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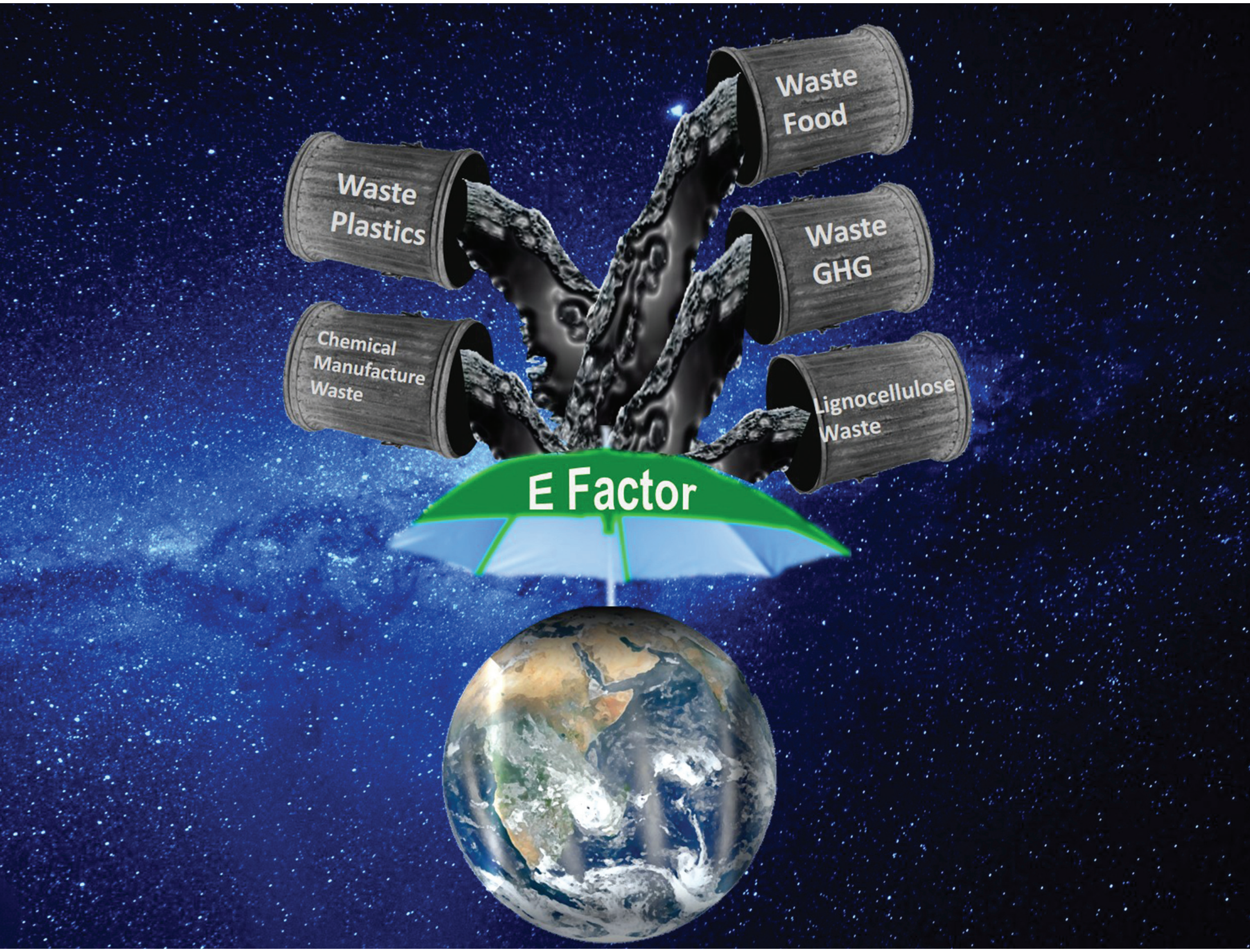

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ROYAL SOCIETY
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CRITICAL REVIEW
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The E factor at 30: a passion for pollution prevention

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The introduction of the E Factor in 1992 focussed attention on the problem of waste generation, defined as everything but the desired product, in chemicals manufacture and gave rise to a paradigm shift in our concept of efficiency in chemical processes, from one based solely on chemical yield to one that assigns value to eliminating waste. Thirty years later, it has become clear that waste is the underlying cause of the major global environmental problems, from climate change to plastic pollution and that the solution to this ubiquitous waste problem is pollution prevention at source enabled by green and sustainable chemistry. The role played by (bio)catalysis, alternative solvents, the emergence of a carbon neutral circular economy based on renewable resources and the electrification of chemicals manufacture based on renewable energy in the drive towards pollution prevention and sustainable industries is delineated.

1. The ubiquity of waste: the source of global environmental problems

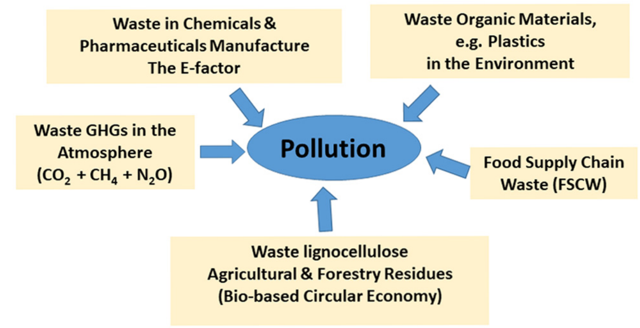
The daunting environmental problems – climate change, degradation of the natural habitat and its biodiversity – that humanity is currently facing on a global scale have a common denominator: WASTE. One could say that finding solutions to this global waste problem is one of the grand challenges of chemistry and chemical engineering for the foreseeable future.

The major environmental concern thirty years ago was the damage caused by ozone depleting chemicals in the atmosphere, particularly chlorofluorocarbons (CFCs) and related halogen compounds. Incidentally, the same compounds are also potent greenhouse gases (GHGs). Now, thirty years later, the major environmental problem is global climate change, the root cause of which is GHG emissions, in particular carbon dioxide (the mother of all waste) methane and nitrous oxide (N_2O). Another waste problem of global proportions is caused by discarded organic materials, in particular single use plastics, that are polluting our natural environment with disastrous consequences for flora and fauna. Recently, attention has focused on yet another major source of organic waste, most of which ends up as land-fill: food supply chain waste (FSCW)[1] arising from the production, distribution and consumption of food. The ubiquity of organic waste is depicted in Scheme 1. The primary solution to pollution is to avoid the formation of waste in the first place. However, not all waste is avoidable; agricultural and forestry residues, for example, are largely unavoidable and valorisation of this renewable organic waste is the answer.

The introduction, thirty years ago, of the E Factor (mass of waste/mass of product), usually expressed as (kgs/kg), constituted a paradigm shift in measuring the efficiencies of chemical processes, from being based mainly on chemical yield to an alternative that assigns value to waste elimination. It highlighted the amounts of waste generated in various segments of the chemicals industry (see section 2)[2] and this struck a chord with the chemical industry, particularly in the pharmaceuticals and fine chemicals segments (Table 1).

1.1 Enter green chemistry and sustainable development

In the 1990s, as a result of increasing environmental awareness, emphasis gradually switched from waste remediation



Scheme 1 The ubiquity of organic waste.

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Table 1 E Factors in the chemical industry

Industry segment	Product tonnage (p/a)	E-Factor (kgs waste/kg product)
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5–50
Pharmaceuticals	10–10^3	25–>100

through end-of-pipe solutions to waste prevention at source This not only eliminates waste treatment costs but also strengthens economic competitiveness through more efficient use of raw materials. It culminated, in the mid-1990s, in the introduction of the term Green Chemistry with the overall guiding element of 'benign by design' and the primary goal of pollution prevention.[3] *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.* The ultimate goal was zero waste production of chemicals.

However, no economic component is implicit in green chemistry and industrial players prefer the concept of sustainable development, launched in the Brundtland report,[4] *Our Common Future*, published in 1987 by the World Commission on Environment and Development. It is defined as *development that meets the needs of the present generation without compromising the ability of future generations to meet their own needs*. A sustainable technology must fulfill two conditions: (i) natural resources must be used at rates that do not unacceptably deplete supplies over the long term and (ii) residues must be generated at rates no higher than can be readily assimilated by the natural environment.[5] In reality, non-renewable fossil resources – oil, coal and natural gas – are being consumed at a much higher rate than that of their replacement by natural geological processes, a situation referred to[6] as "ecological timescale violation", making their use unsustainable in the long term. At the same time, the use of fossil resources is generating carbon dioxide at rates that cannot be assimilated by the natural environment which causes devastating climate change.[7]

1.2 The role of catalysis in sustainable development

A major cause of waste in the production of chemicals, especially advanced pharmaceutical ingredients (APIs) and numerous other fine chemicals, was the widespread use of stoichiometric amounts of organic and inorganic reagents in organic synthesis. Prime examples include the use of metals and metal hydrides such as Na, Mg, Zn and $NaBH_4$ and $LiAlH_4$, respectively, as reducing agents, and chromium(VI) compounds and permanganate as oxidants, to mention but a few. Other major sources include mineral acids such as H_2SO_4 and Lewis acids, $AlCl_3$, $ZnCl_2$ and BF_3 and bases such as NaOH and KOH used as stoichiometric reagents or in work-up. The key to sustainable manufacture of chemicals is clear: broad application of cleaner catalytic alternatives – heterogeneous, homogeneous, biocatalysis and organocatalysis in organic synthesis.[8]

Why were catalytic technologies not widely used in the production of APIs and fine chemicals? A prime reason was that the much smaller volumes involved compared with those in commodity chemicals production made the necessity to minimise waste less acute. Moreover, the economics of commodity chemicals dictate the use of the least expensive reagents that are usually the most atom economical reagents, *e.g.* H_2 for reductions, O_2 or H_2O_2 for oxidations and CO for C–C bond formation. Furthermore, time-honoured, classical stoichiometric technologies generally have the broadest applicability and shortest development times. This resulted in the use of inferior stoichiometric technologies in order to meet stringent market deadlines. Subsequent process changes were generally prohibitive owing to problems associated with gaining regulatory approval.

Nonetheless, motivated by the pressing need to reduce waste, in the last thirty years more emphasis has been placed on the use of catalytic methods in (industrial) organic synthesis. This involved, for example, the application of catalytic technologies such as hydrogenation, carbonylation, hydroformylation and olefin metathesis that were already widely used in the production of commodity chemicals. Furthermore, catalytic technologies are also evolving. For example, there is a discernible trend, both in Industry and Academia, to replace the use of scarce precious metal catalysts, *e.g.* Pd. Pt, Rh and Ru, with non-precious metal catalysts (NPMCs),[9] particularly Fe, Cu and Ni, otherwise known as Earth abundant metals (EAMs)[10] as sustainable, cost-effective alternatives. It is worth noting, in this context, that these are the very same elements contained in the active sites of enzymes catalysing a variety of redox processes in nature.

The evolution of catalysis in industrial organic synthesis is being further stimulated by the ongoing decarbonisation of the energy sector and defossilisation of chemicals production. Renewable (green) electricity, generated using solar, wind and nuclear energy, is becoming increasingly important and has already led to a veritable renaissance in electro- and photo-catalysis (see section 6).

At the same time, the increasing importance of the circular bio-economy is stimulating the application of biocatalysis in chemicals manufacture. This will be manifest in integrated biorefineries involving the conversion of lignocellulose to monosaccharides as the key base chemicals in lieu of olefins in oil refineries.

1.3 The role of the solvent[11]

In 1992 we asserted[2] that: "*So many of the solvents favored by organic chemists are now on the black list that the whole question of solvents in organic synthesis requires rethinking. Not only do organic chemists generally use too much solvent, they very often choose the wrong ones. In the first place, is a solvent really necessary? If a solvent (diluent) is needed it should preferably be water*".

