

# E factors, green chemistry and catalysis: an odyssey

Roger A. Sheldon

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The development of green chemistry is traced from the introduction of the concepts of atom economy (atom utilisation) and E factors in the early 1990s. The important role of catalysis in reducing or eliminating waste is emphasised and illustrated with examples from heterogeneous catalytic oxidations with hydrogen peroxide, homogeneous catalytic oxidations and carbonylations and organocatalytic oxidations with stable *N*-oxy radicals. Catalytic reactions in non-conventional media, *e.g.* aqueous biphasic, supercritical carbon dioxide and ionic liquids, are presented. Biotransformations involving non-natural reactions of enzymes, *e.g.* ester ammoniolysis, and the rational design of semi-synthetic enzymes, such as vanadate phytase, are discussed. The optimisation of enzyme properties using *in vitro* evolution and improvement of their operational stability by immobilisation as cross-linked enzyme aggregates (CLEA<sup>®</sup>) are presented. The ultimate in green chemistry is the integration of catalytic steps into a one-pot, catalytic cascade process. An example of a chemoenzymatic synthesis of an enantiomerically pure amino acid in water and a trienzymatic cascade process using a triple-decker oxynitrilase/nitrilase/amidase CLEA are discussed. Finally, catalytic conversions of renewable raw materials are examined and the biocatalytic aerobic oxidation of starch to carboxy starch is presented as an example of green chemistry *in optima forma* *i.e.* a biocompatible product from a renewable raw material using a biocatalytic air oxidation.

## 1. Introduction to green chemistry and sustainability

Green chemistry can be conveniently defined as:<sup>1</sup> *Green chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.*

Raw materials include, in principle, the source of energy as this also leads to waste generation in the form of carbon dioxide. The guiding principle is the design of environmentally benign products and processes (*benign by design*) which is embodied in the twelve principles of green chemistry as

formulated by Anastas and Warner.<sup>2,3</sup> Green chemistry is primary pollution prevention rather than waste remediation (end-of-pipe solutions). More recently, the twelve principles of green engineering were proposed,<sup>4</sup> which contain the same underlying features—conservation of energy and other raw materials and elimination of waste and hazardous materials—but from an engineering standpoint. Poliakoff and co-workers<sup>5</sup> proposed a mnemonic, **PRODUCTIVELY**, which captures the spirit of the twelve principles of green chemistry in a single slide.

Another concept which has become the focus of attention, both in industry and society at large, in the past decade or more is that of sustainable development, first introduced in the Brundtland report<sup>6</sup> in the late 1980s and defined as: *Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs.*

Biocatalysis & Organic Chemistry, Delft University of Technology,  
Julianalaan 136, Delft, 2628 BL, Netherlands.  
E-mail: r.a.sheldon@tudelft.nl



Roger Sheldon is a native of Nottingham, UK. He received a PhD in organic chemistry from the University of Leicester, UK, in 1967. Following a postdoctoral appointment with Jay Kochi at Case Western Reserve University and Indiana University, USA, he was with Shell Research Amsterdam (1969–1980) and DSM Andeno (1980–1990) before being appointed to the Chair of Biocatalysis and Organic Chemistry at Delft University of Technology in 1991. His research interests are in the general area of green chemistry and catalysis, encompassing the application of homogeneous, heterogeneous and, particularly, biocatalysis in organic synthesis. He is widely known for developing the concept of E factors for assessing the environmental footprint of chemical processes. He is currently Professor Emeritus in Delft and CEO of CLEA Technologies, a start-up biotech company.

In the past decade the concepts of green chemistry and sustainable development have become a strategic focus in both industrial and academic corridors of power and have formed the subject of several books.<sup>1,7-9</sup> Indeed, the two concepts go hand in hand: sustainability is our ultimate common goal and green chemistry is a means to achieve it.

## 2. E Factors and atom utilisation

As we have noted elsewhere<sup>10</sup> our attention was drawn to the problem of waste in the fine chemicals industry in the early 1980s by the closure of a plant which produced *ca.* 100 tons per annum of phloroglucinol by the process shown in Fig. 1. It involved dichromate oxidation of 2,4,6-trinitrotoluene (TNT), in fuming sulfuric acid, followed by Béchamp reduction with iron and hydrochloric acid and subsequent heating of the acidic solution to give phloroglucinol.

Unfortunately, phloroglucinol was not the only 'product' formed. Along with every kg of the desired phloroglucinol, *ca.* 40 kg of solid waste containing  $\text{Cr}_2(\text{SO}_4)_3$ ,  $\text{NH}_4\text{Cl}$ ,  $\text{FeCl}_2$  and  $\text{KHSO}_4$  was produced. The magnitude of this waste is easily understood by examining the stoichiometric equation (see Fig. 1) of the overall process, something very rarely done by organic chemists. This predicts the formation of *ca.* 20 kg of waste per kg of phloroglucinol, assuming 100% chemical yield and exactly stoichiometric quantities of the various reagents. In practice, an excess of the oxidant and reductant, and a large excess of sulfuric acid, which has to be subsequently neutralised with base, is used and the isolated yield of phloroglucinol is less than 100%. This explains the observed 40 kg of waste per kg of desired product.

Our experience with the phloroglucinol process led us to analyse the amount of waste formed in processes for the manufacture of other fine chemicals and pharmaceutical intermediates and even some bulk chemicals. This soon revealed that tens of kg waste per kg of desired product were no exception in the fine chemicals industry which led us to propose the term E(nvironmental) factor (kg waste per kg product) as a metric for quickly assessing the environmental footprint of manufacturing processes.<sup>11</sup> Table 1 illustrates the magnitude of the waste problem in the various segments of the chemical industry.

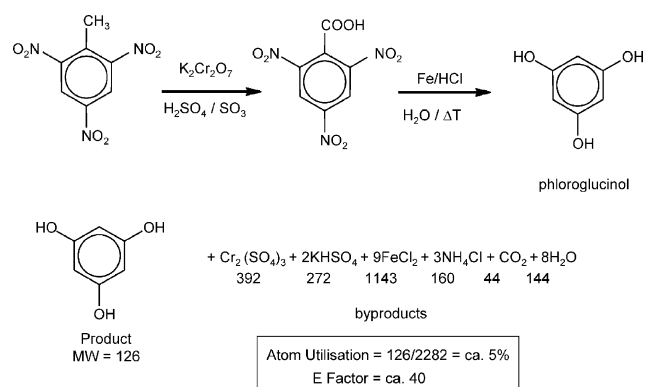


Fig. 1 Phloroglucinol manufacture from TNT.

Table 1 E factors in the chemical industry

Industry segment	Volume/tons per annum <sup>a</sup>	E factor (kg waste per kg product)
Bulk chemicals	$10^4$ – $10^6$	<1–5
Fine chemical industry	$10^2$ – $10^4$	5–>50
Pharmaceutical industry	$10$ – $10^3$	25–>100

<sup>a</sup> Annual production of the product worldwide or at a single site

A knowledge of the stoichiometric equation allows one to predict, before any experiment is performed, the theoretical minimum amount of waste that can be expected. Hence, we began to use what we called the *atom utilisation* concept<sup>12</sup> to quickly assess the environmental acceptability of alternative processes to a particular product. The idea arose by analogy with the concept of 'syn gas utilisation', which we used to roughly assess the commercial viability of various processes for the production of commodity chemicals from syn gas.<sup>13</sup> We reasoned that the more atoms of the syn gas that ended up in the product the better the economics would be. Ethylene glycol synthesis, for example, involves 100% syn gas utilisation, while ethylene utilises only 44%, with the production of expensive water as the co-product (see Fig. 2).

Similarly, we used the concept of *oxygen availability* to assess the economic and environmental viability of different oxygen donors in catalytic oxygen transfer processes (Table 2).<sup>14</sup> The most attractive oxidants are those containing the highest percentage of available oxygen and forming an innocuous co-product, preferably water. On this basis hydrogen peroxide earned the accolade "Mr Clean".<sup>15</sup> This concept can be extrapolated to the use of *hydrogen availability* for assessing reducing agents.

