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The Road to Carbon Neutrality

Sheldon, Roger A.

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Waste Valorization in a Sustainable Bio-Based Economy: The Road to Carbon Neutrality

Roger A. Sheldon*[a, b]

The development of sustainable chemistry underlying the quest to minimize and/or valorize waste in the carbon-neutral manufacture of chemicals is followed over the last four to five decades. Both chemo- and biocatalysis have played an indispensable role in this odyssey. in particular developments in protein engineering, metagenomics and bioinformatics over the preceding three decades have played a crucial supporting role in facilitating the widespread application of both whole cell and cell-free biocatalysis. The pressing need, driven by climate change mitigation, for a drastic reduction in greenhouse gas (GHG) emissions, has precipitated an energy transition based on decarbonization of energy and defossilization of organic chemicals production. The latter involves waste biomass and/or waste CO_2 as the feedstock and green electricity generated using solar, wind, hydroelectric or nuclear energy. The use of waste polysaccharides as feedstocks will underpin a renaissance in carbohydrate chemistry with pentoses and hexoses as base chemicals and bio-based solvents and polymers as environmentally friendly downstream products. The widespread availability of inexpensive electricity and solar energy has led to increasing attention for electro(bio)catalysis and photo(bio)catalysis which in turn is leading to myriad innovations in these fields.

1. Waste as a Resource: the Road to Circularity

In recent years, it has become abundantly clear that waste derived from various human activities is the root cause of our many environmental problems and despair. These include, for example, the increasing levels of waste carbon dioxide, and other green house gases (GHGs) in the atmosphere that is the cause of climate change and waste from single use plastics that is devastating our natural environment. In 2023 global CO_2 emissions were a record 37.2 Gigatons $(37.2\times10^9$ tons)[1] the main source of which is the combustion of fossil resources for heating and electricity generation. Organic chemicals production is responsible for 1.86 Gt, whch represens 5% of total CO_2 emissions but the fate of the chemical industry is inextricably related to that of energy and transportation fuels. For comparison, cement[2] and iron and steel manufacture account for ca. 5% and 7%, respectively, and ammonia production via the Haber-Bosch process for another 1%.[3]

The 2015 Paris Agreement's long-term temperature goal (LTTG) of 1.5°C marked a milestone in the need for commitment to actions to mitigate climate change and coincided with the launch by many countries of net zero strategies with the goal of achieving net zero in 2050.[4] This need was reiterated in a 2022 Assessment Report.[5] Moreover, a 2019 report from the International Energy Agency (IEA) emphasized the need for the development of viable methodologies for the valorization of CO_2 waste.[6]

The way forward is clear: waste must be seen as a resource in a circular economy. Indeed, the attitude towards waste has undergone a metamorphosis in the last 4–5 decades, progressing from waste remediation, through prevention and utilization to finally become waste valorization. Actually, the organic chemical industry has always been largely based on waste, beginning with Perkin's serendipitous synthesis of the first synthetic dye mauveine, in 1856,[7] from coal-tar, a byproduct of coke production. This marked the beginning of an organic chemical industry based on coal-tar as the key raw material.

This scenario changed completely following the first production in 1921 of the petrochemicals, ethylene and propylene, by thermal cracking of waste alkanes from oil refining,[8] It marked the birth of the petrochemical industry based on the use of lower olefins and aromatics as base chemicals and subsequently led to the large-scale production of polyethylene and polypropylene plastics and many other polymers. Now, a century later, this scenario has not changed significantly, despite the fact that the first UN Conference on the Human Environment, held in Stockholm in 1972, raised the question of climate change emanating from steadily increasing GHG emissions. That this was caused by the burning of fossil hydrocarbon fuels, was also mentioned for the first time.[9]

Now, fifty years further on, we find ourselves in a transition period involved in gradually replacing fossil resources by sustainable alternatives, namely, solar, wind, hydroelectric and nuclear energy, as the source of power for heating, transportation and various industries. It entails decarbonization of

[a]   R. A. Sheldon
      Department of Biotechnology, Delft University of Technology, Netherlands
      E-mail: r.a.sheldon@tudelft.nl

[b]   R. A. Sheldon
      Department of Chemistry, University of the Witwatersrand, Johannesburg, South Africa
      E-mail: roger.sheldon@wits.ac.za

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the energy sector, defossilization of chemicals manufacture. and the use of sustainable energy and waste CO_2 or biomass for chemicals production. It also requires the use of a variety of technologies, such as onversion of second generation, lignocellulosic biomass as the raw material in e-biorefineries and biocatalysis using whole-cells and free enzymes, supported by electro- and photo-catalysis. to achieve a circular, bio-based economy with net zero GHG emissions.

2. The Role of Catalysis in Waste Minimization

The publication[10] in 1992 of of E-Factors (Table 1), representing the average amounts of waste generated per kg of desired product in various sectors of the chemical industry, drew attention to the enormous amounts of waste generated in the production of fine chemicals and pharmaceuticals. The E-Factor, succinctly defined as "everything but the desired product", includes, by definition, carbon dioxide emissions but the relevant data was generally not widely available in 1992. Moreover, CO_2 emissions were not at the top of everybody's agenda back in 1992. Another matter for discussion was how to include solvents, the most important contributor to waste,[11] in the E-Factor. Originally, if there was no data available, we assumed that 90% of the solvent was recovered but, in hindsight, this was probably over-optimistic. In any case, if the data is available, E can be calculated and presented with and without solvent.

The copious amounts of chemical waste were a direct result of the widespread use of e.g. reductions and oxidations, involving stoichiometric amounts of mainly inorganic reagents. The solution was clear: replace antiquated stoichiometric methodologies with greener, catalytic alternatives, such as catalytic hydrogenation and catalytic oxidations with dioxygen or hydrogen peroxide.

A pertinent example from commodity chemicals in the 1970s is propylene oxide (annual global production 9–10 mio tons) which was produced by reaction of propylene with HOCl. For every kg of propylene oxide ca. 3 kg of $CaCl_2$ is produced (Scheme 1). In contrast, the Shell process[12] for the manufacture of propylene oxide together with styrene, commercialized in 1974 and still in operation today, involved the Ti-on-silica catalyzed epoxidation of propylene with ethylbenzene hydroperoxide as the key step.[13] Overall the process produced propylene oxide and styrene and one equivalent of water from two petroleum hydocarbons and a molecule of oxygen: a superb example of green and sustainable chemistry *avant la lettre*.
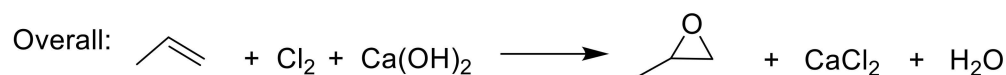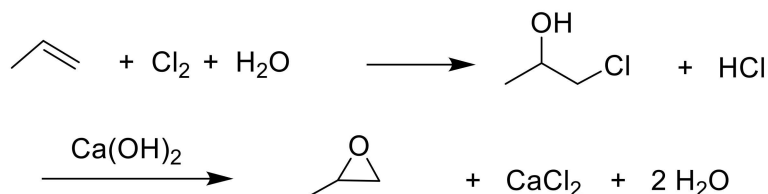
Notwithstanding the elegance and longevity of the Shell process, the use of hydrogen peroxide, derived from catalytic reaction of hydrogen and oxygen,[14] for the direct epoxidation of propylene, in water as the solvent (Scheme 2),[15] is more in line with the present day scenario of defossilization of chemicals manufacture. It could be even more attractive if the hydrogen peroxide is produced by electrolysis of water[16] thus enabling the green and sustainable manufacture of a bulk commodity chemical from a commodity olefin, water and sustainable electricity.

In the 1970s Shell and other petrochemical companies developed several homogeneous and heterogeneous catalytic technologies, e.g. olefin oligomerization, olefin metathesis, hydroformylation and carbonylation, for the bulk chemicals sector, that could also be applied in fine chemicals production. Unfortunately, the fine chemicals and pharmaceuticals industries were not yet ready to implement such catalytic technologies. Incredible as it may seem in hindsight, the fine chemicals and pharmaceuticals industries continued to use mainly archaic stoichiometric methodologies far into the 1990s. However, the pressure to reduce the prodigious amounts of waste finally prevailed and catalytic technologies,

Table 1. The E-Factor in various sectors of the chemical industry.

Industry segment	Product tonnage (tonnes per annum)	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

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1. Chlorohydrin process

Scheme 1. Processes for propylene oxide manufacture.

AE = 58 / 185 = 31%   E-factor = > 2

2. SMPO process
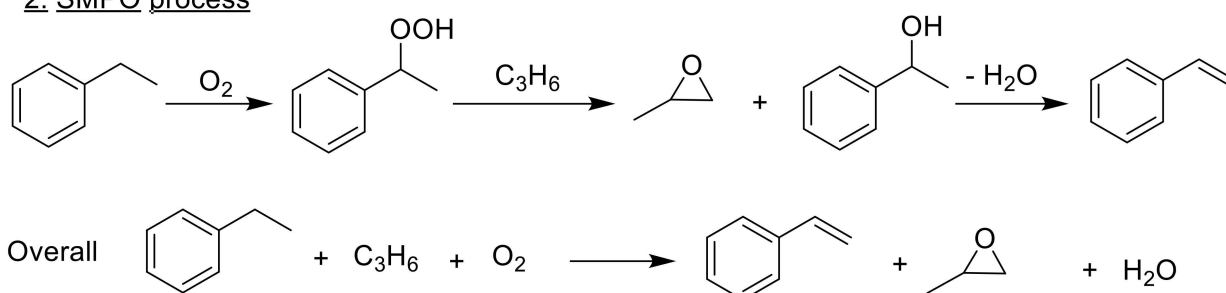
AE = 152 / 168 = 90%   E-Factor = 0.1
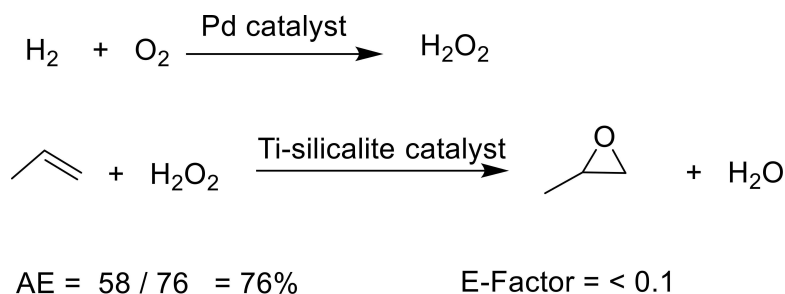
Scheme 2. Direct hydrogen peroxide process for propylene oxide.

AE = 58 / 76 = 76%   E-Factor = < 0.1

such as hydrogenation, hydroformylation, carbonylation and oxidation, were embraced by Pharmaceutical and Fine Chemical companies.[17]

3. The Role of Catalysis in a Defossilized Chemical Industry

Existing catalytic transformations of hydrocarbons will continue to play an important role in the short term. In contrast, the transition to a decarbonized energy sector and a defossilized chemical industry will have an overriding influence on the development of new catalytic technologies for converting the feedstocks of the. future. The most important feedstocks will be captured carbon dioxide[5] and 2nd generation biomass, i.e. lignocellulosic biomass. Hence, it will be necessary to develop economically and environmentally viable catalytic processes for the conversion of these two feedstocks en route to platform chemicals and biofuels (see section 4).

A variety of approaches[18] are potentially available for catalytic conversion of CO_2. The conventional way is to use the reverse water gas shift (RWGS) reaction to convert CO_2 and H_2

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into CO and water,[19] followed by Fischer-Tropsch conversion of the CO and H_2 to hydrocarbons and/or methanol.