Solvents account for 80–90% of the total mass of nonaqueous material used in pharmaceutical manufacture and are responsible for 75–80% of the waste.[12] A survey of solvent usage in the period 1997–2012, led to the conclusion that there was considerable room for improvement throughout the global pharmaceutical industry[13] and the last two decades have been devoted to rethinking the question of solvents in chemical processes.[14] The best solvent is no solvent; reactions can be performed in neat liquid substrates as exemplified by biodiesel production from triglycerides.[15]

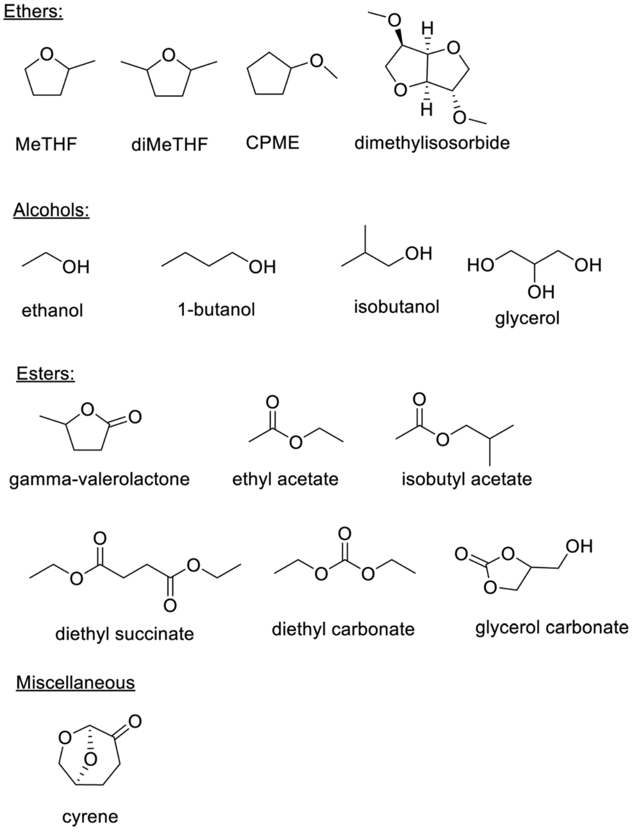
There is currently a marked trend away from the use of chlorinated solvents, low-boiling hydrocarbons and ethers that are classified as hazardous or highly hazardous based on flammability and/or toxicity issues. The list also includes certain polar, aprotic solvents, such as dimethylformamide (DMF) and *N*-methylpyrollidone (NMP) that are reproductive toxicity hazards and are classified as substances of very high concern (SVHCs). Many of these solvents are still being used, despite the availability of greener alternatives, which motivated pharmaceutical companies to develop Solvent Selection Guides (SSGs) to stimulate replacement of environmentally undesirable solvents, in particular chlorinated hydrocarbons.[16] The overall trend is towards the use of lower alcohols, esters and, in some cases, ethers.

Bio-based solvents. Predictably, the drive towards a bio-based economy has focused attention on the use of alcohols, ethers and esters derived from renewable biomass[17–20] many of which are ranked in the CHEM 21 project[21] as 'recommended'. Moreover, fermentation alcohols, such as ethanol[22] and isobutanol have the added advantage of facile biodegradability. Glycerol,[23] a byproduct of biodiesel production, and glycerol carbonate are high boiling solvents that dissolve lipases with retention of activity.[24] The dimethylacetonide of glycerol, otherwise known as solketal and marketed by Solvay as Augeol, is gaining in popularity as an environmentally friendly solvent and fuel additive.[25]

Bio-based esters such as isobutyl acetate, ethyl lactate (derived from two innocuous fermentation products), ethyl levulinate, diethyl carbonate, and γ-valerolactone (GVL)[26] are environmentally attractive solvents. Similarly, bio-based ethers such as methyl-tetrahydrofuran (Me-THF),[27] dimethyl tetrahydrofuran (diMeTHF), cyclopentyl methyl ether (CPME) and dimethylisosorbide, are useful solvents for, *inter alia*, biocatalysis (Scheme 2).[28]

Dihydrolevoglucosenone, marketed as cyrene and produced by pyrolysis of (ligno)cellulose[29] followed by hydrogenation of the resulting levoglucosenone, is a safe bio-based replacement for polar aprotic solvents with toxicity issues, such as DMF and NMP. It combines a good health and safety profile with excellent biodegradability.[30,31] It has been successfully used as solvent, or co-solvent with water, in a wide variety of organic reactions,[32] including biocatalytic transformations.[33] Recently, the enzymatic reduction of levoglucosenone to cyrene, which has the advantage of affording a solvent free of traces of metal catalysts, was demonstrated.[34]

Neoteric solvents: ionic liquids and deep eutectic solvents. The last decade has witnessed the emergence of so-called neoteric solvents – ionic liquids (ILs) and Deep Eutectic Solvents (DESs), alone or together with water – as reaction media for conducting biocatalytic reactions. Biocatalysis in ILs, including protic ionic liquids (PILS), has been widely studied and is the subject of many recent reviews.[35–38] DESs were introduced a decade later than ILs but have also been widely used as solvents for conducting reactions with both whole cells and isolated enzymes.[39–42] In particular, natural deep eutectic solvents (NADESs), prepared from combinations of relatively simple, primary metabolites, including sugars, amino acids and organic acids, are of interest as green solvents for biocatalysis. They are assumed[43] to function as reaction media in the intracellular synthesis of sparingly soluble secondary metabolites, such as flavonoids and steroids, and have been called "Solvents for the 21st century".[44]



Scheme 2 Examples of bio-based solvents.

1.4 Aqueous–organic biphasic catalysis

Aqueous–organic biphasic catalysis[45] is used to facilitate the separation and recycling of water soluble homogeneous catalysts from water insoluble products. The classic industrial example is the Ruhrchemie/Rhône Poulenc process for the hydroformylation of propylene employing a water-soluble Rh(I) catalyst.[46] The process has an E Factor of 0.1 compared to 0.6–0.9 for conventional hydroformylation processes. Moreover, aqueous biphasic catalysis is readily adapted to continuous flow operation.

Enzymes function optimally in water but if the product is only sparingly soluble in water it can be extracted into an environmentally acceptable solvent, such as ethyl acetate.

Alternatively, extraction can be back-integrated into the reaction step by conducting the process as aqueous biphasic catalysis. The company Codexis, for example, developed a variety of cost-effective biocatalytic processes to pharmaceutical intermediates using highly engineered enzymes in this way.[47]

1.5 Micellar catalysis: aqueous micelles as nanoreactors

Another innovative approach, pioneered by Lipshutz and co-workers,[48–50] involves the use of small amounts of environmentally benign designer amphiphiles (surfactants). The latter spontaneously self-assemble in water, at concentrations above their critical micelle concentrations (CMC) of *ca.* 10^{-4} M, to form nanomicelles. The lipophilic interiors of the latter act as nanoreactors for reactions involving water-insoluble substrates and, for example, noble metal complexes or metal nanoparticles.[51] The choice of amphiphile is critical as it determines the size, shape and internal lipophilicity of the nanoreactors. Lipshutz and co-workers[52,53] used small amounts (*e.g.* 2 wt%) of commercially available designer amphiphiles, such as TPGS-750-M (Scheme 3), to perform a variety of noble metal catalysed reactions at room temperature in organic solvent free water. The product was recovered by extraction with a minimum amount of a solvent that is environmentally acceptable and readily recyclable, such as ethyl acetate, while the amphiphile remains in the water phase. The E-Factors of reactions performed in water with 2–5% amphiphile were an order of magnitude less than the same reactions conducted in traditional organic solvents.

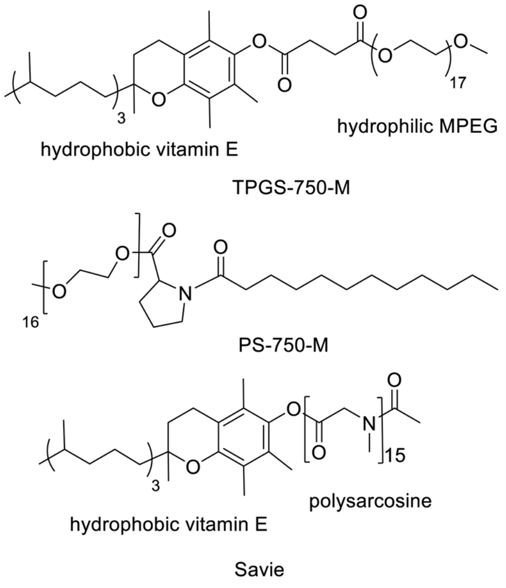
Interestingly, Handa and co-workers[54] recently designed a proline-based amphiphile, PS-750-M (Scheme 3), containing a tertiary amide function. Their goal was to replace polar aprotic solvents such as DMF and NMP through the formation of designer nanoreactors. PS-750-M instantly forms micelles containing a tertiary amide group in the hydrophobic core or at the interface, thus mimicking dipolar aprotic solvents. The micelles of PS-750-M were shown to mediate the formation of amides in water.[55]

Similarly, enzymatic reactions of hydrophobic substrates in water were enabled using designer amphiphiles, particularly TPGS-750-M.[56] This enabled the combination of noble-metal catalysed synthesis of ketones with subsequent enantioselective KRED catalysed reduction to afford a one-pot production of chiral secondary alcohols in high enantioselectivities (Scheme 4). Interestingly, the activity of the KRED increased in the presence of the amphiphile compared to in buffer alone. This was attributed to a 'reservoir' effect in which the micelles control the supply of both substrate and product to the active site of the enzyme, thereby limiting substrate and product inhibition.

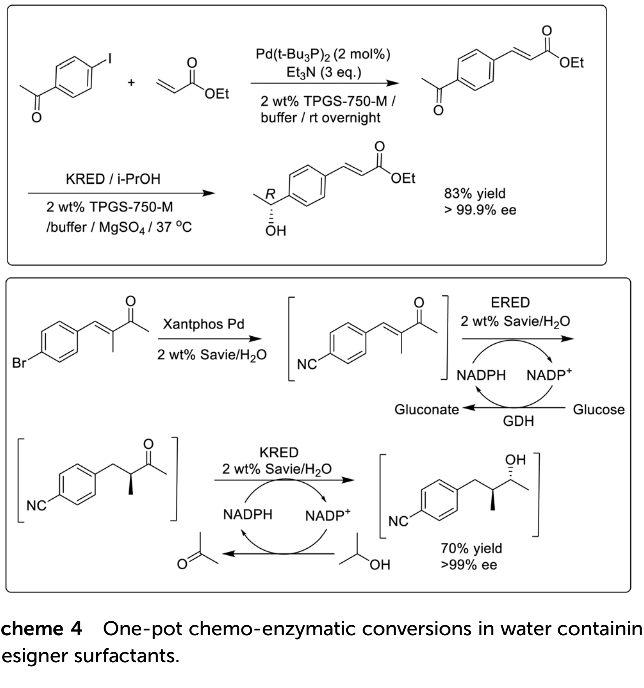
Similarly, micellar catalysis with designer amphiphiles, such as TPGS-750-M, enabled a variety of one-pot cascade processes that combine chemo-catalytic and enzymatic steps.[57–59] Product recovery involved extraction with a minimum amount of an environmentally acceptable solvent, such as ethyl acetate, or precipitation as an insoluble solid with the amphiphile remaining in the water phase. More recently, Lipshutz and coworkers reported[60] the synthesis of a biodegradable amphiphile, Savie, and its use in one pot chemo-enzymatic cascade processes (see Scheme 4).

1.6 The role of circularity in waste minimisation and sustainable development

The increasing focus of attention on pollution prevention and resource efficiency is the major driver in the transition from a traditional linear flow of materials in a 'take-make-use-dispose' economy, to a sustainable, circular economy.[61] The latter eliminates waste by design of products and processes



Scheme 3 Structures of designer amphiphiles.



Scheme 4 One-pot chemo-enzymatic conversions in water containing designer surfactants.

that efficiently use resources and are recycled according to the underlying philosophy of the European Commission's "Roadmap to a resource efficient Europe".[62]

Circularity is not a new concept. Barry Commoner, the iconic industrial ecologist, already observed[63] in the 1960s: "*We have broken out of the circle of life, converting its endless cycles into man-made linear events: oil is taken from the ground, distilled into fuel, burned in an engine, converted thereby into noxious fumes which are emitted into the air*". Unfortunately, the transition from an unsustainable linear economy to a greener circular economy is seriously hampered by not conducting economic evaluations on a level playing field. The true costs of 'take-make-use-dispose' manufacturing chains must take resource efficiency and circularity into account. The currently externalised costs of resource depletion, waste management and environmental pollution must be internalised.

