

On the Sustainability of Palladium in Organic Synthesis: A Perspective

Palladium-based catalysis: its availability and use, today and tomorrow

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What's the long- and short-term prognosis for palladium in organic synthesis, the key platinum group metal (pgm) for transition metal-based catalysis used today by the fine chemicals industries? Are these processes green and sustainable? Are they environmentally respectful of the metals, especially the pgms, so essential to modern day society? Are non-pgm 'earth abundant' metals an attractive alternative? Where does the up-and-coming area of chemoenzymatic catalysis, which combines chemo- and biocatalysis in one-pot processes in water, fit into the future of drug syntheses? And what about agricultural targets also being made that include palladium catalysis? These and related timely topics are discussed in this Perspective.

1. Is Palladium in Crisis?

Ask any card-carrying organic chemist which metal reigns supreme today in synthetic organic chemistry and most, if not all, will quickly identify palladium as the clear winner. But this soft, silver-white metal is only one of six that make up the pgms, which also include ruthenium, osmium, platinum, rhodium, and iridium. According to the

American Chemical Society (ACS) Green Chemistry Institute (1), palladium has "limited availability..."; the other five are also endangered, given their "rising threat from increased use". In brief, they are, in one way or another, all at risk. And while neither osmium nor even ruthenium is considered 'precious' usually based on cost, both platinum and palladium are certainly 'expensive', while iridium, and especially rhodium, are borderline prohibitive, typically being reserved for reactions where catalyst loadings must be very low. During the past few years, the price of palladium has jumped on occasion to >US\$3000 per troy ounce, **Figure 1** (2), and even today remains competitive with that of gold (*ca.* US\$2000 per troy ounce). What does this suggest regarding the prognosis for pgms even in the short term, let alone the prospects for long-term availability? How can we continue today with a 'business as usual' mentality, knowing that these particular resources on the planet are finite? Are we not already operating in crisis mode, if only on the basis of price, where palladium may provide, at least on paper, the solution to an important synthetic problem but its use in the laboratory is simply unaffordable? For many contract manufacturing organisations (CMOs) that make crucial intermediates, that time is already here. What now?

2. Earth-Abundant Metals?

One prevailing sentiment is that base metals will come to the rescue (3, 4). Do we actually have base metal-catalysed processes ready to step in and allow the community to achieve the same goals? Hardly; the science is simply not there yet. Most notably, reactions looking to replace palladium, for example, with typically 5–10 mol% nickel may offer

academic solutions but, in reality, are just replacing one problem of metal scarcity with others. That is, aside from the additional options for mechanistic variations, for example, with nickel having facile access to various oxidation states normally not commonly involved in palladium catalysis (i.e., Ni(I) and Ni(III)) thereby leading potentially to side-product formation, a different array of ligands is usually required to match nickel for the intended chemistry. More vigorous conditions are also common, thereby requiring greater investments of both energy and time. And lastly, looming large in what is rarely acknowledged in publications using such high loadings in catalysis is the all-but-certain elevated levels of residual metal in each product. This may not be an issue for many practitioners, but it is a crucial consideration in the pharmaceutical industry where the limit according to International Conference on Harmonisation (ICH) Q3D guidelines, for example, for nickel in oral drugs is 20 ppm or less than 200 $\mu\text{g day}^{-1}$ (5–7). Even using 1 mol% of a nickel catalyst is virtually guaranteed to lead to >100 ppm nickel in any product, thereby necessitating additional time and expense required for its removal. Taken together, all of these factors might better be viewed as exchanging the more obvious up-front costs with those overall reaction parameters associated with base metal catalysis. Such considerations, likewise, apply to other base metals beyond nickel (such as copper and cobalt) that, notwithstanding their historic roles played in alchemy, are today also endangered (1). Indeed, focusing on current prices as the sole indicator in the selection process may be leading us into a false sense of security. The reality is that this metric

alone is not an accurate measure in choosing a catalyst, whether considering pgms or otherwise.