In a decarbonized energy sector green hydrogen, produced by electrolysis of water using off-peak electricity generated with sustainable energy, such as solar, wind or nuclear power, can be harnessed for direct reduction of the CO_2[20] Most direct CO_2 conversion technologies are in early development stages but low-temperature electrolysis is deemed a promising pathway.[21]

Alternatively, photocatalysis, mediated by semi-conductors, can be employed for the photocatalytic conversion of CO_2 to methanol.[22] TiO_2 is the most widely investigated catalyst owing to its excellent stability, nontoxicity, and low price. The use of titanium carbide, Ti_3C_2/MXene, as a promising co-catalyst for photocatalytic conversion of CO_2 to energy-efficient fuels has recently been reviewed.[23]

Another variation on this theme is photo-biocatalytic conversion. Many organisms, such as plants, microalgae, and cyanobacteria utilize CO_2 as a carbon source in photosynthetic production of carbohydrates. In the same vein, biochemical conversion utilizes enzymes or microbes to convert CO_2 and water to a range of products such as methane, methanol, CO, and biomass.[24]

In microbial electrosynthesis (MES) electrons from an electrode convert a mixture of CO_2 and H_2O to commodity chemicals[25] by coupling green electricity to the carbon and energy metabolism of electroactive acetogenic and methanogenic bacteria. The latter microorganisms mediate the reduction of CO_2 to acetic acid, ethanol, formate, methanol, and methane. Another possibility is to convert the products of CO_2 reduction to downstream products by electrofermentation (EF).[26]

In a defossilized chemical industry another important feedstock will be waste lignocellulose from agricultural and forestry residues and food supply chain waste (FSCW). Electro-catalytic or electro-biocatalytic methodologies will be used in e-biorefineries to produce key platform chemicals and biofuels.[27] Alternatively, waste biomass can be used for the generation of sustainable electricity and hydrogen.[28]

In many cases, the conversion of renewable biomass may involve the use of scarce precious metal catalysts (PMCs) such as platinum, rhodium, ruthenium and particularly, palladium. This presents another potential problem based on the low natural abundance and the significant environmental impact of mining these metals. Hence, considerations of sustainability, cost, and price volatility could present a significant incentive to explore and develop the use of more earth abundant metals (EAMs) as catalysts.[29] However, it was recently pointed out[30] that several factors contribute in various ways to the overall carbon footprint, which led to the conclusion that a far more detailed analysis is required than is typically used!

4. Emergence of Biocatalysis: as a Key Enabling Technology

The use of enzymes in organic synthesis was known already in the early 20th century but was not widely used by organic chemists and certainly not in industry. The exception was the use of enzymes in the industrial synthesis of semi-synthetic. penicillin and cephalosprorin antibiotics.

4.1. Manufacture of Beta-Lactam Antibiotics

6-aminopenicillanic acid (6-APA) is a key raw material in the manufacture of semi-synthetic beta-lactam antibiotics. More than 20,000 tonnes of 6-APA are produced annually from the fermentation product penicillin G (Pen G). A conventional chemical method (Scheme 3), involving protection, de-protection and functional group activation steps, in dichloromethane as solvent under energy intensive conditions, was originally used for this conversion. This resulted in the production of copious quantities of toxic waste. Interestingly, it was the first process for which we calculated the E-Factor, in the late 1980s, a few years before the concept was published.

On the other hand, enzymatic hydrolysis catalyzed by penicillin G amidohydrolase (E.C. 3.5.1.11), better known as Pen-G acylase, is a one step process, in water at 37 °C. The only reagent used is 0.9 kg NH_3 per kg 6-APA to adjust the pH.[31,32] Pen-G acylase was already known in the early 1960 s[33] but it was expensive to produce, had poor thermal stability and low volumetric productivity and was discarded after a single use. Hence, for the next two decades, 6-APA was produced using the chemical procedure. In the meantime, Pen-G acylases with improved stability were developed, by traditional screening, and cost-effective production was eventually achieved with the aid of recombinant DNA technology. Moreover, effective immobilization of the enzyme enabled multiple recycling, up to 1000 recycles,[34] with dramatic reductions in the enzyme cost contribution.[35]

4.2. Biocatalysis in Organic Synthesis

Already In 1984 Zaks and Klibanov[36] reported that certain lipases could function adequately in hydrophobic organic solvents, such as toluene, under almost anhydrous conditions at elevated temperatures, e.g. 100 °C. The importance of this publication in the development of biocatalysis in organic synthesis cannot be overestimated. To understand this one has to appreciate the state of the art at the time of publication. In 1984 catalytic methods were not used in industrial organic synthesis. Synthetic organic chemists used stoichiometric reagents for everything. They even preferred stoichiometric reductions with metal hydride reagents to catalytic hydrogenation. Organic reactions were performed in organic solvents, with no limitations. The use of chlorinated hydrocarbons, such as carbon tetrachloride or dichlorome-
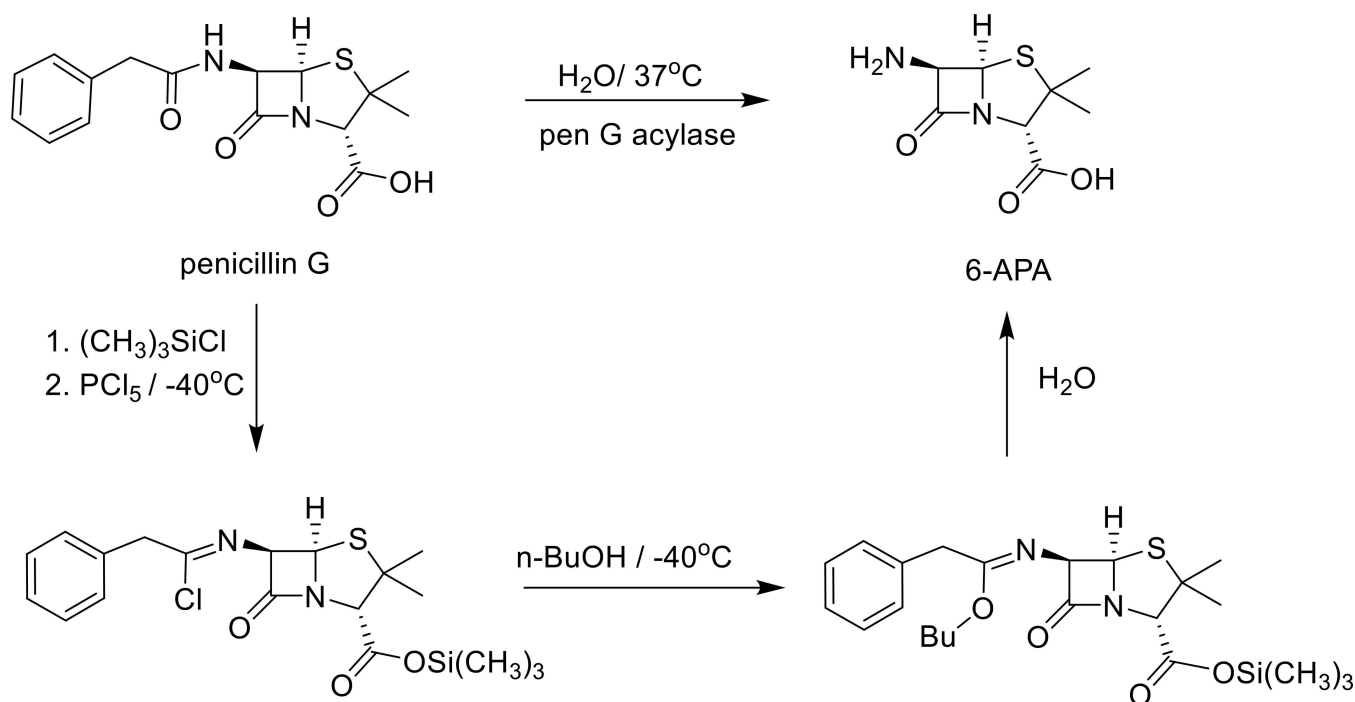
Chemicals used to produce 1 kg 6-APA:

Chemical process		Enzymatic process	
PCl_5	1.2 kg	NH_3	0.09 kg
$(CH_3)_3Cl$	0.6 kg		
$PhN(CH_3)_2$	1.6 kg		
n-BuOH	8.0 kg		
CH_2Cl_2	11.0 kg		
NH_3	0.2 kg		

Scheme 3. 6-APA synthesis.

thane, for example, presented no problem. Add to this the fact that synthetic organic chemists were taught that enzymes can function only in aqueous media at ambient temperature and one can understand that the work of Zaks and Klibanov was nothing short of a revelation that completely redefined the biocatalysis landscape. It meant that its scope in organic synthesis was potentially much broader than previously imagined.

Another important development that redefined the potential of biocatalysis was the introduction of legislation, by the FDA in 1992, that required pharmaceutical companies to fully test both enantiomers of a chiral drug.[37] In practice, this led to the marketing of chiral drugs as the single, pharmalogically active enantiomer. It created, in turn, a need for commercially viable methods, that is chirotechnology,[38] for the synthesis of pure enantiomers of chiral drugs. Catalytic asymmetric synthesis was, at the time, the most promising technology for the synthesis of single enantiomers. Noyori and Knowles collectively received one half of the Nobel prize in Chemistry in

2001 for catalytic asymmetric hydrogenation using noble metal complexes with chiral phosphine ligands as catalysts.[39]

Since most enzymes are highly enantioselective, biocatalysis was clearly an attractive alternative for producing pure enantiomers of chiral drugs. However, at the time it was regarded as not being cost-effective and limited in scope. This scenario rapidly changed at the turn of the century following spectacular developments in protein engineering that helped biocatalysis evolve to be the method of choice for the commercial scale enantioselective synthesis of chiral drugs.[40,41]

Frances Arnold was awarded the Nobel Prize in Chemistry in 2018 for her pioneering work on the use of directed (in vitro) evolution to engineer enzymes.[42] This enabled the engineering of enzymes to exhibit pre-defined properties with regard to, for example, substrate specificity, activity, selectivity, stability and pH optimum. Furthermore, metagenome mining,[43] proved to be an invaluable tool for the discovery of new enzymes and new enzyme activities, without requiring

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prior protein engineering. or provide a better starting point for engineering. Notwithstanding these remarkable advances that have been made in the use of biocatalytic methods in the synthesis of APIs, according to a recent survey[44] the pace at which this is happening is slower than expected. However, one cannot help thinking that this is more a reflection of the pace of the industry than the state of the art.

Enzymes are nature's sustainable catalysts[45] with numerous environmental and economic benefits. They are derived from renewable resources and are biocompatible, biodegradable, essentially non-hazardous and non-toxic. The use of enzymes avoids the use of scarce precious metals and the accompanying costs of removing traces of noble metals, to an acceptable ppm level, from end products. On the other hand, recent developments in the use of designer amphiphiles (see section 5.4) to enable the use of precious metal catalysts, such as palladium, at extremely low loadings should alleviate the price and availability issues.

Moreover, enzymatic reactions are performed at physiological pH and ambient temperature and pressure in water. No functional group activation and protection and deprotection steps are required. In practice this enables shorter syntheses coupled with higher selectivities and affording purer products in processes that are more resource and energy efficient and generate less waste. Furthermore, most enzymatic processes are conducted in standard multi-purpose batch reactors under roughly the same conditions of temperature and pressure and can be readily coupled in multistep biocatalytic cascade processes as well as chemo-enzymatic cascades (see section 3.5).

In the first decade of this century, the use of protein engineering techniques such as DNA shuffling, invented by Stemmer,[46] enabled the optimization of enzymes to afford processes that fit predefined criteria and are sustainable by design. A classic example is the three-step enzymatic synthesis[47] of a key intermediate for atorvastatin, a cholesterol-lowering agent, with an overall E-Factor of 8 or 18 if water is included.[48] All three enzymes were optimized, using DNA shuffling, to meet predefined process parameters. The relevant data for the novel dehalogenation step are shown in Scheme 4.

