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Organometallic Catalysis and Sustainability: From Origin to Date

Rapid progress towards more sustainable processes for industry

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Organometallic catalysis has its origins in the 18th and 19th centuries. Then, the emphasis was on achieving remarkable chemical transformations, but today the focus is increasingly on sustainability. This article summarises the current promising approaches with special regard to those that have commercial potential, including non-aqueous and water immiscible solvents, modified enzymes, micellar catalysis, catalysis with low loading, metal-free catalysis and catalyst recycling. Environmental metrics, a key evaluation tool for any industrial chemical process, are used in micellar catalysis to demonstrate their usefulness, especially to achieve streamlined protocols, reduce losses and eliminate toxic materials.

Introduction

Nature is the best-developed and largest biochemical reactor, synthesising countless chemical entities in high purity and yield without exhausting itself. Beautifully, its processes exhibit quantitative reaction yield, low E factor, excellent atom economy, absence of toxic metals and solvents, ultra-purity of products, excellent chemoselectivity and outstanding reaction reproducibility throughout billions of years – all accomplished at ambient temperature in water (**Figure 1(a)**). Conversely, synthetic processes prevail with breadth of substrate scope and reaction kinetics, but only due to availability of powerful organometallic catalysts, which, in combination with other discoveries in chemistry, materials and other disciplines, have enabled synthetic organic chemists to construct almost any desired molecule. Astonishing catalytic transformations have been developed with modified enzymes (1), nanomaterials (2), photoredox chemistry (3) and organocatalysts (4). Asymmetric catalysis has led to independence from chiral auxiliaries and nonracemic starting materials (5). The 18th and 19th century progenitors of organometallic chemistry, Cadet (6), Frankland (7) and Zeise (8), could not have imagined this boom in organometallic catalysis, which continues into the 21st century with milestones including the birth of nanocatalysis (9), the renaissance

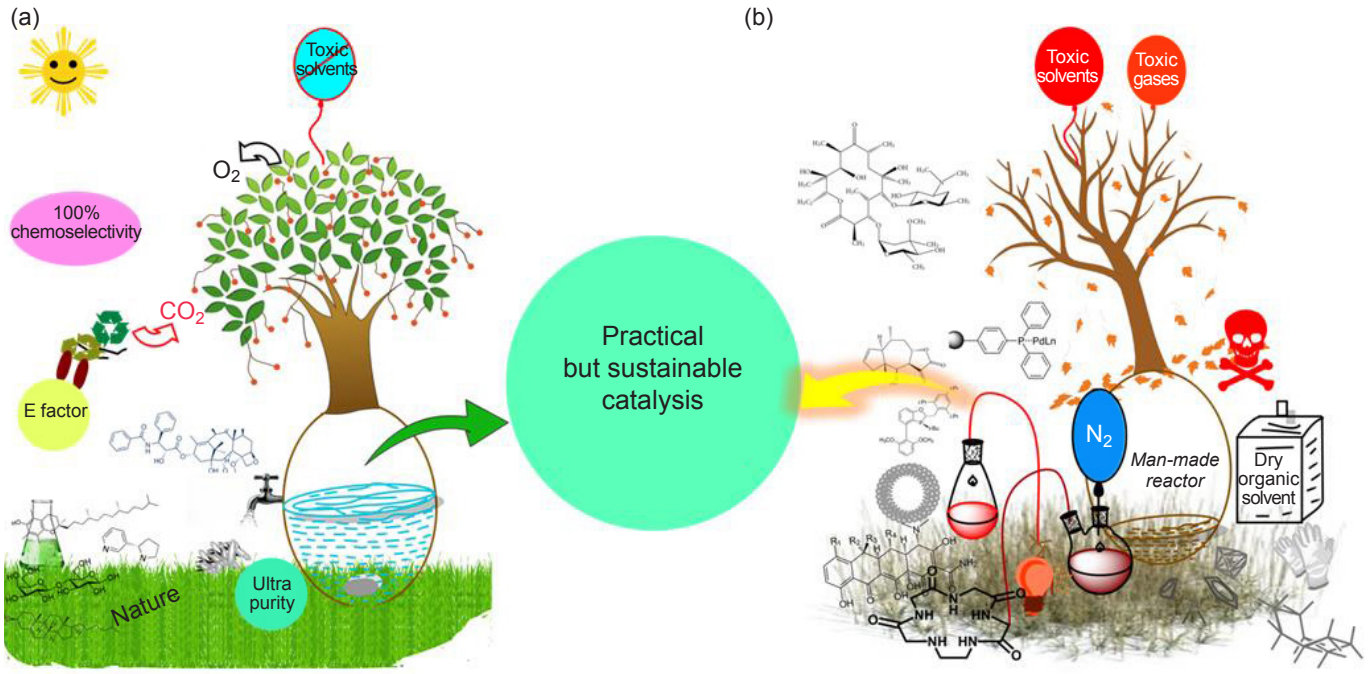


Fig. 1. (a) Nature *versus* (b) man-made catalytic processes

of photoredox catalysis (10) and the harnessing of micellar conditions to perform air-sensitive chemistry in water at room temperature (11).

However, in the big picture, in spite of major advances in the development of novel transformations, ligands, catalysts and technologies, the majority of today's catalytic transformations suffer from many drawbacks in terms of sustainability, as evinced by very high E factors (12), poor atom economy (13), use of hazardous material and toxic organic solvents (12) and the involvement of energy intensive routes (**Figure 1(b)**). A very simple question must strike any organic chemist's mind: when has Nature run any reaction in dry tetrahydrofuran (THF) at –78ºC or in any other organic solvent under very harsh conditions? While following Nature and enjoying the wealth of chemical properties of transition metals, one must marvel at how amazingly our processes differ. Are they not responsible for huge chemical waste generation? This issue is somewhat truer with chemistry laboratories in academia where we put much focus on current trends while ignoring sustainability issues, deferring the topic to process chemists. Our preset perceptions sometimes blind us from important innovations, which may be particularly true for sustainability in chemical catalysis. If Nature can perform biochemical catalysis so ideally, why is it not generally possible to perform chemical catalysis in the same fashion? Perhaps this goal presently seems unrealistic. Due to older beliefs, even gold was considered catalytically inactive (14), leaving Sir Geoffrey C. Bond to remark: "We are at a loss to understand why these catalytic properties of gold have not been reported before, especially since the preparative methods we have used are in no way remarkable". Today, even gold-assisted photoredox chemistry is possible (15), and for the matter at hand, Frances Arnold's inspired work on mimicking natural catalytic processes already provides a guiding light (1). Developments helping to save our reserves of threatened metals through the merger of photoredox chemistry with enzymatic, micellar and nanocatalysis are also noteworthy (1–4). Accordingly, endeavours to discover sustainable new catalysts, transformations and technologies that will preserve our beautiful blue planet should be undertaken with careful attention to all aspects of how Nature performs chemistry. Such attention will yield solutions to many current and even untouched problems.