In 1991 Trost published his elegant paper<sup>16</sup> on *atom economy* which became the widely accepted terminology, although *atom efficiency* is also used. In Fig. 3 we compare the atom utilisation (economy) of the classical chlorohydrin route to propylene oxide with that of oxidation with hydrogen peroxide. We began to promote the use of E factors and atom economy (utilisation) for assessing the environmental acceptability of chemical manufacturing processes in the early 1990s<sup>11,12</sup> and they have now become widely accepted green

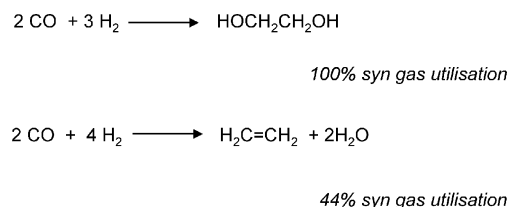


Fig. 2 Syn gas utilisation.

Table 2 Oxygen availability in various oxidants

Oxidant	% Active O	By-product
$\text{H}_2\text{O}_2$	47	$\text{H}_2\text{O}$
<i>t</i> -BuOOH	18	<i>t</i> -BuOH
$\text{CH}_3\text{COOOH}$	22	$\text{CH}_3\text{COOH}$
$\text{NaOCl}$	22	$\text{NaCl}$
$\text{KIO}_4$	8	$\text{KIO}_3$

## 1. PO : Chlorohydrin process

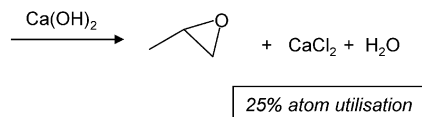
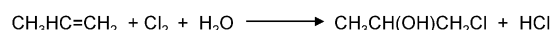
2. PO : Catalytic Oxidation with  $\text{H}_2\text{O}_2$ 

Fig. 3 Atom utilisation.

metrics. The latter is an extremely useful tool for rapid evaluation of the amounts of waste that will be generated by alternative processes. It is a theoretical number, *i.e.* it assumes a chemical yield of 100% and exactly stoichiometric amounts and disregards substances which do not appear in the stoichiometric equation.

The E factor, in contrast, is the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvent losses, process aids and, in principle, even fuel. We generally excluded water from the calculation of the E factor as we thought that its inclusion would lead to exceptionally high E factors in many cases and make meaningful comparisons of processes difficult. A higher E factor means more waste and, consequently, greater negative environmental impact. The ideal E factor is zero. Put quite simply, it is kilograms (of raw materials) in, minus kilograms of desired product, divided by kilograms of product out. It can be easily calculated from a knowledge of the number of tons of raw materials purchased and the number of tons of product sold, for a particular product or a production site or even a whole company. It is perhaps surprising, therefore, that many companies are not aware of the E factors of their processes. We hasten to add, however, that this situation is rapidly changing and the E factor has been widely adopted by the fine chemicals and pharmaceutical industries.<sup>17,18</sup>

As Lord Kelvin pointed out: “*To measure is to know*”. Quantification of the waste generated in chemicals manufacturing, by way of E factors, served to focus the attention of fine chemical and pharmaceutical companies on the need for a paradigm shift from a concept of process efficiency which was exclusively based on chemical yield to one that is motivated by elimination of waste and maximisation of raw materials utilisation. Alternative metrics have been proposed,<sup>19–21</sup> notably mass intensity (MI),<sup>20</sup> defined as the total mass of materials used divided by the mass of product, *i.e.*  $\text{MI} = \text{E factor} + 1$ . In our opinion, however, none of these alternative metrics offers any particular advantage over the E factor for giving a mental picture of how wasteful a process is. The ideal

MI is 1 whereas the ideal E factor is 0, which more clearly reflects the ultimate goal of zero waste.

All of the metrics discussed above take only the mass of waste generated into account. However, the environmental impact of waste is determined not only by its amount but also by its nature. Hence, we introduced<sup>11</sup> the term ‘environmental quotient’, EQ, obtained by multiplying the E factor with an arbitrarily assigned unfriendliness quotient,  $Q$ . For example, one could arbitrarily assign a  $Q$  value of 1 to NaCl and, say, 100–1000 to a heavy metal salt, such as chromium, depending on its toxicity, ease of recycling, *etc.* Although the magnitude of  $Q$  is debatable and difficult to quantify, ‘quantitative assessment’ of the environmental impact of waste is, in principle, possible.  $Q$  is dependent on, *inter alia*, the ease of disposal or recycling of waste and, generally speaking, organic waste is more easy to dispose of or recycle than inorganic waste.

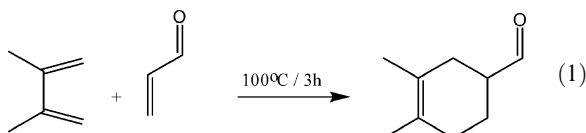
### 3. Catalysis and waste minimisation

Where does this waste originate? It comprises primarily inorganic salts, such as sodium chloride, sodium sulfate and ammonium sulfate, that are formed in the reaction or in downstream processing. One of the reasons that the E factor increases dramatically on going from bulk to fine chemicals and pharmaceuticals is that the latter are more complicated molecules that involve multi-step syntheses. However, the larger E factors in the fine chemical and pharmaceutical industries are also a consequence of the widespread use of classical stoichiometric reagents rather than catalysts. Examples that readily come to mind are metal (Na, Mg, Zn, Fe) and metal hydride ( $\text{LiAlH}_4$ ,  $\text{NaBH}_4$ ) reducing agents and oxidants such as permanganate, manganese dioxide and chromium(vi) reagents. For example, the phloroglucinol process (see above) combines an oxidation with stoichiometric chromium(vi) with a reduction with Fe–HCl. Similarly, a plethora of organic reactions, *e.g.* sulfonations, nitrations, halogenations, diazotisations and Friedel–Crafts acylations, employ stoichiometric amounts of mineral acids ( $\text{H}_2\text{SO}_4$ , HF,  $\text{H}_3\text{PO}_4$ ) or Lewis acids ( $\text{AlCl}_3$ ,  $\text{ZnCl}_2$ ,  $\text{BF}_3$ ) and are major sources of inorganic waste. The solution is evident: substitution of antiquated stoichiometric methodologies with cleaner catalytic alternatives. Indeed, a major challenge in chemicals manufacture in general is to develop processes based on  $\text{H}_2$ ,  $\text{O}_2$ ,  $\text{H}_2\text{O}_2$ , CO,  $\text{CO}_2$  and  $\text{NH}_3$  as the direct sources of H, O, C and N. Catalytic hydrogenation, oxidation, carbonylation and hydroformylation are good examples of such highly atom efficient, low-salt processes. The generation of copious amounts of inorganic salts can similarly be largely circumvented by replacing stoichiometric mineral and Lewis acids and stoichiometric bases, such as NaOH and KOH, with recyclable solid acids and bases, preferably in catalytic amounts.<sup>22</sup> Another major source of waste in the pharmaceutical industry is solvent losses which has stimulated the development of alternative reaction media (see later).<sup>18,23</sup>

### 4. The best catalyst is no catalyst

Although the introduction of clean catalytic methodologies can dramatically reduce the E factors of processes in the fine

chemicals and allied industries, catalysis is not a *conditio sine qua non* for waste minimisation. The ideal reaction is one that proceeds thermally, under relatively mild conditions without the need for any reagents including catalysts, to afford the desired product in 100% atom efficiency. Many (4 + 2) cycloadditions, such as the Diels–Alder reaction (Reaction (1)), fulfil these criteria. Nonetheless, the addition of solid Brønsted or Lewis acid catalysts can sometimes lead to better results.<sup>24</sup>



Strictly speaking, a catalyst is, by definition, not consumed during a reaction. However, in practice losses may occur during work-up or the catalyst may be deactivated. In many cases the catalyst consists of an expensive noble metal, often as a complex with an even more expensive ligand. Hence, from both an economic and environmental viewpoint, catalyst loadings and catalyst losses should be kept to a minimum. Unfortunately, the organic chemist's penchant for adding the standard 5 mol% of catalyst to the reaction militates against this. It is worth noting that many noble metal catalysed reactions may involve colloidal metals as the active catalyst and aggregation of the colloidal particles, which is facilitated by increasing metal loading, could lead to catalyst deactivation.