While the catalyst selection process, therefore, perhaps argues for more widespread use of pgms, we must recognise that pgm availability, eventually, will begin to drop; that for decades the chemistry community continues to be unwilling to accept the shortages that will likely appear at some point, perhaps within the next 5–10 years, **Figure 1** (2). Is it acceptable today, therefore, or at any time in the near future for all 'consumers' to simply ignore this reality? It seems to always be the 'other guy' using pgms at scale in industrial laboratories who is the big offender, since academicians, for example, typically do chemistry with far smaller quantities. Of course, there are far more users in academia (both at the graduate and undergraduate levels, worldwide), and hence, the major offenders from the overall green chemistry perspective are... academicians! Let's also appreciate that while (transition metal) catalysis at any level of usage may be one of the fundamental "12 Principles of Green Chemistry" (1), it is listed at number nine. In other words, while pgms should be an integral part of environmentally responsible synthetic chemistry, where recycling must figure prominently (8), its usage should be viewed as part of a holistic picture.

3. Do We Have Options?

Today, most catalysis is still done, unfortunately, with far too much metal, precious or otherwise. Proof of this pervades the chemical literature and is easily seen; for example, recent work by big pharmaceutical companies (9–10). But beyond



Fig. 1. Price of palladium (per troy ounce) over time (2)

these catalyst issues, synthetic chemistry was developed in, and is 'matched' to, waste-generating organic solvents (6), thereby consuming enormous amounts of our limited petroleum reserves. Rarely acknowledged, of course, is that most of this organic waste is burned giving rise to CO₂, much of which is released into the atmosphere. In addition, there are temperature requirements for catalytic processes, which typically means heating reactions (i.e., investing energy) that lead to byproducts that generate even more waste from subsequent product purification.

Along with transitioning away from organic solvents into alternative reaction media (11) come changes in the rules for doing organic synthesis (12); rules that embrace new opportunities as they appear, and that are in harmony with nature. With all these issues facing traditional organic chemistry, perhaps the overriding question that must be addressed is: should we be betting our future on 200 years of modern synthetic organic chemistry in organic solvents, or millions of years of chemistry by nature in water?

Fortunately, the beginnings of environmentally friendly and economically attractive alternatives are becoming more apparent on a regular basis. Not surprisingly, nature continues to provide guidance that is leading to viable solutions for the practice of organic chemistry that include: (a) minimising the need for organic solvents of any type, thereby dramatically reducing organic waste and allowing for telescoping to become routine, rather than limited due to individual reaction solvent needs; (b) reliance on lower levels of pgm-based catalysts, thereby extending the lifetime of available supplies; and (c) reactions being run under ambient temperatures, thereby avoiding higher temperature-induced byproduct formation,

along with associated investments of time and effort to effect separations.

Recognition of the path forward comes easily once an appreciation of nature's success is recognised... success realised all in water. But most chemistry of carbon involves water-insoluble materials, so what's nature's secret? Answer: 'dirty water'. The 'dirt', of course, corresponds to the numerous chemicals present in the oceans that might have assisted the evolutionary process: vesicles, membranes, salts and yes, micelles in which chemistry of water-immiscible compounds took place. Clearly, the Earth's water through time was not pristine.

Some of this 'dirt' that has led to numerous opportunities for transitioning several of the most heavily used reactions away from organic solvents focuses on development of 'benign by design' surfactants that enable chemistry 'in water'. Newly introduced amphiphiles such as the vitamin E-containing TPGS-750-M (13), proline-derived PS-750-M (14) and the rosin-based APGS-2000-M (15) (**Figure 2**) each spontaneously form micellar arrays upon dissolution in water (above their critical micellar concentrations, which tend to be very low). These are just a few examples of technologies that continue to show considerable promise for use in synthesis.

The potential for modernised micellar catalysis 'in water' to significantly extend pgm usage almost indefinitely (admittedly only with respect to synthetic chemistry) is represented by recently reported processes for the most heavily utilised palladium-catalysed cross-couplings; for example, Nobel Prize-winning Suzuki-Miyaura reactions (16). Hence, by varying either the ligand, as with HandaPhos (17), (**Figure 3**) or more recently biaryl N₂Phos (18), or the substitution pattern on a palladacycle (especially with the most atypical