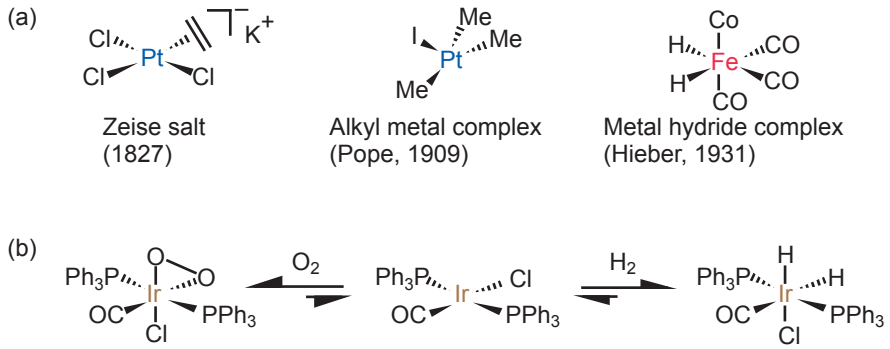
Historical Origins

Organometallic catalysis has a rich history. In 1731, Stahl published a report on the synthesis of Prussian blue, $Fe_4[Fe(CN)_6]_3$ (16). However, the traditional classification of metalloid complexes as organometallics would date the first synthesis of an organometallic

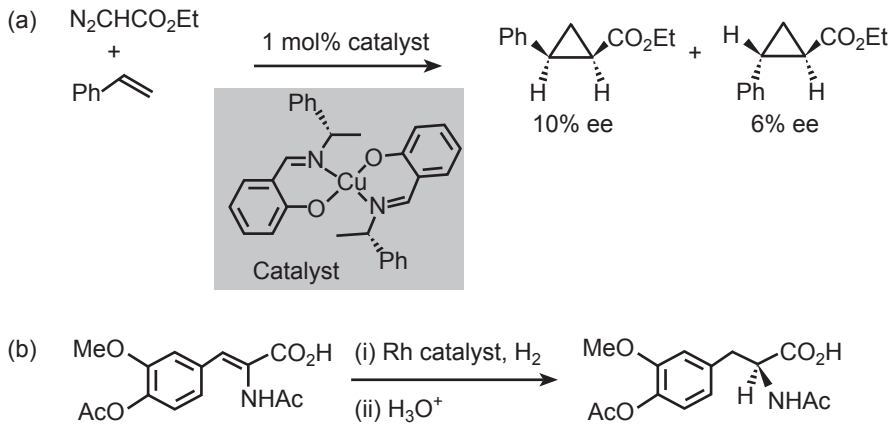
compound to 1757, when Cadet encountered the foul smell of cacodyl oxide and tetramethyldiarsine, generated from arsenic-containing cobalt salts while trying to develop new invisible inks (6). The true genesis of organometallic chemistry happened in 1827 when the first π-complex, trichloro(ethene) platinate(II), now known as Zeise's salt, was reported (**Scheme I(a)**) (17). Further noteworthy metal alkyl complexes were reported between 1849 and 1863, including diethyl zinc, tetraethyl tin, diethyl mercury and trimethylboron (18, 19). The first metal carbonyl complex, dichlorodicarbonyl platinum, was synthesised in 1868, followed by syntheses of binary metal carbonyl complexes, including tetracarbonyl nickel in 1890 and pentacarbonyl iron in 1891. At the time, catalytic utility was unknown, and the bonding and structure of organometallic complexes was a mystery. Early assumptions held that ligands were aligned in a chain with metal at the terminus. The coordination theory proposed by Werner in 1893 based on his experimental data was the first of many models to more correctly explain the nature of bonding in organometallic complexes (20).

The seminal application of organomagnesium compounds to organic synthesis by Barbier, Grignard and Sabatier occurred in 1900 (21, 22), and the birth of organometallic catalysis was soon to follow. Although concurrent discoveries of organometallic reactions facilitated by unconsumed chemical mediators were rationalised into conceptual unity by Berzelius with his articulation of the concept of catalysis in 1835, the fusion of these two domains into organometallic catalysis did not begin until Ostwald's work on chemical equilibria and catalysis in 1902. This work initialised homogeneous catalysis and organometallic chemistry with its reports on the first alkyl metal and metal hydride catalysts (23). Subsequently, Sabatier clearly distinguished homogeneous and heterogeneous catalysis through his method development for hydrogenation of organic compounds in the presence of finely divided metals (24), an achievement that led to a Nobel Prize in Chemistry shared with Grignard in 1912. Important milestones during the next 50 years include the Fischer-Tropsch synthesis of linear hydrocarbons from syngas (25–27), vanadium oxide catalysed oxidation of benzene (28), silver-catalysed epoxidation of ethylene (29), cobalt-catalysed hydroformylation of olefins, the oxo process (30), the Pd-Cu-mediated Wacker process for acetaldehyde formation (31) and the Ziegler-Natta catalysts for olefin polymerisation, which earned their developers the 1963 Nobel Prize in Chemistry. The Wacker process in particular was a bellwether of future directions, being the first useful transformation to employ homogeneous organopalladium catalysis.

The golden period of homogeneous catalysis started in 1962 when Vaska reported a 16-electron iridium complex, now known as Vaska's complex (**Scheme I(b)**), having the unusual property of reversible bonding with oxygen; this complex is the basis for the modern iridium complexes used in photoredox chemistry (32). In 1963 Fischer isolated the first metal-carbene complex (33), a tungsten-based complex that later provided a simple and fascinating means of olefin metathesis (34). Another important achievement was the development of the first homogeneous hydrogenation in 1965, independently reported by Wilkinson and Coffey (35, 36). Control on chirality was first accomplished in 1966 by Nazoki and Noyori who reported synthesis of *cis*- and *trans*-cyclopropane carboxylate (10% and 6% ee, respectively) from styrene and ethyldiazoacetate using 1 mol% of a chiral Cu(II) complex (**Scheme II(a)**) (37). This work marked the



Scheme I Discovery of metal complexes important from catalysis perspective. (a) Early reported examples of metal complexes; (b) unusual properties of the Vaska complex



Scheme II Asymmetric catalysis at a very early stage. (a) The first reported asymmetric catalysis; (b) Knowles application of asymmetric catalysis in the synthesis of *L*-DOPA

advent of asymmetric organometallic catalysis. At about the same time, Kagan reported an asymmetric rhodium-catalysed hydrogenation to obtain chiral amino acids using a C-2 symmetric chiral 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) ligand (38), a discovery that soon led to the synthesis of enantiomerically pure *L*-3,4-dihydroxyphenylalanine (L-DOPA) by Knowles (**Scheme II(b)**) (39). Thereafter, asymmetric epoxidation of allylic alcohols was reported by Sharpless (40). Noyori and coworkers finally accomplished the synthesis of the very important 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) ligand in 1976 after two years of method development, paving the way for many similar ligands that are widely used today (41). These many discoveries in asymmetric catalysis by Knowles, Sharpless and Noyori earned them a Nobel Prize in 2001.