1.7 Waste valorisation in a circular bio-based economy

In the case of unavoidable but renewable organic waste, *e.g.* agricultural and forestry residues, valorisation is the answer. A sustainable circular bio-based economy will be largely based on conversion of waste lignocellulose into carbon neutral liquid fuels, bulk chemicals and novel materials in integrated biorefineries (see section 4).[64] This concurs with the third element of green chemistry: utilisation of renewable resources.[65] Hundreds of millions of tonnes of lignocellulosic waste are generated annually world-wide[66,67] as agricultural residues such as sugar cane bagasse, corn stover, wheat straw and rice husks. The second generation bio-based economy, therefore, is based on the full utilisation of agricultural biomass. Moreover, substitution of existing products by safer bio-based alternatives, *e.g.* biocompatible and biodegradable plastics with reduced environmental footprints, is an added environmental benefit.[68]

1.8 The plastic pollution challenge

Industrial monomers constitute a large portion of the global production of commodity chemicals and in a circular economy the corresponding polymers must be recycled, as such or as the original monomers. The global production of plastics, for example, was 390 million tonnes in 2018, consisting of 174 million tonnes for packaging and 216 million tonnes for non-packaging applications. Virgin plastics represented 360 mio tonnes (92%) of the total and a mere 8% (30 mio tonnes) was recycled plastics. The total consumption of plastic products in the same period was 385 million tonnes resulting in the generation of 250 million tonnes of post-consumer plastic waste. 75 million tonnes of this were landfilled, 50 million tonnes burned for energy recovery, 75 million tonnes were improperly disposed in the environment, and 50 million tonnes were recycled.[69] Packaging plastics consist mainly of polyolefins – polyethylene (PE), polypropylene (PP) and polystyrene (PS) – together with polyethylene terephthalate (PET). Production of the corresponding monomers accounts for *ca.* 4% of the global production of all petrochemicals.[70] A paltry 9% of all the plastics ever produced have been recycled with the remainder being mostly discarded in the environment where they slowly fragment into microplastics and nanoplastics. The associated costs for society are profound, *e.g.* failure to recycle plastics costs the EU Euro 105 billion.[71]

In 2020 a new species of *Eurythenes* amphipod was discovered at a depth of 6900 meters in the Mariana Trench of the North-West Pacific Ocean.[72] It already had microplastic fibers in its gut, with 84% similarity to PET, and was ironically named *Eurythenes plasticus*.

Clearly, a linear take-make-use-dispose economy, that encourages production of virgin plastic over recycling, is not conducive to the goal of zero waste chemicals manufacture. In the post energy-transition era a resource efficient and environmentally benign circular economy, based on the principles of low waste by design, keeping products and materials in the loop, and regenerating natural systems[73,74] will flourish. Particularly single use plastics will be based on renewable carbon and designed for efficient recycling.[75,76]

2. The metrics of waste

If we want to reduce the formation of waste in chemicals manufacture we must have metrics for measuring the mass efficiency of processes. Thirty years ago, two key mass efficiency metrics – atom economy (AE)[77] and the E Factor[2] – were introduced. AE is obtained by dividing the molecular weight of the product by the sum of the molecular weights of all the materials in the stoichiometric equation. It assumes the use of exactly stoichiometric amounts of starting materials and a 100% chemical yield. No experimental data is required and, hence, it is very useful for comparing different routes to a target molecule before performing any experiments.

This contrasts with the E(nvironmental)-Factor which is the actual amount of waste formed, *i.e.* it is the environmental footprint of a process. By definition it is "everything but the desired product" produced per kg of product and includes both solvent losses and ancillary chemicals used. The ideal E Factor is zero in accordance with the first principle of Green Chemistry: "*It is better to prevent waste than to treat or clean up waste after it is formed*". E Factors of multi-step processes are obtained simply by adding E Factors of individual steps.

That chemicals manufacture was responsible for a substantial environmental footprint, expressed as the E Factor, was illustrated with the now well-known Table of E Factors, based on actual data from mature commercial processes in various industry segments, from oil refining to pharmaceuticals. Publication of this table in 1992 laid down an important challenge for the industry, particularly the pharmaceuticals sector, to reduce its waste. The challenge was accepted and major pharmaceutical companies spent the next 2–3 decades cleaning up their manufacturing operations.[78] However, these improvements are not always apparent in lower E Factors owing to the increasing molecular complexity and longer syntheses of APIs that is reflected in higher E Factors that partially neutralise the improvements.[79] On the other hand these more recent APIs tend to be considerably more active than their predecessors and, hence, annual production volumes are substantially less.

The E Factor emphasizes the need for designing cleaner, waste-free processes. The ideal E-Factor of 0 clearly reflects the ultimate goal of zero waste manufacturing plants. In addition, lower E Factors translate to smaller quantities of materials consumed and are manifest in reduced manufacturing and waste disposal costs.[80] The E Factor includes all reagents used and, if the actual amount is not known, 10% of the solvents used on the assumption 90% would be recovered and recycled. In hindsight, this was probably overoptimistic. Organic chemists generally optimise the solvent for each step in a multi-step synthesis, often leading to a different solvent for each step and cross-contamination that impedes solvent recycling. Water was excluded on the grounds that inclusion would produce skewed E Factors. However, disposal or recycling of process water generally involves some sort of pretreatment and we currently calculate E Factors both with and without water for comparison.[81] This led to the designation of simple E Factors (sEF), that exclude both solvents and water, for initial route scouting, and complete E Factors (cEF) that include solvents and water with no recycling.[5] The true E Factor falls between the sEF and cEF and can be calculated when reliable data are available for solvent losses on a production scale.

Inclusion of energy requirements in the E Factor was always implicit since we recognised that energy consumption generates carbon dioxide as waste. On the other hand, fine chemicals and pharmaceuticals production usually involves multipurpose facilities where energy usage is often not allocated to individual product lines. In contrast, energy consumption is an important component of the production of bulk chemicals that is generally in dedicated plants. Consequently, the E^+ Factor, comprising greenhouse gas emissions emanating from electricity used in cooling, heating, stirring and pumping, *etc.*, was proposed.[82]

E Factors refer to chemical processes conducted at a manufacturing site, *i.e.* within gate-to-gate system boundaries, rather than cradle-to-grave.[83] It is dependent on the starting point of the synthesis and E Factors of multi-step syntheses are substantially reduced overnight by purchasing early intermediates rather than producing them in-house. It is essential, therefore, to have a clear definition of what is considered as a starting material. In pharmaceuticals manufacture it has been defined as material that is readily available at a price of <\$100 per kg from a reputable commercial supplier.[84] Any intermediate costing >\$100 per kg is referred to as an advanced starting material (ASM) and the E Factor for its production, the so-called intrinsic E Factor, must be included. Since E Factors are additive, the intrinsic E Factor for an ASM synthesis may be simply added to the main synthesis E Factor to obtain an E Factor for the complete synthetic pathway. For example, in conducting a meaningful comparison of routes to a key HIV protease inhibitor intermediate, it was essential to include intrinsic E Factors for the synthesis of ASMs in order to make comparisons on a level playing field.[85]

The E Factor's durability lies in its simplicity, in terms of concept and application, and broad familiarity. In the first two decades following its publication it was used to assess the extent of waste formation in the manufacture of pharmaceuticals, a broad range of fine chemicals, and a few bulk chemicals including industrial monomers such as caprolactam,[86] in addition to being widely adopted in academic circles. In the last decade it has become increasingly applied in polymer synthesis. The major outlet of bulk chemicals is as monomers for the synthesis of a broad range of polymers and in recent years it has become increasingly apparent that the sustainability of polymeric materials is very much dependent on the amount of waste generated, both in the production of the monomer and in the process for its polymerization.[87–89]

In the drive towards a carbon-neutral bio-based economy there is increasing emphasis on the use of bio-based polymers derived from renewable raw materials, *e.g.* by modification of the most abundant biopolymer, cellulose (see also section 4).[90] However, renewable is not enough: the percentage of bio-based feedstock in the polymer is relevant but the process for its manufacture must also have a low E Factor. For example, Fadlallah and coworkers[91] employed the E Factor, the simple E Factor and atom economy as green metrics for comparing synthetic methods for the production of a wide variety of bio-based monomers from (waste) lignin.

Other mass-based metrics such as process mass intensity (PMI) and reaction mass efficiency (RME) have been proposed[92] but have not attained the scope and broad acceptance of the E Factor. We recognised, however, that a limitation of the E Factor is that it didn't consider the environmental impact of the waste; all types of waste were assigned equal rating. Consequently, the E Factor must be considered in conjunction with other environmental metrics.[93] We proposed the environmental quotient (EQ),[94] where Q represents the nature of the waste, to assess environmental impact but then the problem becomes the quantification of Q. Eissen and Metzger[95] introduced the user-friendly EATOS (Environmental Assessment Tool for Organic Synthesis) software for assessing the potential environmental impact of waste by assigning penalty points based on human and eco-toxicity. It was subsequently further refined by others.[96]

In our experience, the Green Motion penalty point system developed by Mane[97] is very useful for rapid comparison of processes. It involves evaluation of seven fundamental process parameters – raw material, solvent, hazard and toxicity of reagents, reaction efficiency, process efficiency, hazard and toxicity of final product and waste generation using a questionnaire with simple yes/no answers. Penalty points are assigned and deducted from 100 to afford an overall score. The higher the score the more sustainable and the lower the environmental impact of the process.

In order to set meaningful goals for industrial research it is necessary to compare processes with an industry benchmark. The Green Aspiration Level (GAL™) is such a benchmark. It represents the average waste generated per kilogram API in 46 commercial manufacturing processes from nine large pharmaceutical companies.[98] More recently, a further refinement, the innovative Green Aspiration Level 2.0 (iGAL 2.0) was published.[99] However, we note that these tools are only relevant for process evaluations of multi-step syntheses of relatively complex APIs.

2.1 The C factor: the carbon footprint

There is currently an ongoing transition, referred to in the EU as the Green Deal,[100] which has the goal of achieving climate neutrality by 2050. It is motivated by the pressing need for climate change mitigation, through replacing an economy based on fossil resources with a bio-based economy based on renewable energy and raw materials. It is manifest in the decarbonisation of the energy sector and defossilisation of chemicals manufacture. Christensen and co-workers[101] proposed, already in 2008, the use of a (C)limate factor metric, defined as the total mass of CO_2 emitted divided by the mass of product formed (kg CO_2/kg product), to compare the CO_2 footprints of different processes to a given product.

$$\text{C Factor} = \text{kg CO}_2\ \text{emitted/kg product}$$

It is the sum total of kg CO_2 emitted in the production of the raw material(s) and in the conversion of the raw materials to the product(s) and is useful for comparing processes based on renewable biomass *vs.* non-renewable fossil resources.[102] Gallou and co-workers[103] recently used it to assess the ecological footprints of APIs. We note, however, that system boundaries need to be defined for determining the C factor.

Summarising, the extent of waste formation is defined by the following mass-based metrics:

- Atom economy is the molecular weight of the product divided by the sum of the molecular weights of the raw materials *in the stoichiometric equation* expressed as a percentage. It is useful for a rough comparison of possible routes prior to experimentation.

- The E Factor is the total mass of waste formed per kg of product (kg waste/kg product) excluding water but including the solvent if the total amount leaving the plant is known. If not it is assumed that the solvent will be recycled with 10% lost as waste (in hindsight probably over-optimistic).

- The simple E Factor (sEF) excludes water and solvent used.

- The complete E Factor (cEF) includes water and solvent and assumes no recycling.

- E factors are based on gate-to-gate boundaries. If an advanced starting material (ASM) is used the E Factor for the synthesis of the ASM, the so-called intrinsic E Factor, must be included.