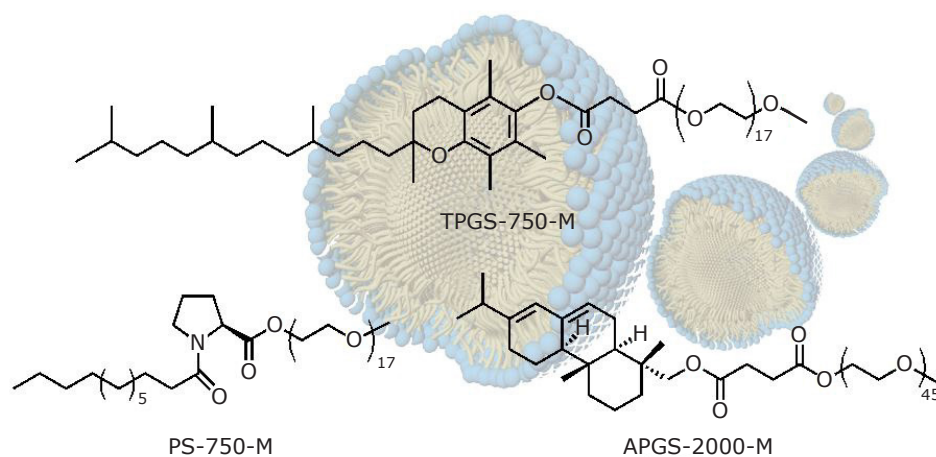


Fig. 2. Structures for three common surfactants used in aqueous micellar catalysis

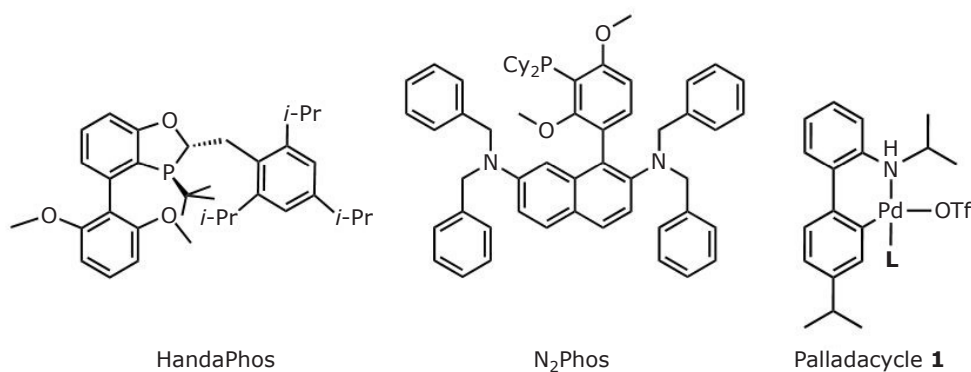
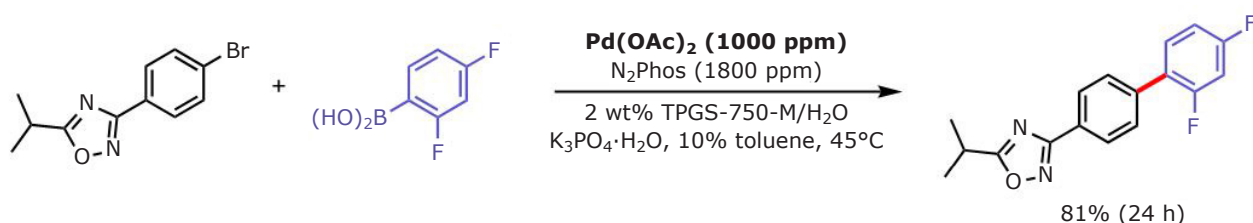


Fig. 3. Structure of ligands HandaPhos and N₂Phos, and palladacycle **1**, for use in parts per million level palladium catalysis



Scheme I. Representative example of a Suzuki-Miyaura coupling in water using parts per million level palladium catalysis

but synthetically significant isopropyl group on nitrogen) (19) as in palladacycle **1**, key biaryl bonds involving highly functionalised reaction partners can now be made in water with loadings of palladium in the parts per million range (for example, as in **Scheme I**; 1000 ppm palladium = 0.1 mol%). Very similar options exist as well for related parts per million level palladium catalysis applied to Sonogashira (20), Stille (21), Mizoroki-Heck (22) and Negishi (23) couplings. The same is true for aminations (i.e., C–N bond formations), also now achievable in water using parts per million loadings of palladium (24–26). As industrial laboratories, especially in the pharmaceutical and agrochemical areas, face continuing regulatory scrutiny and demands that place restrictions on environmentally allowable chemistry (27), not to mention costs to the consumer, the importance of extending access to pgms *via* usage at parts per million levels becomes all-the-more obvious.

