Illuminating a Path for Organic Synthesis Towards Sustainability. No One Said It Would Be Easy…

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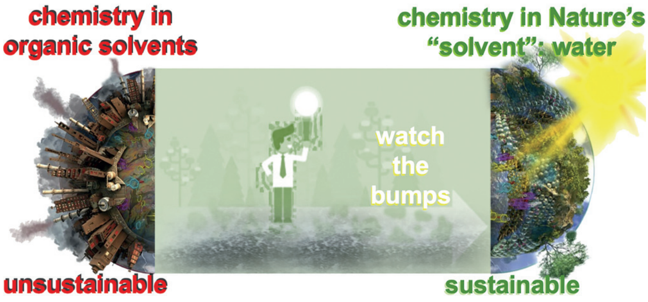

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Abstract A personalized account is presented describing some of the stories behind the scenes in efforts to convert organic chemistry into a more sustainable discipline. These are part of a group 'crusade' started almost 15 years ago aimed at providing technologies illustrative of how key reactions used today can be 'faster, better, cheaper' when run in recyclable water. Hence, the option now exists to do organic synthesis in a far more environmentally responsible fashion. By contrast, most of organic chemistry developed over the past 200 years that relies on organic solvents continues to generate enormous amounts of pollution, while depleting finite petroleum reserves and our supplies of many precious and base metals. Making the switch to water, Nature's chosen reaction medium, akin to that in which bio-catalysis is typically performed, is inevitable.

Key words sustainability, green chemistry, chemistry in water, chemo-catalysis, ppm level Pd

1 The Story Begins: A Different Type of Prejudice

'…*Easy*'? Wow! I had no idea what I was about to get myself into back in 2006. Now, roughly 15 years later, and well along in our group's 'crusade' to convert the petroleum-based field of organic synthesis that relies heavily on the use of organic solvents into a sustainable, water-based science, can I look back and realize what we have been through, and in all likelihood, what lies ahead. The stories being told herein are almost certainly not unique; indeed, there must be many, albeit in other disciplines, who, like me, started out on a very traditional path (a Ph.D. with Harry Wasserman at Yale, then a postdoc with E. J. Corey at Harvard). But then, at some point and for some reason, as in my case, come to realize that as far as traditional academic research in organic synthesis done in organic solvents is concerned, the 'business as usual' mentality is no longer appropriate.

In hindsight, the challenges that we were about to take on were not the typical daily 'mano-a-mano' ones with Nature. Hardly! They were then, and still are today, equally, if not more inspiring, notwithstanding our ongoing struggles to survive in a world that, for the most part, knows only and practices only organic chemistry in organic solvents. Indeed, as organic chemists almost instinctively believe, water is the enemy.[1] This sense is implied, if not said directly, in virtually every classroom from sophomore organic chemistry on. But what is the origin of that type of thinking? Is it the 'pK_a problem'? But let's appreciate that, e.g., we have aldolases that work in water,[2] so isn't the solution already there to be found? Of course, it is! And we are even working now on doing such enolizations in water. I have already told the students involved what the title of this eventual paper will be: 'Who needs LDA?' And what about recent literature using very highly basic reagents…in water, also disproving these time-honored biases?[3] We need to realize that, in fact, the situation is just the opposite; that *water is our best friend*. Water is the medium chosen by Nature; it is the medium in which the vast majority of biocatalysis is practiced.[4] We don't even think about it. For example, when Francis Arnold received the Nobel Prize for her brilliant contributions on directed evolution,[5] did anyone question in which medium those unnatural enzymes are being used? (Shhh…it's water!) Students from her group at CalTech continue to get 'scooped up' by academia to do chemistry along these lines…in water. Is it not obvious that chemo-catalysis is destined to be done in this same medium?[4a]

As new 'advances' are accumulated in organic solvents, are we moving in the wrong direction? Isn't it obvious that our natural petroleum reserves are not limitless? Is our

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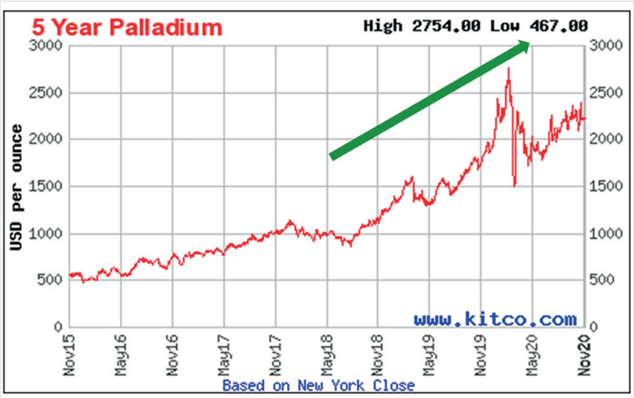

Figure 1 The price of Pd/Troy ounce since 2015

supply of transition metals and the technology needed to access them unlimited, these metals being so crucial for catalysis, whether focusing on, e.g., palladium or nickel? Should we pay more attention to the oceans of organic waste, mostly solvents,[6] that lie buried throughout the world and are subject to unearthing, as once dormant volcanoes come to life, earthquakes open new underground fissures to the surface, and climate change wreaks havoc worldwide, all worsening with time? It seems more and more difficult to come up with cogent arguments against these notions, whether giving a talk in front of an audience or at the dinner table. And yet, we continue to go down the same path, assisted by billions of governmental and private support dollars worldwide, that while generating, for sure, exciting new developments—do they truly have a future when they take place in traditional media? And what about the many ongoing collaborations between academia and industry? Here again, is funding encouraging more of the same traditional synthetic approaches?

For us, the handwriting on the wall is strikingly clear. Even some 'oil and natural gas' companies are getting out of petroleum and into other forms of energy (e.g., electrical and wind), undergoing a transformation that in time will undermine the very foundation of organic chemistry (e.g., our access to organic solvents). It's already happening,[7] as is recognition of the shortages coming for many elements and most notably, precious metals.[8] Unfortunately, even as the price of palladium reaches new heights (up over 500% over the past five years; Figure 1),[9] many in the community continue to deny the wave of sustainability. When we finally realize the inevitable, will it be too late?

It did not take long for me to see just how stacked the deck actually is against us. But I also knew that we would have our victories. So, with each new recruit who joins the team, I offer the same early warnings: We are doing synthetic chemistry unlike the organic chemistry world is used to seeing. We are asking the synthesis community to consider chemistry in water as an environmentally responsible alternative to traditional uses of organic solvents. In essence, we are proposing with each technology that the community considers a paradigm shift. There will be a LOT of pushback, and there will be tough times, as we are going squarely against the grain. But hopefully, in time, this will all be worth it. Perhaps not so remarkably, students have not only bought in, but they continue to come in numbers. Students get it, and quickly. They know that this is their world; that they will inherit the problems left behind, and they want to be part of a solution.

Having completed our very first study on olefin metathesis years ago, spearheaded by an exceptionally talented postdoc, Subir Ghorai (now at Sigma-Aldrich), our initial manuscript on chemistry in water was written and submitted to the *Journal of the American Chemical Society* (*JACS*). We felt that it met the standard 'novelty and urgency' requirements, showing that, for the first time, this Nobel Prize winning chemistry could be done in water at room temperature in very competitive yields, while completely eliminating chlorinated solvents typically needed at reflux (Scheme 1). In that Comm. Ed. we also introduced a new surfactant, PTS (polyoxyethanyl α-tocopheryl sebacate) (Figure 2),[10] that enabled this chemistry to be done in 98% water (by weight), and illustrated effective cross-metathesis using known and commercially available Grubbs II and Grubbs–Hoveyda II catalysts. Also discussed was the first mention that, conceptually, micellar catalysis as an en-

Biographical Sketch

Bruce Lipshutz has been on the faculty at UC Santa Barbara since 1979, following his Ph.D. at Yale (Harry Wasserman) and postdoctoral studies at Harvard (E. J. Corey). Starting in 2006, his research group began focusing on the development of new, environmentally responsible technologies in organic synthesis for use in recyclable water, including the specific goals of: (1) getting wasteful organic solvents out of organic reactions; (2) minimizing the need for investing energy (in the form of heating or cooling) into reactions; (3) reducing the loadings of transition-metal catalysts to ppm levels; and (4) fully integrating chemo- and bio-catalysis as reagents for use in water, such that multi-step, one-pot sequences are the norm, thereby achieving time, pot, and ligand economy.