- Strictly speaking, the E Factor must always include waste, in CO_2 equivalents, from the energy used to drive the process. In practice, however, this is generally not included but when it is it has been referred to as the E^+ Factor.

- The C Factor is kg CO_2 formed/kg product and is the carbon footprint of the process.

- The process mass intensity (PMI) is the total mass of materials used divided by the mass of product formed (kg/kg) and is E +1.

2.2 The ethanol equivalent

Horvath and coworkers[104] proposed a relatively simple mass metric for assessing the sustainability of biomass-based routes to fuels and chemicals: the ethanol equivalent. It is defined as the "mass of ethanol required to deliver the equivalent amount of energy from a given feedstock using energy equivalency or produce the equivalent mass of a carbon-based chemical using molar equivalency". Since ethanol is, *inter alia*, produced by fermentation, the required mass of biomass feedstock, the land area and even the volume of water can be readily calculated. The authors concluded, based on their calculations of ethanol equivalents, that production of the 387 × 10^6 tons of gasoline used in the US in 2008, using 1G corn-based bioethanol technology commercially practiced in the US is not even close to being a viable proposition. In contrast, the conversion of 2G waste lignocellulose to basic chemicals, such as ethylene, propylene and xylenes, *via* intermediate ethanol, could be a sustainable option in the near future.

3. Biocatalysis is sustainable and green

Biocatalytic processes are eminently sustainable. They have definite economic and environmental benefits and conform to 10 of the twelve principles of green chemistry,[105,106] the foremost of which is pollution (*i.e.* waste) prevention. Indeed, one could say that biocatalysis is the key to sustainable chemistry:[107]

(i) The catalysts (enzymes) are derived from inexpensive, renewable resources with stable availability and costs in contrast with the fluctuating prices and availability of scarce precious metal catalysts. Moreover, enzyme production costs are steadily decreasing as a result of using more productive hosts coupled with improved protein expression and downstream enzyme recovery.

(ii) They avoid the need for costly removal of traces of noble metals, to an acceptable ppm level, from end products.

(iii) The catalysts (enzymes) are biocompatible, biodegradable, essentially non-toxic and non-hazardous.

(iv) The processes are conducted under mild conditions, in water at ambient pressures and temperatures. This enables relatively simple coupling of enzymatic steps in cost-effective, environmentally attractive cascade processes.[108]

(v) The processes are step economic.[109] As a result of their exquisite functional group specificity the need for protection and deprotection steps is usually circumvented leading to less waste and more cost-effective processes.

(vi) Optimised enzymes exhibit superb chemo-, regio- and stereoselectivities, including near-perfect enantioselectivities (>99.99%), that are absolutely unparalleled.

(vii) Owing to the exquisite functional group specificity of enzymes, extra functional group protection and deprotection steps are avoided

(viii) Because of the ambient conditions enzymatic processes (but not fermentations) can be conducted in standard multi-purpose batch reactors, thus avoiding extra investments, *e.g.* in high-pressure equipment.

As if all this were not enough, procedures have been extensively optimised in the last decade by the application of immobilised enzymes in continuous processing (see below). Such advantages inevitably beg the question: if enzymatic processes are so good why haven't they been widely used until the last two decades? The answer is: lack of use was largely due to the limited commercial availability and poor stability of most enzymes under the harsh conditions – high substrate concentrations and elevated temperatures with substrates that are poorly soluble in water-characteristic of industrial processes severely limited their applications in industrial organic synthesis.

Two decades ago commercial availability of enzymes was rather limited to hydrolases of animal origin, *e.g.* proteases, lipases, esterases and glycosidases, used in food and beverages and detergents. This changed dramatically in the last two decades. Advances in high throughput genome sequencing in combination with bioinformatics have enabled the identification of an ever-increasing number of new and robust enzymes through metagenome mining.[110,111] Subsequent synthesis of the targeted gene, ready for cloning into a host production organism, requires only two weeks at a cost of <\$1000. Consequently, more enzymes are available and they are more cost-effective. Furthermore, developments in directed (*in vitro*) evolution techniques,[112–114] with the aid of advanced machine learning techniques[115] enable the re-engineering of enzymes to exhibit pre-defined properties with regard to substrate specificity, activity, selectivity, stability and optimum pH[116,117] Two decades ago, the process had to be modified to fit the available enzyme, often resulting in a nightmare process. Today, the enzyme is evolved to fit a pre-defined optimum process that is benign by design. In the last decade this facilitated the broad integration of biocatalysis, as a mature sustainable technology, in mainstream (industrial) organic synthesis,[118–124] particularly for the enantiospecific synthesis of APIs.[125–130] It led to the introduction of the concept of biocatalytic retrosynthesis, with rules and guidelines to aid the identification of biocatalytic pathways to target molecules.[131–133]

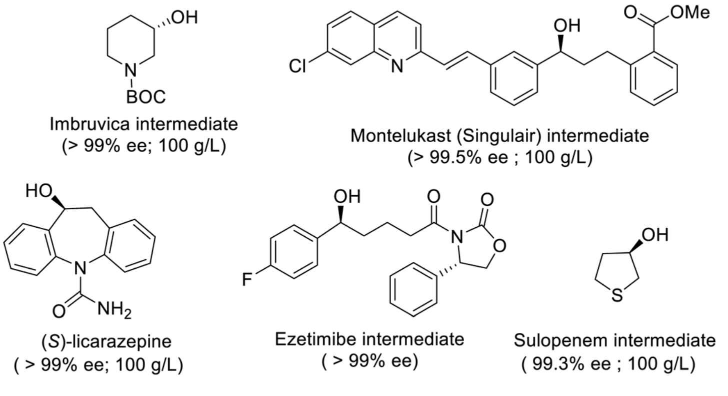
The general discussion of the important role of the solvent in determining the overall greenness of a process, as discussed in section 1.3, is also applicable to biocatalytic processes. Using an organic solvent as such is not a problem. The preferred solvent for enzymatic processes is water but this can be problematic with hydrophobic substrates. In this case aqueous/organic biphasic systems are often used to enable recycling of the organic solvent. Alternatively, hydrophobic solvents, *e.g.* biobased ethers and esters, can sometimes be used, in the absence of a separate water phase, with immobilised enzymes.

3.1 The ever broadening scope of biocatalysis

Clearly catalysis with enzymes has successfully negotiated the long and winding road from laboratory to industrial process. Not only has the number of commercially available enzymes dramatically increased, the scope of biocatalysis has been rapidly widening.[134–137]

Chiral secondary alcohols, for example, are key intermediates in the synthesis of a broad range of APIs. Thirty years ago they were produced either by stoichiometric ketone reduction with chiral hydride reagents or catalytic asymmetric hydrogenation.[138] Thanks largely to vast improvements achieved through directed evolution, ketoreductase (KRED) mediated enantioselective reduction of prochiral ketones has essentially superseded asymmetric hydrogenation as the first choice method for industrial production of enantiomerically pure secondary alcohols (Scheme 5).[139–142] The nicotinamide cofactors, NADH or NADPH, that supply the reducing equivalents are recycled *in situ* by adding a large excess of an alcohol co-substrate, such as isopropanol, or a second enzyme in combination with an inexpensive co-substrate, such as formate/formate dehydrogenase (FDH) or glucose/glucose dehydrogenase (GDH).

Similarly, selective oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, is a key transformation in organic synthesis. Historically, stoichiometric amounts of inorganic oxidants, such as hazardous chromium VI reagents, were used but there is a marked trend towards more sustainable chemocatalytic[143] and biocatalytic



Scheme 5 Enzymatic production of chiral alcohols.

methods.[144] Alcohol oxidases (AOx) employ stoichiometric amounts of dioxygen as the oxidant together with catalase to rapidly degrade the H_2O_2 co-product. Since the reactions are performed in aqueous media, safety issues normally associated with use of dioxygen in combination with volatile organic compounds no longer apply. This is another virtue of enzymatic catalysis *in aqua*.

Typical examples are copper-dependent galactose oxidase (GOase) and flavin-dependent glucose oxidase (GOX) that catalyse substrate specific aerobic oxidations of carbohydrates. New flavin- and Cu-dependent AOxs, with improved stabilities and altered substrate specificities have been developed[145] with the aid of genome mining and directed evolution. A choline oxidase variant, for example, is a broad spectrum primary alcohol oxidase[146] and a GOase variant catalysed the ammoxidation of primary alcohols to nitriles.[147]

Enantiopure chiral primary amines are also key intermediates in the synthesis of a wide variety of pharmaceuticals and can be produced by a suite of biocatalytic methods[148–150] using amine oxidases (AOs), amine dehydrogenases (AmDHs) and imine reductases (IREDs). A synthesis of Boceprevir, for example, involved an AO catalysed desymmetrisation as the key step.[151] Reductive amination of prochiral ketones catalysed by AmDHs was unknown 10 years ago. In contrast, amino acid dehydrogenases (AADHs) were well-known. This inspired Bommarius and co-workers[152,153] to use them as starting points for engineering highly active and enantioselective (>99.8% ee) AmDHs. Subsequently, AmDHs were used in conjunction with cofactor regeneration using glucose/GDH or ammonium formate/FDH (Scheme 7), for the reductive amination of a variety of ketones[154–157] and a new family of native bacterial AmDHs was discovered.[158]

Another fairly recent development is the emergence of imine reductases (IREDs)[159–165] and the closely related reductive aminases,[166–169] that catalyse asymmetric reductive amination of ketones. For example, a synthesis of the JAK1 inhibitor, Abrocitinib, involved an enantioselective reductive amination as the key step (Scheme 6).[170]

The synthesis of chiral amines by AmDH catalysed reductive amination of ketones was taken a step further by combining it with an ADH catalysed oxidation of an alcohol. This afforded a redox-neutral conversion of a racemic alcohol to a single enantiomer of the corresponding amine in a classic example of so-called hydrogen borrowing (Scheme 7).[171] Overall the reaction involves nucleophilic substitution of a hydroxyl group in a secondary alcohol, a transformation on the list of 10 key research areas for greening the pharmaceutical industry.[172] In this case OH is substituted by NH_2, forming an equivalent of water as the sole co-product. Its success depends on the ADH catalysing the oxidation of both alcohol enantiomers,[173] which is not trivial since ADHs are generally enantioselective. The overall efficiency was further improved by co-immobilisation of the ADH and AmDH.[174]

