

The ‘Nano-to-Nano’ Effect Applied to Organic Synthesis in Water

A remarkable opportunity to use not only water as the reaction medium but very little surfactant and catalyst containing only ppm levels of metal under mild conditions

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The remarkable benefits associated with the attraction of polyethylene glycol (PEG)-containing nanomicelles to metal nanoparticles in water allows for varying types of important catalysis to be done under very mild and green conditions.

1. Introduction

Aqueous micellar catalysis is far from new (1, 2). Indeed, although a wealth of information on this topic has been accumulated over many decades (3, 4), an appreciation of the potential for this chemistry to replace organic solvents as the reaction medium in many of the most commonly used reactions in catalysis has only recently been advanced (5–8). The explanations behind this surprising state of affairs may lie in the lack of training received in this area and the normal mindset among synthetic organic chemists that the presence of water in a reaction, in other than selected cases (for example hydrolysis), is to be avoided. Hence, its use as the entire reaction medium is rarely a consideration. Simply put, organic chemistry takes place in organic solvents and so why ‘complicate’ an already challenging science?

The short answer is that times have changed and as environmental and human health issues continue to come into focus, so must our attention take note that the chemistry enterprise is creating huge amounts of organic waste, the most egregious component of which is organic solvents (9). Getting them out of organic chemistry should be a goal that chemists strive to achieve, as the way this field is currently practiced is just not sustainable. How can it be that there is not a single key reaction parameter associated with the way catalysis is done today that overlaps with the manner in which nature continues to practice organic chemistry (**Figure 1**)? Fortunately, there is already strong evidence indicating that by redesigning surfactants for synthetic chemistry (5–8), these form nanomicelles that enable homogeneous catalysis to be efficiently applied to the very same reactions valued by synthetic chemists, but with one major difference: they are done under environmentally responsible conditions.

The two leading nonionic designer surfactants forming micellar arrays in water that accommodate many differing reaction partners, catalysts and additives are DL- α -tocopherol methoxypolyethylene glycol succinate (TPGS-750-M) (10) and β -sitosterol methoxyethyleneglycol succinate (SPGS-550-M) also known as ‘Nok’ (11) (**Figure 2**). Both form nanomicelles that, unlike the majority of surfactants typically found in catalogues frequented by the synthetic community, are of the ‘right’ size or shape leading to bond formations that are usually as good or better than those observed in organic media. But what had originally not been fully

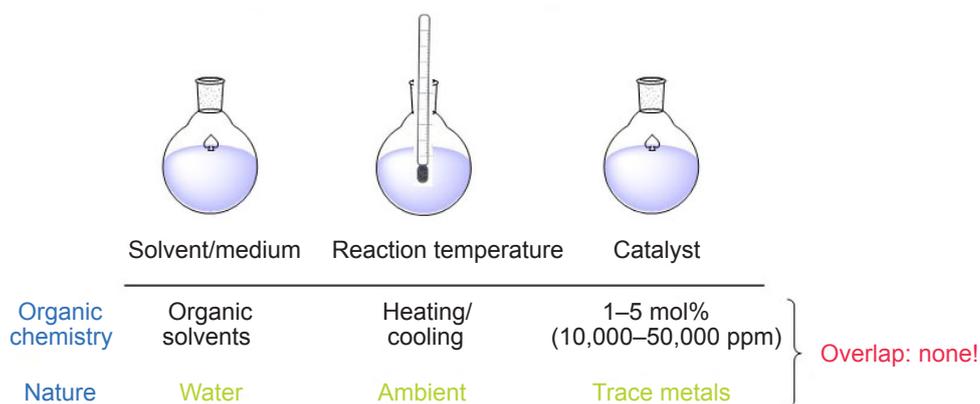


Fig. 1. Extent of overlap as practiced by nature vs. modern organic chemistry: none