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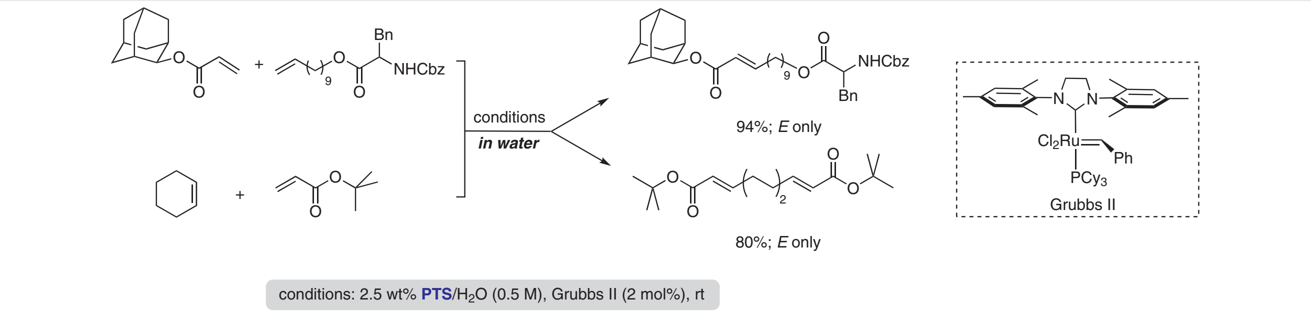

Scheme 1 Representative cross-metathesis reactions in water at room temperature

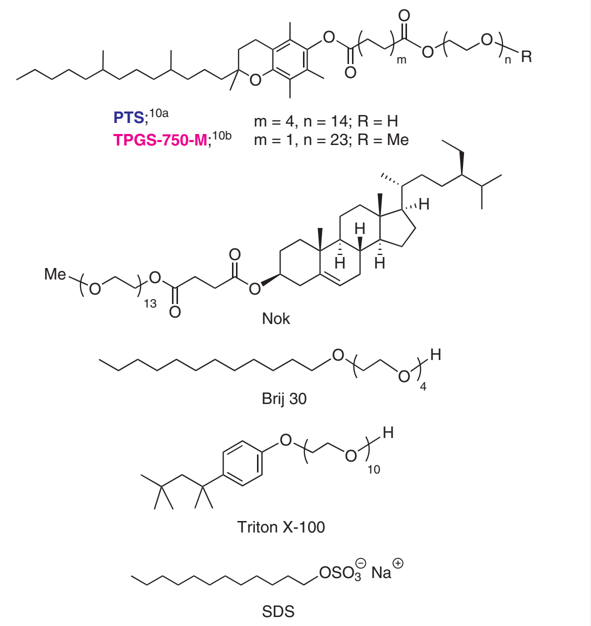

Figure 2 Structures of representative amphiphiles

abling technology was not only possible in water, but also in ocean water, where the chemistry proceeded with even better results! We described how micellar catalysis with ‘designer’ surfactants enabled the desired synthetic goals, and that such a nanoparticle approach to chemistry in water is sensitive to particle size, explaining why alternative nonionic surfactants, such as Brij-30 and Kolliphor (renamed from originally, Cremophor), which might feature a similar hydrophilic lipophilic balance (HLB) (Figure 3), are not *generally* useful for modern transition-metal catalysis. All this new information and ‘greener’ chemistry was favorably reviewed, except by one reviewer; the paper,[11] our first disclosure on micellar catalysis, was promptly rejected. And what did that referee claim was the reason for this rejection? Well, a recent, apparently important publication in this area was cited that we had failed to include among the references within our submission. Although that seemed a bit harsh, I understood that such things happen…until I checked the submission date on that important paper that we seemingly missed: that date was AFTER our submission. In other words, it was impossible for us to have seen this paper cited by the reviewer. Nonetheless, we lost that one!

2 Are We up to the Challenge? Too Late Now…

If only this was a one-time event; a one-off, attributable to the ‘luck of the draw’ in terms of selection of referees. Unfortunately, having been around the block a few times I knew that this was no fluke; rather, it was representative of the many setbacks coming our way. After all, traditional organic chemists like the world they have inherited, and skillfully maintained. They are comfortable in this setting; hey,

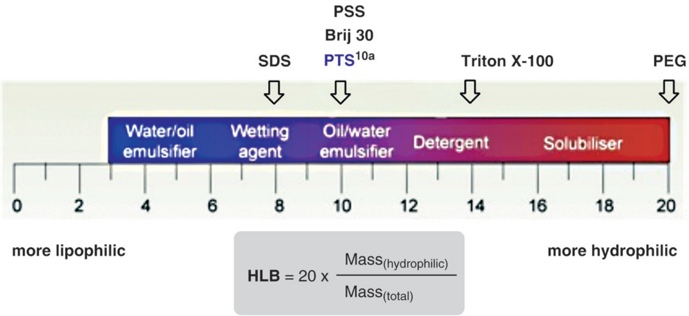

Figure 3 Hydrophilic lipophilic balance (HLB) of representative surfactants

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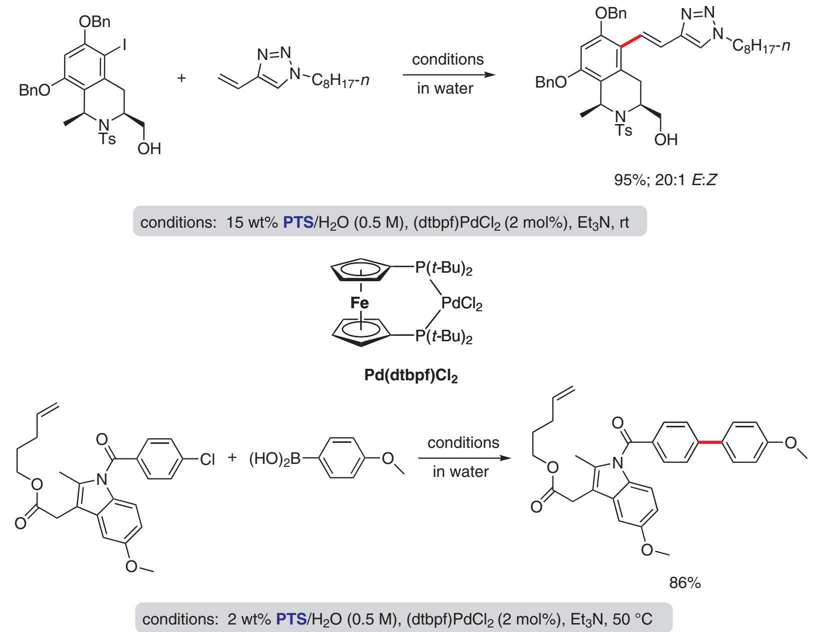
I was, too! We all know the rules, know how to play the game, and how to maintain the positions that we have worked very hard to achieve, especially in academic circles. That's just human nature. But chemistry today, unlike a century ago, is rapidly consuming our resources,[8] and at the expense of the world to be inherited by our children and grandchildren. Those, like mine, will wonder why the planet is so polluted with *our* chemical waste; why the petroleum reserves are so low, and why the metals needed for so many important purposes are extremely expensive, or worse yet, gone. Today, I no longer in good conscience have to look at my beautiful 5-year-old granddaughter, Zoey (Figure 4), and tell her that I continue to knowingly pollute the planet she will occupy for many years to come.

Already back in 2007, we had also completed, in addition to Subir's study on metathesis (*vide supra*),[11] related work using Pd catalysis documenting that this non-traditional approach to synthesis in water seemed to be general. Graduate student teams led by Ben Taft (Novartis), Alex Abela (Gilead) and Tue Peterson had successfully applied our PTS-based technology to both Heck[12] and Suzuki–Miyaura[13] couplings, respectively (Scheme 2). As it was time to publish these, and with the work on olefin metathesis still lacking a home in any journal, I called Amos Smith at Penn, the founding Editor of *Organic Letters*. I explained both the chemistry and the circumstances, and then asked if he would consider not one but all three manuscripts, perhaps even agreeing to publish them 'back-to-back-to-back'. His answer may have come long distance from Philly, but it took him far less than a New York minute to reply: 'I'll take them; all of them.'

Figure 4 Granddaughter Zoey Alvarado (age 5), pictured here during the year 2020, of the COVID-19 pandemic. She deserves the truth, and a better world (reproduced with permission)

Although we knew that metathesis, Heck, and Suzuki–Miyaura reactions could be done in water at (Southern California) room temperature (ca. 21–22 °C) or slightly above, and that PTS formed micelles that seemed to accommodate each coupling, the obvious question was why? Why did Oehme's review in 2005[14] on aqueous micellar catalysis not



conditions: 15 wt% **PTS**/H_2O (0.5 M), (dtbpf)$PdCl_2$ (2 mol%), Et_3N, rt

Pd(dtbpf)Cl_2

conditions: 2 wt% **PTS**/H_2O (0.5 M), (dtbpf)$PdCl_2$ (2 mol%), Et_3N, 50 °C

Scheme 2 Early demonstration of both Heck and Suzuki–Miyaura couplings in water

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discuss a single Pd-catalyzed cross-coupling using a nonionic surfactant? What was it about PTS that enabled these couplings to occur, while so many other surfactants in the Aldrich catalog (cf. Figure 2) were being used, occasionally, on a 'hit or miss' basis? This was chemistry truly 'in water', rather than 'on water', and certainly not 'with water.'[1,15] These are important distinctions to be made early and made unequivocally, especially if we wanted to avoid a future 'debunking' by Donna Blackmond![16] Ouch! Hence, in the spirit of total transparency, it can honestly be said that at that time we had no clue what made PTS special. Traditional means of analysis: IR, NMR, mass spectrometry, etc., were not helpful here. Fortunately, on campus, we have a top-rated Materials Department, and it was time to apply their tools for gaining insight into our problems.

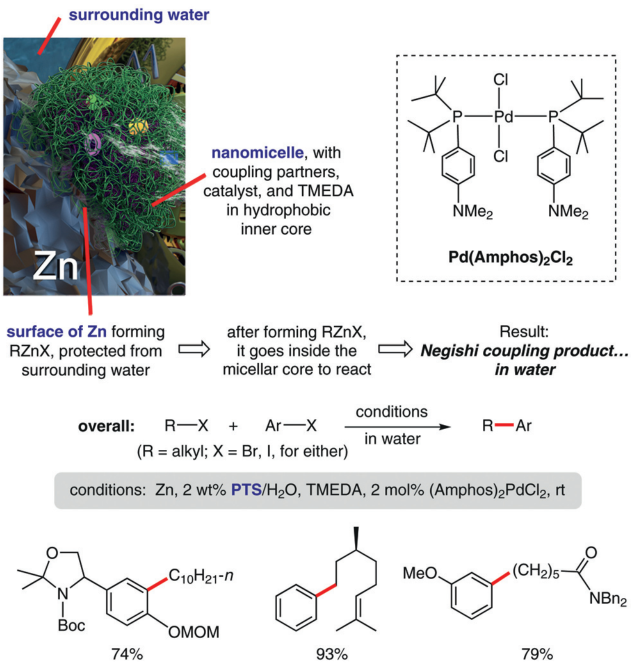
So, we learned a new word: 'nanoparticles' (NPs). To traditional organic chemists operating in solutions based on organic solvents, this term means virtually nothing. But in the world of surfactants,[17] this is what enables aqueous chemistry. The NPs that were forming spontaneously in water, composed of strands of PTS, were seemingly different, unusual; and to gather an appreciation for this, we needed to learn the techniques used routinely in materials science, such as dynamic light scattering (DLS) and low-temperature transmission electron microscopy (cryo-TEM). With access to these two analytical tools we were ready to do more, knowing that we could gain insight as to what we had in terms of both the reaction medium, and possibly even the catalysts being used. It was becoming clear to us that the 'rules' associated with doing chemistry in water[18] are very different from those in the textbooks being taught. But we still needed to come up with something special; something unique that demonstrated what out of the box thinking here could lead to. Who knew then that we would soon accomplish chemistry that organic chemists still think, even today, is impossible.