4.3. Biocatalytic Synthesis of Chiral Pharmaceutical Intermediates

Following the impressive results obtained in the synthesis of the atorvastatin intermediate, ketoreductases (KREDs) became the first choice method for the manufacture of a wide range of enantiopure secondary alcohols.[49–52] Efficient regeneration of the NAD(P)H co-factor is accomplished by adding a second alcohol, e.g. isopropanol, or a second enzyme/substrate combination, e.g. glucose/glucose dehydrogenase (GDH) or formate/formate dehydrogenase (FDH). Indeed, based on the superb enantiospecificities obtained with enzymes, biocataly-
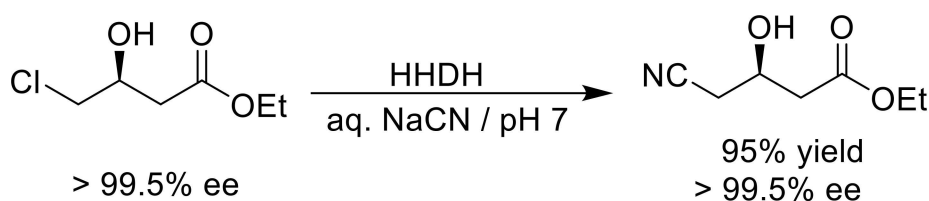
Parameter	Process design	Wild-type	Best variant
[Substrate] (g.L-1)	120	20	140
[Enzyme] (g.L-1)	1.5	30	1.2
Catalyst productivity (g/g)	80	0.7	117
STY (g.L-1day-1)	>360	7	672
Isolated yield (%)	>90	67	92
Chemical purity (%)	>98	>98	>98
ee (%)	>99.5	>99.5	>99.5
Reaction time (h)	8	72	5
Phase separation (min.)	<10	>60	<1

Scheme 4. Enzymatic dehalogenation wiih a dehalogenase.

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sis has become the first choice method for the sustainable synthesis of key pharmacetical intermediates in general.[53]

Chiral primary and secondary amines are even more prolific pharmaceutical intermediates than chiral secondary alcohols. Inspired by the work of Klibanov and Zaks (see earlier) on the use of lipases in organic solvents, extensive research was carried out in the late 1980s and 1990s on the kinetic solution of chiral amines by lipase-catalyzed acylation of amines with activated esters.[54] This formed the basis for the BASF process[55] for the industrial scale kinetic resolution of chiral amines by lipase-catalyzed acylation with 2-methoxy-acetic acid ester. The unwanted enantiomer of the amine is acylated and the resulting amide is waste. Fortunately, penicillin amidase catalyzes its hydrolysis and the 'wrong' amine enantiomer can be racemized using a palladium catalyst to afford an overall dynamic kinetic resolution (Scheme 5).

Notwithstanding the impressive results obtained with the BASF process, it is a kinetic resolution. A catalytic asymmetric synthesis, in contrast, has the advantage of not requiring racemization and recycling of the wrong enantiomer. More-over, in the last decade spectacular advances have been made in the enzyme catalyzed asymmetric synthesis of chiral amines employing a variety of enzyme classes (Scheme 5). Amine transaminases (ATAs), for example, utilize primary amine donors, such as isopropylamine, for the enantioselective conversion of prochiral ketones to chiral secondary amines. The method has been used in the last decade for the highly enantiospecific synthesis of numerous APIs.[56–61]

Noble metal catalyzed reductive amination of ketones, with a mixture of hydrogen and ammonia, is widely used to produce secondary amines.[62] In contrast, the first use of an engineered amine dehydrogenase (AmDH), to catalyze asymmetric reductive amination was reported in 2012.[63] Howev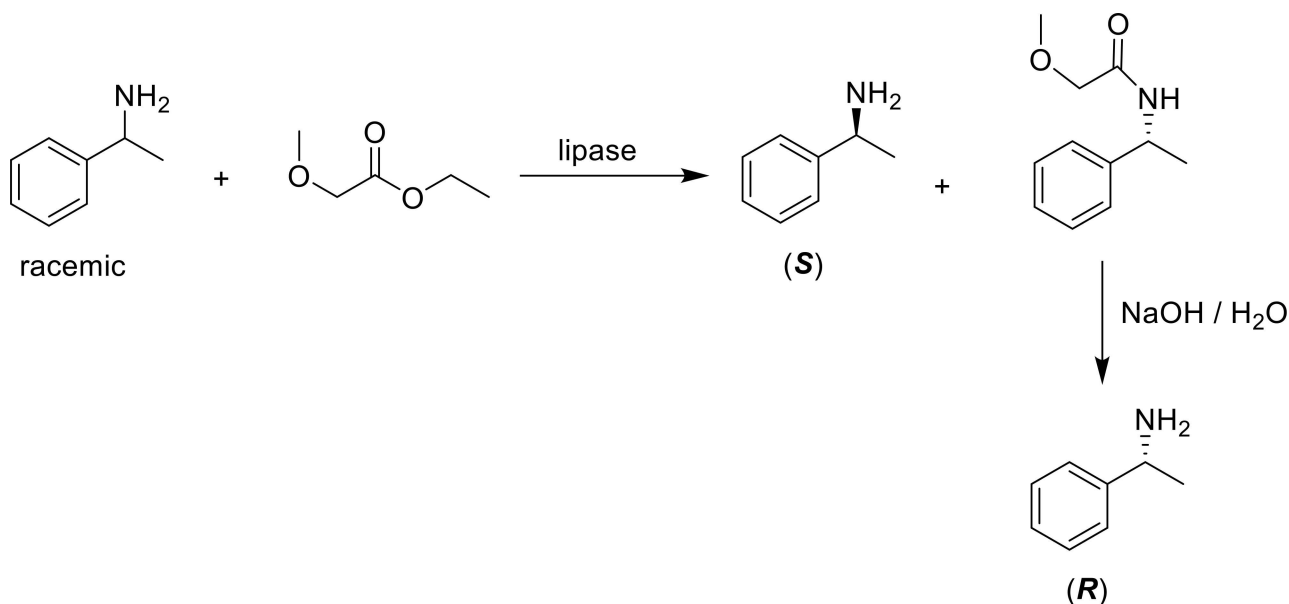er, a decade later AmDHs are widely used in the synthesis of enantiopure amines.[64,65] Similarly, imine reductases (IREDs), another recent addition to the repertoire,[66] are able to catalyze both asymmetric imine reduction and reductive amination of ketones with primary amines (Scheme 6).

By combining directed evolution with mechanism-guided chemomimetic design to generate highly engineered variants of Cyt-P450 dependent monooxygenases, Arnold and co-workers[67,68] were able to expand the biocatalysis toolbox to include new-to-nature reactions. Examples include carbene and nitrene insertion reactions with ethyl diazoacetate and tosyl azide to form cyclopropanes and aziridines from olefins, respectively. An engineered heme enzyme from *Pyrobaculum arsenaticum* protoglobin was subsequently shown[69] to mediate nitrene insertion into C–H bonds using hydroxylamine hydrochloride as the precursor.

Use of protein engineering generally entails finding an enzyme exhibiting the desired activity, albeit at a very low level, and employing directed evolution to improve its activity. Recently machine learning (ML) has emerged as a powerful tool to aid the identification of a suitable starting point enzyme. Subsequent improvement for numerous enzyme applications is predicted to become a fully automated process.[70]

4.4. Enzyme Immobilization and Continuous Processing

In the last three decades biocatalysis, with the help of protein engineering, has proven to be an invaluable tool for the sustainable manufacture of pharmaceuticals and fine chemicals.[71,72] Now, as we stand on the brink of massive defossilization of chemicals manufacture, by switching to renewable waste biomass or waste carbon dioxide as the feedstock, biocatalysis needs to be commercially viable for the production of commodity chemicals.
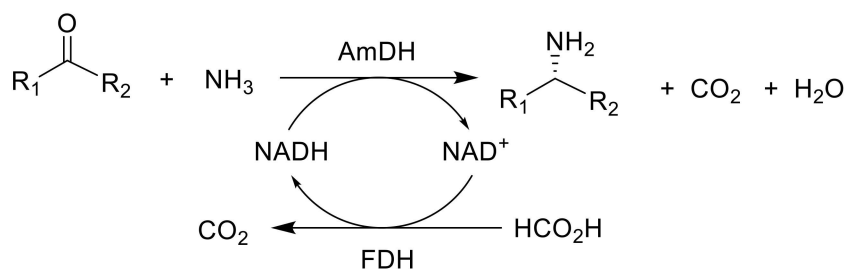

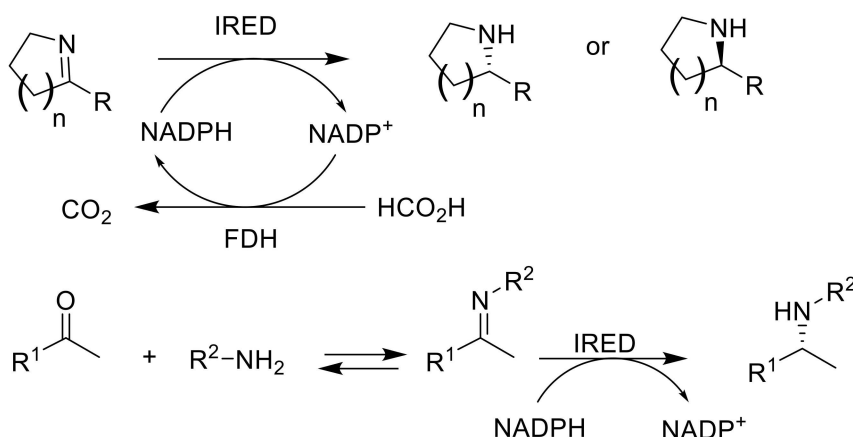**Scheme 5.** BASF process: Biocatalytic resolution of amines.

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.1. Transamination

2. Reductive amination

3. Imine reduction

Scheme 6. Biocatalytic synthesis of enantiopure amines.

Commercial viability will require product concentrations of 200–400 g.L^{-1} and volumetric productivities of 1–10 kg.L^{-1} h^{-1}. Catalyst productivities (kg/kg) will need to be increased by 1–2 orders of magnitude[73,74] to >1000 kgs/kg to compete with heterogeneous catalysts used in petrochemical production, i.e. space time yields (STYs) of 1–10 kg L^{-1} h^{-1}.[75]

Enzymes are water-soluble and were traditionally used on a single use, throw-away basis which is neither cost-effective nor environmentally acceptable. In contrast, the organic chemical industry is accustomed to heterogeneous catalysts in continuous processes, e.g. in packed bed reactors. Thus, In order to be competitive enzymes will need to be immobilized as water-insoluble powders and recycled numerous times. Pen-G acylase is cost-effective in Pen-G hydrolysis (see earlier) because it is immobilized to enable its recycling 1000 times.

The primary method for immobilization of isolated enzymes involves binding to a prefabricated carrier by (i) simple physical adsorption, (ii) ionic bonding, or (iii) covalent attach-ment to a resin These days most proteins are recombinant proteins that are generally produced with a string of six to nine histidine residues, a so-called His-tag, attached to the N- or C-terminus. This enables purification by non-invasive binding of the imidazole groups in the His-tag to immobilized transition metal ions. It forms the basis for affinity immobilization[76] that combines high immobilization yield with high activity retention. It also enables combination of isolation of the enzyme from cell-lysate and its immobilisation into a single efficient step.

Alternatively, enzymes can be immobilized by covalent attachment to carriers or as carrier-free cross-linked enzyme aggregates (CLEAs).[77] This involves random formation of covalent bonds with reactive functional groups, such as the amino groups of lysine residues, on the enzyme. Unfortu-nately, this can cause disruption of its three dimensional structure with accompanying loss of activity.

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Recently, we used bio-orthogonal chemistry, in conjunction with rec-DNA, to obtain highly precise immobilization with no loss of activity.[78] This involved the genetic insertion of non-canonical amino acids (ncAAs) containing reactive functional groups, e.g. azide and alkyne, that can undergo a non-random bio-orthogonal coupling to afford a CLEA with no loss of activity, in a potentially cost-effective combination of enzyme production, purification and immobilization in the cell-lysate.