The intense scientific interest in organometallic catalysis has not abated in the new millennium with Nobel Prizes being awarded for work in the area in 2005 and 2010. At present, however, it is shocking to observe that we seemingly have yet to fully realise the challenges that will be faced for decades into the foreseeable future. Awareness has begun to take root, thanks to the emergence of the green chemistry concept beginning in 1990 and its promotion of a more sustainable and environmentally responsible practice of chemistry (42). More recently, in the USA, establishment of the ACS Green Chemistry Institute has provided better direction for the community, the US Presidential Green Chemistry Challenge Award is encouraging chemists to focus on innovative sustainable methods and the National Science Foundation (NSF) Sustainable Chemistry, Engineering, and Materials (SusChEM) programme is likewise a key initiative to attract more chemists in order to attain long-term sustainability goals.

Advances in General Sustainability

Many advancements in organometallic catalysis and synthesis have been achieved and a few of them are summarised here.

Aqueous Reaction Media

When has Nature ever run a reaction in organic solvent? The answer is ‘never’. So if Nature can do chemistry in an aqueous environment, why then do chemists not do the same? Partly, we are not able to perfectly mimic Nature in every aspect, but conducting catalysis in water, even at room temperature, is certainly possible. However, performing chemistry in water and then introducing that water into the waste stream would still adversely impact our environment and be a topic of criticism. The cost of such contaminated water treatment may even be greater than the disposal of organic solvents, and of course, the impact may be more detrimental.

Is it possible to recycle the water if contaminated from catalytic reactions that are conducted in water? Very recently, a micellar technology has been introduced by Lipshutz and co-workers where dissolution of 2% (w/v) of amphiphile named tocopherol methoxypolyethylene glycol succinate (TPGS-750-M) in water forms nanomicelles (43). The hydrophobic interior of nanomicelles has been harnessed for chemical catalysis. Coupling reactions including Suzuki-Miyaura, Buchwald-Hartwig amination, Sonogashira, Hiyama,

Heck and C–H activation are well reported under micellar conditions. In addition, asymmetric gold catalysis, aerobic oxidation, ring-closing metathesis (RCM), Cu-H reductions, nitro reductions, trifluoromethylation and many more have been explored (**Figure 2**) (44). Interestingly, the authors are able to recycle the catalyst and reaction medium many times. Amphiphile TPGS and its components are environmentally benign and do not yield any toxic fragments. Recycling has been performed without any energy intensive procedure. Products of resulting reactions have been extracted by a minimal amount of organic solvent and the aqueous layer is reused for the next catalytic reaction.

Greener Reaction Media

Reaction medium is an important parameter to the success of any catalytic process and the isolation of its resulting product. Large amounts of organic solvents are annually consumed in chemical transformations. Dissolution of all components of a reaction including the resulting product is traditionally considered as beneficial, especially for reaction yield and determining reaction kinetics and mechanism. With the emergence of green chemistry, this parameter has received fresh attention as chemists have begun to seek alternatives

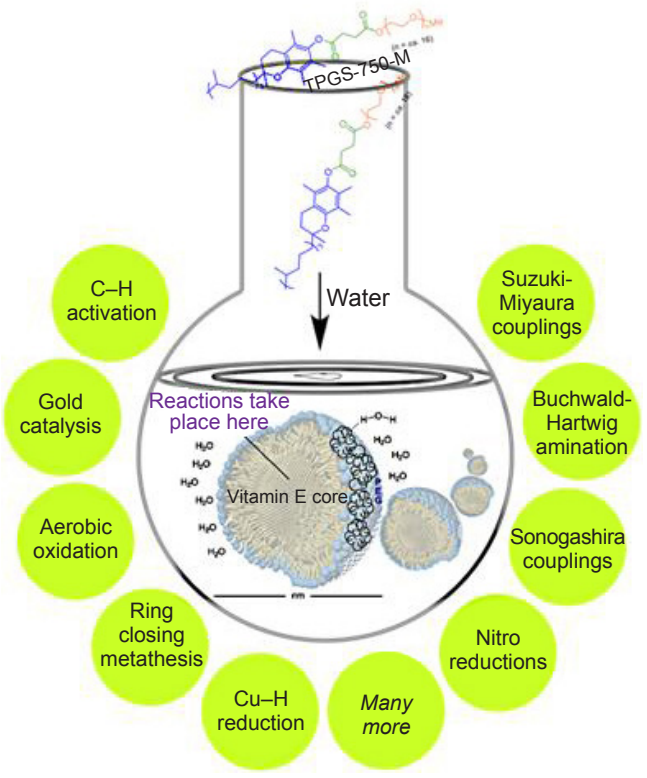


Fig. 2. Versatility of micellar approach for catalysis in water

to conventional, oftentimes toxic, organic reaction media. Financial concerns also prompt this renewed consideration, since with conventional reaction media we first pay upfront for toxic solvents and then pay again in the end for their disposal. While a temporary answer is to focus on the use of greener solvents, such as using 2-methyltetrahydrofuran in place of water-soluble THF, alternative reaction media are currently needed that are not only green but also do not lead to the same waste streams.

One class of alternative reaction medium, ionic liquids, has been put forward as a safer choice than organic solvents (45), but despite the limited volatility, inert nature and relative stability of ionic liquids, risk of their post-reaction release into the environment is a significant concern. As Jordan and Gathergood noted: "The parameters of biodegradability, toxicity – and recently mutagenicity – are becoming more significant" (46).

Supercritical carbon dioxide presents a nontoxic, nonflammable alternative, but high pressure and temperatures are required to maintain CO_2 in its liquefied state. It has been explored as a reaction medium in many valued reactions such as Pd-catalysed Heck reactions and Rh-catalysed hydroformylation (47).

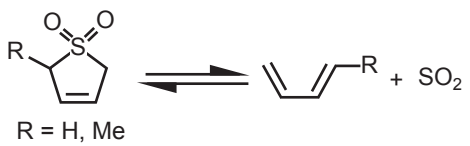
Traditionally, fluorinated solvents have also been considered to be safer and greener media (48). This class includes perfluorinated hydrocarbons, fluorous amines and ethers. The characteristic supporting their greenness is their immiscibility with water, and thus, inability to contaminate water. However, their miscibility with water is temperature-dependent. Heating the fluorous-bound catalyst in a non-fluorous solvent leads to homogeneity, resulting in catalysis. After reaction completion, cooling provides the separation of phases and ease of product separation from the organic solvent layer. New fluorous solvents, catalysts and reagents are now available that drop the costs associated with bond constructions (49).