3 'Impossible' Reactive Metal Chemistry in Water

How about Negishi couplings *in water*?

Can you imagine trying to 'sell' this to anyone back in 2009? The origin of this technology, and its credit, goes back and belongs to the work of two former postdocs in the group, Christophe Duplais and Arkady Krasovskiy (Dow), who had previously been good friends as students in Europe. Christophe was here developing 'UC Pd', a new, recyclable form of Pd/C for effecting Sonogashira couplings in EtOH.[19] When Arkady arrived, they decided to work together on a project of their own creation, and that was totally unknown to me (which is usually referred to as 'submarine chemistry'). After a month or two, their results, finally being relayed to me, were not worthy of mention. It was at this time that I asked both to have a meeting with me in the privacy of my office. I told them diplomatically, but in no uncertain terms, that they are far too talented to be here doing traditional organic synthesis; that they needed to think boldly, creatively, and to take chances; that the rules for chemistry in water are different.[18] So, they went back to their labs to dream. Two weeks later they knocked on my door, claiming that they had some new chemistry in water that I might find very interesting. As they were entering, Christophe was too excited and could not control himself, blurting out in his distinctive French accent: 'How about Negishi couplings in water?' Hearing this seemingly ridiculous claim, I immediately tossed both out of my office, thinking 'you guys are crazy.'

I should have listened to them. It took another two weeks before they would chance this meeting again, but this time, they came fully armed with even more data. I listened in disbelief as they claimed what was to become a very reproducible, general phenomenon, where the water-intolerable organozinc halide could be generated in situ, protected on the metal's surface by the micelle, and once inside the hydrophobic inner core, did what was expected: supplied the species needed for a transmetalation to palladium leading to net C–C bond formation, tantamount to a Negishi coupling (Scheme 3).



Scheme 3 Micellar catalysis applied to net Negishi (reductive) couplings in water

As stunning and useful as this technology is, yet again our attempts to publish this generally applicable chemistry in water was initially met with failure. Notwithstanding all the pK_a arguments claiming that such an approach is simply

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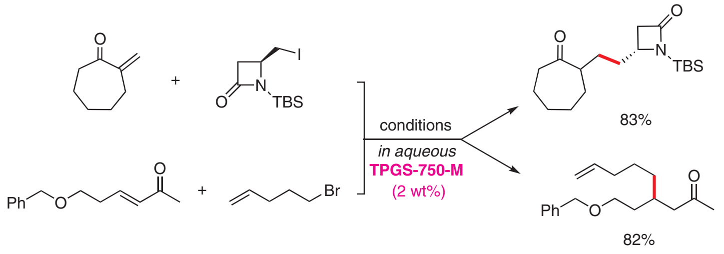
not possible, the reviews by *Science* overall did not go well: The argument by one referee was advanced that 'organozinc chemistry in water is known.' And so, while that comment may have been true at the time for a very limited subset of organozinc reagents (i.e., allylic species),[20] why this was enough to override the enthusiasm expressed by the other reviewers remains unclear. Fortunately, the revised manuscript as a Comm. Ed. to *JACS* went to different referees who, eventually, supported this counter-intuitive work. And while it took more than six months to get this communication in print,[21] we were, nonetheless, very happy to see that there would be those who were not in such disbelief.

Once we had Negishi-like couplings in water under our belts, the alternative transmetalation from Zn to Pd was from Zn to Cu, another energetically favorable event; hence, the expectation: RZnX + CuX going to RCu(X)ZnX. Aside from my decades of interest in organocopper chemistry,[22] the real story behind this project comes from a visit paid to my former postdoctoral mentor, EJ Corey, during the summer months when my youngest son, Mitch, a high school senior applying to colleges and I were making stops at Ivy League schools going north on Route 95. The plan was to start at Penn in Philly and end at Harvard in Cambridge. In my mode as a father, I wanted Mitch to meet EJ and shake hands with a Nobel Laureate. EJ was most welcoming, and it was an opportunity, for both of us, not to be missed. After generously sharing his time and wisdom with Mitch that Sunday afternoon, EJ *insisted* that we take a picture together (Figure 5). On the way out of his office, I happened to mention that we were doing copper chemistry in water, specifically using asymmetrically ligated CuH.[23] Since EJ, as usual, knew the literature extremely well, he looked at me, perhaps wondering why I thought this was work worth mentioning, and proceeded to correctly claim that 'copper hydride is known to be stable in water, so that's not surprising.'[24] But he then went on to immediately state: 'Now, when you can make a *carbon–carbon bond* using copper in water, you call me!'

That was not a meeting I shall ever forget. The challenge had been extended, but it was not such a stretch, given our Negishi couplings in water,[21] to replace palladium with copper and an aryl halide with an enone, looking to do *carbon* conjugate addition chemistry in water. In my gut I really believed that the desired C–C bond should get made inside that hydrophobic micellar core. When this story, along with the synthetic challenge, was relayed to Shenlin Huang, a very talented and experienced graduate student in the group, I could see the look of excitement in his eyes. Both of our phones were placed on speed dial…

Figure 5 Picture taken in EJ Corey's office in 2008, where he questioned organocopper chemistry in water (reproduced with permission)

It did not take long for Shenlin, having enlisted fellow graduate student Nick Isley and visiting student Wendy Leong, to find that, indeed, carbon–carbon bonds could be made under these aqueous conditions by making the reagent and substrate changes anticipated (*vide supra*).[25] However, since an organocopper reagent, formally 'RCu', was presumably being generated and not the corresponding *ate* complex (i.e., R_2CuZnX), its reactivity in water (or any medium) at room temperature was nowhere close to that typically seen with cuprates, even when the latter are used at –78 °C.[26] Hence, the RCu we were generating needed help, i.e., an additive that would enhance the reactivity of its enone partner. The answer was not hard to find. Obviously, $BF_3{\cdot}Et_2O$ in water was out;[27] we needed a Lewis acid that is stable in water. Answer: $AuCl_3$ (Scheme 4). With the modified conditions in hand, and generality established, the manuscript went in to *JACS*, and after some tough questioning by the referees, it made it through. Yes, it was time



conditions: $Cu(OAc)_2{\cdot}H_2O$ (3–5 mol%), Zn powder (4 equiv), TMEDA (2 equiv), **$AuCl_3$** (5 mol%), rt

Scheme 4 Formation of C–C bonds via organocopper chemistry, *in water*

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to make that call. So, did that call happen? No way! I am sure that not one member of the Corey 'mafia' is surprised about that…

After this second contribution appeared that, in all likelihood, was also found to be hard to believe (as with the one featuring Negishi couplings in water), things settled down for a while; perhaps the community was beginning to believe that 'designer' surfactants are, indeed, enabling, and that the 'rules' under which chemistry in water are operating are just different. But this period was just a lull before the next storm came along, and this one was, well, let's just say that it was not fun!

4 Didn't I Once Say: 'It's All about the Ligand'?[23,28]

One of the lessons that Nature had taught us in doing chemistry in water is to pay attention to the old adage 'like dissolves like.' Hence, if organic substrates and, in particular, catalysts are insoluble in water, then they are competing for space inside the micellar lipophilic inner cores that function as 'solvent.' And since one cannot usually do anything about the choice and nature of the reaction partners of interest, the ligand that goes hand-in-hand with the metal seemed ripe for 'adjustment', applying this simple concept to its design. Or, to put this another way, we were getting into the ligand design business that by all yardsticks was a crowded arena, already having several very 'well-established' names associated with it. But we had an advantage, knowing that, for example, phosphine ligands complexing Pd and thereby forming catalysts had been designed for use *in traditional organic solvents* and not based on the new rules[18] for doing chemistry in water. Moreover, we also knew that the secret to success for getting a catalyst into a micelle and keeping it there is to maximize its binding constant for the 'grease' that serves as the organic solvent within each nanoparticle. Hence, those ligands that might be terrific in toluene and dioxane were not necessarily a 'match' for chemistry in water. Ok, but where to start the search?

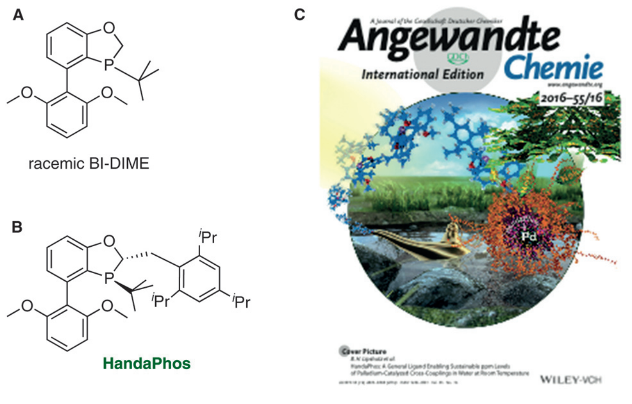

Figure 6 Structures of ligands based on the oxaphosphole skeleton. Cover image reprinted with permission from *Angew. Chem. Int. Ed.* **2016**, *55*, 4914. Copyright 2016 Wiley-VCH.