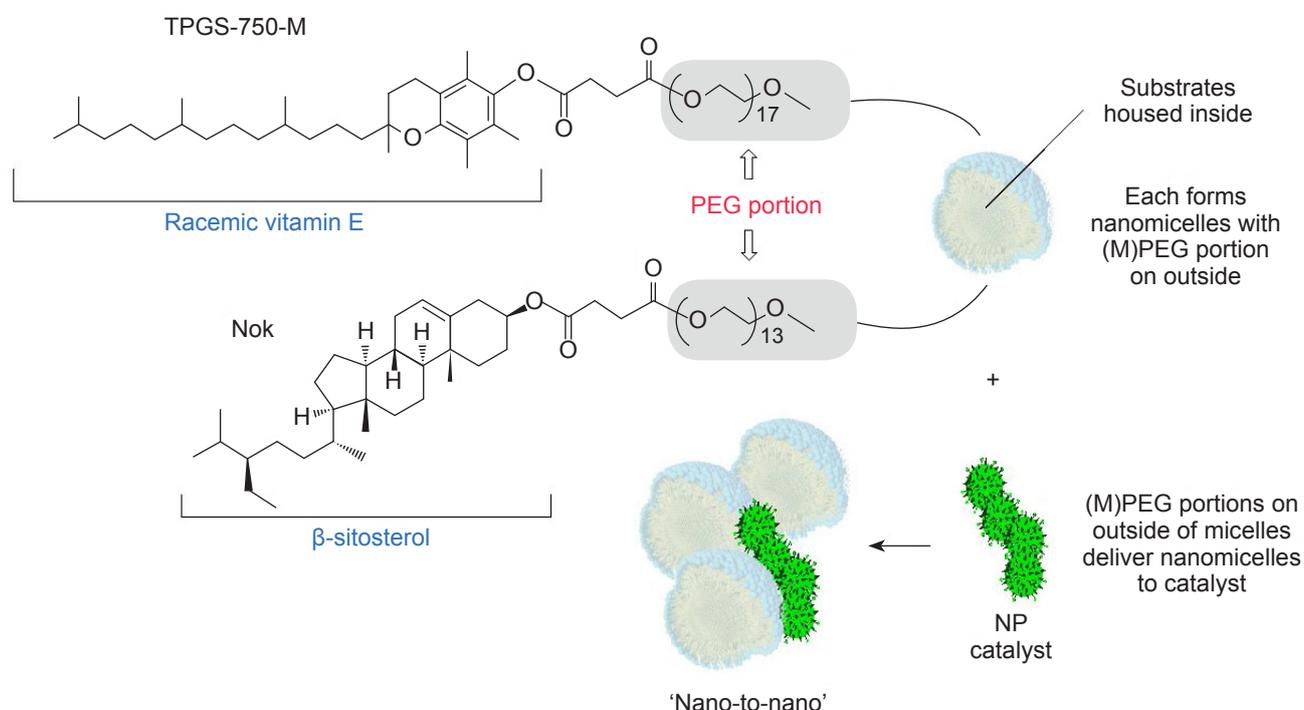


Fig. 2. Designer surfactants leading to nanomicelles that participate in 'nano-to-nano' effect

appreciated is that the methoxy polyethylene glycol (MPEG) (or polyethylene glycol (PEG), in general) present in these 40–60 nm spheres of TPGS-750-M or rods of Nok has a natural tendency to function as a stabilising ligand around metal nanoparticles (NPs) (12, 13) that are also present as catalysts in the water. In other words, generation of metal nanoparticles as catalysts attract the MPEG-containing micelles, which is tantamount to an internal delivery system of the reaction partners housed within the micelles

to the catalyst. This 'nano-to-nano' effect offers a remarkable opportunity to use not only water as the reaction medium, but very little surfactant and catalyst containing only ppm levels of metal, and to do such heterogeneous catalysis under atypically very mild conditions (between 22°C and 45°C).

That this phenomenon is not only happening but also likely to be responsible for the facile catalysis observed is clear from cryo-transmission electron microscopy (cryo-TEM) analyses. These data show an unequivocal

preponderance of nanomicelles aggregated around metal NPs, whereas in the absence of such NPs an otherwise even distribution of micelles in the surrounding water is seen. While such an association does not prove that the observed catalysis is taking place as proposed, it does document the ‘nano-to-nano’ effect that localises the high concentration of substrate within the micelle directly at the catalyst surface, potentially accounting for the lack of energy (in the form of heat) needed to enhance interactions in these heterogeneous mixtures that otherwise might be needed in organic solvents where no such formal delivery mechanism exists.