For example, many industrially important palladium catalysed C–C coupling reactions, such as the Heck and Suzuki couplings, are now known to involve colloidal palladium (probably giant palladium clusters as described by Moiseev and co-workers<sup>25</sup> or what have become more recently known as palladium nanoparticles) as the active catalyst. Aggregation of the palladium leads to the formation of inactive palladium black. De Vries and co-workers<sup>26</sup> showed that smooth, ligand-free Heck and Suzuki couplings of aryl bromides (Fig. 4) could be performed with “homeopathic” catalyst loadings (0.01–0.1%). One wonders how many more (noble) metal catalysed reactions could benefit from “homeopathic” catalyst loadings.

## 5. Heterogeneous catalytic oxidation with hydrogen peroxide

Although catalytic oxidation is widely applied in the bulk chemicals industry<sup>27</sup> there are still a few processes which use

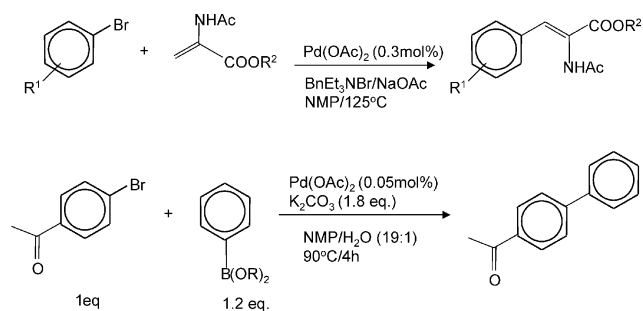
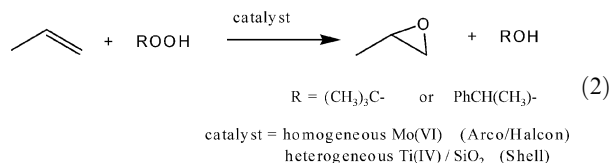


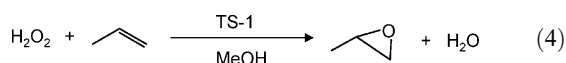
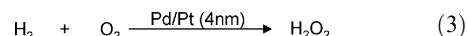
Fig. 4 Heck and Suzuki coupling with “homeopathic” palladium.

stoichiometric inorganic oxidants. A case in point is propylene oxide (PO) manufacture. The chlorohydrin route, which generates *ca.* 2 kg of CaCl<sub>2</sub> for each kg of PO, accounts for more than half of the *ca.* 4 million tons of propylene oxide produced annually. In the late 1960s the Halcon and ARCO companies developed processes for the epoxidation of propylene with an alkyl hydroperoxide, catalysed by soluble molybdenum compounds.<sup>28,29</sup> In contrast, the Shell SMPO process for the co-production of styrene monomer and propylene oxide involves the epoxidation of propylene with ethyl benzene hydroperoxide over a heterogeneous Ti(IV)-on-silica catalyst (Reaction (2)).



We attributed<sup>30</sup> the high activity of the Ti(IV)–SiO<sub>2</sub> catalyst to the electrophilicity (Lewis acidity) of the Ti(IV) being increased by the silanoxyl ligands and to its site isolation in the silica framework preventing the formation of inactive  $\mu$ -oxo oligomers. Interestingly, the Shell catalyst was completely inactive when aqueous hydrogen peroxide was used as the oxidant owing to the strong inhibitory effect of water and other protic solvents on the Ti(IV)–silica catalyst.<sup>30</sup> In stark contrast, Enichem workers reported,<sup>31</sup> in the mid 1980s, that the analogous titanium(IV) substituted silicalite-1 (TS-1) was an effective catalyst for the epoxidation of olefins with 30% aqueous hydrogen peroxide in methanol as solvent. This contrasting behaviour could be rationalised on the basis of the hydrophobic nature of silicalite-1, which enables the selective adsorption of hydrophobic olefins into the pores of this molecular sieve, even in the presence of water or alcohols.

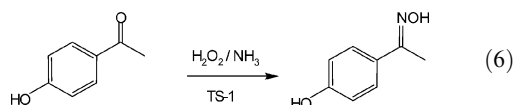
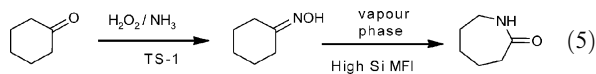
Although the TS-1 catalyst was developed in the mid 1980s, its application in PO manufacture was hindered by the relatively high price of hydrogen peroxide. More recently, Headwaters Technology Innovation (HTI) developed palladium–platinum nanoparticles which catalyse the direct synthesis of hydrogen peroxide from hydrogen and oxygen (Reaction (3)), in high selectivity, below the flammability limit of hydrogen.<sup>32</sup> Combination of this development, for which HTI received a 2007 Presidential Green Chemistry Challenge Award, with the Enichem technology (Reaction (4)) affords a direct synthesis of propylene oxide from propylene, hydrogen and oxygen, with water as the sole by-product, which is currently being commercialised in partnership with Evonik (formerly Degussa).



Similarly, Sumitomo has commercialised a process for caprolactam, the raw material for nylon 6, which involves combining the TS-1 catalysed ammoxidation of cyclohexanone, with NH<sub>3</sub>–H<sub>2</sub>O<sub>2</sub>,<sup>33</sup> with a novel vapour phase Beckmann rearrangement over a high-silica MFI zeolite,<sup>34</sup> affording caprolactam



in >98% yield based on cyclohexanone and 93% based on  $\text{H}_2\text{O}_2$  (Reaction (5)). The conventional process involves the reaction of cyclohexanone with hydroxylamine sulfate (or another salt), and Beckmann rearrangement in the presence of stoichiometric amounts of sulfuric acid or oleum, generating *ca.* 4.5 kg of ammonium sulfate per kg of caprolactam. In contrast, the Sumitomo process generates two molecules of water as the sole co-product, *i.e.* it is essentially salt-free. We similarly showed that the same methodology could be used for the ammoximation of *p*-hydroxy acetophenone (Reaction (6)).<sup>35</sup> The oxime product is an intermediate in the manufacture of the analgesic paracetamol.

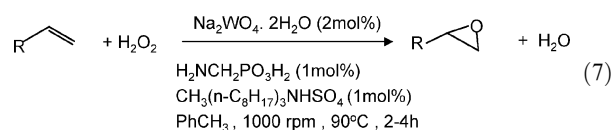


The remarkable success of TS-1, as a catalyst for a variety of oxidations with the green oxidant hydrogen peroxide, led to frenetic activity towards the synthesis of related heterogeneous catalysts.<sup>36</sup> This was largely based on the expectation that TS-1 was the prototype of families of so-called “redox molecular sieves” with unique properties.<sup>36</sup> Site-isolation, in the constrained environment of the pores and cavities of molecular sieves, of elements capable of catalysing oxidation processes, was expected to produce robust, recyclable catalysts with enzyme-like properties.

To this end we synthesised, *inter alia*, chromium-substituted molecular sieves, such as chromium aluminophosphate-5 (Cr-ALPO-5) which proved to be an active, recyclable catalyst for the oxidation of alcohols and alkylaromatic hydrocarbons with alkyl hydroperoxides or molecular oxygen.<sup>37</sup> However, a subsequent, more detailed investigation,<sup>38</sup> involving a “hot filtration test”, revealed that small amounts of chromium(vi) were being leached into the solution, by reaction with the alkyl hydroperoxide, and that amounts of soluble Cr(vi) as low as 1–2 ppm could account for the observed catalysis. Such a catalyst can be recycled many times because each time a small amount of the active species is released into the solution, like Greek warriors from the Trojan horse.<sup>39</sup> This obviously places severe limitations on the practical utility of such catalysts and the hot filtration test has been adopted by many workers as a standard protocol for establishing true heterogeneity. In this way, catalysis observed with many redox molecular sieves has been shown to be homogeneous in nature and a result of leaching of the metal from the framework. This induced us to switch our attention to the use of existing protein scaffolds as a basis for designing novel catalysts for oxidations (see later).

