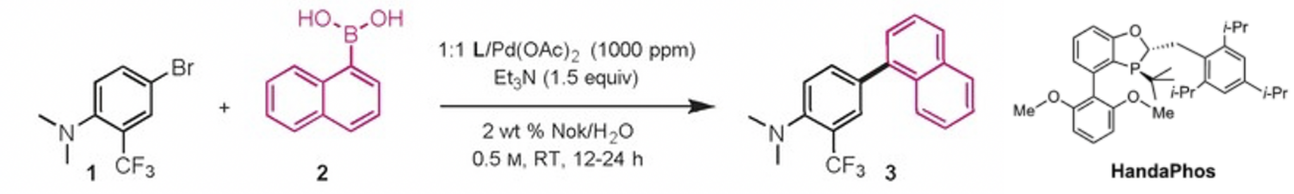
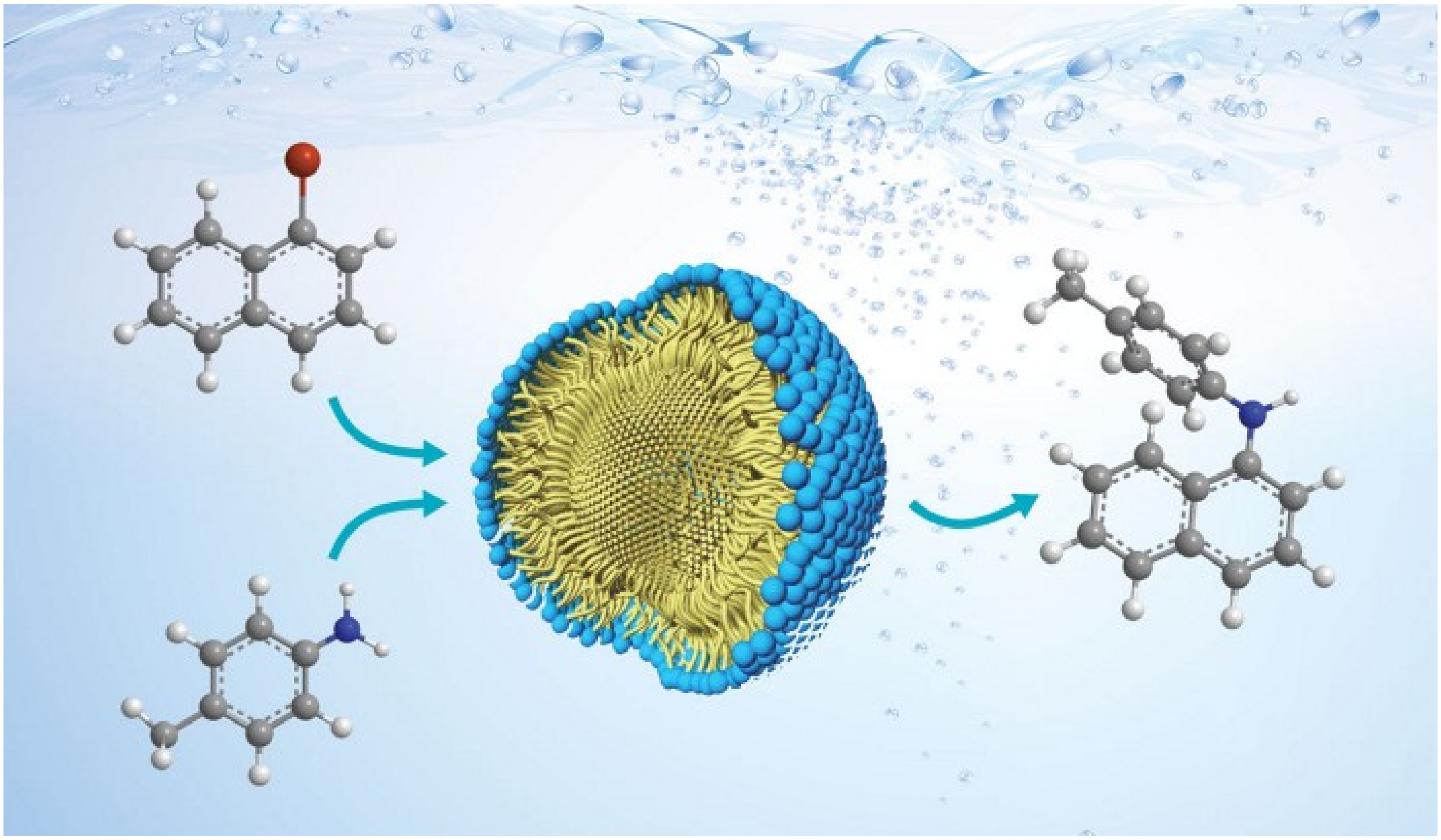


Figure 10. Ppm level Pd-catalyzed Suzuki-Miyaura (SM) cross couplings in water [21].

@Jorge Pinto

Conclusion

As discussed throughout this paper, the strategy of developing alternative solvents and using water as a reaction medium provides the possibility of addressing the problem of generated organic solvent wastes. Although water is not an optimal solvent in organic chemistry, it has been selected as Nature's solvent in optimizing reactions for millions of years and it is possible to become one of the most optimal solvents in the future!



Pd-catalyzed Buchwald-Hartwig amination in TPGS-750-M (Bruce H. Lipshutz / Yang H. Ku , C&EN) [22]

Although synthetic organic methodologies in water increased dramatically during the two decades, it is still a "black box" for chemists and remains a secret. "It's still too much driven by trial and error," says Dr. Fabrice Gallou, who is an expert of micellar chemistry in water at Novartis [22]. Most of the reactions were still batch-size, which are only micrograms or grams. The next step is to scale up this technology to at least kilograms scale for medicinal process chemistry. In the words of Nobel Laureate Professor Ryoji Noyori "Green Chemistry is not just a mere catch phrase; it is the key to the survival of mankind [23]."

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