2. The ‘Nano-to-Nano’ Effect: Palladium, Nickel and Copper Nanoparticles

2.1 Palladium

The first observation came unexpectedly when Pd NPs were generated from the combination of palladium acetate ($\text{Pd}(\text{OAc})_2$) and sodium borohydride (NaBH_4) in aqueous TPGS-750-M at room temperature (14). The resulting heterogeneous aqueous mixture could be used to great advantage, converting a variety of unsymmetrically disubstituted alkynes to the corresponding *Z*-alkenes, typically with >99:1 *Z*:*E* selectivity (Figure 3). Part of the success observed in these net Lindlar-like reductions is the facility with which the reaction mixture could be recycled, including the water, the surfactant therein, and the Pd catalyst. Thus, an ‘in-flask’ extraction with an ethereal solvent (for example methyl *tert*-butyl ether (MTBE)) afforded the product, leaving behind all other ingredients ready for

introduction of the same or an alternative educt, along with fresh reductant. The overall reliance on organic solvents, therefore, was shown to be at least an order of magnitude lower than amounts often required with similar reactions in the literature (15). Moreover, these differences are to be realised prior to recycling of the aqueous mixtures.

A similar ‘nano-to-nano’ effect was seen with new NPs derived from the reduction of iron(III) chloride (FeCl_3), where either the naturally occurring content of Pd within FeCl_3 or by externally doping with $\text{Pd}(\text{OAc})_2$ at the ppm level sufficed to arrive at active catalysts useful for important cross-couplings (Figure 4) (16). That is, given the threshold presence of ca. 350 ppm Pd, NP formation upon treatment of the mixture (i.e., FeCl_3 + 350 ppm Pd) with methylmagnesium chloride (MeMgCl) in tetrahydrofuran (THF) at ambient temperatures affords the desired NP catalysts. When prepared in the presence of SPhos, the resulting NPs mediate Suzuki-Miyaura couplings in aqueous nanomicelles between room temperature and 45°C. Extensive analyses of this isolable powder, including a cryo-TEM experiment conducted on the reaction medium (TPGS-750-M + water) again confirmed the aggregation of nanomicelles together with the solid iron nanoparticles containing ppm levels of palladium (here designated Fe/ppm Pd NPs).

This newly developed NP platform, consisting of mostly Mg, Cl and THF, with Fe accounting for only ca. 2.5% of the mix, can be altered as a function of the ligand added prior to their preparation. Changing the recipe from inclusion of SPhos to XPhos now allows for efficient ‘nano-to-nano’ catalysis of Sonogashira

Lindlar-like reductions using Pd NPs: alkynes to *Z*-alkenes:

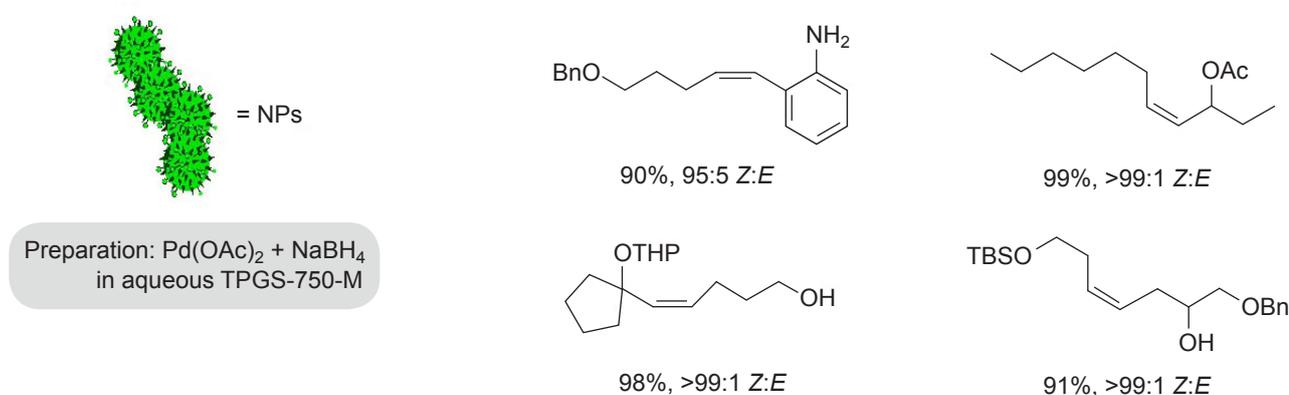


Fig. 3. Representative Lindlar-like reductions of alkynes to *Z*-olefins (14)