Traditionally, fine chemicals and pharmaceuticals were produced in batch and large volume commodity chemicals in continuous operation. The last decade, however, has seen a marked trend towards the production of pharmaceuticals in continuous flow operation, in packed bed reactors. Biocatalysis in flow, enabled by the development of cost-effective immobilization techniques, is rapidly becoming a key technology in biotransformations.[79–83]

A hydrogen borrowing cascade for chiral amine synthesis from the corresponding alcohols has, for example, been performed in continuous flow[84] with the two enzymes co-immobilized on controlled porosity glass Fe^{3+} ion-affinity beads. Biocatalysis in flow eliminates downtime, increases productivity, optimizes resource utilization and reduces the amount of waste. In short, it is more cost effective and more sustainable

4.5. Biocatalytic and Chemo-Enzymatic Cascades

The fact that most enzymes operate at roughly ambient temperature and pressure in an aqueous medium creates ideal conditions for combining different enzymatic steps into multi-enzyme cascade processes for sustainable pharmaceutical syntheses.[85–87] They are more cost-effective and sustainable than performing the different steps separately. It includes the use of cascades of highly evolved enzymes for the synthesis of complex molecules[88] and the use of multi-enzyme cascades in continuous flow.[89] It is also eminently feasible to combine the two worlds of biocatalysis and chemocatalysis to afford cost-effective and environmentally favorable chemo-enzymatic cascade processes.[90–92] The use of chemo-enzymatic cascades for upgrading bio-based resources has also been described.[93]

5. Defossilization and the Bio-Based Circular Economy

We are currently in a transition period from an unsustainable, linear take-make-use-dispose economy based on finite fossil resources as the source of both carbon and energy. The goal is a bio-based, defossilized circular alternative that utilizes renewable carbon in combination with a sustainable energy source.[94] The latter will consist of green electricity generated using photovoltaic panels, wind turbines, hydroelectric power or nuclear energy. The renewable carbon currently in use consists mostly of first generation (1G) feedstocks, such as

corn or wheat starch and sugar cane or beet, that are not sustainable in the longer term owing to competition with food production.

In contrast, second generation (2G) feedstocks, consisting of unavoidable lignocellulosic waste, such as agricultural waste and forestry residues, are not competing with food production.[95–97] There is more than enough of this, primarily polysaccharide waste, to sustain the total global production of commodity chemicals in e-biorefineries.[98] Such a waste-to-chemicals scenario can also include other souces of waste, such as food supply chain waste.[99,100] In the longer term, aquatic carbohydrates, derived from micro- and macro-algae and consisting of a variety of structural polysaccharides that differ in structure from their terrestrial counterparts, are the potential feedstocks for third generation (3G) biorefineries.[101,102]
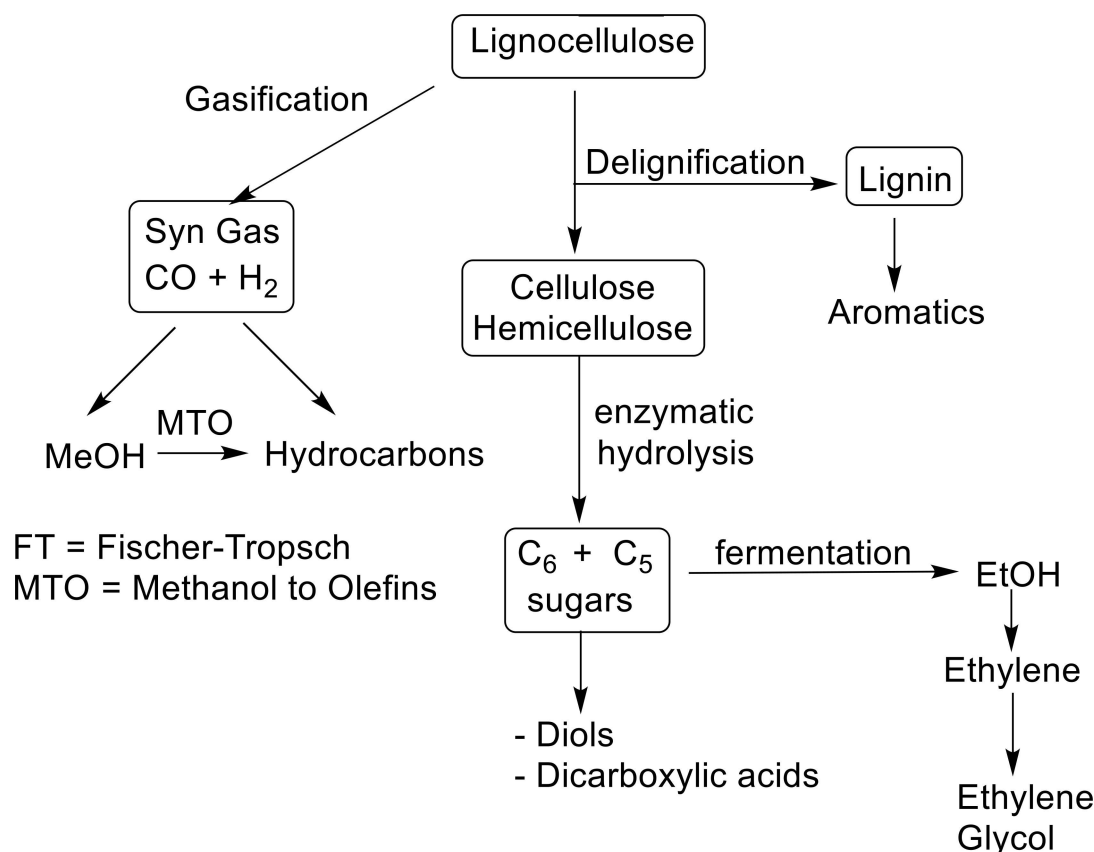
5.1. Conversion of Lignocellulosic Biomass to Platform Chemicals

Already in 1973 an oil crisis stimulated major petrochemical companies to think about how they could produce chemicals if there was no oil. The answer was to convert syn gas (CO/H_2), produced by coal gasification, to a mixture of hydrocarbons using the Fischer-Tropsch (FT) technology developed in Germany in the 1930s.[103] In fact, any source of biomass could be used but coal was the obvious choice at the time. Technologies were also available or were developed to convert syn gas directly to various oxygenated chemicals, such as ethylene glycol.[104]

Now, fifty years on, carbon neutrality is the ultimate goal and coal is not an option but various sources of waste lignocellulose biomass are viable options. The main challenge in a biorefinery is that, from both a commercial viability and a net zero GHG emissions viewpoint, all of the lignocellulose, i.e. lignin, cellulose and hemicellulose, must be valorized to produce marketable liquid fuels and commodity chemicals.[105] This is also driven by a convergence of green chemistry with industrial biotechnology.[106] Sustainable electricity will be the source of the energy required in e-biorefineries.[107]

As Scheme 7 shows, there are more options than in 1974, mainly as a result of advances in biotechnology. It is now eminently feasible to produce chemicals directly from syn gas by fermentation.[108] Acetogenic bacteria, for example, convert syn gas to ethanol and acetic acid.[109] Alternatively, the syn gas can be converted to a wide variety of commodity chemicals in noble metal catalyzed processes.[110,111]

In yet another alternative, the lignin can be separated, with the so-called lignin first strategy,[112,113] and the remaining cellulose and hemicellulose hydrolyzed to mixtures of C_6 and C_5 sugars.using a cellulase enzyme cocktail.[114] This is followed by selective conversion of the hexoses and pentoses into platform chemicals using sustainable biocatalytic or chemo-catalytic methods. These include, *inter alia*, production of alcohols, diols, and carboxylic acids by fermentation and a variety of chemocatalytic reductions and oxidations. Thus,

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Scheme 7. Conversion of lignocellulose to commodity chemicals.

defossilization of feedstocks involves a switch from hydrocarbons to carbohydrates as the base chemicals and further conversion to a variety of platform chemicals and industrial monomers, using chemo-catalysis or whole cell or cell-free biocatalysis.[115]

Three scenarios are envisaged. First, dehydration of alcohols to drop-in olefin monomers that constitute the cornerstone of the petrochemical industry, e.g. bio-polyethylene via bio-ethanol. Second, direct conversion to oxygenates as platform chemicals using chemo- or biocatalysis or combinations thereof. Third, direct conversion to a new biopolymer that has to compete with an existing oil-based polymer, e.g. carbon fibers from lignin.

Various lower alcohols, e.g. 1-butanol and isobutanol, can be produced cost-effectively by fermentation and are in the process of being commercialized. Similarly, 1,3-propanediol, 1,2-propanediol, 2,3-butanediol (2,3-BDO), and 1,4-butanediol (1,4-BDO) can be produced industrially by fermentation and can be considered as green platform chemicals. A variety of hydroxy acids and dicarboxylic acids can also be produced effectively by fermentation and converted to existing or new (to the market) polymers.

Similarly, routes can be envisaged for converting hexoses and pentoses to a variety of oxygenates using catalytic hydrogenation or chemo- or biocatalytic aerobic oxidations. For example, hydrogenation affords a variety of sugar alcohols

with commercial applications. On the other hand, the 1,2-diols, e.g. ethylene and propylene glycol are much more important, commercially, and can be produced by a chemocatalytic conversion involving retroaldol condensation followed by hydrogenolysis.[116]

Acid catalyzed dehydration of pentoses and hexoses affords furfural and 5-hydroxymethyl furfural (HMF), respectively. Furfural is already an important commodity chemical and HMF has enormous potential as a platform chemical for the production of various bio-polymers, chemicals and biofuels. Cost-effective production of HMF, is challenging owing to the low stability of HMF under the acidic conditions. Hence, much effort has been devoted to the optimization of this step.

The problem is circumvented by converting the glucose to the more stable, hydrophobic, 5-chloromethylfufural (CMF) which is separated by extraction (the choice of solvent will important for the overall sustainability). A mixture of CMF and furfural is obtained by hydrolysis of (ligno)cellulose with highly concentrated HCl (40%) at ambient temperature and pressure.[117] It is a modern version of the process, developed by Bergius in the 1920s,for the saccharification of (ligno)cellulose.[118] The vision of Bergius was to supply the world with non-food sugars for cattle feed, commodity chemicals and bio-based materials. Avantium has scaled up the process to obtain a 96.7% yield of CMF from the C_6

fraction of sugars from lignocellulose saccharification in continuous operation.