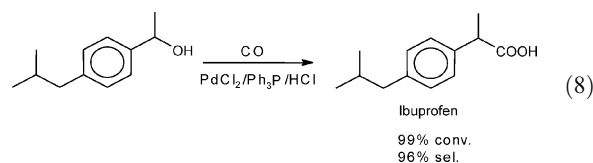
At the same time that Enichem workers were developing the TS-1 catalyst, Venturello and co-workers<sup>40</sup> adopted a different approach. They showed that a mixture of tungstate and phosphate, in the presence of a tetraalkylammonium halide as a phase transfer agent, mediated the epoxidation of olefins with hydrogen peroxide in a two-phase dichloroethane–water system. Since its discovery in 1983 the Venturello and related

systems have been extensively studied.<sup>41</sup> Noyori and co-workers<sup>42</sup> reported a halide-free and chlorinated hydrocarbon solvent-free system which constituted a significant improvement to the original system. A combination of a phase transfer agent, comprising a lipophilic tetraalkylammonium cation and a bisulfate anion, with a catalytic amount of  $\text{H}_2\text{NCH}_2\text{PO}_3\text{H}_2$  and sodium tungstate, was an effective catalyst system for olefin epoxidation with  $\text{H}_2\text{O}_2$  in toluene–water or in the absence of an organic solvent (Reaction (7)).



## 6. Homogeneous catalysis and alternative reaction media: the best solvent is no solvent

Homogeneous catalysis is widely used in the chemical industry in, for example, carbonylation, hydroformylation, olefin metathesis and oxidation. However, despite its advantages, such as high activities and selectivities, compared to heterogeneous counterparts, it suffers from serious shortcomings. Recovery of the catalyst in an active form suitable for recycling is often cumbersome and the product can be contaminated with catalyst residues. An illustrative example is the Boots–Hoechst–Celanese (BCH) process for the manufacture of the analgesic ibuprofen, with an annual production of several thousand tons. A key step is a homogeneous palladium catalysed carbonylation of an alcohol (Reaction (8)), which proceeds with high activity and selectivity in addition to 100% atom efficiency.<sup>43</sup> A serious drawback, however, is the cumbersome separation of the catalyst from the product and contamination of the latter, the active pharmaceutical ingredient, with unacceptably high amounts of palladium. Consequently, an expensive purification procedure is required to obtain a product of acceptable purity. Indeed, this is a problem with homogeneous catalytic processes in general. Attempts to heterogenise homogeneous catalysts by attachment to organic or inorganic supports have, generally speaking, not resulted in commercially viable processes, for a number of reasons, such as leaching of the metal, poor catalyst productivities, irreproducible activities and selectivities and degradation of the support.



There is a definite need, therefore, for systems that combine the advantages of high activity and selectivity of homogeneous catalysts with the facile recovery and recycling characteristic of their heterogeneous counterparts. This can be achieved by employing a different type of heterogeneous system compared to the traditional solid catalyst with liquid or gaseous reactants, namely liquid–liquid biphasic catalysis, whereby the catalyst is dissolved in one phase and the reactants and

product(s) in the second liquid phase. The catalyst is recovered and recycled by simple phase separation. Preferably, the catalyst solution remains in the reactor and is reused with a fresh batch of reactants without further treatment or, ideally, it is adapted to continuous operation.

This meshes with another important issue in green chemistry: organic solvents. So many of the solvents favoured by organic chemists, such as chlorinated hydrocarbons, have been blacklisted that the whole question of solvent use requires rethinking and has become a primary focus, especially in the pharmaceutical industry.<sup>18,44,45</sup> In our original studies of E factors of various processes we assumed, if details were not known, that solvents would be recycled by distillation and that this would involve a 10% loss. A recent benchmarking exercise performed by the Green Chemistry Institute Pharmaceutical Round Table (see the GCI website: <http://www.acs.org/greenchemistry>) revealed that solvents were a major contributor to the E factors of pharmaceutical manufacturing processes. Their use results in substantial atmospheric emissions and pollution of ground water. These issues surrounding a wide range of traditional organic solvents have stimulated the fine chemical and pharmaceutical industries to seek more benign alternatives. The problem with solvents is not so much their use but the seemingly inherent inefficiencies associated with their containment, recovery and reuse. Alternative solvents should, therefore, provide for their efficient separation from the product and reuse.

Various non-conventional reaction media have been intensely studied in recent years, including water,<sup>46</sup> supercritical CO<sub>2</sub>,<sup>47</sup> fluorous biphasic,<sup>48</sup> and ionic liquids,<sup>49</sup> alone or in liquid–liquid biphasic combinations. We also note that the use of water and supercritical carbon dioxide as reaction media is consistent with the current trend towards the use of renewable, biomass-based raw materials, which are ultimately derived from carbon dioxide and water.

The best solvent is no solvent, but if a solvent (diluent) is needed then water has many benefits: it is non-toxic, non-flammable, abundantly available and inexpensive. Furthermore, performing the reaction in an aqueous biphasic system,<sup>50</sup> whereby the catalyst resides in the water phase and the product is dissolved in the organic phase, allows for recovery and recycling of the catalyst by simple phase separation. An example of a large scale application of this concept is the Ruhrchemie–Rhône Poulenc process for the hydroformylation of propylene to *n*-butanal which employs a water-soluble rhodium(i) complex of trisulfonated triphenylphosphine (tppts) as the catalyst and has an E factor of 0.1 compared to 0.6–0.9 for conventional monophasic hydroformylation processes.<sup>51</sup>

We developed the use of an analogous palladium(0) complex of the tppts ligand, Pd(tppts)<sub>3</sub>, for the aqueous biphasic carbonylation of alcohols and olefins (Fig. 5).<sup>52</sup> For example, when the above-mentioned ibuprofen synthesis was performed with tppts in an aqueous biphasic system, product contamination by the catalyst was essentially eliminated. Similarly, we used a water soluble palladium complex of a sulfonated phenanthroline ligand for the highly selective aerobic oxidation of primary and secondary alcohols in an aqueous biphasic system, in the absence of any organic solvent (Fig. 5).<sup>53</sup> The

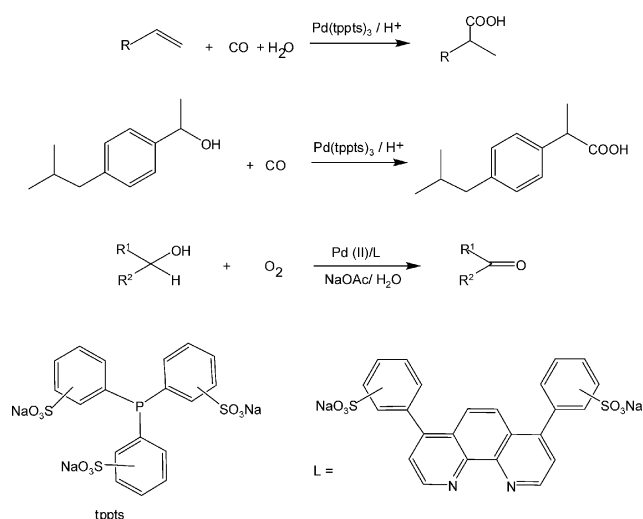


Fig. 5 Catalytic aqueous biphasic carbonylations and oxidations.

liquid product could be recovered by simple phase separation and the aqueous phase, containing the catalyst, used with a fresh batch of alcohol substrate, affording a truly green method for the oxidation of alcohols.