Suzuki-Miyaura cross-couplings with Fe/ppm Pd NPs

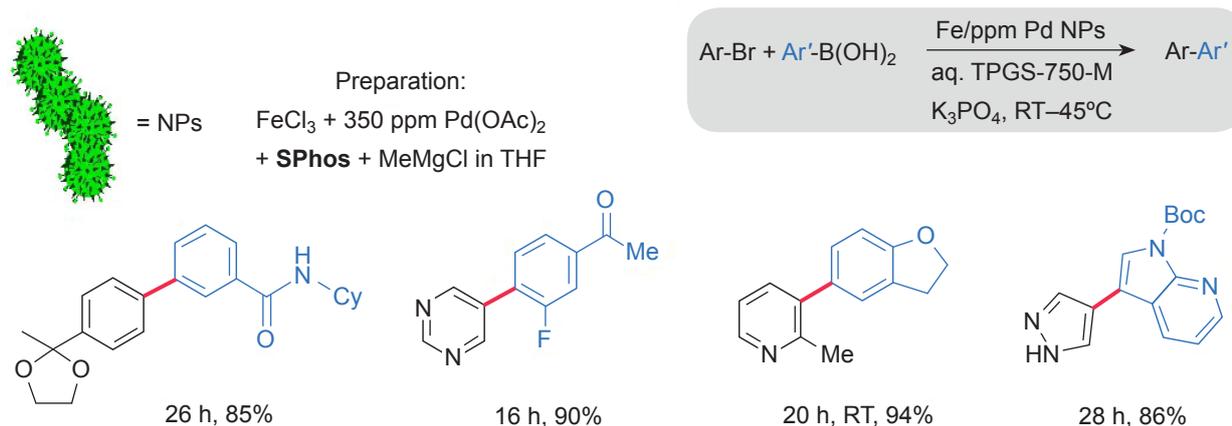


Fig. 4. Fe/ppm Pd NPs that enable Suzuki-Miyaura couplings in aqueous TPGS-750-M NPs based on the 'nano-to-nano' effect (16)

couplings in the same recyclable aqueous mixtures (Figure 5) (17). Recycling is smoothly orchestrated using very limited amounts of a single and recyclable, organic solvent for 'in flask' extraction.

These NPs derived from FeCl_3 can also be prepared in the absence of any ligand, otherwise required for Pd-catalysed cross-couplings. In this case, the 'nano-to-nano' effect can be used to effect reductions of aromatic and heteroaromatic nitro groups in water at room temperature (18, 19). The stoichiometric reductant is NaBH_4 , although as recently updated at Novartis in Basel, Switzerland, the addition of potassium chloride (KCl) or the use of fresh potassium borohydride (KBH_4) appears to be the hydride source of choice (20). Only 80 ppm of palladium (as Pd(OAc)_2) is required for these NP reductions, again implicating a palladium hydride species (Figure 6). The mild reaction conditions account for the tolerance of many functional

groups. Importantly, use of hydrogen gas in place of a borohydride is totally incompatible with this catalyst and in fact, is detrimental to the overall reduction.

2.2 Nickel

Notwithstanding the reported success of the catalyst ($\text{Fe/ppm Pd NPs} + \text{BH}_4^-$) applied to nitro group reductions (above) (18, 19), doping of this NP platform with metals other than Pd offers either additional benefits to existing processes, or potentially new opportunities to lower both base and precious metal usage to ppm levels. Part of the incentive to further investigate along these lines is that the amount of residual metal(s) in the desired products has been found to be below tolerance levels as established by the US Food and Drug Administration (FDA). That is, going into these reactions with ppm amounts of transition metal catalysts, rather than the more typical 1–5 mol% range (10,000–50,000 ppm),

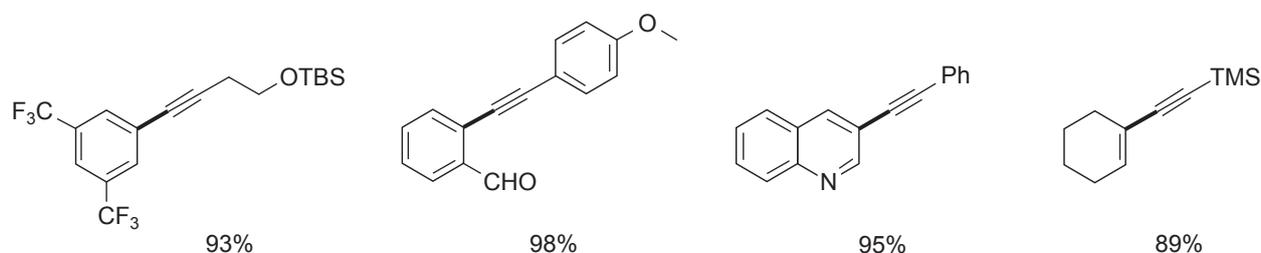


Fig. 5. Fe/ppm Pd NPs used for Sonogashira couplings in aqueous TPGS-750-M (17)