CMF is a platform chemical.[119] It is converted, by hydrolysis, back to HMF and HCl and the HCl recycled. The HMF can be converted to a variety of bio-monomers (Scheme 8). Hydrogenation of CMF affords 2,5-bishydroxymethylfuran (BHMF), an interesting monomer.[120,121] Alternatively, it is converted to 2,5- diaminomethyluran, a raw material for polyamides, via the dialdehyde. However, the most important of these bio-monomers is furan 2,5-dicarboxylic acid (2,5-FDCA) produced by chemocatalytic or biocatalytic[122] aerobic oxidation of HMF. FDCA is the raw material, together with bio-ethylene from bio-ethanol, for producing polyethylenefuranoate (PEF) a fully bio-based alternative for polyethylene terephthalate (PET).
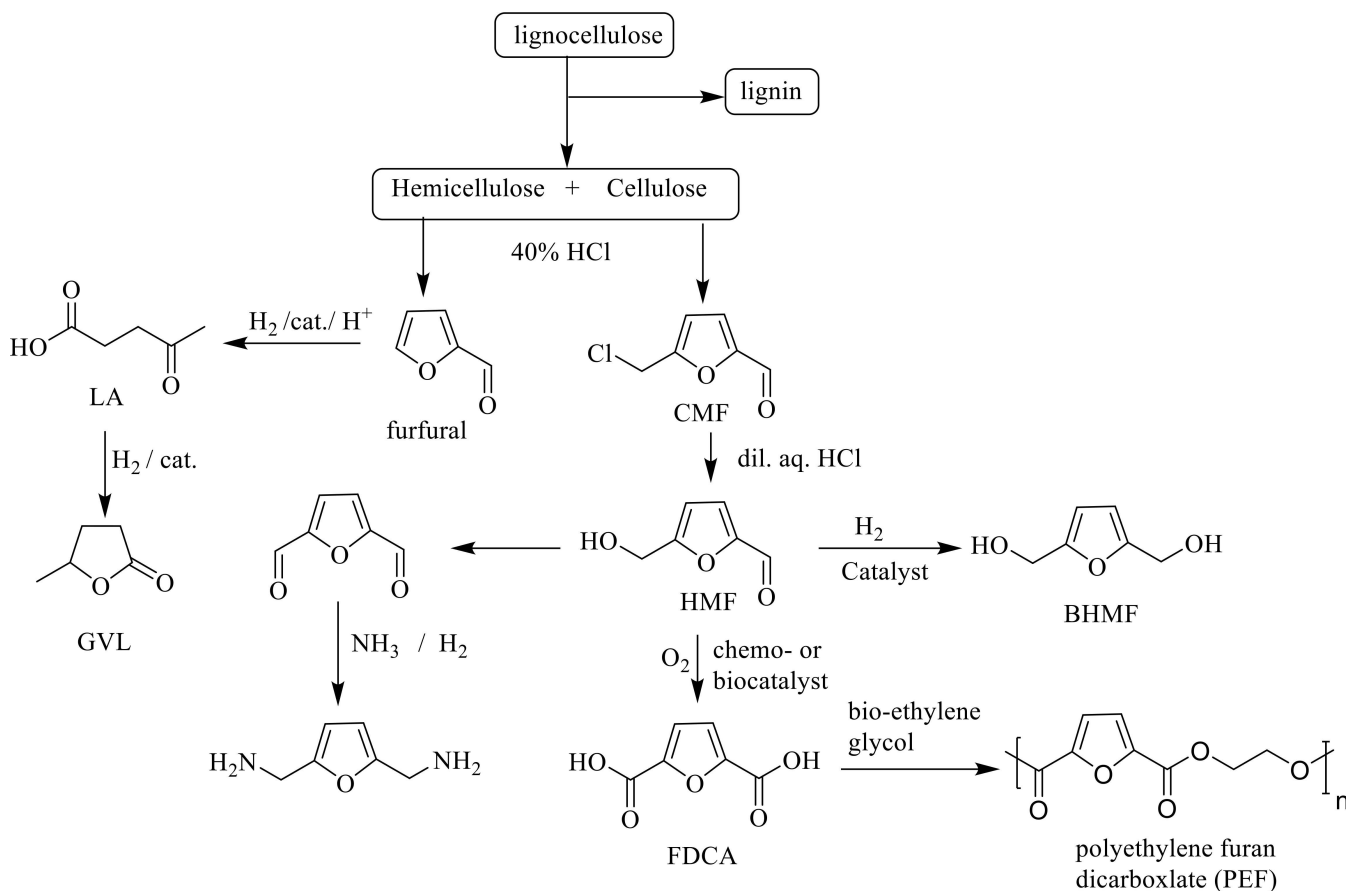
5.2. Bio-Based Polymers and the Plastic Pollution Conundrum

The numerus societal benefits of plastics, notably the big five – polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) polystyrene (PS) and polyethylene terephthalate (PET) - for health, safety, energy saving and materials conservation, are undeniable.[123] Many vital activities, e.g in medical appliances, are completely dependent on specialty plastics. The problem begins when they become plastic waste in the environment. Only 30% of all the plastics that were ever produced are currently in use.[124] The remaining 70% (> 6 billion tonnes) has primarily accumulated in land-fills or was directly disposed in the environment. A business-as-usual scenario predicts that a further 6–12 billion tonnes of plastic waste will be generated by 2050.

Clearly such an unsustainable linear take-make-use-dispose economy inust be supetseded by a circular bio-based economy that optimizes resource utilization through multiple rounds of recycling.[125] The waste problem is primarily caused by single use plastcs (SUPs) for packaging that account for ca. 40% of the annual global production of 400 mio tonnes. They consist, almost entirely, of three polyolefins and a polyester, namely, polyethylene (PE), polypropylene (PP), polystyrene (PS), and polyethylene terephthalate (PET), They are the plastic pollution problem.

A recent review of the environmental impact of bio-based plastics[126] concluded that substitution of two thirds of the global plastics demand with bio-based alternatives would deliver an annual reduction of 241–316 million tonnes of CO_2 equivalents. However, their high production costs and lower mechanical stability make widespread commercialization a challenge. Nevertheless, appropriate application of extended producer responsibility measures to PE and PP could change this scenario overnight.

Scheme 8. CMF and furfural as platform chemicals.

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Landfill is no longer a viable option and chemical recycling by converting waste plastic to e.g. fuel is not an attractive proposition. The most sustainable and sensible option is closed loop recycling by conversion to the original monomers to produce new plastic.This presents a problem for two of the four, namely the PE and PP, which are by far the largest volume SUPs but recycling back to the monomers is not tchnically feasible.

On the other hand, the replacement of fossil resource derived olefins by renewable hexoses and pentoses, as the base chemicals in a biorefinery, creates a window of opportunity to replace unrecyclable polyolefins with eminently recylable bio-based polyesters and polyamides.

Enzymatic hydrolysis of polyethylene terephthalate (PET) to the original monomers, for example, has been widely studied.[127] The current status of research on PET-hydrolyzing enzymes for industrial scale application[128] and the biotechnological recycling of plastics in general was recently reviewed.[129,130] It appears to be just a matter of time before this technology is commercialized. Alternatively, the fully bio-based polyethylene furanoate (PEF) developed by Avantium, and polybutylene succinate (PBS), and related bio-based polyesters can be converted to the original monomers by acid- or base-catalyzed or enzyme-catalyzed hydrolysis (see Scheme 9).

Polyhydroxyalkanoates (PHAs) are a particularly interesting sub-class of polyesters because they are available from fermentation of low-cost waste streams. They can even be produced by fermentation of the lignin fraction in a lignocellulosic biorefinery.[131] and are biodegradable. They function as a carbon and energy source for acetogenic bacteria and can represent up to 90% of the dry weight of the organism. Some PHAs have physical properties that are comparable with those of PE and PP and could be suitable for applications as SUPs for packaging.[132]

5.3. Electrolytic Valorization of Waste Biomass

A primary source of energy for future manufacture of chemicals and liquid fuels will be green, i.e. renewable, electricity.[133] So-called Power-to-X (P2X) technologies use "excess" and underutilized renewable electricity to convert abundant molecules, such as water and CO_2 into hydrogen, syngas and methanol and air and water into hydrogen peroxide, and ammonia. This provides a versatile, low capital intensive decarbonization strategy for producing green fuels and an abundance of downstream organic molecules in electrobiorefineries (e-biorefineries)[134–137] Schmidt and co-workers,[138] for example, produced butanol and hexanol from CO_2 and H_2O by electrolytic reduction to syn gas (CO/H_2) followed by fermentation with *C. autoethanogenum*.

Alternatively, bio-based polyesters such as PHAs could be produced by reduction of CO_2 to short-chain fatty acids that are further converted by PHA accumulating microorganisms.[139] P2X was also be used to exploit the synergy of microbial and electrochemical transformations in the valorization of waste polysaccharides, e.g. lignocellulose (2G) and algal polysaccharide (3G) biomass. It has been used,
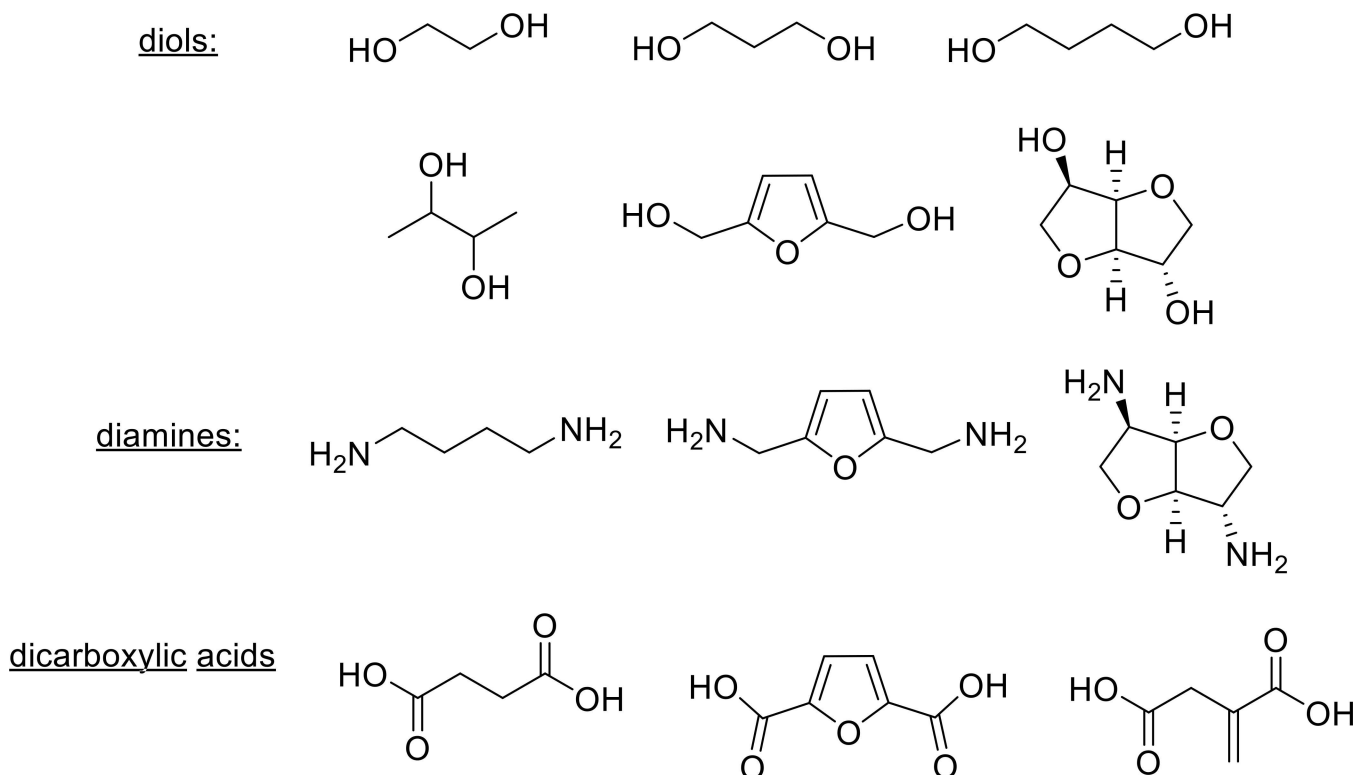
Scheme 9. Bio-based monomers for polyesters and polyamides.

for example, in the valorization of waste lignin from the processing of waste lignocellulose.[140]

The projected availability of inexpensive renewable electricity is a major driver for a veritable revival in electrosynthesis.[141–145] Electrobiocatalysis[146] can also be utilized for electrochemical regeneration of redox cofactors such as NAD(P)/NAD(P)H, as an alternative to conventional regeneration systems involving a second enzyme and a sacrificial co-substrate, in reactions with isolated oxidoreductases. It was successfully used, for example, in the electrolytic, nickel-catalyzed oxidation of the biomass-derived platform chemical, 5-hydroxymethylfurfural (HMF) to 2,5-FDCA the monomer for the fully bio-based plastic, PEF (Scheme 10).[147]

5.4. Photolytic Valorization of Waste Biomass

In vivo, photoautotrophic organisms such as green plants, algae, and cyanobacteria are able to convert solar energy and CO_2 into chemical energy in the process of photosynthesis. On the other hand, traditional photochemical processes were performed with UV light. This changed with the introduction of photocatalysts, in particular photoredox catalysts, that are activated with low-energy photons. They paved the way for sustainable photolytic processes driven by an environmentally friendly reagent, namely visible light.[148] Subsequently, visible light directed photoredox catalysis became a powerful tool that can be combined with conventional transition metal catalysis or organocatalysis to create new synthetic methodologies.[149]

Similarly, *in vitro*, synergistic combinations of photocatalysis and biocatalysis enable sustainable biotransformations[150,151] including photobiocatalytic cascade processes.[152,153] Numerous light-dependent enzymes have evolved *in vivo*. A FAD-dependent fatty acid photodecarboxylase (FAP), for example, catalyzes the photo-decarboxylation of fatty acids.[154] This can be used to convert long chain fatty acids derived from renewable biomass to hydrocarbon fuels, in a defossilized bio-based economy.