That turned out, fortunately, as the U.S. press core might claim, to be a 'softball' question: Enter a new postdoc into the group by the name of Sachin Handa (Prof., University of Louisville). He quickly decided to apply this concept to create a new series of ligands to test, including one based on the Boehringer-Ingelheim (BI) biaryl platform, the parent ligand being BI-DIME (Figure 6, A). Previous modifications in the literature had led to a series of substituted BI-DIME ligands that worked well in organic media,[29] but these were simply not lipophilic enough to achieve our goal: i.e., its use as a ligand on Pd that led to a general method for catalysis of Suzuki–Miyaura couplings in water *at the ppm level of precious metal.* Eventually, Sachin found the magic residue that fulfilled our requirements (i.e., the 2,4,6-triisopropylbenzyl group) (Figure 6, B), allowing for these valuable couplings to occur typically starting with only 1,000 ppm (0.10 mol%) of ligated Pd, and sometimes, with even less (Figure 7). Although the research went very well, as did the characterization of this new ligand (which was rightfully named HandaPhos) and its 1:1 complex with palladium, publication of this work was met, euphemistically speaking, with 'unexpected resistance.' The manuscript had been submit-

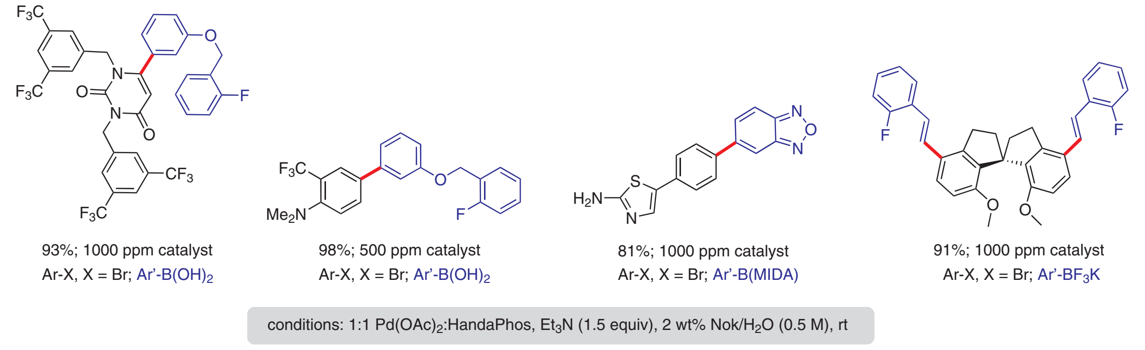

Figure 7 Products of ppm (HandaPhos)Pd-catalyzed Suzuki–Miyaura couplings in water

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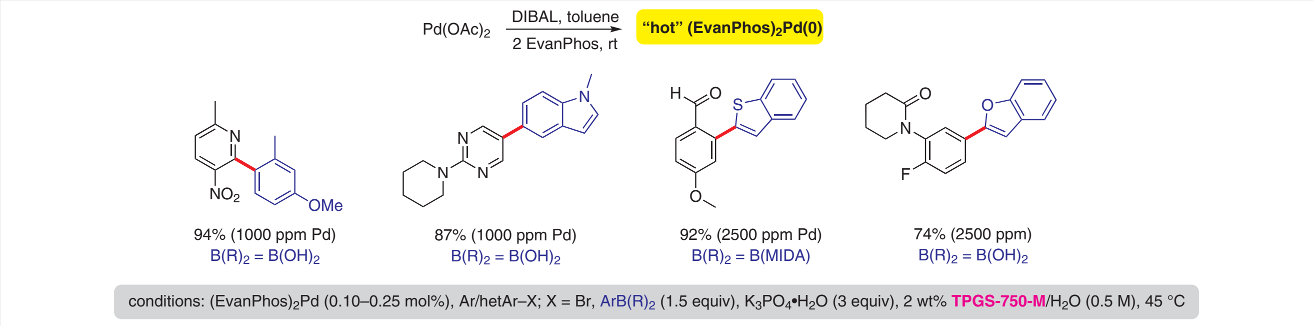

Scheme 5 Suzuki–Miyaura (SM) couplings using catalytic (EvanPhos)$_2$Pd in aqueous micellar media

ted to *Angewandte Chemie International Edition (ACIE)*, finding its way to a reviewer who took exception to our name for this ligand, claiming that any species, known or otherwise, based on the BI-DIME skeleton belonged to BI. Recommendation: Manuscript rejected. Really? On that basis? The name!? We argued against such specious logic; what about the *science*? Fortunately for us, once I addressed the *legitimate* concerns by all referees, the work was not only eventually formally accepted,[30] but was actually invited to be featured on the cover of the issue in which this paper was to appear (Figure 6, C).

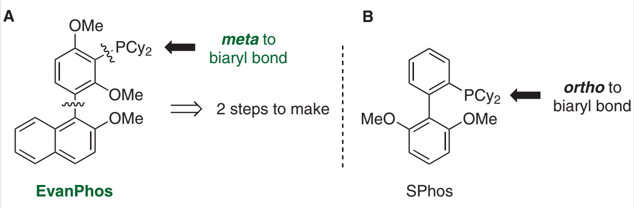

Figure 8 Structural comparisons of EvanPhos and SPhos

The paper that disclosed HandaPhos to the community (i.e., a ligand that is commercially available from Sigma-Aldrich; catalog #799580), brought us closer to one of our goals of developing ppm level transition-metal catalysis in water. We had learned from the Green Chemistry Institute about 'endangered metals';[31] how so many, both precious and base, are being consumed at an alarming rate; that even with recycling technologies in place, we are going to run out within, say, the next 100 years or less.[8] At issue with HandaPhos (*vide supra*) is its required 10-step synthesis,[30] and so we decided to design a new phosphine ligand-containing scaffold that might approach its effectiveness, but required far fewer steps to make. The biaryl array that seemed to meet these criteria was successfully pursued by an advanced graduate student in the group, Evan Landstrom, who did not put up the slightest resistance when I proposed that we call it 'EvanPhos' (Figure 8, A). That it could be made in only two steps from readily available materials was a huge plus, and for many of the Suzuki–Miyaura couplings studied, it could be used in aqueous surfactant (TPGS-750-M)[10b] as the 2:1 complex at the 1000–2500 ppm level of Pd (0.10–0.25 mol%) (Scheme 5). Although this ligand itself was new, also part of this study was its use in *organic solvent* (yes, this part of the project was tough to accept!). Apparently, this was the first use of EtOAc for Suzuki–Miyaura (SM) couplings. Our strategy behind initially documenting how this organic solvent (gulp!), in fact, is far better than the other commonly used media, such as toluene of dioxane, was to entice consumers to switch to EvanPhos-complexed Pd in an organic medium, which we guessed would appeal to the reader's comfort zone. We found that if good quality Pd(OAc)$_2$[32] is initially reduced by DIBAL, after which the resulting catalyst is used in EtOAc (Figure 9), subsequent SM couplings are typically better (yields and reaction rates) than those routinely done in more common solvents in which the in situ conversion of Pd(II) into Pd(0) comes at the expense of excess boronic

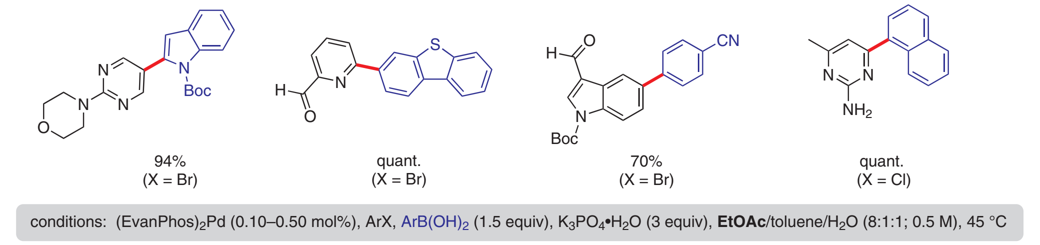

Figure 9 Use of catalytic (EvanPhos)$_2$Pd for SM couplings in *EtOAc*

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acid in the pot. And if this happened to attract users, then showing in this study that the exact same chemistry done in water was even better might turn some heads.

Well, that was the plan, and while the chemistry panned out nicely, where to publish all of this? Would referees appreciate the new ligand, let alone the unprecedented use of EtOAc for Suzuki–Miyaura couplings? Apparently, judging from the reviews, not only did the reviewers not take note of any of these features, one went so far as to claim that what we were offering in the manuscript was nothing more than 'just another Buchwald ligand' (e.g., SPhos; Figure 8, B). This comment, in particular, taught us that a referee might go to any extent to convince an associate editor, potentially for mistaken reasons, to decide against a manuscript submitted in good faith. It seems almost impossible that any PhD in organic chemistry does not know the difference between *ortho*- and *meta*-substitution (of the phosphine relative to the biaryl bond; Figure 8, A vs 8, B) on an aromatic ring. And yet, this was the basis of the rejection received; there was nothing 'novel' about EvanPhos, notwithstanding that it is *not* based on the *ortho*-phosphine biaryl platform that is so crucial to its involvement in Pd catalysis.[33] Although this work was ultimately accepted,[34] it is hoped that those doing traditional Suzuki–Miyaura cross-couplings realize that their results might be improved using commercially available EvanPhos (Sigma-Aldrich catalog #902292), complexed with Pd, and used in EtOAc.