4. Platinum Group Metals and Biotechnology, or Platinum Group Metals vs. Biotechnology?

Another area impacted, perhaps to the greatest extent by 'dirty water' that is destined to play an increasingly important role in the future of organic

synthesis, is chemoenzymatic catalysis (28). That is, featuring one-pot reaction sequences where both chemocatalysis and biocatalysis occur utilising the same 'solvent': water. The presence of an aqueous micellar medium accommodates the requirements of each type of catalysis: chemocatalysis, focusing on the type and amounts, for example, of pgms being used, and biocatalysis that relies mainly on enzymes present in the water, whether natural or engineered *via* directed evolution (29). Thus, as shown in **Figure 4**, the combination is especially powerful not only in allowing for tandem processes to take place, but also in its avoidance of unsustainable levels of precious metal catalysts (note the use of only 2500 ppm palladium, or 0.25 mol%). Moreover, the switch to water (11), rather than using organic solvents that typically involve aqueous workups of any intermediate(s), avoids waste-generating purification(s). The enzymes involved, with all their innate virtues, can thus be used either in the initial reaction; for example, a lipase, leading to esterification (30), or, in a subsequent step, for example, an initial transition pgm-catalysed reaction (such as a palladium-catalysed Sonogashira coupling) followed by an asymmetric carbonyl reduction mediated by a ketoreductase (KRED; such as, ADH101) to give a nonracemic

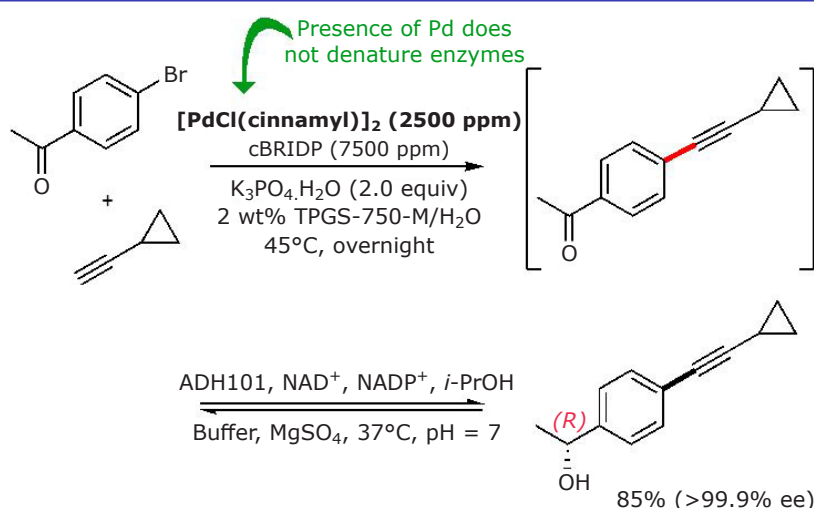


Fig. 4. Representative example of chemoenzymatic catalysis, where parts per million levels of palladium suffice

product alcohol, not surprisingly in high ee's (31). It should also be noted that the same surfactant technology that enables chemoenzymatic catalysis also ensures minimal enzyme denaturing due to the presence of pgms that continue being used in the unsustainable 1–10 mol% range (9, 10). Presumably, the nanomicelles provide alternative 'housing' for the pgm-based ligated catalyst, rather than its typical localisation in the aqueous buffered medium. Thus, with an order of magnitude less pgm present in the reaction medium, which is all that is now needed for chemocatalysis, chances are that the compatibility question associated with even highly sensitive enzymes might soon end up as a solved problem.

5. What's 'Wrong' with this Picture?

While the issues of sustainability noted above apply to all users of pgm catalysts, what's the view from industrial companies that process the raw materials leading up to the availability of pgm catalysts? After all, isn't there an implied assumption that they have unlimited access to metals, and pgms, in particular, needed by the chemistry enterprise? Assumptions aside, where are we today on this front (8), and just how much do other factors, such as geopolitical issues figure into the equation, for example, given that >40% of the world's supply of palladium comes from Russia (32)? In other words, what is being done to address future needs of pgms? Even when nature provides unexpected sources; for example, the finding that palladium is present to varying degrees as an 'impurity' in the mining of the truly Earth-abundant iron ore (33), the community at large still sees most of these discoveries not as opportunities (34) but as

experimental failures (35). These attitudes must change, and these questions must be addressed sooner than later. Otherwise, fundamental organic synthesis that depends so heavily on pgm-based catalysis in organic solvents will simply continue digging that 'rabbit hole', using more and more resources being taken from future generations. How much longer will it take before the obvious is acknowledged: that organic chemistry as currently practiced is unquestionably unsustainable?