3.2 Chemomimetic biocatalysis: new to nature reactions

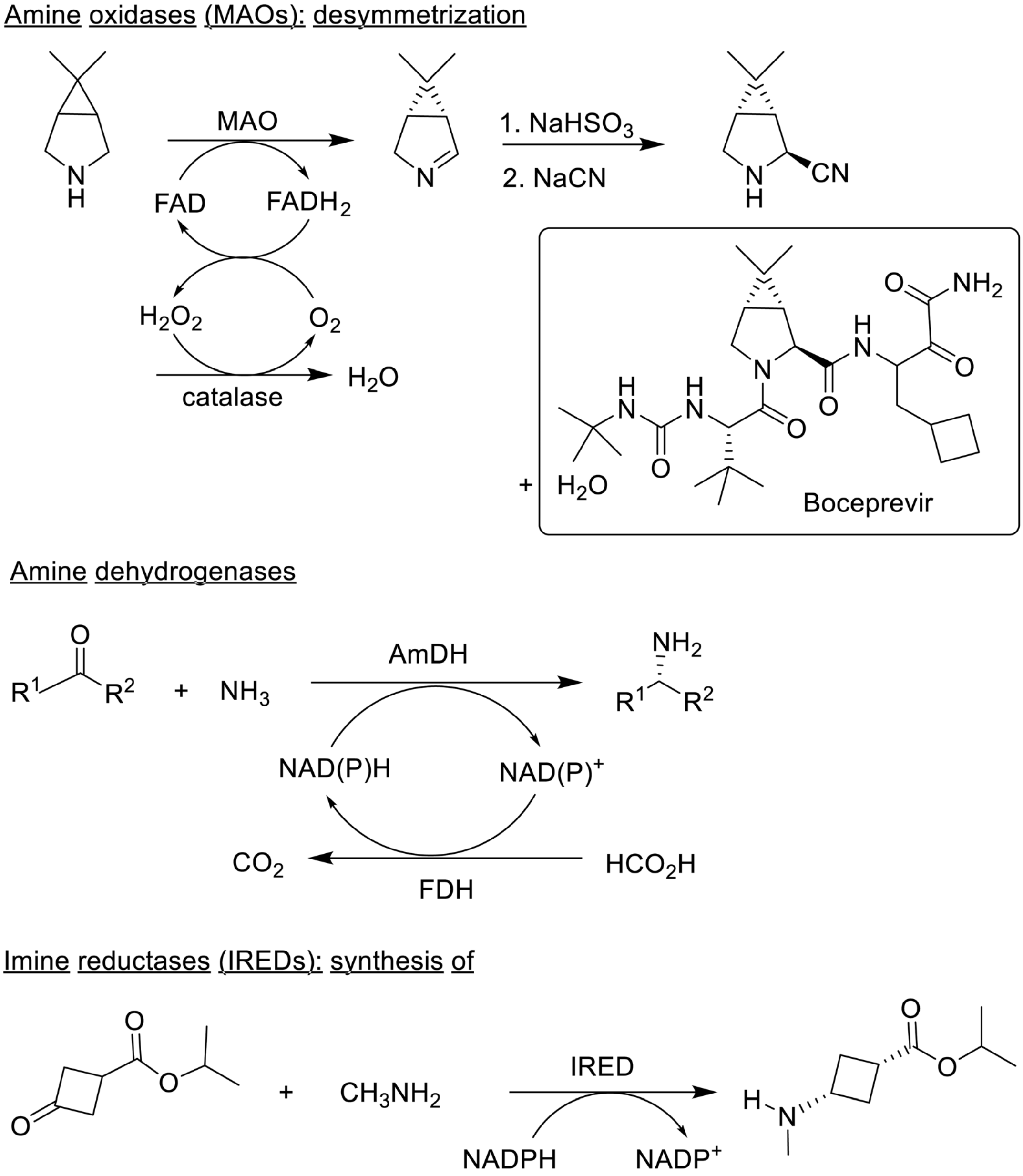
One way to develop new biocatalytic reactions is to use a chemomimetic approach,[175] that is by imitating known chemo-catalytic reactions. Combining this concept with protein engineering using directed evolution afforded new-to-nature biocatalytic reactions (Scheme 8).[176,177] For example, metalloporphyrins are known to catalyse cyclopropanations and aziridinations of olefins, by carbene and nitrene insertion, respectively, and C–H bond insertion reactions *via* high valent oxo-metal species. Arnold reasoned[178,179] that heme-dependent enzymes, in particular cytochrome-P450-dependent mono-oxygenases, that catalyse olefin epoxidations *via* high-valent oxoiron intermediates should also be able to catalyse cyclopropanation and aziridination of olefins.

This proved to be the case: the P450BM3 from Bacillus megaterium catalysed olefin cyclopropanation and aziridination by reaction with ethyl diazoacetate and tosyl azide, respectively. More recently, Arnold and co-workers extended this to the cyanomethylation of sp^3 and sp^2 (arene) C–H bonds[180] catalysed by two different P-450-based, carbene transferases, even in the same molecule, using diazoacetonitril as the stoichiometric reagent (see Scheme 8). New-to-nature reactions, developed with the help of directed evolution, can also be used for the synthesis of a wide variety of non-canonical amino acids that are structural motifs in many modern therapeutics.[181]

3.3 Enzyme immobilisation, biocatalysis in flow and cascade processes

Notwithstanding their many advantages enzymes have two shortcomings: (i) limited stability under the harsh conditions of industrial processes and (ii) limited recyclability. Enzymes are soluble in water and are typically used as homogeneous catalysts in an aqueous medium on a once-through, throw-away basis, which is not conducive to sustainability. This hurdle can be overcome by immobilising the enzyme as a solid heterogeneous catalyst that is recoverable by centrifugation or filtration and can be subsequently recycled.[182] This is essentially a *conditio sine qua non* for developing sustainable processes with high catalyst productivities.[183]

Enzymes are immobilised by attachment to an insoluble support (carrier), usually a natural or synthetic organic polymer or an inorganic solid such as silica or alumina or as insoluble cross-linked enzyme aggregates (CLEAs) formed by intermolecular cross-linking of enzyme molecules. Simple adsorption and ionic binding with carriers are widely used but have the drawback that they are susceptible to leaching of the enzyme under aqueous conditions, depending on the pH, ionic strength and temperature, especially under the harsh conditions of many industrial processes. Covalent bonding between the enzyme and the carrier has the advantage of stability towards leaching but the limitation that random covalent bonding at various positions in the enzyme can lead to loss of activity. There is a definite need, therefore, for less invasive

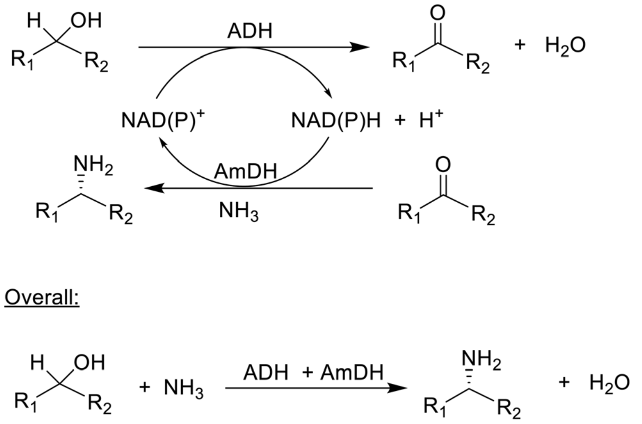


Scheme 6 Enzymatic production of chiral amines.

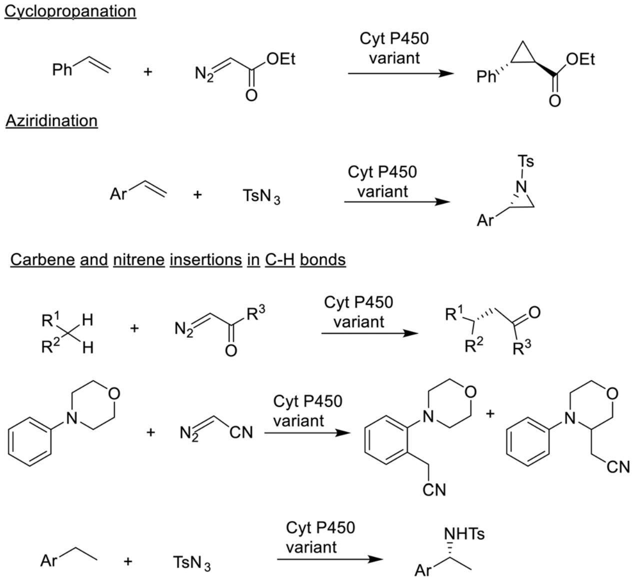
methods for forming covalent bonds between the enzyme and the carrier, *e.g.* by employing bio-orthogonal chemistry to affect precision covalent bonding at preselected sites in the enzyme.[184]

Alternatively, affinity immobilisation makes use of polymers containing surface chelating functionalities, such as iminodiacetic acid, preloaded with metal ions – Ni^{2+}, Zn^{2+}, Fe^{2+}, Co^{2+} and Cu^{2+} – that exhibit a strong affinity for the imidazole groups in surface histidine residues of the enzyme. It affords high activity recoveries through non-invasive binding. In addition, recombinant proteins are usually produced containing a so-called His-tag – a string of six to nine histidine residues – attached to the N- or C-terminus – to enable purification through affinity binding. This makes it possibile to combine enzyme isolation, purification and immobilisation into a single, cost-effective operation.[185]

Multi-step processes of APIs can often be significantly shortened through the use of biocatalytic reactions to circumvent the need for functional group protection and deprotection and functional group activation steps. Multi-step processes can be further shortened by combining steps in multi-enzyme or chemo-enzymatic cascade processes.[186] Most enzymatic reactions are conducted under roughly the same conditions of temperature and pressure and, hence, it is relatively easy to integrate multiple steps into eco-efficient catalytic cascade processes.[187–189] thus avoiding the separation, and purification



Scheme 7 Enzymatic hydrogen borrowing.



Scheme 8 New to nature reactions.

of the products from individual steps characteristic of conventional processing. This also improves conversions by limiting product inhibition.[190] It can involve the co-immobilisation of enzymes to afford a multi-functional biocatalysts, *e.g.* as genetically fused multi-enzymes[191] or combi-CLEAs.[192]

The success story of biocatalysis in pharma is further underlined by the fact that more than 60% of all FDA-approved antiviral drugs were made accessible through biocatalytic processes,[193] often involving multiple enzymes. Superb examples are provided by the synthesis of Islatravir, a nucleoside HIV inhibitor, in a three-step cascade involving nine enzymes[194] and molnupiravir,[195] the first SARS-coV-2 oral antiviral, in three steps and 69% overall yield from simple raw materials with isolation of only one intermediate (Scheme 9). The latter process replaced the original 10 step chemical synthesis that had an overall yield of 10%.

The pharmaceutical industry in general, and biocatalysis in particular,[196–198] is rapidly evolving towards safer and more sustainable continuous processes[199–201] that generate less waste and have lower E factors than conventional processes. Biocatalysis in flow facilitates process intensification[202] and integration of multiple process steps in biocatalytic and chemo-enzymatic cascade processes.[203,204] Conducting cascade processes in a continuous flow mode[205] overcomes limitations resulting from reaction and reagent batch incompatibility.[206,207] It was applied, for example, in transaminase catalysed continuous amination of ketones.[208–210] In an interesting variation on this theme, Mutti and co-workers[211] recently reported the use of 3D printing technology to facilitate the merging of biocatalysis and continuous processing.

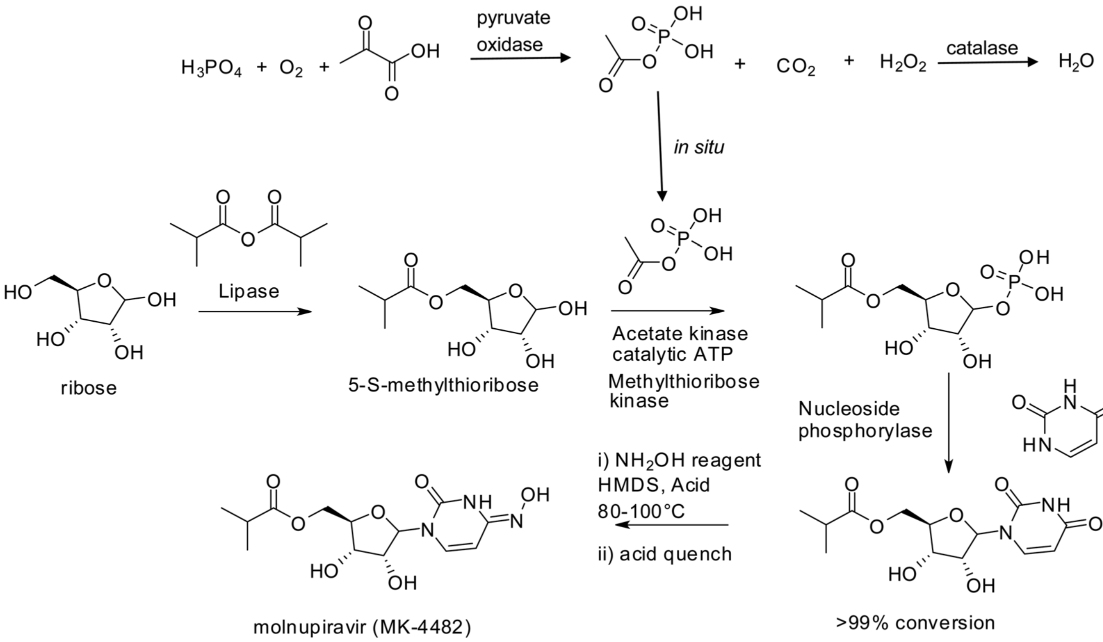
4. The biobased economy: waste valorisation

Publication of the table of E Factors thirty years ago challenged the fine chemical and pharmaceutical industries to make the paradigm shift from a concept of process efficiency that was exclusively focused on chemical yield to one motivated by elimination of waste and conservation of resources. It played an undeniable role in the shaping of more sustainable chemicals manufacture by substitution of archaic wasteful technologies and toxic or hazardous solvents and reagents with more sustainable alternatives. This will continue to be an important driver in the future but will be underpinned by two additional developments. The first is the so-called defossilisation of chemicals manufacture by substituting fossil resources with renewable, bio-based feedstocks in the manufacture of commodity chemicals and materials. The second is the transition from an unsustainable linear economy to a circular alternative involving the deliberate design of products and processes with conservation of resources and elimination of waste in mind.