5 What Happens When Our Supply of Palladium Runs Out?

It is fully appreciated that there will be those who scoff at the notion of the community depleting our access to palladium. Academicians, in particular, have told me in no uncertain terms that their reactions that utilize a milligram of Pd are not adding to the shortage, and so they are not going to change their chemistry over this. Unfortunately, most do not appreciate that endangered metals get their classification not by the amount of metal left on the planet; there are far more quantities of metals in the world than we could ever begin to use up. The problem is that we do not have the technology to access these metals below a certain level of the Earth's crust. Mining metals is both a tough and expensive proposition, and it can only get us to a certain point, …and that's it! If we accept these facts, as reported by independent agencies that have no particular interest in the chemistry associated with these metals,[8] then there are only two options facing us: (1) Find a way to do the same chemistry with another, less costly and available metal, or (2) develop chemistry that requires an order of magnitude less of these endangered metals but that accomplishes the same synthetic goals. The reasons behind our choice of option (2) are very simple: Firstly, we already know how to do catalysis with Pd; why invent alternative (base) metal catalysis when Pd works so well? And secondly, if we can reduce our consumption of palladium by moving the decimal point to the left by one, then imagine what that does to the time we have gained in terms of prolonging the use of this metal in catalysis. In other words, if we have ca. 100 years remaining of access to palladium, that time frame has just been extended to 1,000 years; problem solved!

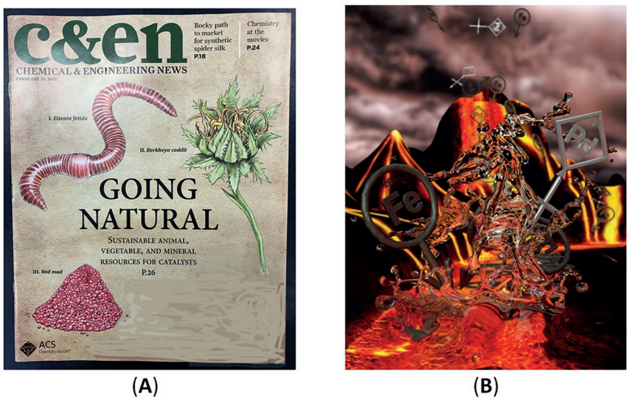

Figure 10 Anticipating precious metal treasures from (A) various natural sources (Illustration by Will Ludwig/C&EN. Reprinted with permission from *Chemical & Engineering News* (© 2017 American Chemical Society), and (B) mined iron ores (credit: Peter Allen)

Technically, there is a third option for dealing with the coming shortage of endangered metals, and Pd in particular, that the chemistry community tends to overlook. That is, why not look to see where metals are present, e.g., within numerous 'spent' items that are available and can be purposed, or re-purposed, a topic already highlighted by *C&E News* ca. four years ago (see Figure 10, A), or that are 'gifts from Nature', i.e., sources of materials containing, e.g., Pd, that can be converted into catalysts such that the Pd is essentially for free? That latter notion intrigued us, and represented another challenge in the group overseen, yet again, by Sachin Handa. He had the idea to convert $FeCl_3$ into new nanoparticles, and so, we speculated that when iron is mined, especially that coming from the depths of the Earth (as UCSB former graphic artist Peter Allen represented in Figure 10, B), other metals (Ni, Cu, Co, etc.) are surely present as 'impurities' and so, why not Pd? In other words, instead of chastising our colleagues who, in the composite, have identified (perhaps unknowingly, in the Barton sense of invention) sources of metal contaminants that are the true catalysts for a given type of reaction, we should celebrate such discoveries, and encourage others to find similar treasures.

So Sachin looked, and Sachin found. By obtaining ICP data on several commercial sources of $FeCl_3$, he found that the material sold by Chem-Impex, a company that sources iron and chlorinates in Asia, had a remarkable 320 ppm Pd as an 'impurity.' By processing this salt into nanoparticles (NPs) (Scheme 6) for use in an aqueous micellar medium

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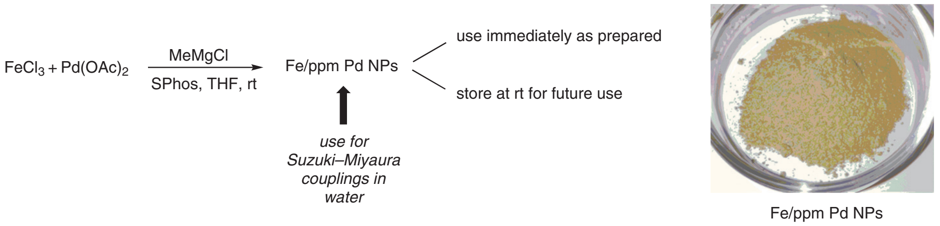

Scheme 6 Preparation and appearance of NPs containing ppm levels of Pd

derived from TPGS-750-M, Suzuki–Miyaura couplings could be efficiently run, and done so with *functionalized* educts (Scheme 7). And what was the cost for the Pd associated with this new technology, ultimately obtained from the mining of iron that was converted into $FeCl_3$? \$0.00. But could the same NPs be fashioned by doping 99.999% pure $FeCl_3$ with 320 ppm of a palladium salt and used in the exact same manner? Yes.

With results such as these, we continued to even out the scorecard, as our manuscript was enthusiastically received at *Science*.[35] Interestingly, within days of its appearance, this $FeCl_3$ was removed from the Chem-Impex catalog; really! Perhaps we tipped them off that there is something more valuable than gold in that ore! For us, this initial reagent set the stage for additional, related NPs that could be made and used (in situ or stored on the shelf) for related ppm Pd-catalyzed processes, such as copper-free Sonogashira couplings[36] and, most recently, Mizoroki–Heck reactions[37] (Scheme 8). Each new NP reagent required, perhaps to no one's surprise, a different ligand for successful C–C bond formations, as summarized below:

Suzuki–Miyaura couplings:	SPhos (>320 ppm Pd/reaction)[35]
Sonogashira couplings:	XPhos (≥500 ppm Pd/reaction)[36]
Mizoroki–Heck couplings:	*t*-Bu_3P (2500 ppm Pd/reaction)[37]

Our continuing interest in ppm level Pd catalysis next turned to the up-and-coming use of aminations of aromatic and heteroaromatic rings, in particular in medicinal chemistry circles. Although the review by Colacot and Snieckus[38] almost ten years ago clearly indicated that such C–N bond-forming reactions were not highly utilized in the first decade of the new millennium, they are now far more popular. They have recently celebrated their 25th anniversary since being introduced by both Buchwald and Hartwig, and a recent review has appeared to acknowledge this well-known type of coupling.[39] Our concern, however, was that these aminations typically, according to this review, require 2–10 mol% Pd, which clearly accounts for the lack of applications *at scale*. The status of this 'name reaction' was also appreciated by a former postdoc in the group, Yitao Zhang, who, after a talk I gave at Penn during his graduate student days in the Chenoweth group, decided that he was going to join us at UCSB, whether I knew it or not. So, *he did*, and wow, was I lucky! Yitao took it upon himself to find a (pre-)catalyst that could be used at the 1000–2500 ppm level to effect these same aminations in water under very mild conditions. And again, *he did* (Scheme 9 and Figure 11). That's 0.10–0.25 mol%, or *over an order of magnitude less Pd* than was currently being used,[40] and featured recyclable water as the reaction medium. Also noteworthy was the observa-