Perhaps the graph in **Figure 1** illustrating the price of palladium over time helps tell the story (2). What will this picture look like 5–10 years from now? And even as society gradually moves away from gasoline-powered engines that dramatically increases supply as the need for catalytic converters eventually dwindles, in terms of long-term availability, aren't we just postponing the inevitable? Isn't the solution obvious: let's find a way, today, to do more with less. Just moving the decimal point in terms of usage one unit to the left solves the problem, both short and long term. And while hints that technology that relies on only parts per million loadings of palladium is already in hand (25, 33, 36, 37), any workable solution must include collaborations with industrial colleagues, especially those who not only share this vision for the future of pgms, but who also have their fingers at all times on the pulse of the field as to where we are and, perhaps more importantly, where we are going (8).

6. Conclusions

In summary, pgm-containing catalysts will continue to play crucial roles in processes currently in use or under development in academic and many

industrial laboratories, alike. Technologies already exist in the toolbox for reducing consumption of pgms to ensure that access to these absolutely essential metal-containing catalysts are available for both immediate and future use, with many more additions to this toolbox coming. Nonetheless, in the big picture sense, how pgms are viewed today must include both short-term and long-term perspectives. Short-term swings in availability are just that: short term. But overall, the chemistry community must appreciate that we are, today, stewards of a very important finite planetary resource requiring a holistic approach that ensures that tomorrow's needs in catalysis, mainly defined by having similar access to pgms, can be met.

