Review

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Review

Enzyme Catalysis for Sustainable Value Creation Using Renewable Biobased Resources

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Abstract: Enzyme catalysis has traditionally been used by various human cultures for creating value, long before its basic concepts have been uncovered, by preparing useful products through the transformation of raw materials available from natural resources. Tremendous scientific and technological progress has been accumulated globally in understanding what constitutes an enzyme, what reactions enzymes can catalyze, and how to search, develop, apply and improve enzymes to make desired products. The exquisite properties of enzymes as nature's preferred catalysts, such as high selectivity, diversity and adaptability, enable their optimal work, whether in single reactions or in multiple reactions. Excellent opportunities for resource efficient manufacturing of compounds needed are provided by the actions of enzymes working in reaction cascades and pathways within the same reaction space, like molecular robots along a production line. Enzyme catalysis plays an increasing role for industrial innovation and responsible production in various areas, such as green and sustainable chemistry, industrial or white biotechnology. Sources of inspiration can be current manufacturing or supply chain challenges, the treasure of natural enzymes or the opportunities of engineering tailor-made enzymes. Making best use of the power of enzyme catalysis is essential for changing the way how current products are manufactured, how renewable biobased resources can replace fossil-based resources, and how the safety, health environment aspects of manufacturing processes can be improved towards cleaner and more sustainable production.

Keywords: biomanufacturing; biocatalysis; enzymes; industrial biotechnology; sustainable chemistry; white biotechnology; green chemistry

1. Introduction

Fermentation has been traditionally used for creating value by transforming raw materials available from natural resources to useful products, such as fermented food and beverages, in numerous human cultures, as demonstrated for example by the isolation and characterization of live yeast cultures in ancient vessels [1]. Bio-archeology tools enable to shine light on these important human activities making use of enzyme catalysis towards value creation, for example processing milk to valuable non-perishable milk products like cheese which are easier to transport [2], or winemaking after the cultivation of grapes [3], long before the basics of science, the concepts of enzymes, molecules, and money were developed. The word ferment has been coined by Wilhelm Kühne [4] and was in use by German workers. The replacement of the old word ferment by the word enzyme, which was used by English workers [5], has been discussed also in terms of widening its meaning towards all catalytic reactions occurring in biological cells. The experimental demonstration by Eduard Buchner in 1897 that whole yeast cells are not needed and a cell-free extract prepared from yeast cells is sufficient for converting D-glucose to ethanol [6] has been a breakthrough discovery, for which Eduard Buchner received in 1907 the Nobel Prize in Chemistry as sole recipient. One hundred years later Eduard Buchner has been considered the father of experimental molecular bioscience [7] due to the tremendous influence of his pioneering experiments in cell-free biocatalysis, which have been key for further advances in enzyme catalysis. The first purification and crystallization of urease

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in 1926 by James B. Sumner [8], and the subsequent purification and crystallization of pepsin by John H. Northrop [9] have been further milestones recognized by Nobel Prizes in Chemistry and demonstrated enzymes to be proteins. These key discoveries inspired the purification and crystallization of a large and increasing number of enzymes, which have been classified by the four digit EC number given by the Enzyme Commission (EC) [10]. This enzyme classification systems is unique among the classifications of catalysts and enables a modular expansion as novel enzyme classes are being discovered.

The importance of enzymes to the living organisms of the biosphere as nature's privileged catalysts and the long history of successful applications of enzyme-catalyzed processes have widely increased the interest in the science and technology of enzyme catalysis. The fast growth of structural, functional, mechanistic and application knowledge about enzymes, the tools and technologies available today and the universe of natural, engineered and *de novo* enzymes have moved enzyme catalysis to a key technology for sustainable value creation in a variety of analytical, synthetic, diagnostic and therapeutic applications. Enzyme catalysis has been of major importance for advancing biochemical analysis, both in measurements of enzyme activities as well as for the determination of analytes by the use of enzymes in analytical and diagnostic applications [11]. The fast and precise analysis of nucleic acids has been revolutionized by amplifying DNA *in vitro* with a thermostable DNA polymerase in the Polymerase Chain Reaction (PCR) technology, for which Kary Mullis received the Nobel Prize [12]. The inherent chirality and excellent selectivity of enzymes make them also attractive catalysts for preparative applications in organic chemistry [13], asymmetric synthesis [14], green and sustainable chemistry [15,16] and industrial biotransformations [17,18]. The excellent properties of enzymes are also of much interest for preparative applications in industrial and white biotechnology [19,20]. The development of directed evolution of enzymes, for which the 2018 Nobel Prize in Chemistry has been awarded to Frances Arnold [21], enabled the engineering and optimization of the properties of enzymes to fit the needs for enantioselectivity, or for certain reaction and process conditions, such as pH, temperature, or substrate [22–24]. Enzyme technologies are essential for innovation in various industrial sectors [25–27] and manufacturing environments [28]. A variety of benefits, such as higher resource efficiency and selectivity, shorter routes, improved safety, health, environment and sustainability aspects, can result from the inclusion of enzyme technologies in novel production processes and from the creation of novel value chains starting from renewable resources. In addition to the pharmaceuticals developed and manufactured by the use of enzymes [29], the development and direct application of therapeutic enzymes has provided tremendous benefits [30].