'Switchable solvent' is another technology assisting organic chemists to move away from using traditional organic solvents (50). Generally, switchable solvents reversibly change their physical properties in response to external stimulus such as a change in external temperature and addition or removal of gases. The 'switchable' solvent is also widely recognised for its practical applications to wastewater treatment, CO_2 capture and solvent recovery. For example, dimethyl sulfoxide (DMSO) is a high boiling solvent and this property makes product isolation very difficult. Piperylene sulfone (51), a switchable solvent,

has been used to replace DMSO for nucleophilic substitution reactions. It is synthesised by reaction of *trans*-1,3-pentadiene and sulfur dioxide in the presence of a radical inhibitor. Heating the piperylene sulfone above 110ºC causes thermal decomposition back to the low-boiling starting materials (**Scheme III**). Thus, it is more convenient to recover the solvent and reaction product.

Modified Enzymes as Biocatalysts

An aqueous environment is also ideal for enzymatic processes, and many known transformations of synthetic utility can be effectively conducted (52). Extension of the repertoire to other valued but unknown organic transformations catalysed by naturally occurring enzymes is the area of directed evolution (**Scheme IV**) (53). With the aid of protein engineering, enzymatic properties can be fine-tuned through iterative mutagenesis, and then can be utilised as biocatalysts to perform target-oriented synthetic organic chemistry and enantioselective biocatalysis. In a Perspective titled 'The Nature of Chemical Innovation: New Enzymes by Evolution', Arnold elaborated on several 'non-natural' reactions that can be carried out by modifications of cytochrome P450-derived enzymes (54). Representative transformations using this approach include cyclopropanations (55), aziridinations (56) and regio-divergent aminations (57). Very recently, directed evolution of cytochrome c for carbon–silicon bond formation has been reported (58). Enzymes had not previously been known to catalyse C–Si bond formation. This conjuncture between living systems and synthetic organic chemistry is a stepping stone to mimic Nature. Using a similar approach, the same group were able to achieve enhanced catalytic activity of cytochrome c by a 15-fold increase in turnover rate relative to the state-of-the-art synthetic catalyst for C–Si bond forming reactions. The reaction proceeded with excellent yields and enantioselectivities over a broad substrate range. Such discoveries and developments represent a significant step forward for mimicry of Nature in catalysis and a move away from scarce metal catalysed processes.



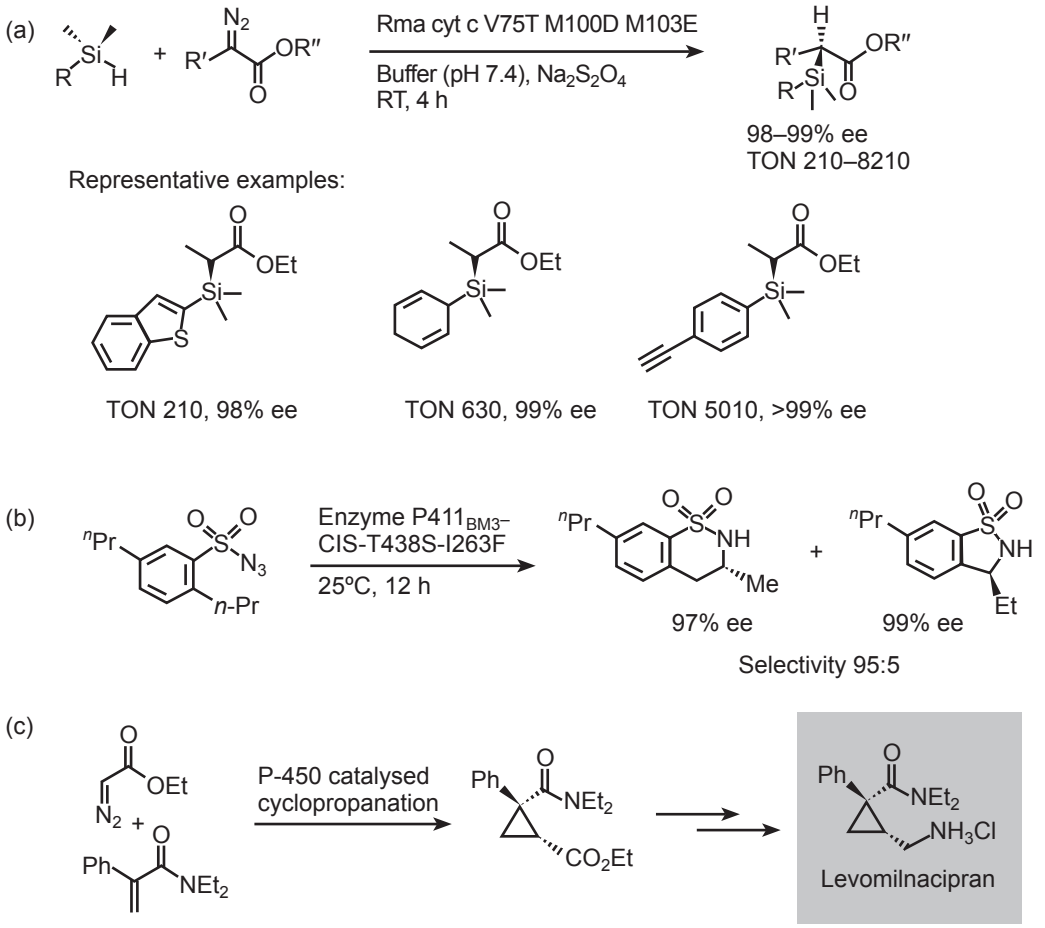
Scheme III Switchable solvent approach. Piperylene sulfone as a DMSO equivalent

'In Water' and 'On Water' Catalysis

Notwithstanding, these milestones in exploring enzyme-mediated transformations in water are not the only simpler alternatives to traditional non-sustainable organometallic catalysis and organic solvents. Much better catalytic activities (ee's, functional group tolerance and yields) have been observed while conducting the reactions with modified enzymes in water. Although reactions 'on water' are very well explored (59, 60), further advances are still needed regarding the interactions involved between substrates, catalysts and water (61), this knowledge gap remains atypical within the synthetic community. Nonetheless, recent studies by Kobayashi and co-workers further demonstrate the synthetic potential of water in catalysis (62). In their report, a new nonracemic Cu(II) catalyst leads to asymmetric conjugate additions of the Fleming dimethylphenylsilane ($PhMe_2Si$) residue in enones and enoates as well as unsaturated nitriles and nitro olefins, with ee's ≥90%. Interestingly, neither the reaction partners nor the copper catalyst is soluble in water. Use of organic solvents including dichloromethane, THF, DMSO, methanol and ethanol provided lesser reaction yields and ee's. The superior results with water may be due the formation of higher order aggregated states of the catalyst.