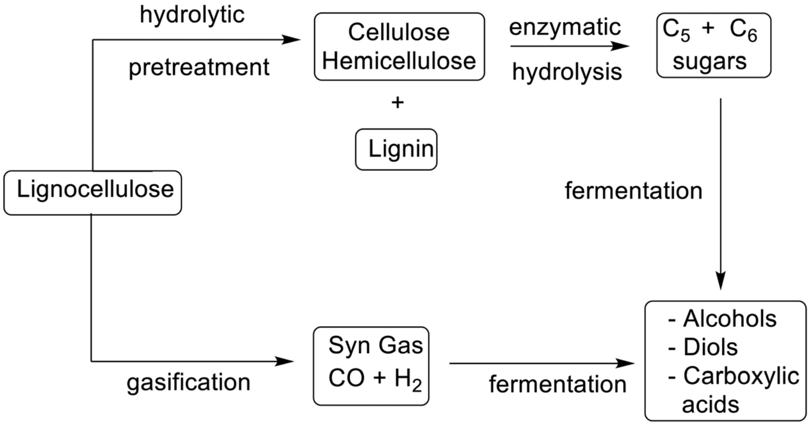
In a bio-based economy unavoidable waste, such as agricultural and forestry residues, composed of lignocellulose, are the feedstocks in biorefineries. However, lignocellulose is more difficult to process than first generation feedstocks such as sucrose and starch. It consists of three polymeric components: lignin (*ca.* 20%), cellulose (*ca.* 40%), and hemicellulose (*ca.* 25%) that must be depolymerised and partially deoxygenated, using thermochemical or hydrolytic processes (Scheme 10).[212]

Gasification, for example, affords a mixture of carbon monoxide and hydrogen (syn gas) that is converted into biofuels and platform chemicals using established chemo-catalytic or fermentation technologies.[213] Hydrolytic processes involve some form of pre-treatment, such as steam explosion, to open up the intractable lignocellulose, followed by hydrolysis of the cellulose and hemicellulose, catalysed by a cocktail of enzymes.[214] This affords a mixture of hexoses and pentoses that are converted to platform chemicals by fermentation and/or chemo-catalysis.[215] Traditionally the lignin was used to generate electricity but a commercially more attractive option is (bio)catalytic valorisation to commodity chemicals.

Although the cost contribution of the enzyme cocktail has decreased substantially over the last decade,[216] the pretreat-



Scheme 9 Molnupiravir synthesis.



Scheme 10 Conversion of lignocellulose to commodity chemicals.

ment and enzymatic hydrolysis contribute significantly to the overall costs. Further reductions may be achievable by enabling multiple recycling of the enzymes through suitable immobilisation, *e.g.* as cross-linked enzyme aggregates (CLEAs).[217] An extra challenge in this context is the need to separate the immobilised enzyme cocktail from other insoluble solids present in the feedstock. This can be achieved using magnetic CLEAs in combination with magnetic separation equipment that is common in the mining industry.[218]

Currently, much attention is focused on the use of alternative reaction media such as ILs, and DESs, particularly if they are derived from renewable raw materials, to facilitate both saccharification of lignocellulose and subsequent conversion of the sugar building blocks to biofuels and commodity chemicals.[219–221]

4.1 Carbohydrates to commodity chemicals

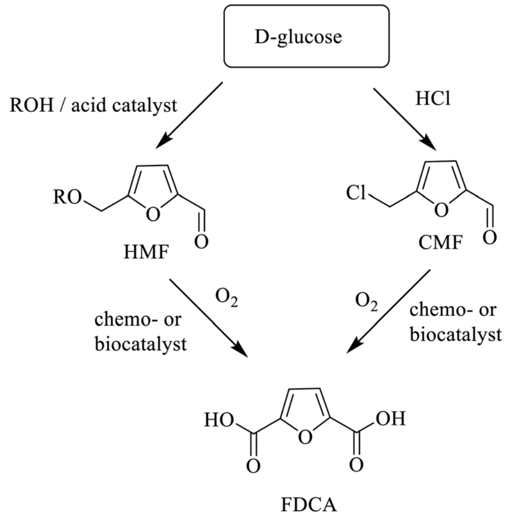
Production of commodity chemicals from C_6 and C_5 sugars involves either (i) conversion to 'drop-in' petroleum hydrocarbons and further processing *via* established petrochemical technologies or (ii) direct, redox-economic conversion to oxygenates as platform chemicals.

Various chemo- or biocatalytic methods are employed for converting hexoses and pentoses to petroleum hydrocarbons.[222] For example, lower alcohols – ethanol and 1-butanol and isobutanol – are produced by fermentation and dehydrated to ethylene, 1-butene and isobutene, linking seamlessly with existing petrochemical supply chains and the optimum use of bioethanol could well be as a platform chemical rather than as a biofuel.[223] Efficient production of isopropanol from ethanol by fermentation, using a metabolically engineered strain of *E. coli*, was recently reported.[224] Subsequent dehydration of ethanol and isopropanol affords two of the top ten petrochemicals: ethylene and propylene. Similarly, 2,3-butane diol and 1,4-butane diol can be produced by fermentation and be subsequently dehydrated to butadiene. Alternatively, metabolic engineering can be used to re-engineer the isoprenoid pathway in bacteria or yeast, to directly produce hydrocarbons, such as isobutene and isoprene, by fermentation.[225]

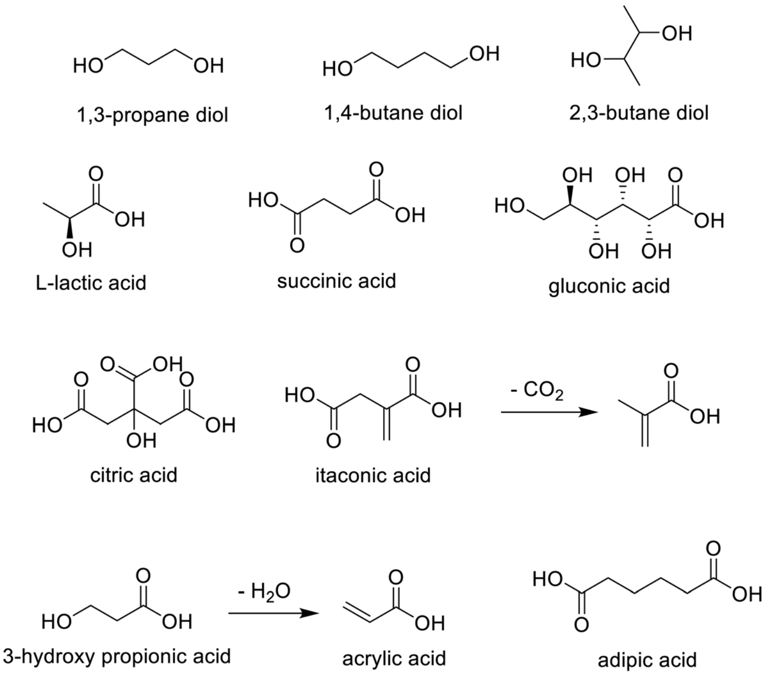
Thanks to advances in metabolic engineering and synthetic biology in the last two decades, a wide variety of diols and mono- and di-carboxylic acids can be produced, in a redox economic and cost effective manner, by fermentation. Citric acid and lactic acid are examples of first generation, large volume commodity chemicals produced by fermentation. There are many examples of second generation (di) carboxylic acids, such as succinic acid and acrylic acid, and diols, such as 1,3-propane diol, 1,4-butane diol and 2,3-butane diol that are produced cost-effectively by fermentation (Scheme 11).

In yet another approach, so-called aqueous phase reforming (APR), over supported Pt or Pt–Re catalysts, pioneered by Dumesic and co-workers,[226] is used to produce, *inter alia*, furfural, 5-hydroxymethyl furfural (HMF) and levulinic acid (LA), that are further hydrogenated *in situ* to a mixture of mainly C_4–C_6 alkanes.

Alternatively, direct conversion of hexoses and pentoses, derived from lignocellulose hydrolysis, to platform chemicals can be achieved using chemo- and/or bio-catalysis.[227,228] For example, acid catalysed hydrolysis of pentoses and hexoses produces furfural[229] and HMF, respectively. Furfural is an existing commodity chemical with broad applications and HMF has enormous potential[230] as a feedstock for chemicals, polymers and biofuels. Aerobic oxidation of HMF affords 2,5-diformylfuran (DFF) that can be converted to the corresponding diol or diamine, potential polymer building blocks, by hydrogenation or reductive amination, respectively (Scheme 12). Alternatively, chemo-[231,232] or biocatalytic oxidation[233–237] produces furan-2,5-dicarboxylic acid (FDCA),[238] the building block for polyethylene furanoate (PEF) (see section 5).



Scheme 12 Production of furanics from glucose.



Scheme 11 Carbohydrates to commodity chemicals.

However, cost-effective dehydration of hexoses, in particular glucose, to HMF presents a significant challenge, mainly owing to the low stability of HMF under the acidic conditions where it decomposes to form humin, a polyfuranic resin.[239] A possible option is to bypass HMF altogether by converting the hexose precursor directly, under mild conditions in high yield, to 5-chloromethyl furfural (CMF) by reaction with aq. HCl.[240] CMF can be further converted to FDCA or to levulinic acid. The combination of good stability with lipophilicity for facile isolation from aqueous media make CMF an interesting platform chemical for production in 2G biorefineries.

5. The circular economy: waste-free by design

5.1 The plastic pollution challenge

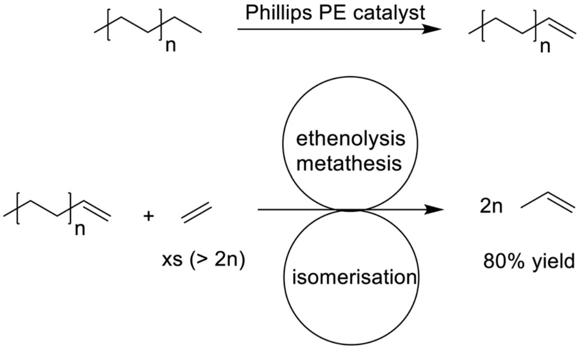
Only 30% of all the plastics that have ever been produced are currently in use.[241] Most of the rest, amounting to more than 6 billion tonnes, has accumulated in landfills or in our natural environment. Furthermore, the projected production of plastics in the period 2020–2050 will generate a further 12 billion tonnes of waste.

There is clearly a pressing need to replace this linear take-make-use-dispose economy with a circular plastic economy that reduces waste and optimises resource utilisation through multiple rounds of recycling. The preferred option is closed-loop recycling to the original plastic by recovery of the corresponding monomers. The second option is open-loop recycling to afford lower value products by, for example, pyrolysis or energy recovery by incineration. Landfill is no longer a viable option.

Depolymerisation to the olefin monomers is the preferred option for recycling the largest volume plastics, *i.e.* polyethylene (PE) and polypropylene (PP). It is technically feasible with polystyrene (PS)[242] but depolymerisation of PE and PP are highly endothermic processes. On the other hand, pyrolysis to a naphtha-like mixture of hydrocarbons and subsequent steam cracking to afford a mixture of lower olefins is feasible. More recently, a more selective approach to PE depolymerisation, involving catalytic transfer dehydrogenation, with a small amount of ethylene mediated by the Phillips ethylene polymerisation catalyst, followed by tandem catalytic isomerisation and olefin metathesis, afforded propylene in 80% yield (Scheme 13).[243,244] The method is reminiscent of the Shell Higher Olefins Process (SHOP), started up in 1977, for the synthesis of higher olefins from ethylene,[245] but operating in reverse.