In natural photosynthesis, visible light is the thermodynamic driving force that promotes the oxidation of water, with concomitant formation of dioxygen and reduced nicotinamide cofactors as biogenic reducing equivalents. It inspired chemists to search for robust inorganic photocatalysts that can mimic this *in vivo* process. Hollmann and coworkers,[155] for example, found that the thermodynamic driving force can be derived from UV and visible light by reaction of water with titanium dioxide-based photocatalysts with liberation of electrons. It was used to reduce an unsaturated ketone with water (Scheme 15).
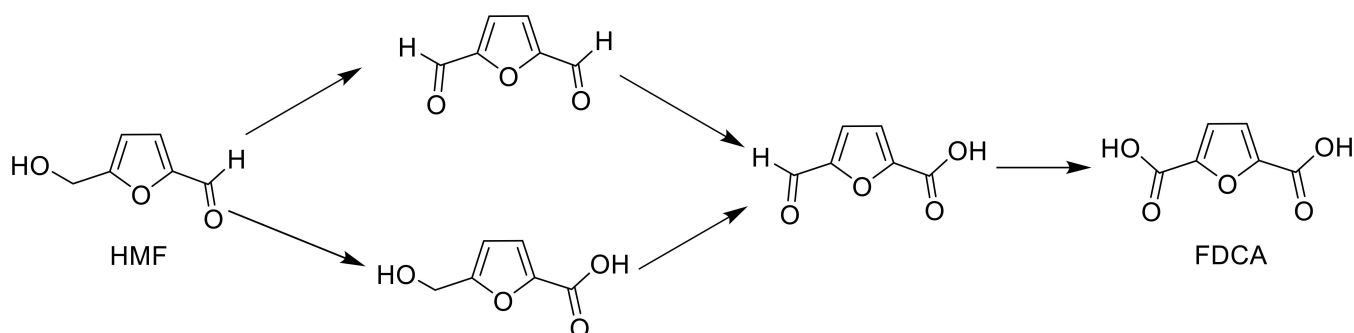
A variety of photocatalytic systems have been used.[140] However, they rely on a limited set of photocatalysts, such as homogeneous indium and ruthenium complexes, a few organic dyes and semi-conducting materials. A major drawback of such methodologies is their limitation to highly energetic visible light. The key to sustainability is the application of photocatalytic strategies that use the entire visible light spectrum. This would enable efficient solar harvesting and sustainable photochemical reactions with sunlight instead of artificial light sources. Hence, recent efforts are geared towards the use of the entire visible light spectrum. Moreover, strategies that utilize near-infrared (NIR) light are suitable for use in biological and medical applications.

We have recently described such a system.[156] Photolytic regeneration of the NAD(P)H cofactor, in the enantioselective KRED-catalyzed reduction of prochiral ketones, was achieved using an NIR-driven artificial photosynthesis system with H_2O as the sacrificial reductant and TiO_2/reduced graphene quantum dots (r-GQDs), combined with a novel rhodium electron mediator (Scheme 11).

Indeed, the future of photobiocatalysis may lie in chromoselective photocatalysis, whereby the outcome of a photocatalytic process is determined by the choice of wavelength. It presents exciting new possibilities in reaction design and controlling reactivity and stereoselection in organic synthesis.[157] Wavelength does matter!

6. Defossilization of Solvents

The second major application of commodity chemicals, after polymers, is solvents. The latter are a major contributor to waste generated and resulting environmental impacts in pharmaceuticals manufacture. A 1997–2012 survey of solvent usage indicated that there was much room for improvement.[158] and led to a rethinking of solvent usage.[159]

Scheme 10. Electrocatalytic oxidation of HMF to FDCA.

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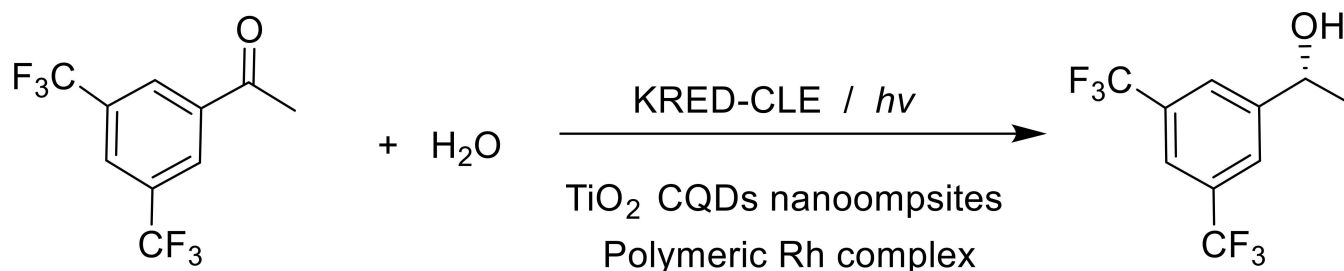
Scheme 11. NIR-mediated photo-enzymatic reduction of a prochiral ketone with water.

An appropriate choice of solvent can improve both the environmental and commercial performance of a process and, hence, its sustainability.[160] Pharmaceutical companies developed Solvent Selection Guides (SSGs) to stimulate replacement of environmentally undesirable solvents, in particular chlorinated hydrocarbons.[161,162] Indeed, the quest for improved solvents, e.g. aided by *in silico* machine learning methods, continues unabated.[163]

In addition to chlorinated solvents many hydrocarbons and low-boiling ethers are classed as hazardous or highly hazardous on the basis of toxicity and/or flammability issues. In addition, widely used dipolar aprotic solvents, typified by dimethyl formamide, dimethylacetamide and N-methylpyrrolidone, are classified as substances of very high concern (SVHCs), based on reproductive toxicity issues, and replacements are desperately needed.

6.1. Bio-Based Solvents

Various mono- and bi-phasic systems, involving solvents derived from renewable biomass, have been proposed as alternatives for less environmentally acceptable volatile organic solvents.[15,164,165] They include a range of bio-based alcohols, including bio-ethanol,[166] isobutanol and glycerol[167] and bio-based esters such as isobutyl acetate, ethyl lactate, ethyl levulinate, diethyl carbonate, glycerol carbonate and γ-valerolactone (GVL)[168] Interestingly, lipases dissolve in glycerol and glycerol carbonate with retention of activity.[169] Similarly, a variety of bio-based ethers such as 2-methyltetrahydrofuran (Me-THF),[170] dimethyl tetrahydrofuran (diMeTHF), cyclopentyl methyl ether (CPME), dimethylsorbide and dihydrolevoglucosenon (cyrene)[171,172] are excellent media for biocatalysis (Scheme 12).[173]

6.2. Water as a Reaction Medium

The best solvent is no solvent but if a solvent (diluent) is really necessary it should preferably be water.[174] Water has much to offer: it is non-toxic, non-inflammable, abundantly available and inexpensive. However, if water is the reaction medium, the remaining water after separation of product and catalyst, is contaminated with trace amounts of organics and will require some form of treatment before being discharged to effluent treatment facilities. This problem is further aggravated if organic solvents are used to extract the product from the reaction mixture.[175] Furthermore, water has the highest heat capacity of all liquids which is a serious disadvantage for chemical processes.
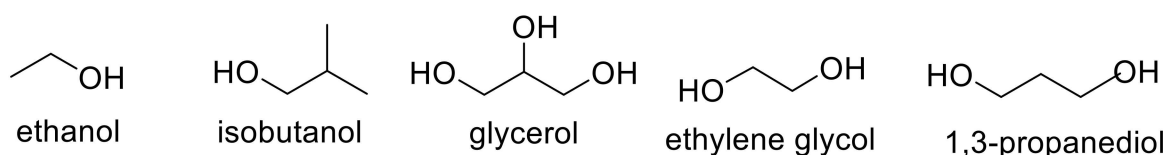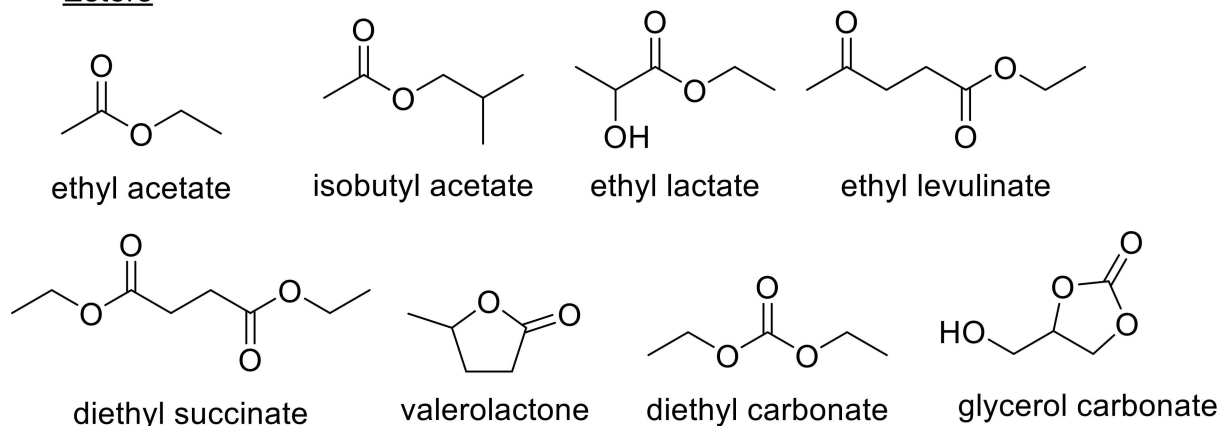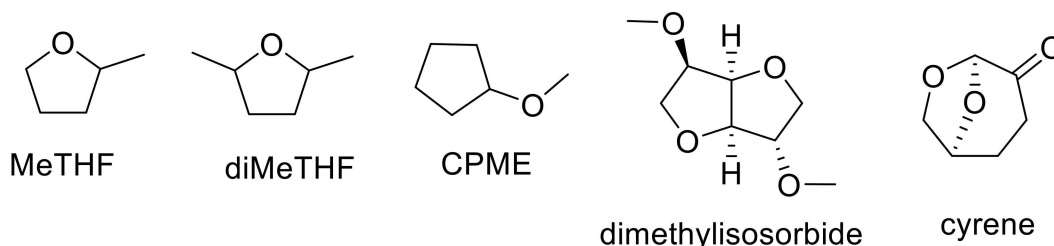
Notwithstanding these issues, there is a clear trend towards the use of water as a reaction medium, sometimes with remarkable results. For example, a dramatically improved five-step synthesis of an API, with the same overall purity of ca. 99.8%, was obtained by Bailey and co-workers[176] at Takeda Pharmaceutical, by conducting it almost entirely in water. In both cases the API was obtained in an overall purity of

6.3. Aqueous Biphasic Catalysis

Catalytic reactions can be performed in water by employing water soluble catalysts. When the substrate is immiscible with water the reactions are performed as aqueous biphasic catalysis. and the product is recovered by phase separation The substrate should be at least slightly soluble in water as the reaction takes place in the aqueous phase. The catalyst-containng aqueous phase remains in the reactor and is recycled. Catalytic processes in general, including enzymatic processes, can be performed under aqueous biphasic conditions. The most well-known example is the Ruhr-Chemie/Rhone-Poulenc process for propylene hydroformylation emploing a water-soluble Rh(I) complex as the catalyst (Scheme 13a).[177] The process is used to produce 600,000 tonnes per annum of butanal and rhodium losses amount to 1 kg in 10^9 kgs of product. Similarly, Pd-catalyzed aqueous biphasic carbonylation of 1-(4-isobutylphenyl)ethanol afforded the non-steroidal anti-inflammatory drug, ibuprofen (Scheme 13b).[178] Other prominent examples of aqueous biphasic catalysis include hydrogenation, olefin metathesis and aerobic alcohol oxidations.[179–181]

6.4. Aqueous Micelles as Nanoreactors

The rates of aqueous biphasic catalysis decrease dramatically with increasing molecular weight, i.e. decreasing solubility of the substrate in water. Attempts to use phosphine ligands that combine the functions of a ligand and an amphiphile (surfactant) to generate micelles, in which the substrate is

Alcohols

ethanol
isobutanol
glycerol
ethylene glycol
1,3-propanediol

Esters

ethyl acetate
isobutyl acetate
ethyl lactate
ethyl levulinate

diethyl succinate
valerolactone
diethyl carbonate
glycerol carbonate

Ethers

MeTHF
diMeTHF
CPME
dimethylisosorbide
cyrene

Scheme 12. Bio-based solvents.

solubilized, were not successful.[36] Lipshutz and co-workers[182] followed a different approach that took the concept to a new level of sophistication and was more successful. They used small amounts (e.g. 2 wt%) of designer amphiphiles that spontaneously self-assemble in water above their critical micelle concentration (ca. 10^{-4} M), to form nanomicelles with lipophilic interiors in which reactions can occur between water-insoluble substrates and catalysts. The choice of amphiphile is critical as it determines the size, shape and internal lipophilicity of the nano-micellar reactors.