Low Catalyst Loadings

Annually, about a billion tonnes of bulk and fine chemicals are produced through metal-catalysed processes. A catalyst is generally used in sub-stoichiometric quantity as it is regenerated after completion of each catalytic cycle. From a pharmaceuticals industry perspective, it is equally important that the resulting product must be free from trace metal impurities which usually come from organometallic catalysts used in the process. Thus, process chemists prefer to use such metal catalysts at early steps of the synthesis. However, sometimes it becomes more challenging to remove trace metal impurities, especially if the product is either an active pharmaceutical ingredient or its intermediate. This problem can be easily solved if there is a provision of more robust catalysts, requiring very low levels of loading in accordance with the notion 'low in, low out'. Thus, catalyst loading is also a very crucial parameter



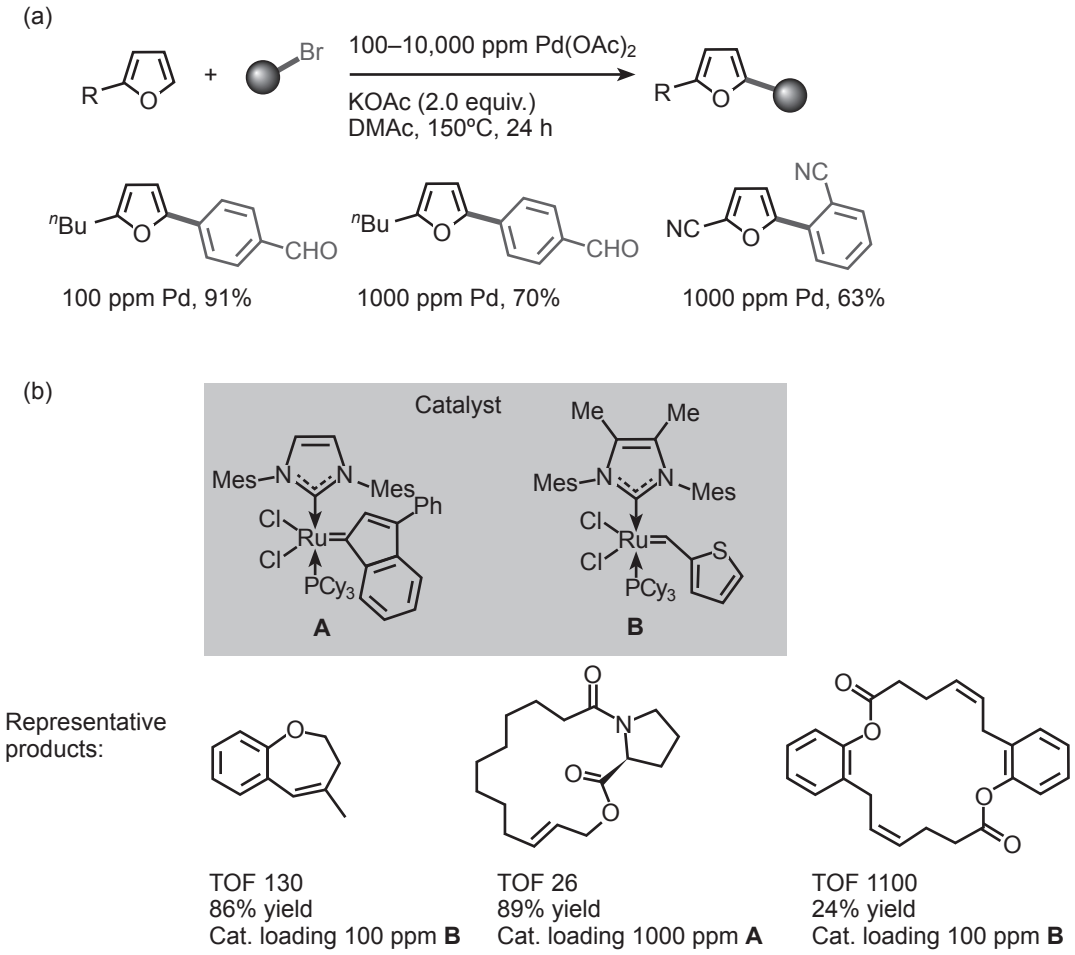
Scheme IV Nature directed enzymatic catalysis. (a) Enantioselective carbon-silicon bond forming reactions; (b) enzyme controlled regiodivergent amination; (c) enantioselective synthesis of levomilnacipran *via* enzymatic cyclopropanation

for product purity, especially for pharmaceutical and material chemists.

There are many precedents for chemical transformations achieved with a very low catalyst loading (63, 64). However, many of them involve elevated temperature, microwave assistance, toxic organic solvents, dry reaction conditions, no opportunity to recycle the catalyst, limited substrate scope or excessive amounts of reactant. Despite these pitfalls, such contributions are steps toward sustainable catalysis.

Doucet and co-workers reported a low catalyst loading for ligand-free palladium-catalysed direct arylation of furans (**Scheme V(a)**) (65). Key features of this work include high reaction yield, better atom economy than traditional Suzuki-Miyaura couplings, very low catalyst loading, high turnover number (TON), high reaction yield and greater functional group tolerance with broad substrate scope.