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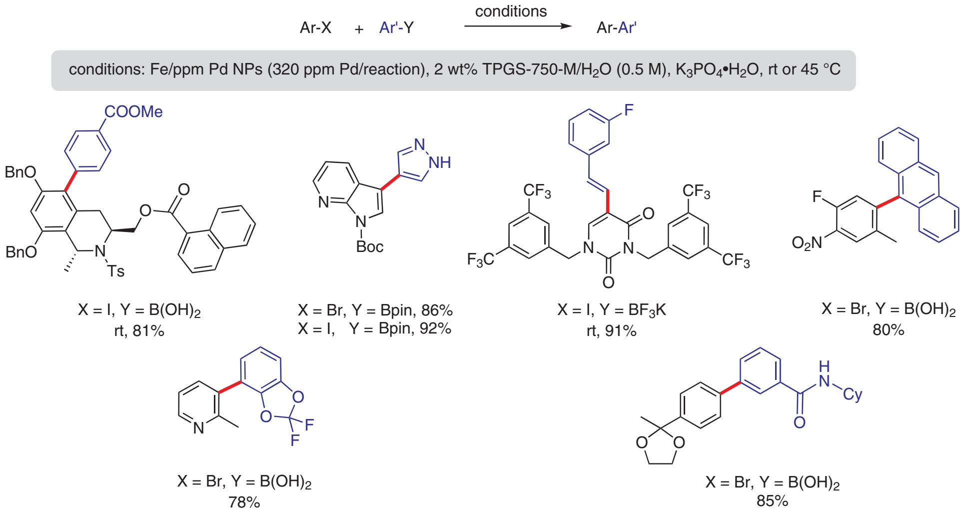
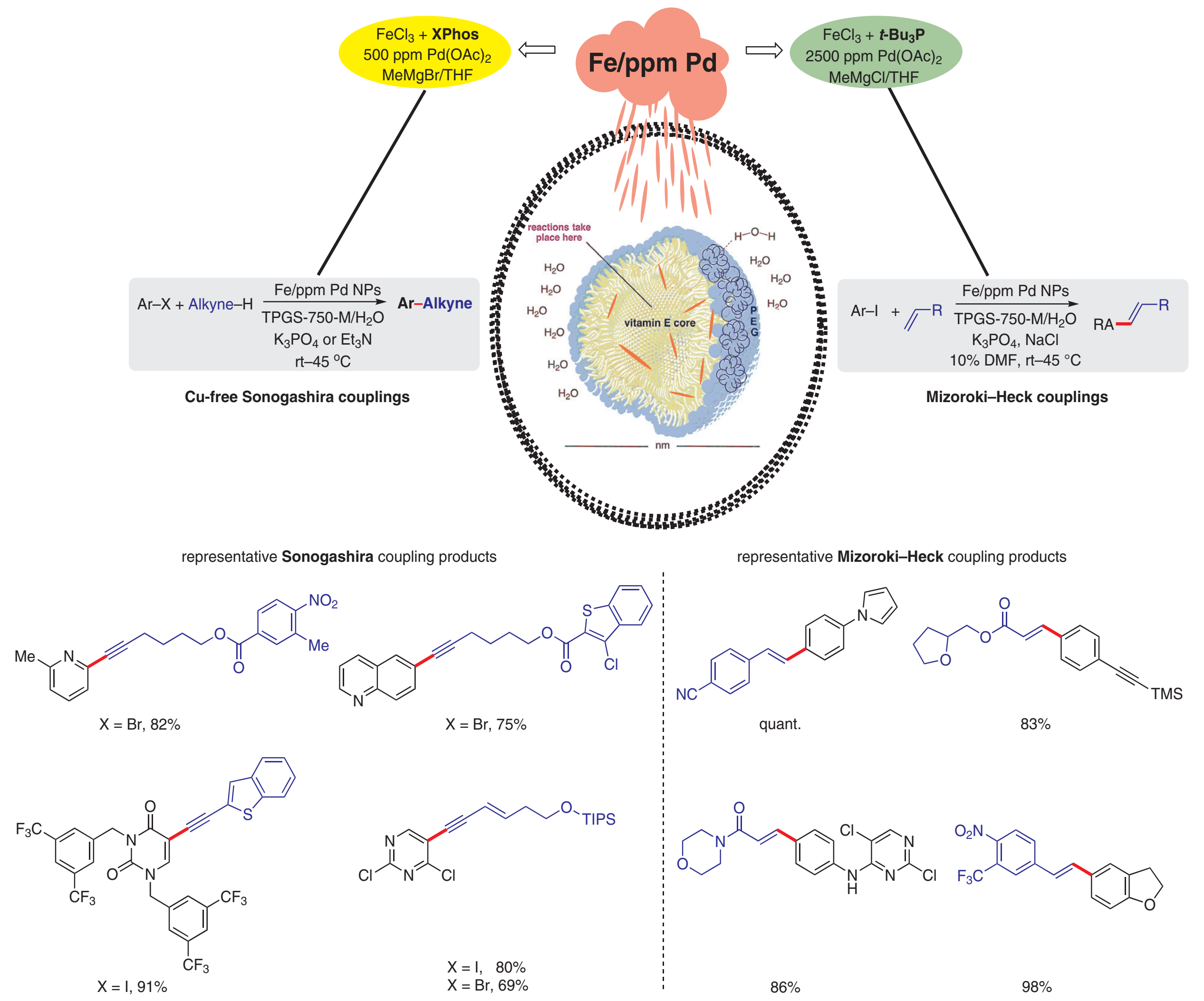
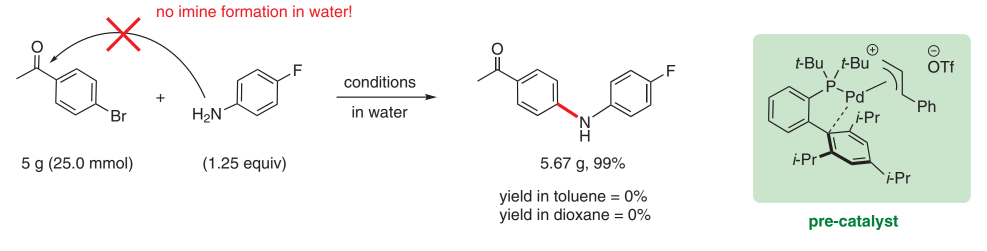


Scheme 7 Representative examples of Suzuki–Miyaura couplings in water catalyzed by ppm Pd NPs



Scheme 8 Different ligands lead to different NPs for heterogeneous Pd-catalyzed couplings. Representative examples of Sonogashira and Mizoroki–Heck couplings using NPs in water.

tion that if the coupling partner contained an aryl ketone in addition to the aryl halide partner, a primary amine reacted as expected within the nanoparticles in water, while in organic media (toluene or dioxane), the corresponding imine was formed to the total exclusion of the product of amination (Scheme 9). Boom! More new rules for chemistry in water.



conditions: [t-BuXPhosPd(π-allyl)]OTf (1000 ppm; pre-catalyst), KO-t-Bu (1.5 equiv), TPGS-750-M/H_2O (0.5 M), 45 °C, 45 min

Scheme 9 Gram-scale amination; note selectivity over imine formation in water

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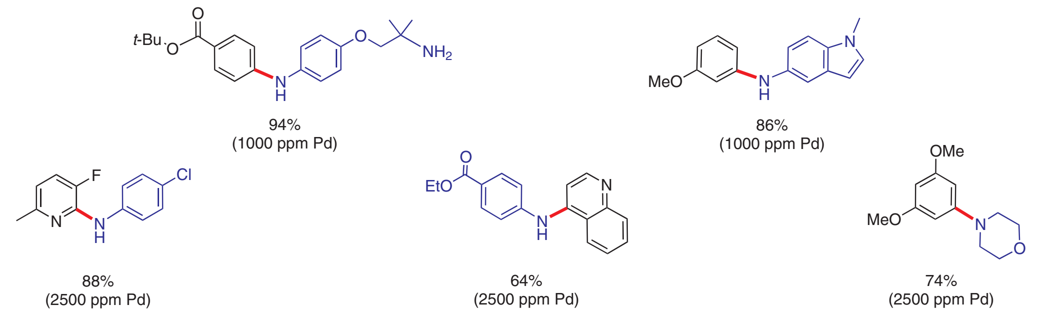

Figure 11 Aminations using 0.10–0.25 mol% Pd in TPGS-750-M/H_2O (0.5 M)/base at 45 °C

So, again, with all this new chemistry and much more embedded within our manuscript (e.g., including a reaction at the 5+ gram scale; applications of the coupling to make six known drug intermediates using far less Pd than that needed from prior art, etc.), we submitted this work to *Chemical Science*. And then we waited…and waited. Finally, the reviews came back and while both were positive, one referee insisted that we do additional experiments, even though we argued that the results to be gleaned from these did little (actually, nothing) to enhance the tenor of this paper. But we ultimately agreed, did the work, altered the text, and then submitted the revised manuscript knowing that all the concerns had been met. We then waited, again, …and waited until it seemed like far too much time had passed for a hardly modified, revised manuscript to be re-examined by the same reviewer. As time moved on, I happened to take note of the Roger Adams award lecture that an old friend, Steve Buchwald (from our days together at Harvard; congratulations, Steve!) was delivering at an upcoming (2019) National Organic Chemistry Symposium (NOS) meeting, and the topic to be discussed on that Tuesday included a heavy dose of amination reactions. Interestingly, after the talk, that next day, we received notice that our revised manuscript was officially accepted as is, and that it could be moved ahead to rapidly appear as an 'Accepted Manuscript' in this journal.[41]

More recently, we had turned our attention to what has come to be called 'late stage functionalization.' The introduction of an especially valued nitrogen-containing residue, such as an amine or nitrile group, into a molecule that is already heavily adorned with functionality is usually very challenging. We were quite aware that several reports on this topic had appeared of late in high-profile journals,[42–44] notwithstanding the fact that very high loadings of metal were involved, including in one case stoichiometric use of palladium.[44] Our efforts were in the area of cyanation, where existing procedures involving complex substrates were not, in my opinion, respectful of the endangered status of palladium, and certainly were far from environmentally responsible in terms of reaction medium. In the hands of mainly two (married) postdocs, Ruchita Thakore and Balaram Takale, and graduate student Vani Singhania, a very effective protocol was worked out that led to the introduction of the nitrile group onto aromatic and heteroaromatic rings. Remarkably, in most cases only 5000 ppm (0.50 mol%) of a commercially available palladacycle (**1**) (Scheme 10) was required as a pre-catalyst for effective use under aqueous micellar catalysis conditions. Literature procedures typically require far greater loadings of endangered Pd.[43,44] Several of our chosen substrates were notably those from the Merck informer library,[45] and were converted in typically modest-to-good yields into their targeted adducts (Figure 12), while simpler cases led to the corresponding adducts very efficiently. Several drug-related intermediates were also synthesized and included in this study, as were a handful of direct comparison cases with existing literature examples. Thus, on all fronts: substrate scope, overall efficiency, loadings of catalyst, greenness of the procedure, etc., there really is no comparison. But as usual, we were faced, yet again, with the same question: Where to publish this work?

We were all very enthusiastic about what had been accomplished; that is, we knew that the technology in hand could be used by medicinal chemists immediately. Moreover, should these new C–CN bonds lead to further development in the hands of a process chemist, that the conditions, i.e., in recyclable water involving <1 mol% of a Pd catalyst…well, they might be an attractive starting point from which to scale up. Considering where other reports had already appeared,[42–44] including journals such as *Nature Chemistry* and *Science*, we unanimously decided to go that route. Unfortunately, after this manuscript sat at *Science* for two weeks, the decision came back not to even consider evaluating the work for publication. Then it was pushed along to *Science Advances*. After yet another month, the *single* referee report came back. It was very complimentary, but said, 'No'. Hmmm! What's the lesson here for the students? We regrouped and decided to send the manuscript to *Angewandte Chemie International Edition* (*ACIE*), but unfortunately without success.