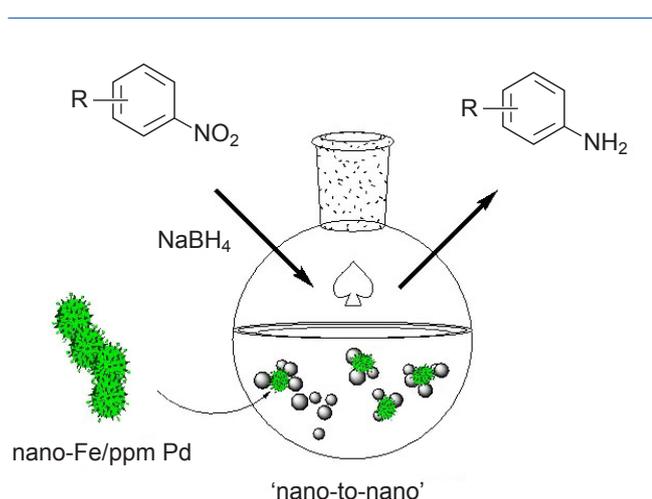


Fig. 6. Ligandless Fe/ppm Pd NPs applied to nitro group reductions (18–20)

leads to acceptable ppm levels of metal impurities that obviate additional time and cost for their removal, a very common occurrence under traditional conditions in organic solvents. In work soon to appear (21), doping these Fe-based NPs with additional ppm levels of a Ni(II) salt affords a reagent that has been found, likewise, to efficiently reduce nitro group-containing aromatic or heteroaromatic compounds, but often at a far greater rate under otherwise identical conditions of concentration, time and temperature. **Figure 7** shows a few comparison cases.

2.3 Copper

Another metal used extensively in organic chemistry is copper and hence, doping the iron nanoparticles with ppm levels with a Cu salt, rather than Pd or Ni (Fe/ppm Cu NPs) might form a potentially useful

reagent, presumably benefiting from the same 'nano-to-nano' effect. Indeed, related NPs are formed using Cu(I) admixed with the same FeCl₃, followed by standard treatment with MeMgCl in THF (*vide supra*). Akin to observations with other NPs in this series, the catalyst can be generated and used *in situ* or isolated for use at a later date. The first type of catalysis examined has been click chemistry between a terminal alkyne and an azide; when performed in aqueous TPGS-750-M at room temperature, cycloadditions to the anticipated triazoles take place quite readily (22). In addition to representative examples shown in **Figure 8**, products formed upon recycling of the aqueous reaction mixture are suggestive that the catalyst does not lose its activity when handled under an inert atmosphere to prevent autoxidation to the otherwise inactive Cu(II) form.

3. Summary

Micellar catalysis has been made highly effective by virtue of newly engineered nanoreactors in water, offering the synthetic community an environmentally responsible alternative to waste-generating organic solvents as reaction media. The green attributes of this approach to synthesis, however, go well beyond this simple solvent switch. In fact, metal NP catalysts present in such aqueous solutions populated by MPEG-containing nonionic surfactants TPGS-750-M and Nok are active under very mild conditions due to this 'nano-to-nano' effect, a phenomenon not found in traditional organic solvents. Applications of metal NPs that can be formed containing either base (for example Ni or Cu) or precious (for example Pd) metals to important reaction types, such as reductions and