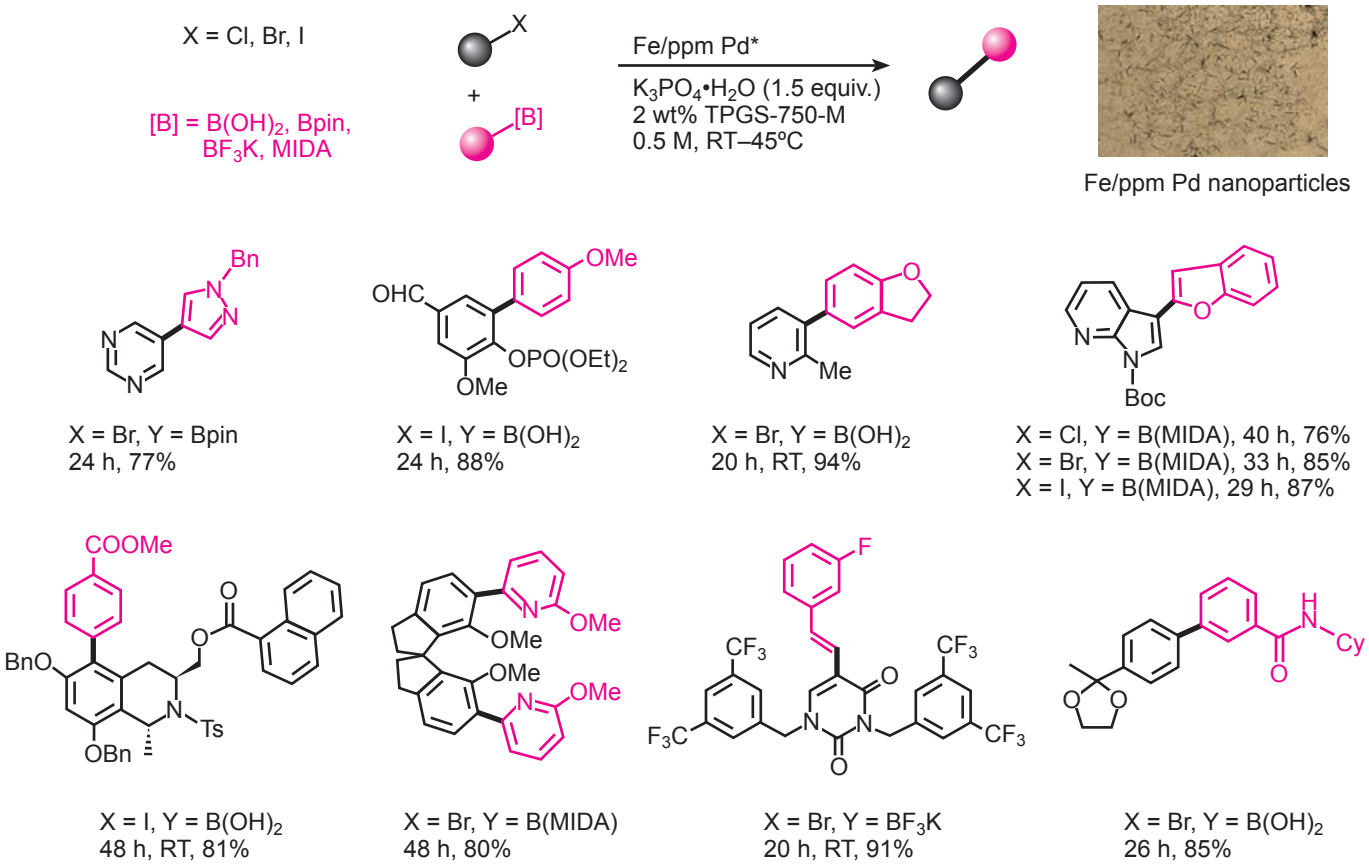
A discovery of an artful RCM reaction by Dider Villemin and its further development through Grubbs and Schrock catalysts provided a new route to synthesise cyclic hydrocarbons (66). With low catalyst loading, it has been explored on many substrates (**Scheme V(b)**). In his study, Kadyrov observed the efficiency enhancement with volatilisation of byproduct ethylene, leading to an increase in turnover frequency (TOF) up to 4173 per minute at 50 ppm catalyst loading (67). With the catalyst loading between 50 and 1000 ppm, 5- to 16-membered heterocyclic moieties have been synthesised. Key features of this methodology were its high TOF and broad substrate scope. A representative 7-membered cyclic ether was obtained with 86% yield at 100 ppm loading of **B**. Similarly, 16- and 18-membered lactones were obtained at 100–1000 ppm catalyst loading. However, yield of the 18-membered lactone was poor.



Scheme V Transition-metal catalysis at ppm levels of catalyst loading. (a) Direct arylation of furans; (b) ring-closing metathesis

Catalysis under mild conditions with low catalyst loading along with the opportunity for in-flask recycling of a reaction medium, all in a single package, is well developed by our team (68). A highly valuable and truly general Suzuki-Miyaura cross-coupling catalysed by ppm levels of palladium is just the tip of the iceberg. In one of our reports, a very general, high yielding cross-coupling process with broad substrate scope operating by way of an iron-based nanomaterial containing ppm levels of palladium impurity has been disclosed (**Scheme VI**) (69). A specific method of nanomaterial generation was crucial for the catalytic activity, namely SPhos as an ancillary ligand, THF as a solvent for formation of nanoparticles, $FeCl_3$ as the iron source, a Grignard reagent as a reductant, and above all, correct stoichiometry of all components. Stability and composition of the nanomaterial was very well established from the physical data including thermogravimetric analysis (TGA), scanning electron microscopy (SEM), X-ray photoelectron spectroscopy (XPS), atomic force microscopy (AFM) and transmission electron microscopy (TEM). The reaction medium was also crucial for catalytic activity and TPGS-750-M aqueous solution was the optimal choice with the added benefit of being a greener solvent. Both the catalyst and reaction medium were recycled without any energy intensive separation processes. Extraction of product with a minimum amount of organic solvent usually left the aqueous components containing the active catalyst.

This technology is applicable to a wide range of substrates including a variety of aryl chlorides, bromides and iodides. Different boron nucleophiles such as aryl boronic acids, boronic acid pinacol (Bpin) esters, potassium trifluoroborate salts and *N*-methyliminodiacetic acid (MIDA) boronate esters are well tolerated. The beauty of this process lies in the participation of earth-abundant metal, the small excess of boron nucleophile needed, mild reaction temperature, no trace metal contamination to the product and the



Scheme VI Fe/ppm-Pd catalysed sustainable and truly general Suzuki-Miyaura couplings. *$FeCl_3$ (5 mol%), SPhos (5 mol%), MeMgCl (6 mol%), K_3PO_4•H_2O

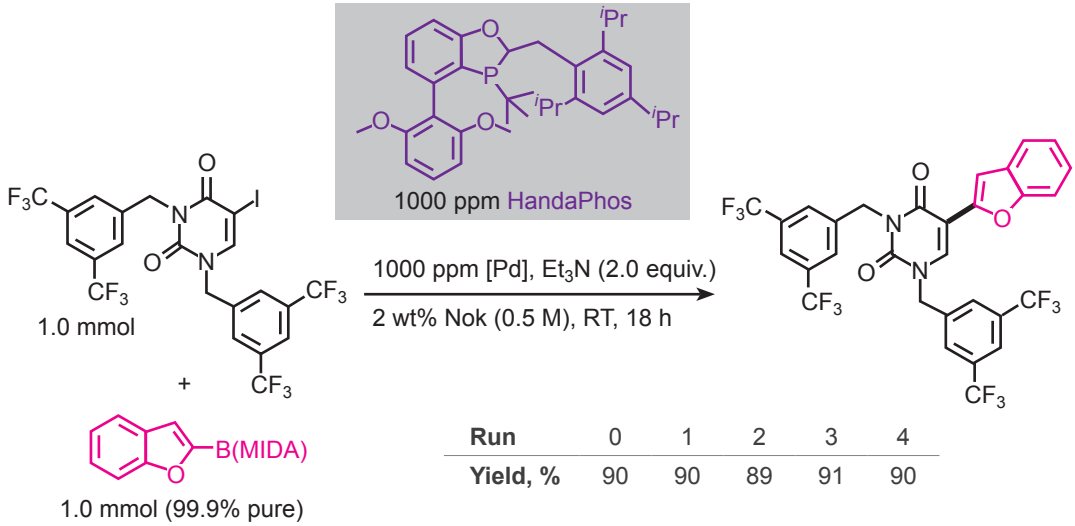
recyclability of the catalyst as well as of the reaction medium. Good functional group tolerance and high reaction yields further lend to its practical application.