References

1. 'Endangered Elements', American Chemical Society, September, 2019, Washington, USA
2. 'Palladium Prices – Interactive Historical Chart', MacroTrends, Seattle, USA: <https://www.macrotrends.net/2542/palladium-prices-historical-chart-data> (Accessed on 28th July, 2022)
3. M. J. Goldfogel, X. Guo, J. L. Meléndez Matos, J. A. Gurak, M. V. Joannou, W. B. Moffat, E. M. Simmons and S. R. Wisniewski, *Org. Process Res. Dev.*, 2022, **26**, (3), 785
4. S. Handa, E. D. Slack and B. H. Lipshutz, *Angew. Chem. Int. Ed.*, 2015, **54**, (41), 11994
5. 'ICH Q3D Elemental Impurities – Scientific Guideline', European Medicines Agency, Amsterdam, The Netherlands: <https://www.ema.europa.eu/en/ich-q3d-elemental-impurities> (Accessed on 28th July 2022)
6. A. M. Thayer, 'Trace Metals Debate', *Chemical Engineering News*, Washington, DC, USA, August, 2013
7. 'Committee for Human Medicinal Products (CHMP): Guideline on the Specification Limits for Residues of Metal Catalysts', Doc. Ref. CPMP/SWP/QWP/4446/00 corr., European Medicines Agency, Amsterdam, The Netherlands, January, 2007, 32 pp
8. E. Schofield, *Johnson Matthey Technol. Rev.*, 2023, **67**, (3), 285
9. S. Pithani, M. Malmgren, C.-J. Aurell, G. Nikitidis and S. D. Friis, *Org. Process Res. Dev.*, 2019, **23**, (8), 1752
10. G. L. Beutner, E. M. Simmons, S. Ayers, C. Y. Bemis, M. J. Goldfogel, C. L. Joe, J. Marshall and S. R. Wisniewski, *J. Org. Chem.*, 2021, **86**, (15), 10380
11. B. H. Lipshutz, *J. Org. Chem.*, 2017, **82**, (6), 2806
12. B. H. Lipshutz, *Curr. Opin. Green Sus. Chem.*, 2018, **11**, 1
13. B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston and R. C. Gadwood, *J. Org. Chem.*, 2011, **76**, (11), 4379
14. J. Brals, J. D. Smith, F. Ibrahim, F. Gallou and S. Handa, *ACS Catal.*, 2017, **7**, 7245
15. Y. Zhang, B. Zhu, Y. Zheng and S. Huang, *J. Organomet. Chem.*, 2022, **965–966**, 122321
16. N. Miyaura and A. Suzuki, *J. Chem. Soc. Chem. Commun.*, 1979, (19), 866
17. S. Handa, M. P. Andersson, F. Gallou, J. Reilly and B. H. Lipshutz, *Angew. Chem. Int. Ed.*, 2016, **55**, (16), 4914
18. N. Akporji, R. R. Thakore, M. Cortes-Clerget, J. Andersen, E. Landstrom, D. H. Aue, F. Gallou and B. H. Lipshutz, *Chem. Sci.*, 2020, **11**, (20), 5205
19. R. R. Thakore, B. S. Takale, F. Gallou, J. Reilly and B. H. Lipshutz, *ACS Catal.*, 2019, **9**, (12), 11647
20. B. Jin, F. Gallou, J. Reilly and B. H. Lipshutz, *Chem. Sci.*, 2019, **10**, (12), 3481
21. B. S. Takale, R. R. Thakore, G. Casotti, X. Li, F. Gallou and B. H. Lipshutz, *Angew. Chem. Int. Ed.*, 2021, **60**, (8), 4158
22. H. Pang, Y. Hu, J. Yu, F. Gallou and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2021, **143**, (9), 3373
23. Y. Hu, M. J. Wong and B. H. Lipshutz, *Angew. Chem. Int. Ed.*, 2022, **61**, (39), e202209784
24. Y. Zhang, B. S. Takale, F. Gallou, J. Reilly and B. H. Lipshutz, *Chem. Sci.*, 2019, **10**, (45), 10556
25. R. R. Thakore, K. S. Iyer and B. H. Lipshutz, *Curr. Opin. Green Sustain. Chem.*, 2021, **31**, 100493
26. J. R. A. Kincaid, M. J. Wong, N. Akporji, F. Gallou, D. M. Fialho and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2023, **145**, (7), 4266
27. J. Becker, C. Manske and S. Randl, *Curr. Opin. Green Sustain. Chem.*, 2022, **33**, 100562
28. L. Bering, J. Thompson and J. Micklefield, *Trends Chem.*, 2022, **4**, (5), 392
29. F. H. Arnold, *Angew. Chem. Int. Ed.*, 2018, **57**, (16), 4143
30. V. Singhania, M. Cortes-Clerget, J. Dussart-Gautheret, B. Akkachairin, J. Yu, N. Akporji, F. Gallou and B. H. Lipshutz, *Chem. Sci.*, 2022, **13**, (5), 1440
31. M. Cortes-Clerget, N. Akporji, J. Zhou, F. Gao, P. Guo, M. Parmentier, F. Gallou, J.-Y. Berthon and B. H. Lipshutz, *Nat. Commun.*, 2019, **10**, 2169
32. 'Value of Palladium Exports from Russia from 2018

- to 2021 (in Million US Dollars)', Statista Inc, New York, USA, May, 2022
33. S. Handa, Y. Wang, F. Gallou and B. H. Lipshutz, *Science*, 2015, **349**, (6252), 1087
34. S. K. Ritter, 'A More Natural Approach to Catalysts', *Chemical Engineering News*, Washington, DC, USA, February, 2017
35. L. K. Boerner, 'Metal-Free? The Mistake that Chemists Seem Doomed to Repeat', *Chemical Engineering News*, Washington, DC, USA, February, 2022
36. B. H. Lipshutz, J. C. Caravez and K. S. Iyer, *Curr. Opin. Green Sustain. Chem.*, 2022, **38**, 100686
37. B. H. Lipshutz, *Synlett*, 2021, **32**, (16), 1588

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Bruce Lipshutz is currently a Distinguished Professor of Chemistry at the University of California, Santa Barbara (UCSB), USA. His research group continues to develop new technologies that are environmentally responsible by enabling key transition metal-catalysed cross-couplings and many other of the most common reactions to be carried out in water under mild conditions. The Lipshutz group has also focused its attention on developing new catalysts for key palladium and several other transition metal-catalysed reactions that enable C–C, C–N and C–H bond formation, typically involving both precious and base metals at the parts per million level. Most recently, these newly developed technologies in chemocatalysis have been merged with biocatalytic processes, commonly referred to as 'chemoenzymatic catalysis', which allow for tandem, one-pot reactions, all enabled by designer surfactants in water.