An aqueous biphasic system is not the answer in all cases, however. Since the reaction takes place in the aqueous phase the substrate must be at least sparingly soluble in water. Consequently, other alternative reaction media: perfluorocarbons, supercritical carbon dioxide, and ionic liquids, have been extensively studied, in both mono- and biphasic systems. Ionic liquids, for example, have been extensively studied as media for performing chemocatalytic<sup>49</sup> and biocatalytic transformations.<sup>54</sup> Following the first report of successful performance of enzymatic reactions in water-free ionic liquids (Fig. 6) in 2000<sup>55</sup> research in this area has undergone explosive growth.<sup>54</sup>

The problem still remains, however, of separation of the product from the ionic liquid and recycling of the catalyst. This can be achieved by, for example, solvent extraction. This does not necessarily mean that we are back to square one where we have the problems associated with the use of an organic solvent. It is conceivable that an undesirable organic solvent, *e.g.* a chlorinated hydrocarbon, used in the original reaction step could be replaced by a more environmentally organic solvent for extracting the product from the ionic liquid. An interesting variant is the use of supercritical carbon

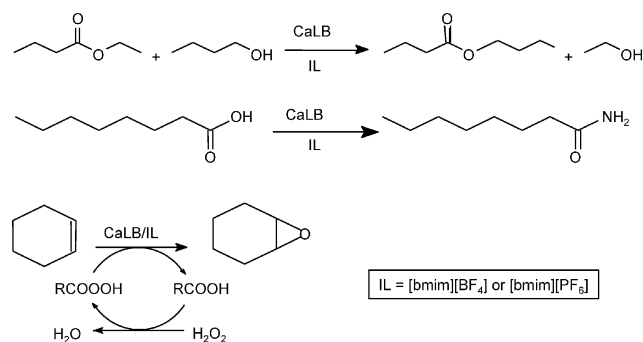


Fig. 6 Biocatalysis in anhydrous ionic liquids.

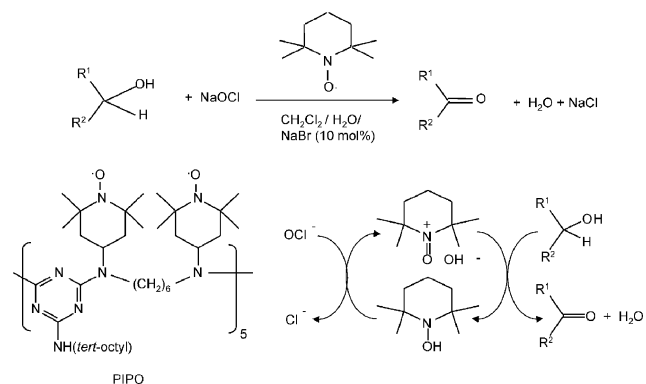
dioxide as the mobile phase, to continuously extract the product, while the chemical catalyst<sup>56</sup> or enzyme<sup>57</sup> remains (dissolved or as a suspension) in the ionic liquid phase. In a recent variation on this theme,<sup>58</sup> the so-called 'miscibility switch' was used to perform a catalytic reaction smoothly in a monophasic ionic liquid–scCO<sub>2</sub> mixture followed by lowering of the pressure to afford a biphasic system whereby the catalyst was contained in the ionic liquid phase and the product in the scCO<sub>2</sub> phase, thus enabling their facile separation.

## 7. Organocatalysis: oxidations catalysed by stable nitroxyl radicals

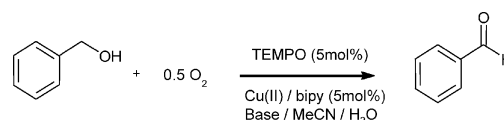
Recent years have witnessed a burgeoning interest in organocatalysis<sup>59</sup> which circumvents many of the problems associated with the use of (homogeneous) metal catalysts (see above). We were attracted to the use of stable nitroxyl radicals, such as TEMPO (tetramethylpiperidinyloxy radical) and its derivatives, as organocatalysts for the selective oxidation of alcohols.<sup>60</sup> For example, the system comprising catalytic amounts of TEMPO, in conjunction with aqueous sodium hypochlorite (household bleach) is now a widely used method in the fine chemicals industry (Fig. 7).<sup>61,62</sup> The active oxidant is the oxoammonium cation which is reduced to the corresponding hydroxylamine. Oxidation of the latter by hypochlorite completes the catalytic cycle. Although the use of NaOCl as the stoichiometric oxidant is not particularly green it is certainly greener than stoichiometric chromium(vi). There are many shades of green.

Shortcomings of the standard protocol for oxidations with TEMPO–NaOCl are the use of substantial amounts of bromide as a co-catalyst and of dichloromethane as the co-solvent, in addition to the relatively high cost of the soluble TEMPO catalyst, which cannot be readily recycled. Hence, we introduced<sup>63</sup> the use of an oligomeric piperidinyloxy radical, PIPO, derived from a commercially available and relatively inexpensive polymer additive, chimassorb 944. PIPO was more reactive than TEMPO, which enabled the use of more acceptable solvents, such as ethyl acetate or methyl *tert*-butyl ether, without the need for a bromide co-catalyst (Fig. 7).

The use of hypochlorite as the stoichiometric oxidant still remains, in the context of green chemistry and waste mini-



**Fig. 7** TEMPO and PIPO catalysed oxidations of alcohols with NaOCl.



**Fig. 8** Copper(II)–TEMPO catalysed aerobic oxidation of alcohols.

misation, a shortcoming of these methods. It was originally shown by Semmelhack *et al.*<sup>64</sup> that TEMPO, in conjunction with copper(I) as a co-catalyst in DMF as solvent, enabled the use of the greener and less expensive molecular oxygen (air) in the oxidation of alcohols. We showed that PIPO could also be successfully used under the same conditions. We subsequently showed that a system comprising TEMPO, a bipyridyl complex of copper(II), and a base formed an excellent catalyst for the selective aerobic oxidation of alcohols (Fig. 8).

The almost complete specificity for primary *versus* secondary alcohol moieties endows this system with enzyme-like qualities. Indeed, copper-dependent oxidases, such as galactose oxidase, catalyse the selective oxidation of primary alcohol moieties *in vivo* and we have shown<sup>60</sup> that the above-mentioned Cu(II)–TEMPO systems involve a similar active oxidant to that used by the galactose oxidase, namely an 'oxy' radical coordinated to a copper(II) centre. Another copper-dependent oxidase, laccase, in conjunction with TEMPO, is able to catalyse the aerobic oxidation of alcohols. We have shown, by measuring isotope effects, that the reaction involves an oxoammonium cation as the active oxidant, analogous to the TEMPO catalysed oxidations with NaOCl but different from the above mentioned copper–TEMPO systems.<sup>65</sup> The different mechanisms can be ascribed to the high redox potential of Cu(II) in fungal laccases which is needed for their *in vivo* catalysis of lignin degradation. It is an example of the so-called entatic effect<sup>66</sup> whereby the coordination of transition metal ions in proteins in unusual (high-energy) geometries can lead to substantial increases in redox potential.

## 8. Biocatalysis: inventing non-natural biotransformations

Biocatalysis has many attractive features in the context of green chemistry: mild reaction conditions (in water at physiological pH and temperature) and an environmentally compatible, biodegradable catalyst (an enzyme) derived from renewable raw materials, combined with high activities and chemo-, regio- and stereoselectivities in reactions of multifunctional molecules. Furthermore, the use of enzymes generally circumvents the need for the functional group activation and protection often required in traditional organic syntheses, affording more environmentally and economically attractive processes with fewer steps and, hence, less waste. Illustrative examples are provided by the substitution of classical chemical processes with enzymatic ones in the synthesis of semi-synthetic penicillins and cephalosporins.<sup>67</sup>

Two advances that form the basis of modern biotechnology have paved the way for the widespread application of biocatalysis. Recombinant DNA techniques have made it, in principle, possible to produce virtually any enzyme for a commercially acceptable price and *in vitro* evolution has

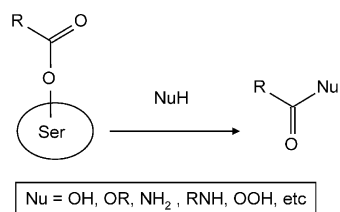


Fig. 9 Lipase catalysed ammoniolysis of esters.

enabled the manipulation of enzymes such that they exhibit the desired substrate specificity, activity, stability, pH profile, *etc.*<sup>68</sup>

In our approach to the rational design of novel, non-natural biotransformations with practical utility we have generally used what we call the mechanism-based organic chemistry strategy. An example is provided by the invention of lipase catalysed ester ammoniolysis, an entirely new enzymatic reaction.<sup>69</sup> The mechanism of lipase catalysed hydrolysis of an ester bond (in a triglyceride) involves the acylation of a serine hydroxyl group in the active site, affording the so-called acylenzyme intermediate. The latter subsequently reacts with water to afford the observed carboxylic acid product (see Fig. 9). We reasoned that replacement of the water, by non-natural nucleophiles could afford an enantioselective route to various carboxylic acid derivatives. For example, use of ammonia in *tert*-butanol, in order to suppress competing hydrolysis, afforded a mild method for the (enantioselective) synthesis of amides from the corresponding esters. We subsequently found that the free carboxylic acid could also be used.<sup>70</sup> The method has broad scope and can be used for the resolution of chiral esters including  $\alpha$ -amino acid esters.<sup>71</sup> It is an excellent method for the synthesis of amides under mild conditions and is, therefore an industrially attractive alternative to chemical amidation which usually requires forcing conditions.