Continuing the evolution of sustainable cross-coupling chemistry using ppm levels of palladium, ligand-based technology has also been reported to facilitate low loading levels in water (68). In addition to the salient features of the Fe/ppm palladium approach, this technology includes rational ligand design supported by density functional theory (DFT) calculations, operational simplicity, no elevated reaction temperature and no need for excess of coupling partners. In this methodology, the highly effective ligand HandaPhos combined in a 1:1 ratio with palladium acetate leads to a precatalyst that upon *in situ* reduction yields a very powerful catalyst to achieve the desired catalysis at room temperature under micellar conditions (**Scheme VII**).

Although transition-metal free Suzuki-Miyaura cross-couplings have been claimed (70), reassessment of such microwave assisted reaction conditions confirmed the involvement of palladium species in the catalytic cycle, albeit at parts per billion levels (71). Thus, metal still appears necessary for these processes, but exceptionally low loadings are possible.

Metal-Free Catalysis

Another alternative to strengthen sustainable chemical catalysis is the metal-free platform of organocatalysis (72). However, organocatalyst-promoted reactions suffer from many drawbacks including low catalyst efficiency, long reaction time, difficulty in recycling the catalyst and almost no activity for activation of challenging chemical bonds such as the *m*C–H bond of an aryl ring. *L*-proline has been thoroughly explored in asymmetric organocatalysis, especially for conjugate addition reactions (73). The limitation of such transformations is the same as in typical organocatalyst-promoted reactions, and thus, not truly sustainable in



Run	0	1	2	3	4
Yield, %	90	90	89	91	90

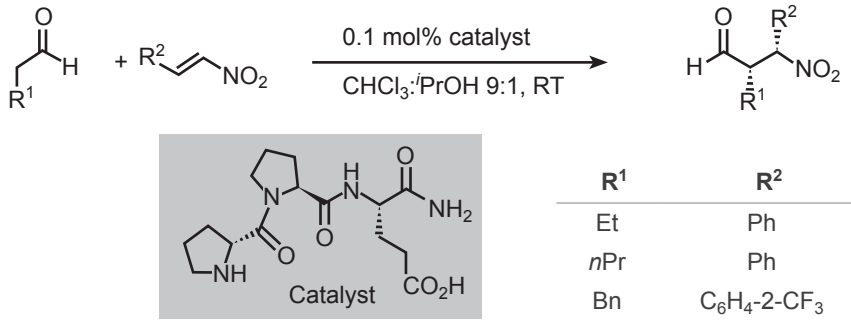
Scheme VII Ligand-mediated sustainable Suzuki-Miyuara couplings at ppm level of palladium. No organic solvent is used for extraction or purification

nature. Very cleverly, through mechanistic insights, Wennemers and co-workers achieved catalyst loadings down to 1000 ppm without affecting the ee and overall yield (**Scheme VIII**) (74). In their study, it was found that the presence of water slowed down the formation of the key enamine intermediate. Therefore, dry reaction conditions are required to achieve this metal-free catalysis at ppm levels. The need for dry conditions is a major problem that chemists usually encounter while designing practical sustainable catalytic methods.

Recent growth in the area of photocatalysis is another step toward mimicry of natural catalysis (75). However, typical involvement of the scarce metal iridium may be an issue in the long run. Fortunately, many metal-free and main group element-promoted photoredox processes have been reported, helping to address this concern (75). Elegant advancement in the area of metal and peroxide-free, scalable and clean photoinduced trifluoromethylation of arenes by C.-J. Li and co-workers has eased the installation of the highly valuable trifluoromethyl group on various arenes (**Scheme IX**) (76). So far, this is the most sustainable way to achieve such trifluoromethylation, especially at gram scale under very mild conditions and with good functional group tolerance. However, there is still plenty of room for further advancement as this process is comparatively less efficient for electron-poor arenes.

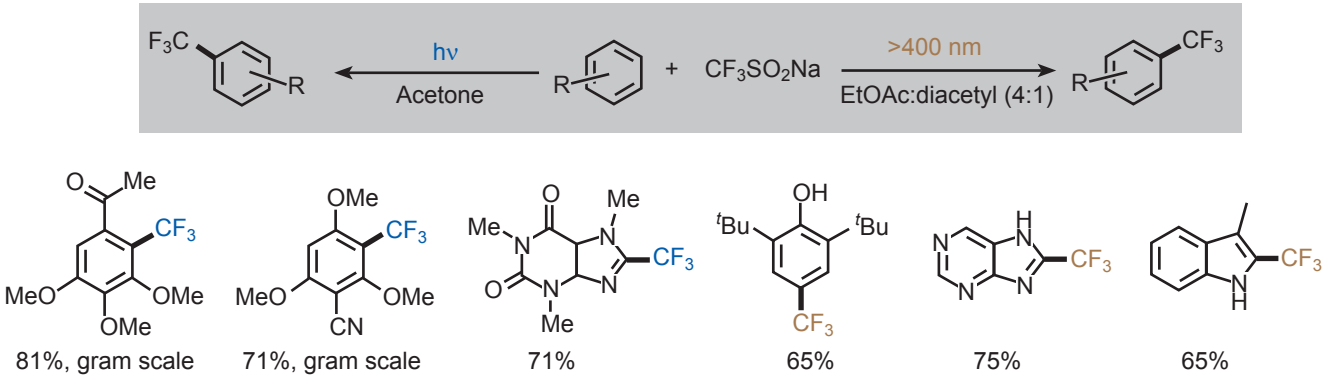
Catalyst Recycling

By definition, a catalyst facilitates reactivity without being consumed in the process. If it is not consumed, then why is it predominantly treated as waste? Sometimes, in systems where catalyst recycling is not attempted, it survives exactly the length of the process, at which point it is still promptly destroyed as waste! The obvious financial and environmental costs of such an unsustainable approach have long spurred



R1	R2	ee, %	Yield, %
Et	Ph	97	87
*n*Pr	Ph	96	98
Bn	C_6H_4-2-CF_3	92	99

Scheme VIII Asymmetric organocatalysis with ppm level of a catalyst



Scheme IX Clean, peroxide- and metal-free trifluoromethylation

chemists to seek ways to reuse these catalysts across multiple reactions (77). Strategies for catalyst recovery generally involve catalyst immobilisation on separable supports or in biphasic solvent systems (78).