Amphiphiles, PTS and TPGS-750-M derived from vitamin E (see Scheme 14 for stuctures), (Editor please note that Scheme 14 contains mistakes and needs to be replaced) were used to perform a variety of noble metal catalyzed reactions,[183–186] such as hydrogenation[187] and palladium catalyzed C–C coupling reactions[188] at room temperature in organic solvent free water. The product was recovered by extraction with a minimum amount of an environmentally acceptable solvent, such as ethyl acetate. Traces of amphiphiles remaining in the aqueous effluent also need to be borne in mind.[189].More

recently, the same group showed that Pd nanoparticles in nanomicelles can be used to catalyze C–N coupling reactions at very low levels of Pd.[190]

Water is also an excellent solvent for enzymatic reactions and products can be extracted into an environmentally acceptable solvent, such as ethyl acetate, or the reaction can be conducted as aqueous biphasic catalysis. Codexis, for example, developed cost-effective biocatalytic processes for various pharmaceutical intermediates using highly engineered enzymes in this way.[191] Enzymes, e.g. ketoreductases (KREDs), were fully compatible with aqueous suspensions of micelles derived from TPGS-750-M[192] which enabled the highly enantioselective one-pot production of chiral secondary alcohols by combining metal catalyzed synthesis of the prochiral ketone substrate followed by enantioselective KRED catalyzed reduction (Scheme 15). Moreover, the activity of the KRED was 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
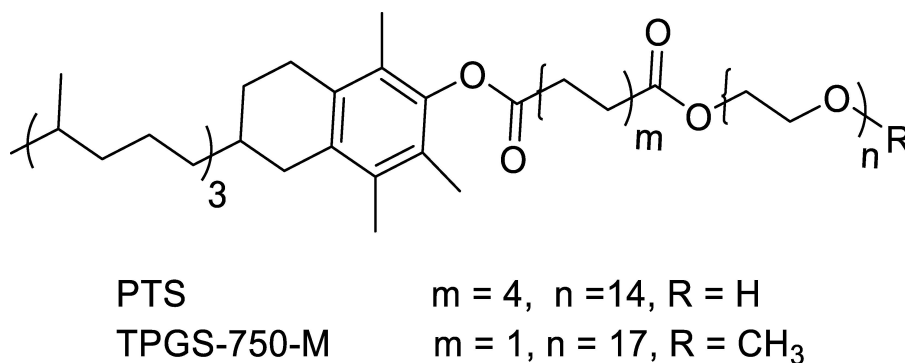
a. Ruhr-Chemie / Rhone-Poulenc process for propylene hydroformylation

94%   6%

Rh losses 1 kg in 10^9 kgs product
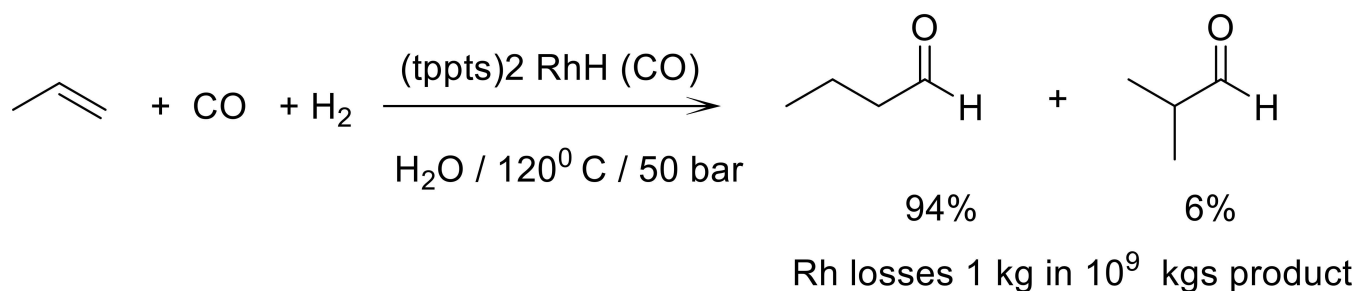
b. Aqueous biphasic carbonylation

Ibuprofen
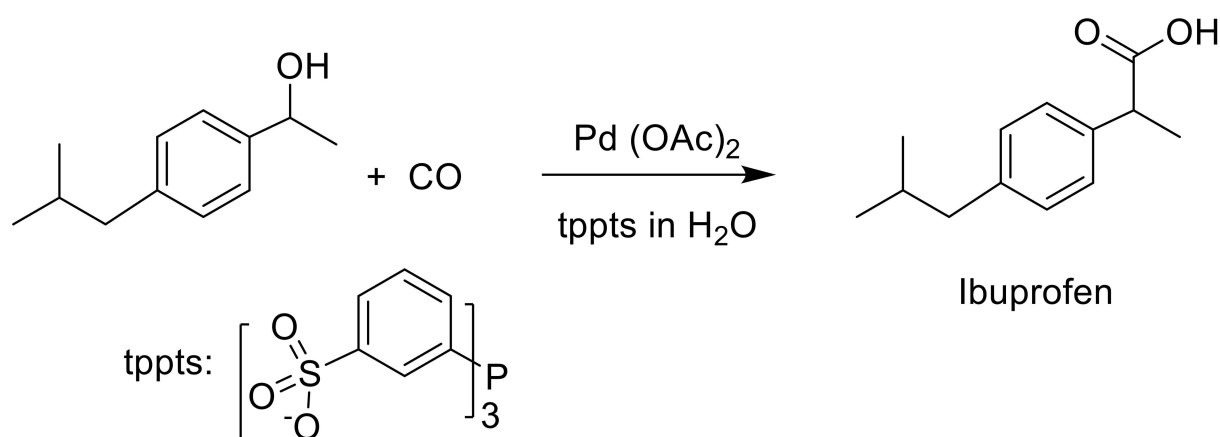
Scheme 13. Aqueous biphasic hydroformylation and carbonylation.

PTS   m = 4, n =14, R = H
TPGS-750-M   m = 1, n = 17, R = CH$_3$

Scheme 14. Structures of Amphiphiles.

to the active site of the enzyme, thereby limiting substrate and product inhibition.

6.5. Enzymatic Acylations in Aqua

There is considerable interest in the hydrolase-catalyzed synthesis of carboxylic esters and amides in water.[193] What is sometmes referred to as reverse hydrolysis in water has been used for more than two decades in the industrial synthesis of semi-synthetic ß-lactam antibiotics catalyzed by penicillin G amidase[194] So-called acyl transferases, in particular that from *Mycobacterium smegmatis* (MsAcT) similarly catalyze the kinetically controlled formation of esters and amides in water.[195] Based on its hydrophobic active site and protein scaffold, MsAcT exhibits a higher affinity for alcohols, amines, and hydrogen peroxide than water and, hence, displays a high synthetic activity in water. It catalyzes, for example, the formation of a variety of esters,[196,197] including flavor esters[198] and the acylation of primary amines in water (Scheme 16).[199]

More recent developments include expansion of the scope to include the synthesis of sugar esters in water,[200] obviously

2
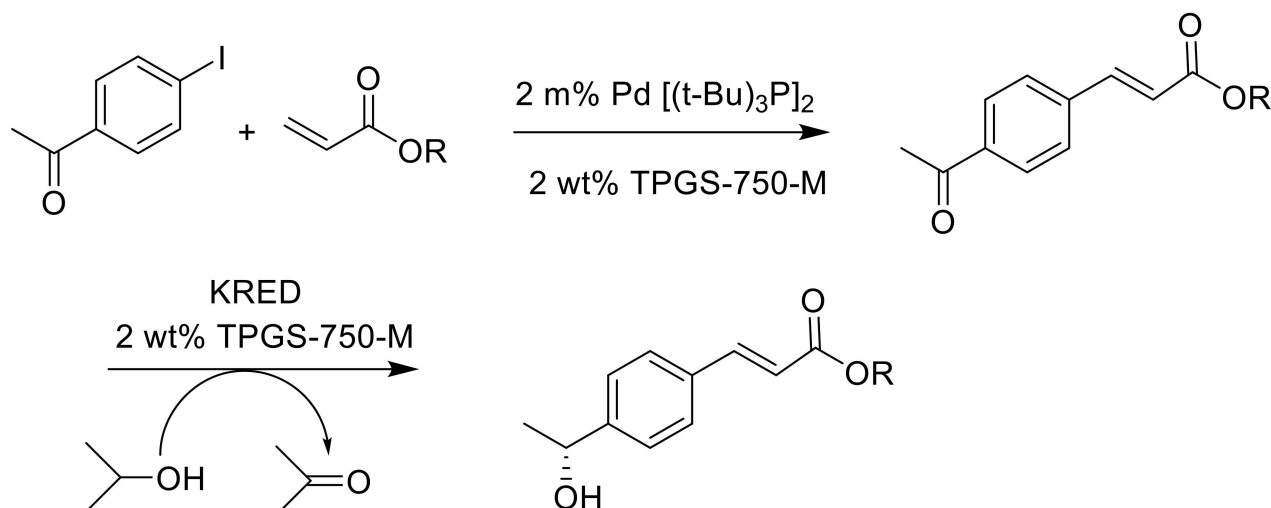
Scheme 15. Chemo-enzymatic synthesis of a chiral alcohol in aqua.