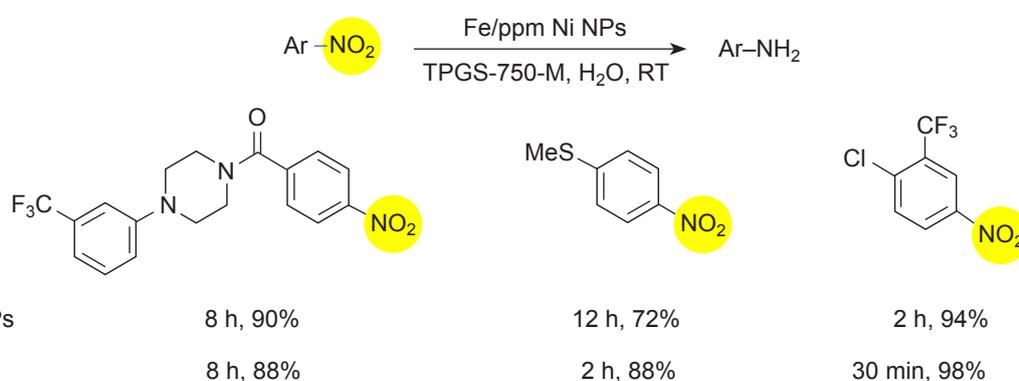


Fig. 7. Faster reductions with new NPs doped with Ni (21)

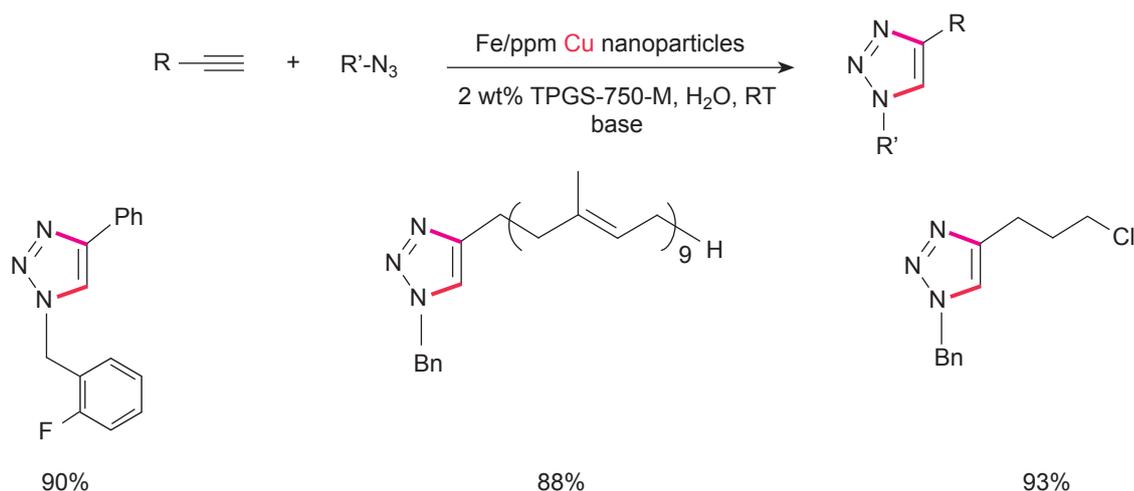


Fig. 8. Representative examples of Fe/ppm Cu NPs applied to click chemistry

cross-couplings, have been demonstrated. Future developments involving other precious metals, such as rhodium and iridium, seem ripe for investigation, furthering the appeal of this new green chemistry.

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The Author



Bruce Lipshutz spent four years at Yale University, USA, (1973–1977) as a graduate student with Harry Wasserman. After a two-year postdoctoral stint with E. J. Corey at Harvard University, USA, as part of the team involved with the total synthesis of the antitumour agent maytansine, he began his academic career at the University of California, Santa Barbara, USA, in 1979, where today he continues as Professor of Chemistry. His programme in synthesis focuses on new reagents and methodologies, mainly in the area of organometallic chemistry. While these contributions tended to fall within the area of ‘traditional’ organic synthesis, more recently his group has shifted in large measure towards the development of new technologies in green chemistry, with the specific goal being to get organic solvents out of organic reactions. To accomplish this, the Lipshutz group has introduced the concept of ‘designer’ surfactants that enable key transition metal-catalysed cross-couplings, and many other reactions, to be carried out in water at room temperature. Most recently, his group has turned its attention to developing new catalysts for key Pd- and Au-catalysed reactions that involve bond formations requiring only parts per million levels of metal, each being conducted in water under very mild conditions. The potential for his group’s work in this field to significantly influence, and in time transform the way in which organic chemistry is practiced in the future, led to a Presidential Green Chemistry Challenge Award in 2011.