Heterogenisation is a widely-employed technique that often comes at the cost of catalytic activity, selectivity and metal leaching, which can limit the extent of recyclability. A compelling illustration of the potential for this approach to overcome these limitations was recently provided by Tu and co-workers, who reported the development of a robust ruthenium-NHC coordination polymer for solvent-free reductive aminations (79). The solid catalyst could be easily recovered by centrifugation and decanting. It was able to catalyse the synthesis of 5-methyl-2-pyrrolidone from levulinic acid at a 1500 ppm catalyst loading through 37 recycles without significant loss of activity. A second strategy, magnetic-metal nanoparticles, represents an alternative 'semi-heterogeneous' system for organometallic catalysts that is easily separable from the bulk reaction medium by use of an external magnet. Catalysts anchored to metal nanoparticles have competitive activities and enantioselectivities compared to their homogeneous analogues (80).

A third strategy, biphasic solvent system, allows for recovery of unmodified homogeneous catalysts by dissolving the products in one layer while retaining the catalyst in another. As noted above, a similar but distinct approach is micellar catalysis. Micellar catalysis has been advanced as a viable strategy to both recover catalysts and minimise solvent waste (12). A key appeal of this strategy is its generality: rather than requiring development of a new immobilised catalyst system for each specific reaction, this approach readily accommodates existing homogeneous technology into a recyclable gross reaction medium. The extent of the generality is so great that multiple, diverse transformations can be performed sequentially in one pot.

Environmental Metrics

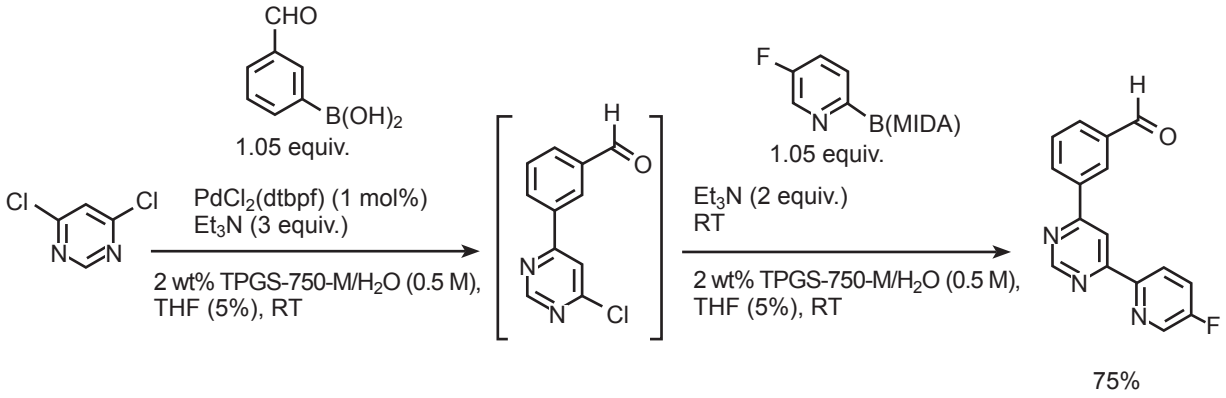
Environmental metrics are important evaluation tools for any chemical process, especially from an industrial point of view (81). Micellar chemistry is an important development in the field of synthetic methods to address issues pertaining to sustainability. Indeed, a most outstanding feature of this chemistry is the overall high mass efficiency. This approach, particularly to novices, appears as counterintuitive, but the micellar environment in which the chemistry occurs possesses some remarkable features.

There are two key components responsible for the efficiency of methods involving micellar chemistry. Firstly, reactions are usually best facilitated by very high concentrations of substrates and catalyst. While transformations in traditional organic solvents tend to proceed at concentrations of 1% to 20% by weight, with 5% being routine after optimisation, corresponding reactions in water under micellar conditions are typically achieved at 10% to 50% by weight, and routine use of 20% is possible with limited effort. The dynamic exchange between the medium and the micelles, a site where actual chemistry takes place whether at the interface or inside the micelles, makes the chemical transformation possible, despite the very minute solubility of reaction partners. Secondly, such transformations typically exhibit very high reactivity and selectivity. Hence, they require very minimal post-reaction processing. Sometimes after the reaction

completion, only a simple filtration of almost pure solid product is required; otherwise, a simple one-time extraction with a minimum amount of solvent for direct isolation of the product is usually sufficient. Perfect reaction selectivity is possible due to the very mild reaction conditions with almost ideal stoichiometry of reactants. The simple filtration procedure is typically favoured for catalytic transformations where a limited amount of side-products are formed. Due to the very limited excess of reaction partners and very low catalyst loading, this approach requires limited effort in product processing. Extraction is the preferred option for stoichiometric transformations where the amount of side-products formed is still substantial.

Standard catalytic and stoichiometric processes performed on scale in our laboratories and production facilities highlight the performance of the technology, as can be exemplified by **Scheme X** with standard depiction of the key operations in processes, and their corresponding metric analyses (**Table I**). Efforts were made to find better practical ways of addressing the safety and environmental impact of the process. Our efforts span over a range of concerns such as the identification of the most efficient synthesis with regard to atom economy and reaction yields, the use of safe and less hazardous chemicals, the elimination or reduction of waste and the number of operations, all with the additional goal of reduced presence of toxic materials. These basic principles, the foundations of green chemistry, are well known to the scientific community (42). However, practical examples that illustrate their relevance are still scarce. We, therefore, wanted to demonstrate quantitatively the relevance of some of the well-accepted green chemistry metrics.

As a result of this work, it has proven possible to replace commonly used polar aprotic solvents, which suffer from reprotoxicity. The overall cycle time also improved dramatically due to a much-reduced number of operations and streamlined workup protocols. In addition, the new process increased the overall yield, mostly due to reduced mechanical losses (loss of material in the workup and purification steps in the original synthesis and during the isolation and purification operations). Finally, the streamlined synthesis minimised the need to handle potentially toxic material.



Scheme X One-pot double Suzuki-Miyaura couplings

Table I Comparisons of Environmental Metrics for One-Pot Double Suzuki-Miyaura Couplings shown in Scheme X

Metrics	Standard process in organic solvents after optimisation	Process in surfactant
PMI[a]	110	72
PMI solvents	57	30
PMI aqueous	38	35
PMI reagents	15	7
E factor	109	71

[a]PMI = process mass intensity

Conclusion

In concluding remarks, it can be inferred that organometallic catalysis is now a well-developed field. However, in terms of sustainability, considering the looming challenges, it is still in its infancy. Merging of various sub-disciplines has contributed significantly towards the emulation of Nature, but the discovery of new reaction pathways, especially for obtaining desired products from readily available starting materials, lags behind other efforts. Beyond C–H functionalisation, sustainable methods for C–F and C–C functionalisation need to be developed in order to include intensive use of biomass. Weighting curricula to green synthesis at undergraduate and postgraduate levels can help to disseminate more awareness to future generations of chemists. Tremendous discoveries made by our chemical community in the past ten years have made the challenging path forward a little easier, and with focused effort it will become much easier to sustain our blue planet.

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