Similarly, lipase catalysed acylation of a primary amine moiety can be used for the resolution of chiral primary amines and BASF successfully developed a process, which is operated on a multi-thousand ton scale, for the synthesis of a variety of enantiopure amines.<sup>72</sup> Commercially acceptable rates were obtained by using a methoxyacetic acid ester as the acyl donor which is attributed to hydrogen bond formation with the ether oxygen in the active site of the enzyme.<sup>73</sup> As shown in Fig. 10, the process affords an amide of the reacting enantiomer together with the other enantiomer as the free amine.

In order to recover both amines in optically active form the amide is hydrolysed chemically by reaction with NaOH in aqueous ethylene glycol at 150 °C. This “brute force” method would certainly lead to problems with amines containing other functional groups and is in stark contrast with the elegant enzymatic procedure used for the first step. Hence, we reasoned that the use of an enzymatic deacylation would afford an overall greener process. An example of what we have called an *easy-on-easy-off* process is shown in Fig. 11. Penicillin G

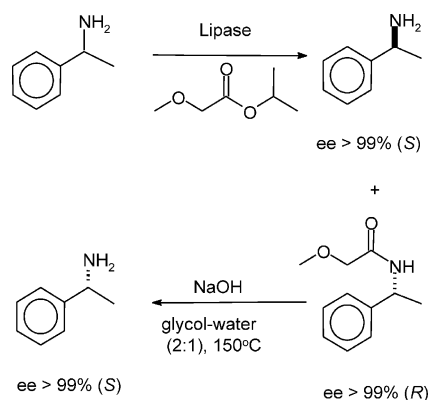


Fig. 10 BASF process for enzymatic resolution of amines.

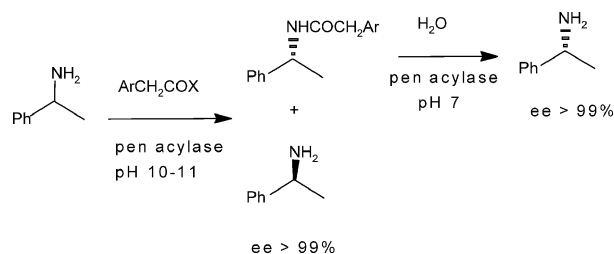


Fig. 11 Easy-on-easy-off resolution of amines with penicillin G amidase.

amidase from *Alcaligenes faecalis*, which is used in the manufacture of semi-synthetic penicillins and cephalosporins, was used in both steps.<sup>74</sup> The acylation was performed in an aqueous medium at pH 10–11 and, after separation of the remaining amine enantiomer, the acylated amine was hydrolysed with the same enzyme by lowering the pH to 7.

In order to obtain a commercially viable process it is necessary to racemise the unwanted amine enantiomer, preferably *in situ* in a so-called dynamic kinetic resolution (DKR). The palladium-on-charcoal catalysed racemisation of amines was first reported by Murahashi and co-workers<sup>75</sup> and was later combined with lipase catalysed acylation to afford a DKR by Reetz and Schimossek.<sup>76</sup> We were able to achieve a DKR of  $\alpha$ -methyl benzylamine by performing the lipase catalysed acylation in the presence of a palladium nanoparticle catalyst (Fig. 12).<sup>77</sup>

## 9. Biomimetic chemocatalysis, chemomimetic biocatalysis and enzyme promiscuity

Why should Nature have a monopoly on good catalysts? Nature's redox catalysts, metalloenzymes, are based on

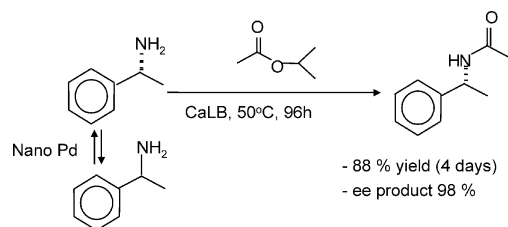


Fig. 12 DKR of  $\alpha$ -methyl benzylamine.



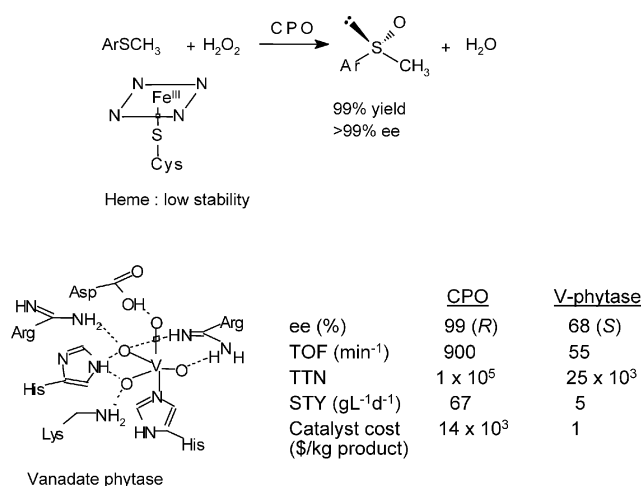


Fig. 13 Enantiosulfoxidation with hydrogen peroxide.

abundant elements such as iron and copper. In the laboratory, in contrast, we are not limited to this narrow choice and much effort has been devoted to designing biomimetic chemical catalysts capable of emulating the activity of enzymes but with increased operational stability. However, the three dimensional protein structure is the culmination of millions of years of evolution and is difficult to emulate. Hence, we adopted a different approach, which we have dubbed the chemomimetic biocatalysis strategy for the rational design of novel redox enzymes. Various transition metals are known to catalyse a variety of oxidations with oxygen or hydrogen peroxide. We reasoned that nesting such a metal in the active site of a hydrolytic enzyme (analogous to situating a redox element in the framework of a molecular sieve) would afford a semi-synthetic enzyme capable of mediating (enantioselective) oxidations. Using this strategy we were able to develop a semi-synthetic peroxidase, vanadate phytase. It was already known that the heme-dependent enzyme, chloroperoxidase (CPO), from *Caldariomyces fumago* is able to catalyse a variety of enantio- and regioselective oxidations, such as sulfoxidation (see Fig. 13), with the green oxidant hydrogen peroxide.<sup>78</sup> However, CPO is rapidly deactivated by hydrogen peroxide *via* oxidation of its sensitive porphyrin prosthetic group which severely limits its practical utility. On the other hand, vanadium is known to catalyse epoxidations and sulfoxidations with alkyl hydroperoxides or hydrogen peroxide and vanadium-dependent peroxidases are also known. They are more stable than the heme peroxidases, because they are not encumbered by the sensitive porphyrin ring, but they are expensive and not readily available.