The story, however, did not end there. Interestingly, our manuscript was passed on; actually, 'fast-tracked' at a sister journal, *ChemCatChem*, with the sole request that we submit a rebuttal to the claims by the two referees. Given the

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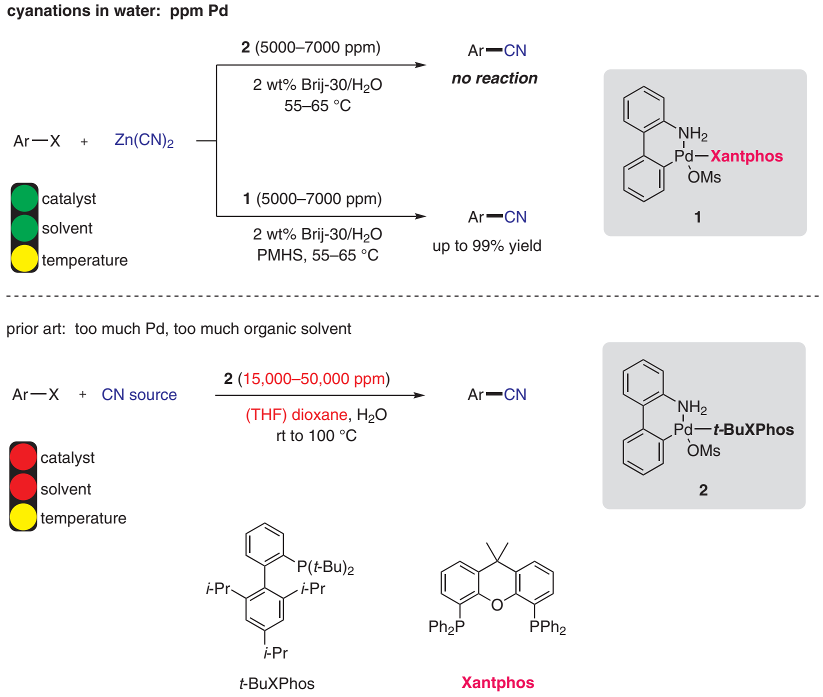

Scheme 10 Cyanations: in water vs literature conditions

nature of these reviewer remarks, our responses were easily scribed and quickly submitted on a Sunday night. The next day the paper was accepted, and by that same Monday evening it had already appeared as an Accepted Article.

Overall, though, quite frankly, Bala and Ruchi were heartbroken; and so was I for them; this might have been their best work yet. In such circumstances, what words can a mentor offer our students? After days of consideration, it occurred to me that in looking back over these past years, that like most in organic chemistry, we have won some and lost some. So, my best advice to them was to know that such events were not personal (well, one would at least like to think so), and that the next outcome could even out the score; that eventually, we are helping to create a future for catalysis, and it's in water wherever our work is published. This was the best that I could do at the time, but I knew that, with some luck, I might have an ace in the hole. This card was not to be played, however, until the outcome of their pending manuscript at *ACIE* was known. We had another good shot at success with this one, showing the world not only how to do Stille couplings in water at the ppm level of palladium (500–1000, or 0.05–0.10 mol%), but also dis-

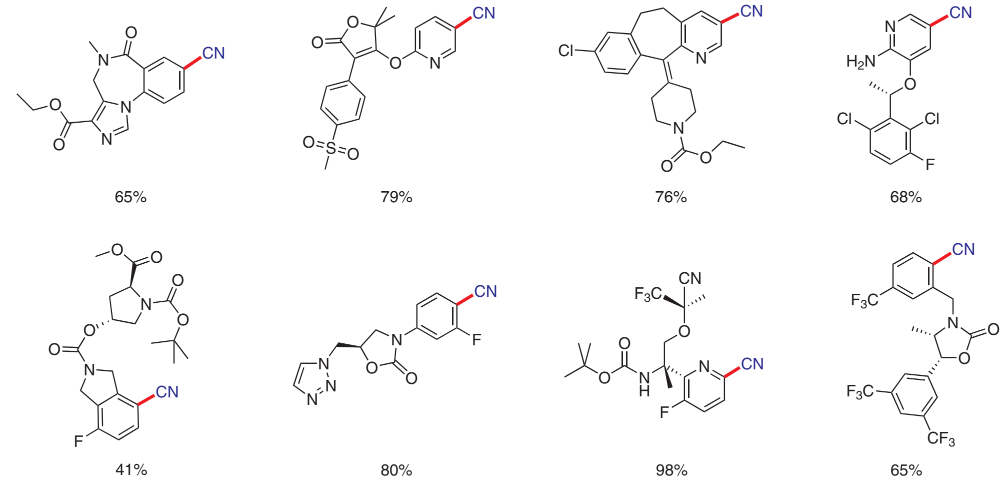

Figure 12 Representative late-stage cyanations of educts from the Merck informer library[45]

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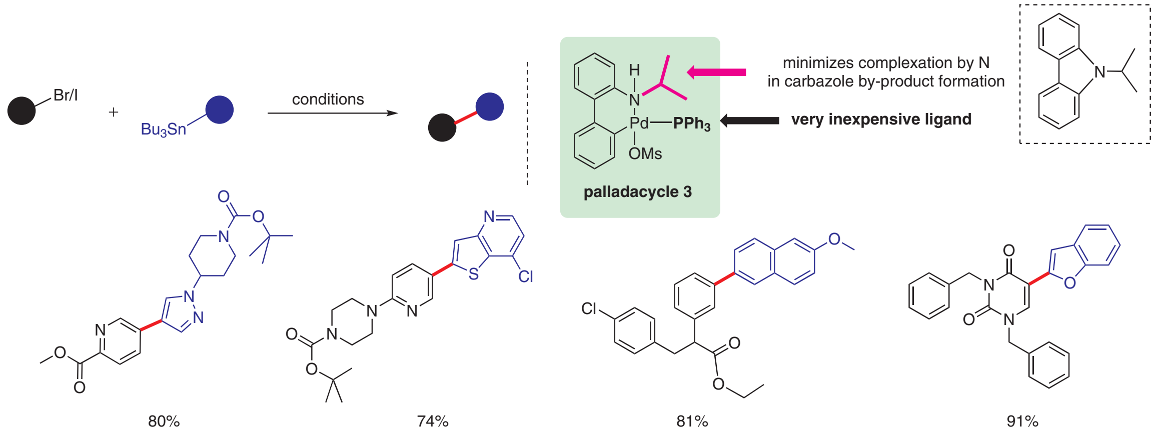

conditions: 500–1000 ppm **palladacycle**, 500–1000 ppm PPh_3, CuI (5 mol%), TBAC (10 mol%), KF (3 equiv), 2 wt% Brij-30/H_2O (0.5 M), 55–60 °C

Scheme 11 Stille couplings in water using ppm levels of new palladacycle **3** containing Ph_3P

closing a new palladacycle (**3**) (Scheme 11)[47] that accomplishes these valued couplings where the ligand is Ph_3P! That's right, triphenylphosphine. And when the reviews came back and both referees rated it as a VIP (very important paper), ranking it in the top 5% of papers published by this high-profile journal, I immediately shared the news, much to their delight. Their faces now acknowledged that my earlier comments made to them were not total nonsense. All was right again in their chemistry world. And I could breathe a sigh of relief as well, since I really needed both of them to tackle one of the biggest challenges in my career: The total syntheses of two antimalarial drugs using our chemistry in water, assigned to them, as part of the recently funded project by the Bill and Melinda Gates Foundation.[48]

6 What are the Implications from These Tales for Today and Tomorrow?

This sounds, yet again, like another 'softball' question; it should not be that tough to interpret these events, to see where chemistry in water is now and what is in store for it going forward. Let's consider, on the one hand, what the downside might be for companies, and even for those in academia, to make this switch from the use of organic solvents to aqueous media.[49] And on the other hand, how does this approach to the same chemical ends fit within the growing wave of sustainability that, finally, is becoming more in focus, more a topic of discussion, and more relevant than ever before?[50]

As for the 'downside', it is probably rather naïve at least for today and the immediate future to think that chemistry in water is going to solve every synthetic problem. We are all taught at some point that 'nothing works in the lab for everything', that there are always exceptions, special cases with special needs that require alternative solutions. Perhaps that will end up being the situation with chemistry in an aqueous medium, but let's not forget that efforts by the community at large have barely begun to think, let alone address, the challenges associated with switching to a water-based discipline. The chemistry world has yet to buy in, to begin making discoveries and applying the new rules of our evolving trade. Nature is still waiting, maybe even laughing at how long it is taking to see what is right there in front of us. So far, there are no major hurdles to using water for chemo-catalysis. If there were, then a big pharma company like Novartis, which through the efforts of process chemists in Basel, most notably Fabrice Gallou and Michael Parmentier,[51] would have found them during our ongoing 10-year collaboration. And while David Constable, a PhD synthetic chemist formerly at GSK and currently Senior Director at the ACS Green Chemistry Institute rarely forgets to remind me that clean water is not available for use in many places in the world, that is a very significant but different challenge facing mankind. For right now and the foreseeable future, for the locations in the world where chemistry is practiced and choices exist, there are no obstacles to choosing water. Even the constant concern expressed by representatives from a few companies (as members of the ACS Green Chemistry Institute's (GCI) Pharma Roundtable (PRT)) that the question of waste water produced using chemistry in water has yet to be fully addressed, has been laid to rest by a team from Novartis under the direction of Fabrice Gallou.[52] Moreover, the old argument that it would be 'too costly' has been thoroughly discredited, as from the standpoint of economics, we now know unequivocally (e.g., from the EPA Presidential Green Chemistry Challenge Awards to several companies each year)[53] that going green is *always* favorable in this regard.