R = H; CH$_3$CH$_2$; CH$_3$CH$_2$CH$_2$;
(CH$_3$)$_2$CH; (CH$_3$)$_2$CHCH$_2$

R^1 = CH$_3$(CH$_2$)$_4$; (CH$_3$)$_2$CHCH$_2$; C$_6$H$_5$; C$_6$H$_5$CH$_2$; C$_6$H$_5$CH=CHCH$_2$

R^2 = H, CH$_3$; CH$_3$CH$_2$; CH$_3$CH$_2$CH$_2$
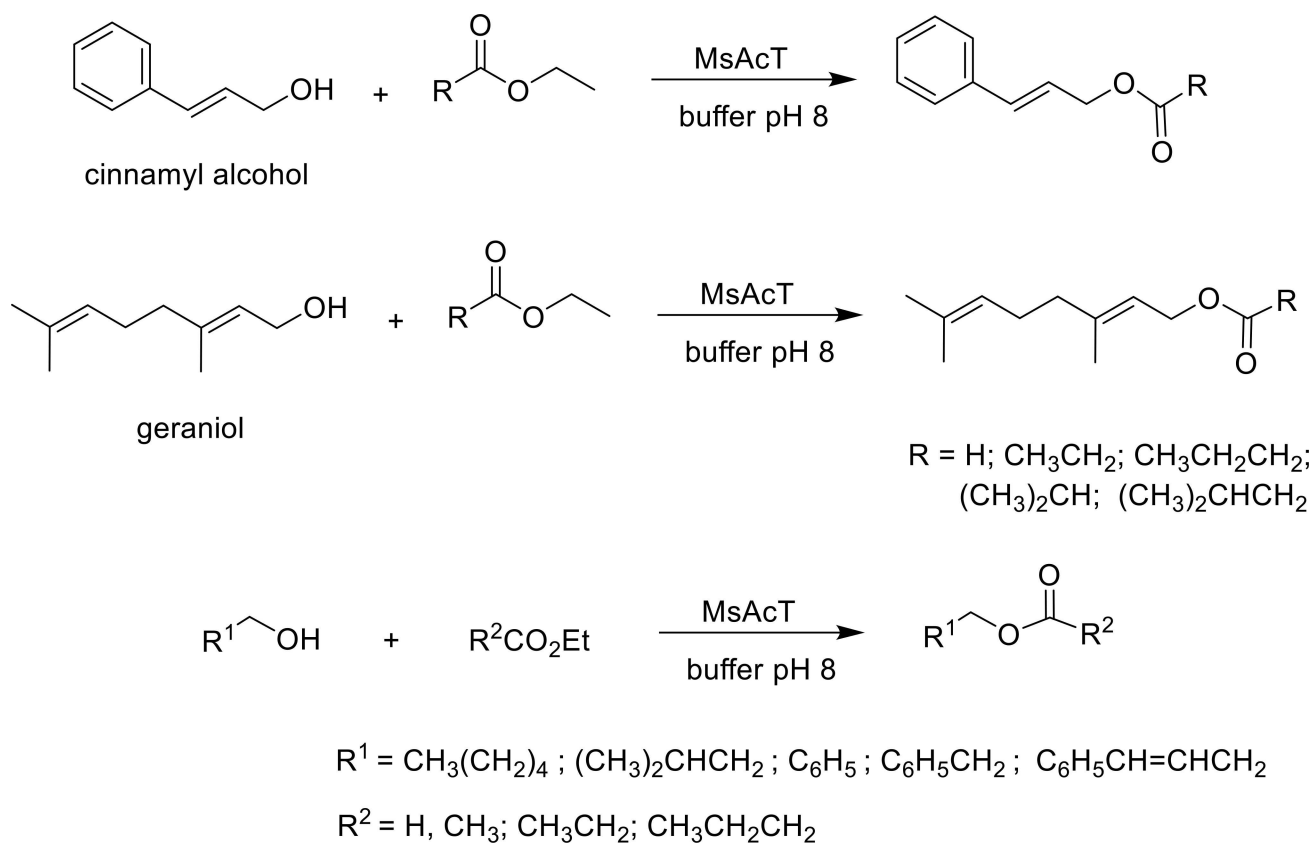
Scheme 16. MsAcT-catalyzed acylations in water.

of particular interest in the context of a move towards renewable carbohydrates as base chemicals. MsAcT variants exhibiting higher acyl transfer-to-hydrolysis ratios and broader scope were produced using protein engineering.[201] MsAcT was also used in the synthesis of polyesters.[202] Furthermore, MsAcT immobilized on polypropylene beads was used to catalyze flavor este synthesis in continuous flow and it has even been suggested that MsAcT is the big new player in biocatalysis.[203]

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6.6. Biocatalysis in Ionic Liquids and Deep Eutectic Solvents

Although many currently available bio-based solvents are useful for conducting biocatalysis in aqueous biphasic systems, if the enzymes are used as suspensions in organic solvents catalytic activities are generally two or more orders of magnitude lower than those observed with the enzymes dissolved in water. Fortunately, the activities of enzymes in organic media can be dramatically increased by the addition of large amounts of insoluble inorganic salts. This observation led, at the turn of the century, to the successful idea to use suspensions of enzymes in hydrophobic ionic liquids that had been pre-dried over P_2O_5.[204]
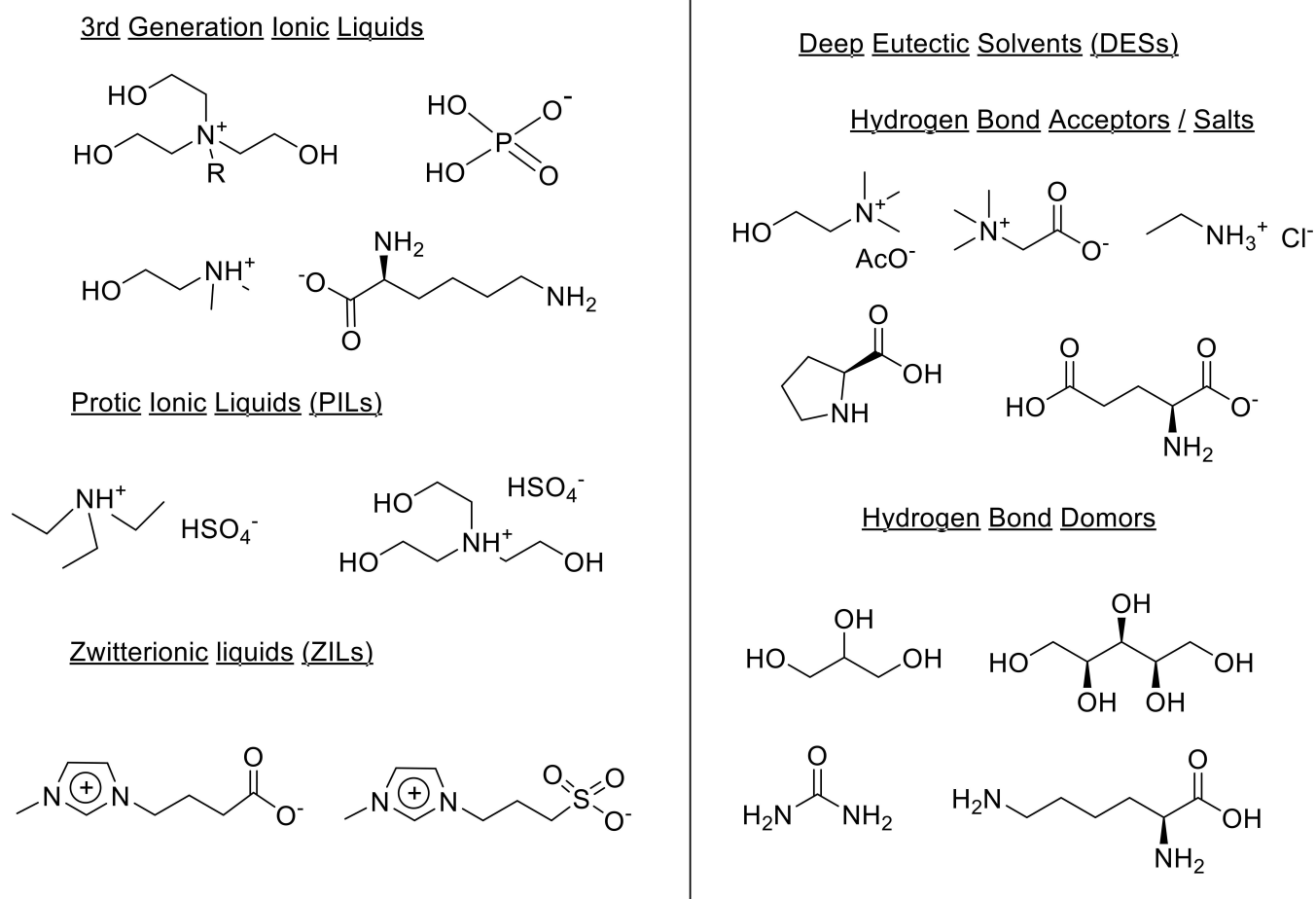
Unfortunately, the hydrophobic ILs used for proof-of-principle consisted of quaternary ammonium cations and expensive and environmentally unacceptable perfluorinated anions.

Since an important motivation for using ILs was to replace volatile organic solvents, product extraction with an organic solvent would, a priori, not appear to be an attractive option. However, certain bio-renewable solvents, such as 2-methylTHF, could constitute an acceptable improvement. Alternatively supercritical carbon dioxide, $scCO_2$, can be used to extract the product. ILs and $scCO_2$ form biphasic systems in which $scCO_2$ is highly soluble in the IL but the IL essentially insoluble in the $scCO_2$ phase.[205]

Nevertheless, the ILs also needed to be optimized in order to achieve cost-effective, environmentally acceptable processes. Second and third generation ILs contained environmentally acceptable anions that are compatible with enzymes but to be cost-effective they really need to be protic ionic liquids (PILs) derived from neutralization of a tertiary amine with an inexpensive acid (see Scheme 17 for examples). Biocompatible ILs and PILs and zwitterionic liquids (ZILs) and the related deep eutectic solvents (DESs) were developed (see Scheme 17 for structures) for performing mono- or biphasic catalysis with enzymes.[206–208]

Many of the envisaged applications of ILs (and DESs) in defossilized chemicals manufacture could be in the production of platform chemicals and biofuels by deconstruction and valorization of polysaccharides and triglycerides in waste biomass. This will probably involve, for commmercial viability, the use of immobilized enzymes in continuous flow operation.[209,210]

Scheme 17. Structures of ionic liquids and deep eutectic solvents.

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7. Conclusions and Prospects

The electrification and defossilization of chemicals production based on sustainable electricity, driven by solar, wind, nuclear or hydroelectric energy, and waste biomass or CO_2 as the source of carbon, constitutes a veritable sea change that paves the way to carbon neutrality. Waste, in the form of CO_2 emissions, waste biomass from agricultural and forestry residues and food supply chain waste, will be a resource for chemicals production in a bio-based economy.

The major base chemicals will be syn gas, from reduction of waste CO_2 with green hydrogen and hexoses, pentoses and lignin produced from lignocellulose. This is a vastly different scenario to base chemicals from oil refining that consist of lower olefins and aromatics i.e. a switch from hydrocarbons to oxygenates as the primary products.

Ninety percent of the downstream products of the petrochemical industry are polymers and the majority of these are polyolefin plastics, mainly polyethylene and polypropylene. These just happen to be the main cause of the disastrous effects of plastic pollution on the natural environment. In the circular bio-economy, in contrast, it is more logical to produce bio-based plastics from oxygenates. This process would be accelerated by application of the principle of extended producer responsibility (EPR) to polymer production and waste remediation.

In the new world of the bio-based economy there will be a renaissance of carbohydrate chemistry involving chemocatalytic and biocatalytic processes with whole cells and immobilized cell-free enzymes. Reactions will be performed in aqueous biphasic media with bio-based solvents or in water containing designer amphiphiles that spontaneously form micellar nanoreactors. In this context, it is worth noting that Nature has been solubilizing water-insoluble compounds in water, *in vivo, for billions of years* by placing them in vesicles such as liposomes. The use of designer surfactants in micellar arrays constitutes an *in vitro* version of this.

The use of both electrocatalysis and photocatalysis in e-biorefineries will flourish based on the electrification of power generation and the availability of inexpensive solar energy and improved catalytic methods for its utilization.

The widespread use of enzyme immobilization coupled with continuous processing will also play an important enabling role in the design of sustainable biocatalytic processes in genera[211,212] and particularly in multi-enzyme and chemo-enzymatic cascade processes.[89]

In short, the extensive decarbonization of energy and defossilization of chemical feedstocks will underpin a sustainable, carbon neutral chemical industry based on waste valorization. In this respect, we acknowledge the prophetic words of the iconic German organic chemist, A. W. von Hofmann, who already noted in 1884, in the early days of the fledgeling chemical Industry that:

"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."

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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PERSPECTIVE
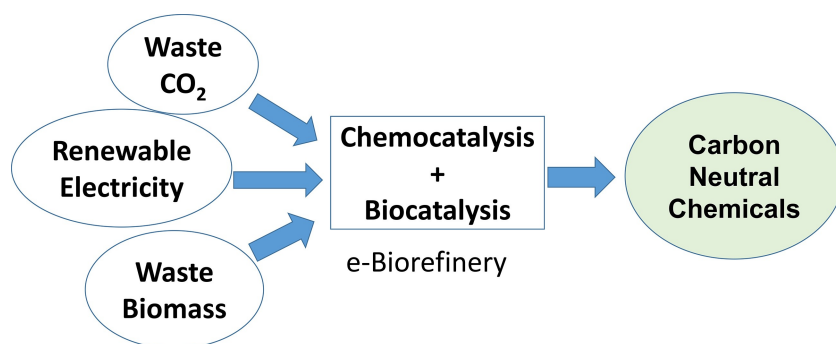
e-Biorefinery

Important developments, over the last five decades, towards realization of sustainable chemicals manufacture, are discussed. They include the use of waste biomass and CO_2 as a raw material, renewable electricity as the energy source and chemo- and biocatalysis, with whole cells or cell-free enzymes, including the use of electro(bio)catalysis and photo(bio)catalysis, as the facilitators.