5.2 Biocatalytic recycling of plastics

The polyolefin recycling problem can be circumvented altogether by substituting polyolefin plastics with more readily recycled polyesters or polyamides. Polymers containing hydrolysable bonds, *e.g.* polyesters and polyamides, such as PET, polybutylene succinate and Nylon, can be converted to the original monomers by acid- or base-catalysed or enzyme-catalysed hydrolysis. The possibilities and limitations of biotechnological recycling of plastics was recently reviewed by Blank and Bornscheuer and co-workers.[246,247]

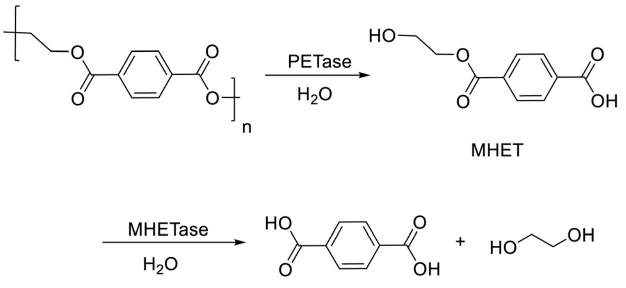


Scheme 13 Catalytic conversion of PE to propylene.

In 2016, a bacterium, *Ideonella sakaiensisin*, was discovered[248,249] in soil from an industrial waste PET-recycling facility, that catalysed the hydrolysis of PET. It secreted two different hydrolases: so-called IsPETase that catalyses hydrolysis of PET to mono-2-hydroxyethyl terephthalic acid (MHET) and a second enzyme that catalyses the hydrolysis of MHET (Scheme 14)

The IsPETase[250–252] was subsequently shown to have structural features in common with both lipases and the plant cell-wall degrading cutinases[253] that catalyse PET depolymerisation *via* hydrolysis.[254,255] Kanaya and co-workers[256] identified a cutinase, from leaf-branch compost (LCC) in a Japanese public park, which catalysed the hydrolysis of PET at 70 °C. Computer-aided protein engineering was subsequently used[257] to produce a variant which catalysed the hydrolysis of PET to 90% conversion in less than 10 h at 72 °C using an enzyme loading of 3 wt%, and a Space Time Yield of 16.7 g l^{-1} h^{-1}. The cost was estimated to be *ca.* 4% of the cost of virgin PET.

Similarly, an anaerobic thermophilic bacterium, *Clostridium thermocellum* was genetically engineered to enable high-level secretory expression of LCC.[258] In addition to catalysing the depolymerisation of PET at 60 °C the microbial cells catalysed the efficient hydrolysis of cellulose, suggesting that they could be used to recycle textile waste containing both polymers.



Scheme 14 Enzymatic hydrolysis of PET.

The current state of research on PET-hyrolysing enzymes was recently reviewed by Kawai.[259] They can be divided into mesophilic (*e.g.* IsPETase) and thermophilic cutinases. The former have the disadvantage that large scale hydrolysis requires a temperature close to the glass transition temperature of 65–70 °C in water. Economic viability is still a key issue for PET recycling but bio-recycling is expected to be the optimum solution as it is eco-friendly with low energy consumption.[260] More recently, machine learning-aided engineering of PET hydrolases was used to produce a robust and active PETase that showed good performance in the degradation of thermoformed PET products.[261]

Clearly, (bio)catalytic depolymerisation of polyesters to the coresponding monomers will be industrially viable in the near future, particularly when costs of virgin *vs*. recycled plastic are compared on a level playing field.

5.3 Biodegradability of plastics

Biodegradability is widely viewed as a desirable property for plastics but technical and socio-economic arguments are not generally in favour of biodegradable plastics.[71] Plastics that readily degrade remain an environmental hazard in a marine environment. Moreover, the biodegradable label will be interpreted by many as meaning that littering is not a problem. In contrast, plastics that are biodegradable-on-demand at their end-of-life (EoL), after multiple recycling, are attractive. For example, Carbios embedded an extremely thermostable esterase, that could withstand the extrusion temperature of 170 °C during its production, to afford polylactate (PLA) that is self-degrading at its EoL.[256]

5.4 Bio-based plastics for sustainability

The sustainable macromolecular materials of the 21st century will have reduced environmental footprints and be based on the carbon neutral utilisation of polymers derived from renewable raw materials.[262,263] Utilisation of renewable biomass is a *conditio sine qua non* for lower GHG emissions. PLA production from corn-starch, for example, affords a 27% reduction in GHG emissions compared with PE from fossil resources[264] and bio-based PET is responsible for 25% less GHG emissions than PET from fossil resources.[265,266] Indeed, the recent publication of several reviews on polymers from renewable feedstocks,[267–271] and the current trends and challenges in their production,[272] attests to its current importance.

Bio-based plastics can be drop-in products, *e.g.* PE produced from ethylene derived from bioethanol. Alternatively, they can be totally new polymers *e.g.* PHAs (see later). An important advantage of drop-ins is that the product is already known in the marketplace and there is no need to change production equipment and processes. In contrast, if the bio-based resin is different, *e.g.* PLA to replace PET, different additives and processing technology may be required and the product will have different mechanical and diffusion barrier properties to *e.g.* water and oxygen. Such problems can sometimes be overcome by using polymer blends.[273]

The primary motive for switching to bio-based plastics is climate change mitigation through reductions in CO_2 emissions but the envisaged facile recyclability and biodegradability will be welcome bonuses. However, the use of renewable feedstocks should not compete with food production or cause deforestation and/or loss of biodiversity. This will be avoided by utilising waste streams as the raw material in 2nd generation (2G) biorefineries, *e.g.* lignocellulosic waste from agricultural and forestry residues and food supply chain waste.[274] Looking further into the future, they will be produced from 3rd generation (3G) polysaccharides from algae and photosynthetic bacteria, that have the advantage that arable land and fresh water are not necessary for their cultivation. Alginate and carrageenan from macroalgae (seaweed), for example, can function as feedstocks for bio-based plastics.[275]

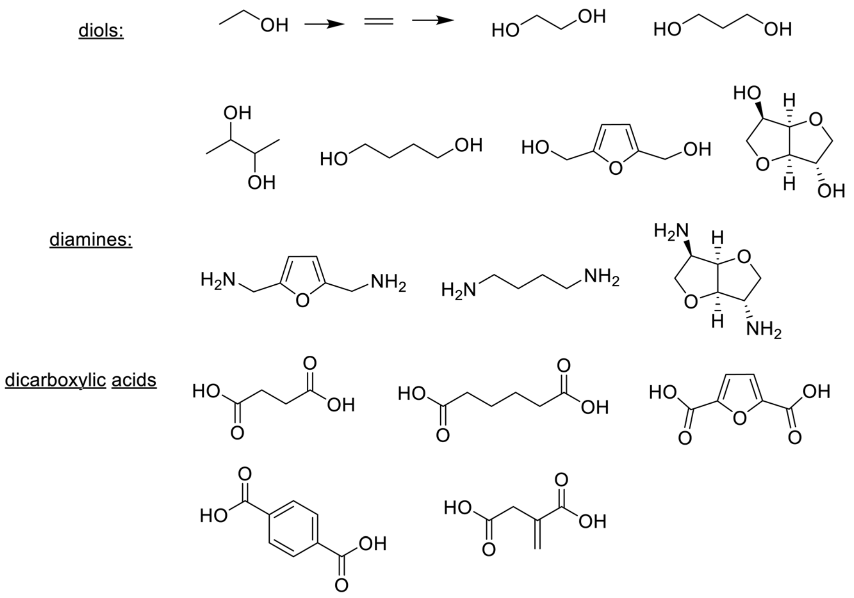
In short, bio-based plastics are produced (i) directly from bio-based monomers, *e.g.* PLA from lactic acid produced by fermentation, (ii) directly by fermentation, or (iii) by conversion of natural biopolymers such as starch, cellulose and chitin.[276] Examples of bio-based monomers – diols, dicarboxylic acids and diamines[277] produced by fermentation or chemocatalytic conversion of glucose, are depicted in Scheme 15. In addition to using bio-based monomers there is also a growing trend towards the use of biocatalysis in the polymerisation process, *e.g.* in the synthesis of polyesters.[278,279]

Drop-in bio-based PET, currently market leader, is 20% bio-based with 2 carbons from bioethanol and 8 carbons from fossil-based *p*-xylene (Scheme 16). Considerable research effort is currently being devoted to developing an industrially viable route to bio-based terephthalic acid to enable production of 100% bio-based PET.[280,281]

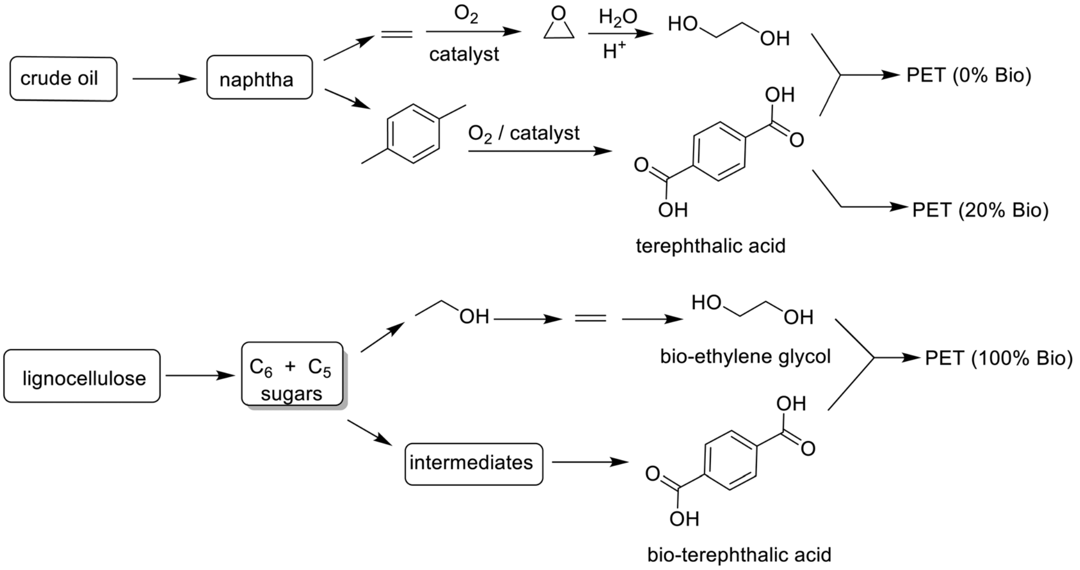
Polyethylene furan 2,5-dicarboxylate (PEF), developed by Avantium,[282] is 100% bio-based (Scheme 17), with a reduction in GHG emissions of up to 55%, and superior thermal, mechanical, and gas barrier properties, compared to PET.[283,284] A 100% bio-based equivalent of polytrimethylene terephthalate (PTT) has been produced from FDCA and bio-based 1,3-propane diol.[285]

Polyhydroxyalkanoates (PHAs) function as a carbon and energy source for acetogenic bacteria and can represent up to 90% of the dry weight of the bacterium. They are particularly interesting plastics because they can be produced by fermentation of low-cost waste streams, *e.g.* municipal[286,287] and paper mill[288] waste water, even waste polystyrene,[289] and they are biodegradable. Their physical properties are comparable with those of PE and PP, making them suitable for, *inter alia*, applications in single-use plastic packaging. Newlight Technologies produced a PHA by aerobic fermentation of methane or biogas from landfills and converted it to a thermoplastic, 'AirCarbon', that was licensed to IKEA for use in home furnishing products.[290] Composites of PHAs with inexpensive natural fibres with superior physico-mechanical properties have also been described.[291]

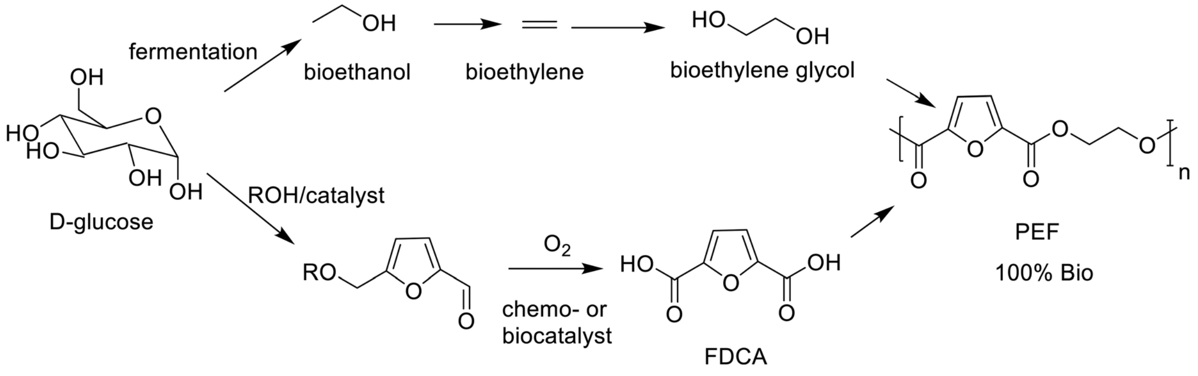
According to a recent review of bio-based plastics in food packaging[292] the total production of bio-based plastics has reached 7.5 million tonnes per annum, including bio-based



Scheme 15 Bio-based monomers for thermoplastics.