It was further known, from the work of Messerschmidt and Weber,<sup>79</sup> that the acid phosphatase phytase, a very inexpensive and readily available hydrolase that is added to poultry and pig feed, has an active site structure very similar to that of vanadium peroxidases, but without the vanadium. Furthermore, in its natural reaction it accommodates a phosphate ester in its active site and phosphorus(v) exhibits similar coordination geometries to vanadium(v). Hence, we reasoned that the addition of vanadate to phytase should afford a robust and inexpensive peroxidase and this proved to be the case (see Fig. 13).<sup>80</sup>

Recently there has been a flourish of interest in the rational design of novel, non-natural reactions of enzymatic transformations by both of the approaches outlined above which have become collectively known as enzyme (catalytic) promiscuity.<sup>81</sup> For example, Okrasa and Kazlauskas<sup>82</sup> exchanged the zinc atom in carbonic anhydrase with manganese to obtain a semi-synthetic enzyme which, in the presence of bicarbonate, acted as a peroxidase. Combination of the concept of enzyme promiscuity with the technique of directed evolution could provide a powerful tool for the design and optimisation of novel reactions with enzymes.<sup>81</sup>

## 10. Optimisation of biocatalysis: evolution in the fast lane

The enzymes found in Nature are the result of aeons of cumulative natural selection but they were not evolved to be suitable for the biotransformations of non-natural, commercially interesting molecules. In order to make them suited to these tasks they need to be re-evolved but we do not have millions of years to do it. Fortunately, modern advances in biotechnology have made it possible to accomplish this in weeks in the laboratory using *in vitro* techniques such as gene shuffling.<sup>83</sup>

An illustrative example is provided by the Codexis process for the production of an intermediate for Pfizer's blockbuster drug atorvastatin (Lipitor). The two-step process (Fig. 14), for which Codexis received a 2006 Presidential Green Chemistry Challenge Award, involves three enzymes (one for cofactor regeneration). The low activities of the wild-type enzymes formed a serious obstacle to commercialisation but *in vitro* evolution of the individual enzymes, using gene shuffling, afforded economically viable productivities.<sup>84</sup>

## 11. Enzyme immobilisation: cross-linked enzyme aggregates (CLEAs)

Notwithstanding the many benefits of enzyme catalysis, their commercial application is often impeded by low operational stability and shelf-life in addition to their cumbersome recovery and re-use and the product contamination that is a characteristic feature of most homogeneous catalysts (see earlier). Although these problems can be alleviated by *in vitro* evolution, another approach to rendering enzymes more robust and recyclable is to

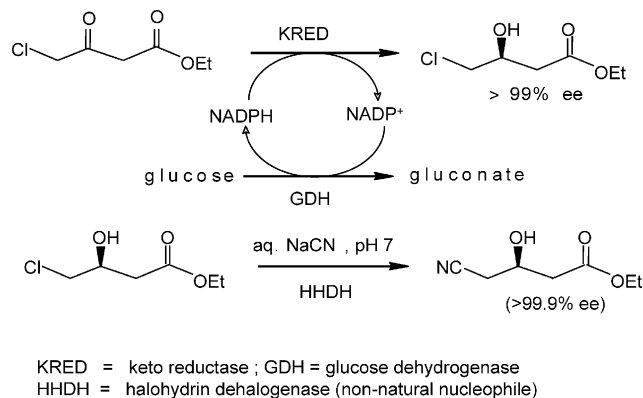


Fig. 14 Codexis process for atorvastatin intermediate.

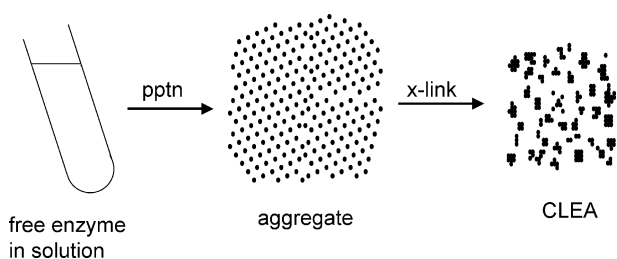


Fig. 15 Cross-linked enzyme aggregates (CLEAs).

immobilise them.<sup>85</sup> Among the several methodologies for enzyme immobilisation, one that is particularly effective is immobilisation as cross-linked enzyme aggregates (CLEAs®).<sup>86</sup> The technique is exquisitely simple, involving standard precipitation of the enzyme from aqueous buffer, *e.g.* with ammonium sulfate, and cross linking of the resulting physical aggregates of enzyme molecules with a bifunctional reagent such as glutaraldehyde (Fig. 15). Since selective precipitation is often used to purify enzymes, 'cleation' essentially involves combination of purification and immobilisation into a single unit operation and there is no need for the enzyme to be of high purity. Indeed, it could even be possible to isolate an enzyme in immobilised form directly from a fermentation broth.

The method is applicable to a broad range of enzymes.<sup>86</sup> Since they consist almost entirely of protein, CLEAs invariably exhibit high productivities. Furthermore, they often show increased stability towards denaturation by heat, organic solvents or proteolysis, which translates to improved operational stability and shelf-life, and they are readily recovered by filtration or centrifugation and recycled. Alternatively, a fixed-bed of CLEA or a suspension of a CLEA in a membrane slurry reactor can be used in continuous operation.

## 12. Catalytic cascade processes

As we have noted elsewhere,<sup>11</sup> brevity is the soul of synthesis. Catalytic processes have the advantage that they are often more direct and shorter than their classical counterparts. In biocatalytic processes, for example, protection and deprotection steps are generally avoided. A reduction in the number of steps in a synthesis, what Wender *et al.* have called step economy,<sup>87</sup> will in most cases lead to a reduction in the amount of reagents and solvents used and, hence, in the waste generated. Indeed, the ultimate in green catalytic methodologies is to integrate several catalytic steps into step economic, one-pot procedures without the need for isolation of intermediates.<sup>88</sup> This is truly emulating the elegant orchestration of enzymatic steps in metabolic pathways in the living cell. Such 'telescoping' of multi-step syntheses has several advantages: fewer unit operations, less solvent, and reactor volumes, shorter cycle times, higher volumetric and space time yields and less waste (lower E factor)—which translates to substantial economic and environmental benefits. Furthermore, coupling of reactions can be used to drive equilibria towards product thus avoiding the need for excess reagents. On the other hand, there are problems to be overcome: catalysts are often incompatible with each other (*e.g.* an enzyme and a metal catalyst), rates and optimum conditions can be very

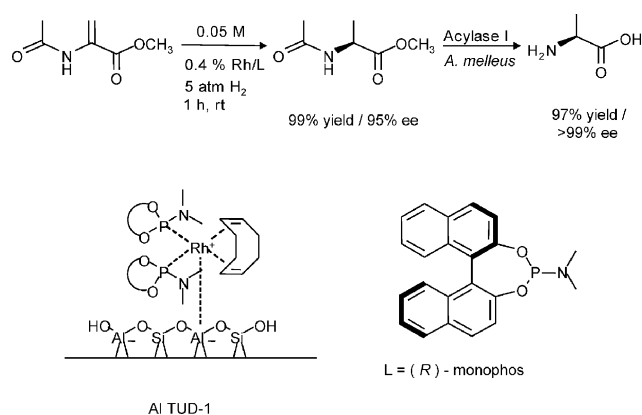


Fig. 16 Catalytic cascade process.

different and catalyst recovery and recycling complicated. Nature solves the problem of compatibility by compartmentalisation of enzymes in different parts of the cell. Hence, compartmentalisation *via* immobilisation could be the solution to these problems in cascade processes. In this context we note that biocatalytic processes generally proceed under roughly the same conditions—in water at around ambient temperature and pressure—which facilitates their integration in cascade processes.

An interesting example, involving combination of a chemocatalytic asymmetric hydrogenation with a subsequent enzymatic deprotection, is shown in Fig. 16.<sup>89</sup> The first step involves a rhodium catalysed asymmetric hydrogenation of a prochiral *N*-acyl dehydroamino acid ester. The (*S*)-product was obtained in 99% yield and 95% ee. In the second step an amino acylase was used to catalyse the hydrolysis of both the amide and ester moieties. This resulted in an upgrading of the enantiopurity, from 95% ee to >99% ee, with little loss in yield, because the acylase was highly *S*-selective. The overall reaction could be performed, without isolation of the intermediate, in water as the only solvent, using an immobilised form of the Rh catalyst in combination with the soluble enzyme or as a CLEA.