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And what about sustainability? It's a topic, finally, that we hear about almost every day. Google it and be prepared to spend hours. How does chemistry impact this broad term that encompasses, beyond environmental factors, not only economic but also social aspects? What is our role in maintaining 'sustainable development', which Wikipedia defines as 'meeting the needs of the present without compromising the ability of future generations to meet their own needs.' For the past 200 years of modern organic chemistry we have all but ignored our continuing consumption of natural resources, becoming overly dependent upon petroleum for both solvents and so many chemicals used every day. How is it that no one debates the notion that petroleum reserves are finite, or that our supplies of several transition metals, as well as other elements are dwindling, and at the current pace of consumption, are likely to be fully consumed within the next 100 years. What then?

Assessing the sustainability of synthetic organic chemistry through green glasses, what are our options now, and what is in store for us looking ahead? What should we be telling our students? If the assumption that chemistry in water (at least in good measure) is an integral part of our future for all the reasons noted herein and elsewhere,[28,54] then continued progress by an increasing number of research groups is likely, and in fact, is already underway (e.g., as discussed in a variety of recent reviews).[55] The involvement of many more groups is to be expected, especially if various agencies offer attention to, and (perhaps more importantly) funding for, this direction of research. It certainly is a good sign that, as examples, the ACS GCI Pharma Roundtable has recently awarded grants specifically for this purpose,[56] that a member of the GCI PRT, Dan Bailey from Takeda, was presented with the 2020 Dunn Award for his synthesis of TAK-954 in water,[57] and the US Congress has begun to consider an initiative to support sustainable chemistry.[50] These recent developments, together with the ever increasing body of work already in existence, suggests that the sustainability 'wave' is gaining momentum.

Nonetheless, and notwithstanding these leading indicators, synthetic chemists still want, maybe even demand, more; more evidence that going green is not only 'interesting', but that it is here to stay. Translated, those especially in industry are (diplomatically) 'screaming', in a Jerry McGuire sense, 'Show me the money!'[58] How to respond? Answer: Bring in bio-catalysis. Say what?

Every organic chemist hopefully sees by now that water is destined to become the common denominator to both chemo- and bio-catalysis; that by using water as the reaction medium ppm levels of endangered metals, and little, if any, energy beyond ambient temperatures are needed for most reactions. Once we acknowledge these important virtues in chemo-catalysis, let's envision what happens when we meld chemo- with bio-catalysis: doing several reactions—2, 3, 4, 5 steps—in a single pot, in water. Imagine such a scenario becoming routine, intermixing both types of reagents. After all, in addition to the Nobel Prizes of 2018 highlighting directed evolution,[5] together with the many known applications of natural enzymes to synthesis[59] and the commitment today being made by several major pharma companies to bio-catalysis[60]…isn't the future of 'catalysis' obvious? No need for descriptors 'chemo' and 'bio'; no need, as Paul Anastas has claimed for years, to call this 'green' chemistry. Let's just call what we do, in water, 'organic chemistry.'

But do traditional organic chemists realize, or even care, that the know-how to make this happen is already here! Is it so difficult to envision this; where there is no need for replacement of organic solvent, or its evaporation, with water; no creation of huge waste streams composed of highly mixed organics and aqueous media? To date, notwithstanding their perceived incompatibilities (i.e., between the use of chemical reagents in water, and enzymes in organic solvents), as others have suggested might exist,[61] none has as yet prevented such retrosynthetic analyses. If true (i.e., that both approaches can be used in the same pot), doesn't synthesis achieve a new level of sophistication? Doing synthesis along these lines may follow new rules, but think about the benefits from new selectivities, the opening of new opportunities for discovery, and the huge economic and environmental savings to be realized. Lengthy syntheses become far shorter in terms of the number of reaction vessels and involve far fewer workups, while the number of individual product purifications drops precipitously, as does waste generation and the time needed to carry each intermediate to the next step in a series. Whether a sequence calls for a reagent from the 'chemo-' or 'bio-' toolbox matters not; both are on the shelf; both do their jobs, added consecutively and interchangeably into the same reaction medium: water.[62,63] Such enabling technologies satisfy what Hayashi has been promoting, albeit in organic media, for years: 'pot'[64] and 'time'[65] economy.

As initiated in the group by Dr. Margery Cortes-Clerget (Dow) in collaboration with graduate student Nnamdi Akporji (Merck), we have already shown that having a surfactant in the water is the 'magic' ingredient: it enables, e.g., chemo-catalysis (Rh and Au) followed by bio-catalysis with a KRED (i.e., a ketoreductase; Scheme 12).[66] And many more combinations featuring 4–5 sequential reactions with different chemo-catalysis reagents together, in water, with various enzymes (e.g., ene-reductases, lipases, and transaminases) are coming, in varying orders of appearance within each scheme.[62,63,67]

Remarkably, the presence of a surfactant may also discourage enzymatic inhibition by providing, in micellar form, a 'reservoir' effect whereby the lipophilic product can be re-localized, drawn away from buildup in and around the enzymatic pocket. The same aqueous nanomicellar medium also provides a location for chemo-catalysts to reside, thereby decreasing their potential denaturing effect to-

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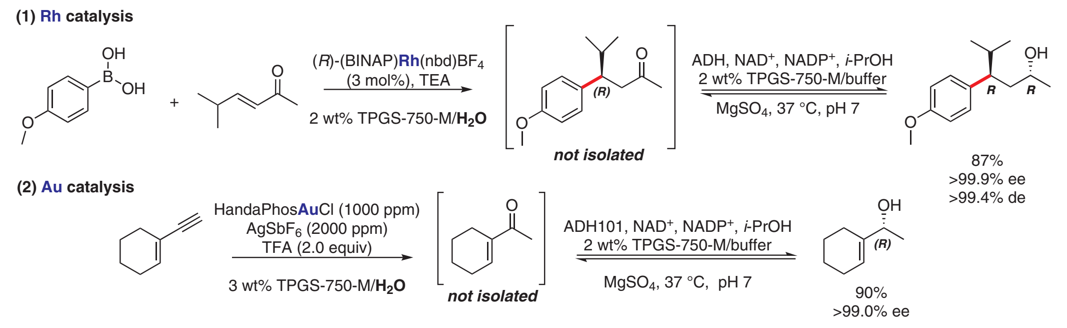

Scheme 12 Two representative examples of one-pot chemo-/bio-catalysis in water

wards enzymes (especially those with metals). Imagine: All that by just adding a well-tolerated surfactant to the water![66]

7 What Is the 'Broader Impact' of This Work?

Among the many valuable comments received from the reviewers of this manuscript, which are most appreciated, came one that asked the important question regarding how chemistry in water is being viewed in a context that extends beyond ongoing and future research. Smart money has it that this referee was in the middle of scribing an NSF proposal, as such a subsection on this topic is nowadays an essential feature of such a document! This aspect, indeed, should be addressed herein.

The answer that this author has come to realize is that for any 'sea change' to be virtually guaranteed, one needs to take the 'Apple' approach. That is, new thinking, in this case regarding the practice of organic synthesis, *needs to be brought to the students*, and this includes not just undergraduates but those at the high school level as well. What is absolutely clear is that these aspiring young scientists 'get it'; that it is soon to be their planet. They immediately understand their inheritance, including: the growing levels of pollution from organic solvents, the metal shortages, the releases ongoing to the atmosphere adding to climate change, and the limited attention these issues have attracted to date. There are signs that progress at these levels is being made, as educational efforts such as those by the ACS Green Chemistry Institute, and *Beyond Benign*,[68] are especially noteworthy. But we must, nonetheless, do more as individual organic chemists, regardless of where we hang our hats. For example, we are looking to the local high schools, inviting chemistry instructors to spend time over the summer in our labs learning green chemistry that each can bring to their classrooms. High school students are getting trained over the summer in our labs, and with proper guidance, have been remarkably responsive.[69,70] We are also in the process of using our decade-plus of experience with so many important reactions now doable in water to create an undergraduate lab *Manual* that will bring the same level of pedagogy to sophomore organic labs, but with experiments (e.g., click reactions, nitro group reductions, Pd-catalyzed couplings, etc.) that rely totally on chemistry in water. The model study being used here at UCSB focused on an S_NAr reaction in water is continuously a 'hit'; every year brings email inquiries from students looking to get involved. Surely others, especially those in academia, will have many alternative suggestions. Now is the time!

8 The Bottom Line…

…is that organic chemists must acknowledge that, through no fault of our own, a mistake was made generations ago that set organic chemistry on an unsustainable path. And that…

…more of the same means less of a future.

The day will surely arrive when we reach that point of inflection; when one or more events *force* the move away from synthetic chemistry in organic solvents and into aqueous media. But as this *Account* hopefully points out in no uncertain terms, there are many 'challenges' that must be overcome before the world of organic chemistry begins, in earnest, to move towards a sustainable discipline. Some of these are purely economic, some are surely cultural, and still others are simply ego-based. And on occasion, it can be all of the above. Nonetheless, it really does not matter which stand in the way. The switch to water must happen; there is no Hollywood ending waiting for us if organic chemistry continues down its current path. We can no longer keep doubling down on chemistry that has no future. Which path makes the most sense? Put another way: Which are *you* betting on: A future based on 200 years of 'modern' organic chemistry in organic solvents, or Nature's billions of years of chemistry in water? This one, for me, was finally a *very* easy call: Nature wins.

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Conflict of Interest

The author declares no conflict of interest.

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It continues to be both an honor and privilege to work with so many students over the past 15 years who have the passion and who share the vision for what all of us see must be the future of organic chemistry. It has also been our good fortune to have attracted the needed financial support to make this chemistry in water a reality. The companies that believe in our mission, and to which we are truly grateful, include: Novartis, PHT International, Anthem Biosciences, Takeda, and Greentech SA. Likewise, crucial research support in the form of grants from the US National Science Foundation is also warmly acknowledged with our sincere appreciation. Lastly, a hearty 'thank you' to Peter Vollhardt for not only providing the opportunity to write this opus, but for the 'poetic license' extended yet again, to this, my third Account to appear in *Synlett*.[22b,24b]

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