Scheme 16 Production of fossil *vs*. biobased PET.



Scheme 17 Production of PEF.

polyurethanes, that is 2% of fossil-based plastics. It is worth noting, however, that the manufacture of fossil-based plastics has been optimised over a period of more than half a century and it is not surprising, therefore, that their bio-based cousins, such as PLA and PHAs, are currently more expensive.[293] This gap is steadily decreasing albeit too slowly to seriously impact the plastic pollution challenge in the short term. This situation would change overnight, however, if EPR were implemented in the pricing of polyolefins, as was the case with the introduction of lead-free gasoline in the 1970s. A recent study of the environmental impact of bio-based plastics concluded that if two thirds of the global plastics were bio-based the annual generation of CO_2 equivalents would be reduced by 241–316 million tonnes.[294]

Bio-based plastics are also produced by direct conversion of natural biopolymers, such as starch and cellulose. Less explored polysaccharides such as chitin,[295] the second most abundant natural polymer after cellulose, are potential sources of packaging plastics. Chitin nanofibers, for example, afforded packaging materials that combine excellent gas barrier properties with flexibility and optical transparency.[296] Similarly, polyamide and polyurethane plastics are derived from long-chain fatty acids present in plant oils (*e.g.* castor oil, sunflower oil)[297] and waste proteins, such as the vast amounts of keratin from wool, hair and chicken feathers[298] constitute another commercially viable source of novel polymer materials.

Finally, production of plastics directly from carbon dioxide will be facilitated by the envisaged future availability of sustainable green hydrogen from water electrolysis using renewable electricity.[299] Carbon dioxide can be converted to syn gas as a source of monomers for plastics produced by existing petrochemical technologies or by fermentation.[300] Alternatively, PHAs can be produced directly from light, CO_2 and water.[301]

6. The energy transition and beyond: decarbonisation of energy and electrons *versus* reagents

The pressing need for reductions in GHG emissions to mitigate climate change has led to a so-called energy transition in which decarbonisation of the energy sector and defossilisation of chemicals manufacture are expected to play primary roles. Our reliance on finite fossil resources, for generating energy and materials, is clearly not sustainable in the long term and will be systematically reduced over the coming decades with the goal of completing the transition by the turn of the century. It will involve replacement of fossil resources by renewable, carbon neutral forms of energy: hydroelectric, geothermal, wind and solar energy. However, it is unlikely that this will generate enough energy to drive highly industrialised economies and sustainable nuclear energy[302] will inevitably be part of the energy mix. Indeed, the anticipated replacement of classical uranium reactors by molten salt thorium reactors[303,304] will make an important contribution to significantly reducing CO_2 emissions and will afford serious reductions in long-lived radioactive waste, another waste problem of global proportions.

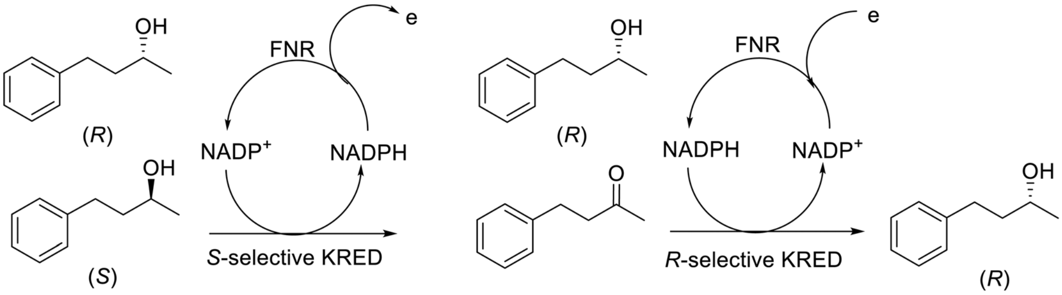
In the envisaged scenario for energy decarbonisation, electricity will play a primary role as an energy source and off-peak electricity will be used for the production of renewable liquid fuels and chemicals, using electrons instead of 'reagents' to drive a so-called Power-to-X (P2X) industry[305–308] in e-refineries. The importance of P2X is underlined by the rapidly growing number of demonstration plants worldwide (190 in 2019).[309] It could involve, for example, the production of renewable hydrogen by electrolysis of water and its use in heating and the production of steel,[310] transportation fuels and base chemicals. Alternatively, electrolysis of a mixture of carbon dioxide and water could be used to produce a mixture of CO and H_2 (syn-gas) that is subsequently converted to hydrocarbons using the classical Fischer–Tropsch (FT) process or to oxygenates using chemo-catalysis or fermentation.[311] The production of e-diesel in an electrically driven FT process will substantially reduce its global warming impact but the total environmental impacts of the two processes need to be compared for a complete evaluation (caveat emptor).[312] Replacing energy intensive steam crackers, that use gas-fired furnaces and generate huge amounts of carbon dioxide, by electric cracking of hydrocarbons using renewable electricity is also a possibility.[313]

Electrolytic reduction of carbon dioxide can be utilised to produce methanol as a high-energy-density liquid fuel and raw material for commodity chemicals manufacture, in a methanol economy as envisaged by Olah and co-workers.[314,315] Ammonia is also a serious contender for energy carrier in a global distribution of renewable energy.[316] Ammonia is already, in a fossil resource-based industry, one of the top ten bulk chemicals with an annual production of 8 mio tonnes. In a sustainable economy it will be produced by hydrogenation of nitrogen with renewable hydrogen or by direct electrolytic reduction of nitrogen.[317]

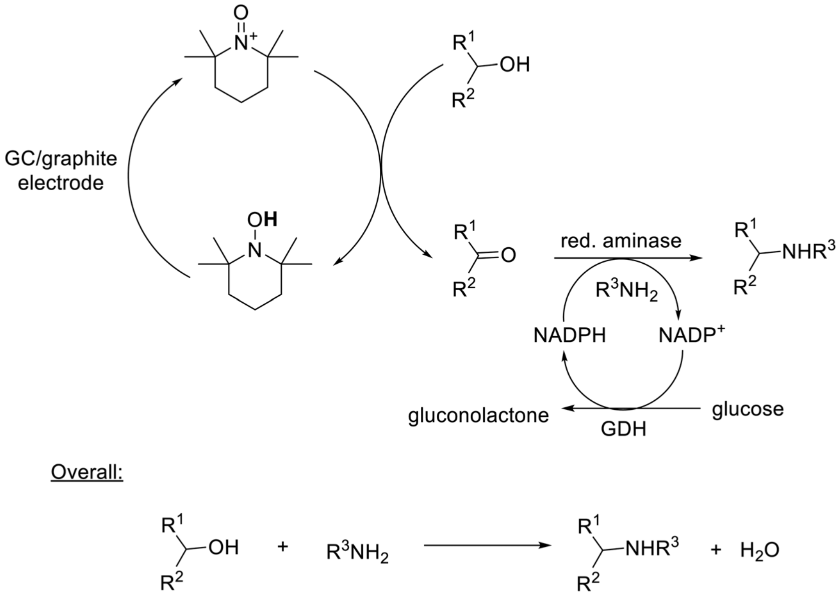
The world-wide attention currently focused on P2X strategies for bulk chemicals production has also provoked a veritable renaissance in organic electrosynthesis.[318–325] Moreover, microbial electrosynthesis (MES), involving coupling of renewable electricity generation with the metabolism of electroactive acetogenic and methanogenic microorganisms (electroautotrophs), in e-biorefineries, can drive the *in vivo* reduction of CO_2 to acetic acid, ethanol, formate, methanol and methane.[326,327]

6.1 Electrobiocatalysis

Alternatively, electricity can drive reactions catalysed by isolated oxidoreductases through replacement of conventional co-factor regeneration systems, requiring a second enzyme and a co-substrate, with electrochemical regeneration. A broad range of NAD(P), FMN, FAD and PQQ-dependent metallo- and non-metallo-oxidoreductases, using both oxygen and hydrogen peroxide as terminal oxidants, has been studied.[328] Enzymatic oxidations with hydrogen peroxide catalysed by peroxidases, for example, have the limitation that the enzymes undergo com-



Scheme 18 Electrobiocatalytic deracemisation of *sec*-alcohols.



Scheme 19 Electrochemoenzymatic conversion of *sec*-alcohols to chiral amines.

peting facile oxidative degradation by hydrogen peroxide. An advantage of *in situ* electrolytic generation is that the hydrogen peroxide concentration is maintained at a low level. Deactivation of chloroperoxidase from *Caldariomyces fumago* (CPO), that catalyses a variety of oxidations including enantioselective olefin epoxidation and sulfoxidations,[329] for example, was reduced by using electrolytic *in situ* hydrogen peroxide generation.[330]

In the innovative 'electrochemical leaf' concept[331] an NADP(H)-dependent dehydrogenase and a small photosynthetic flavo-enzyme – ferredoxin-NADP$^+$ reductase (FNR) – that supplies electrons to generate the NADPH cofactor are entrapped in a nanoporous metal oxide electrode. FNR is ubiquitous in nature where it channels electrons into biosynthesis.[332] This concept can be used to drive a variety of reactions, including multi-enzyme cascade processes[333,334] such as a one-pot deracemisation of chiral secondary alcohols (Scheme 18).[335]

Alternatively, chemocatalytic oxidations can be integrated with biocatalytic steps, *e.g.* combination of TEMPO-catalysed aerobic oxidation of alcohols with enzymatic reductive amination of the resulting ketones to afford an enantioselective, environmentally attractive route to chiral amines from alcohols, with a molecule of water as the sole coproduct, in an aqueous medium (Scheme 19).[336]

7. Conclusions

Thirty years ago the E Factor drew attention to the problem of waste generation in chemicals manufacture and caused a paradigm shift in how the efficiency of chemical manufacturing processes is assessed. In the meantime, it has become increasingly clear that waste is the common denominator in the major environmental problems, such as climate change and pollution of our natural habitat. It is also clear that finding solutions to the ubiquitous waste problem, in its many facets, is one of the grand challenges for chemistry and chemical engineering.

Hopefully, we have shown in this review that there is sufficient reason for optimism. The answer is not less chemistry but better more sustainable chemistry, based on a more efficient use of resources in a circular economy underpinned by advances in (bio)catalysis and coupled with extensive decarbonisation of the energy sector and defossilisation of chemicals manufacture.[337] Technologies will be sustainable, and products recyclable, by design and the key words will be *pollution prevention*.

The organic chemist, A. W. von Hofmann, already said it almost 200 years ago:

"*in an ideal chemical factory there is, strictly speaking, no waste but only products. The better a real factory makes use of its waste, the closer it gets to its ideal, the bigger is the profit*".

Conflicts of interest

There are no conflicts to declare.

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