A second example (Fig. 17) involves a trienzymatic cascade process using a triple-decker combi-CLEA containing an oxynitrilase, a nitrilase and an amidase.<sup>90</sup>

## 13. Renewable raw materials and green product design

Another important goal of green chemistry and sustainability is the substitution of fossil resources—oil, coal and natural

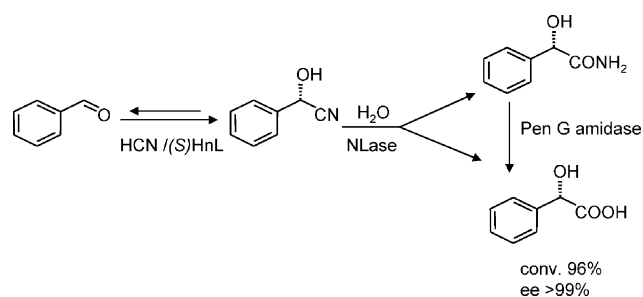


Fig. 17 A trienzymatic cascade with a triple-decker combi-CLEA.

gas—by renewable raw materials. The utilisation of biomass for sustainable fuels and chemicals has become a top priority on the international political agenda.

It goes without saying that processes for the conversion of renewable carbohydrates, triglycerides and terpenes, should involve optimum utilisation of raw materials and elimination of waste, *i.e.* have low E factors, by employing catalytic methodologies. They should also employ environmentally friendly solvents, preferably water, alone or in combination with carbon dioxide (see below). Ionic liquids are also of interest since they can, depending on their structure, dissolve large amounts of carbohydrates, including polysaccharides.<sup>91</sup> If they are also derived from renewable raw materials, are biodegradable and have low ecotoxicity, all the better.<sup>92</sup> In addition, there are special issues associated with renewables, *e.g.* the food *vs.* fuel dilemma and comparative land usage. Consequently, in order to be meaningful, a green metric for comparing different methodologies for biomass conversion should take these issues into account.

There is currently considerable interest in a biobased economy employing the conversion of renewable feedstocks in biorefineries as a sustainable source of liquid fuels and commodity chemicals.<sup>93</sup> First generation processes currently in use involve the utilisation of maize and oil seeds, such as rapeseed, as feedstocks for bioethanol (and commodity chemicals, such as lactic acid and 1,3-propane diol), and biodiesel, respectively. However, it is evident that, in order to avoid the food *vs.* fuel dilemma, second generation biofuels and bio-based chemicals will be based on lignocellulosic materials (preferably agricultural waste) and/or microalgae. Conversion of lignocellulose could involve gasification to syn gas or enzymatic hydrolysis to a mixture of lignin and polysaccharides followed by depolymerisation of the latter to fermentable monosaccharides.<sup>94,95</sup> Metabolic pathway engineering<sup>96</sup> is used to optimise the production of the required product based on the amount of substrate (glucose) consumed, *i.e.* the atom efficiency.

Alternatively, carbohydrates can be converted to valuable chemicals by chemocatalysis, *e.g.* dehydration and/or hydrogenation,<sup>97</sup> carbonylation,<sup>98</sup> oxidation,<sup>99</sup> or biocatalysis.<sup>100</sup> For example, hydroxymethyl furfural (HMF) and levulinic acid are biomass-derived platform chemicals obtained by acid catalysed dehydration of hexoses (Fig. 18). In our original studies of carbonylations in aqueous media, catalysed by the water soluble  $\text{Pd}(\text{tppts})_3$  complex, we were interested in the carbonylation of carbohydrates as renewable raw materials and we studied HMF as a model substrate.<sup>52,98</sup> HMF underwent selective carbonylation to give 5-formylfuran-2-acetic

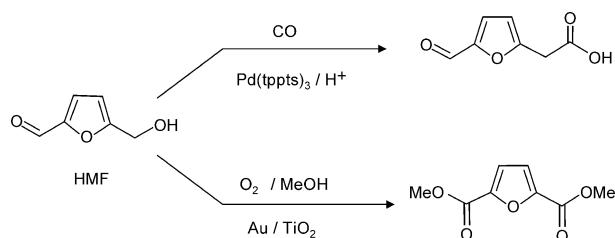


Fig. 18 Metal catalysed carbonylation and oxidation of HMF.

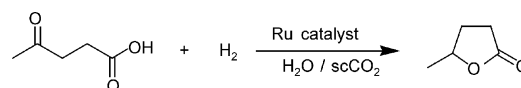


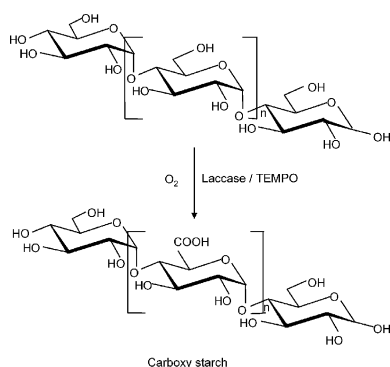
Fig. 19 Hydrogenation of levulinic acid in  $\text{scCO}_2$ - $\text{H}_2\text{O}$ .

acid (FFA), as the sole carbonylation product (Fig. 18). There is currently much interest in the selective oxidation of renewable carbohydrate feedstocks over gold nanoparticle catalysts following the pioneering studies of Rossi and co-workers who showed that gold can be more selective than palladium or platinum in, for example, the oxidation of glucose to gluconic acid.<sup>101</sup> More recently, Taarning, Christensen *et al.* reported<sup>102</sup> that aerobic oxidation of HMF in methanol over  $\text{Au-TiO}_2$  afforded dimethyl furan-2,5-dicarboxylate in 98% yield.

Poliakoff and co-workers<sup>103</sup> recently reported a continuous process for the ruthenium catalysed hydrogenation of levulinic acid to  $\gamma$ -valerolactone in a biphasic mixture of water and  $\text{scCO}_2$  as solvent (Fig. 19). By careful manipulation of the phase behaviour, reaction and separation could be integrated into a single process with reduced energy requirements, the product being obtained in pure form from the water phase. The product lactone has been proposed as a sustainable liquid fuel and raw material for commodity chemicals.<sup>104</sup>

The shift from oil to renewable raw materials will have far-reaching consequences for the commodity chemical industry. The structure of chemical supply chains will be radically altered, creating new opportunities for innovation in green chemistry and sustainable technologies. For example, a direct consequence of the recent enormous increase in biodiesel production is that the co-product, glycerol, has become a low-priced commodity chemical which is an interesting raw material for other bulk chemicals such as 1,2- and 1,3-propane diol and acrylic acid by catalytic reduction and oxidation, respectively.<sup>105,106</sup> These processes will also have to be efficient in raw material utilisation and generate minimum waste.

Alternatively, the switch to renewable raw materials could be an opportunity to substitute existing products by greener products, *e.g.* polymers based on renewable feedstocks. For example, acrylic acid is mainly used in the manufacture of polyacrylates. The latter are water super absorbents but their poor biodegradability is a serious shortcoming. Hence, an innovation for the longer term could be to produce a polymer, from renewable feedstocks, that is both a super water absorbent and readily biodegradable. Carboxy starch is such a polymer and it can be produced by TEMPO catalysed bleach oxidation of starch. However, as discussed earlier, a greener process would be obtained by substituting the  $\text{NaOCl}$  with molecular oxygen. This is possible using laccase as a co-catalyst (see earlier) but the process (Fig. 20) is not commercially viable owing to high enzyme costs, a direct result of the low operational stability of laccase. It has been shown that the operational stability of a laccase CLEA is much improved compared to the free enzyme. This paves the way for green and economically viable production of carboxy starch: green chemistry and sustainability *in optima forma*, a biodegradable product derived from a



**Fig. 20** Production of carboxy starch by laccase–TEMPO catalysed oxidation of starch.

sustainable raw material by a biocatalytic process with water as the co-product.

## 14. Conclusions and prospects

In the past fifteen years green chemistry and sustainability, supported by the underlying concepts of E factors and atom economy (atom utilisation), have become an unstoppable juggernaut. The concepts have been widely embraced by the chemical industry and the academic community. The importance of chemo- and biocatalysis and non-conventional reaction media in eliminating waste and circumventing the use of hazardous reagents and solvents is also widely accepted. More recently, another important trend towards green, sustainable technologies has come to the fore: utilisation of renewable raw materials. The ingenuity of chemists and chemical engineers is now being brought to bear on the development of green catalytic processes for the conversion of these alternative feedstocks. This will result in a total reshaping of the chemical industry, the ultimate in sustainability being the manufacture of biocompatible products from biomass *via* green catalytic processes. As Albert Einstein wisely remarked: “*The significant problems that we face today cannot be solved by the same level of thinking we were at when we created them*”.

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