The aim of this work is to outline advantageous features of enzyme catalysis which are important not only for creating economic value by research, development and innovation towards products, but also towards resource-efficient and sustainable production processes. The consideration of the type of raw materials, the manufacturing route, the process characteristics and its E-factor, which designates the ratio of waste generated to product [31], are highly significant for implementing the UN Sustainable Development Goals.

2. UN Sustainable Development Goals and Sustainable Value Creation at Micro- and Macro-Levels within the Earth System Boundaries

The impact of the activities of a growing human population on various parameters of the earth system has been increasing since the beginning of the industrial revolution. The impact of human activities on the global environment is no longer negligible, compared with the impact of natural systems, as in previous periods of history, on the contrary, various indicators of anthropogenic influence have changed to such an extent that they have reached the level of natural influence on a global scale. It has even be estimated that we stand at a turning point where the global mass made by humans exceeds the biomass of all biological organisms living on planet earth [32]. These combined anthropogenic effects at planetary scale have inspired the proposal to introduce an define the widely discussed term Anthropocene for a new geological epoch different from the Holocene [33–36]. A proposal to recognize formally the Anthropocene as an epoch within the Geological Time Scale

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has been brought forward by the Anthropocene Working Group [37]. A date in the mid-20th century has been proposed for the onset of the Anthropocene at 12 different sites on five continents [37].

A system approach which analyzed the types of boundaries and their status with respect to a safe space for life on planet earth [38,39] has attracted much interest. The need for urgent action is evident from finding some planetary boundaries at high risk of being passed beyond the safe limits, such as the biodiversity loss, and the biochemical flows of nitrogen and phosphorus [38,39]. While the knowledge of the boundaries and a safe space for life is also of fundamental interest for searching a habitable space and living organisms outside planet earth, among the thousands of exoplanets discovered in the universe [40,41], the resolution on the 2030 Agenda for Sustainable Development and the associated UN Sustainable Development Goals (SDGs) adopted by the United Nations General Assembly on 25 September 2015 [42] address life and development on planet earth. Over the course of the years from the launch in 2015 until now the 2030 Agenda for Sustainable Development has already reached its midterm, but progress towards many SDGs requires acceleration, course correction and a sense of urgency according to the Global Sustainable Development Report 2023 [43].

Demands are increasing for energy, materials and products satisfying the needs of a growing human population, while the amount of waste accumulated along its production chain and from its consumption is also becoming larger. It is however not only the amount but also the type and chemical composition of the waste which requires attention for balancing global cycles. With the increasing amount and diversity of materials and products, there will also be a parallel increase of the interactions, not only of the products and materials but also of the related waste, with the biosphere. Therefore the minimization of adverse impacts caused by chemicals and waste requires urgent actions, as the size of the global chemical industry in 2017 was already greater than 5 trillion US dollars. This has been expected to double by 2023 due to emerging economies, as outlined in the Global Chemicals Outlook II, which was launched 2019 in Geneva before the reality of the various crises such as the COVID-19 pandemy [44].

Multiple crises at micro- and macro-levels are however nothing new and have been accompanying human history at numerous locations on planet earth. Multiple crises which have reached global dimensions and are interconnected have been outlined as megathreats which need to be addressed and require action [45]. The various sorts of actions needed for a habitable planet and providing transitional paths towards overcoming the multiple crises can be guided by the planetary boundaries [38,39]. Resource efficiency, recycling, re-utilization and damage repair, which are hallmarks of living biological organisms, can also provide inspirations for the use of enzymes in creating sustainable value. Empowering human ingenuity and investing into scientific research and innovation can lead to future breakthroughs, more responsible production, more sustainable value chains and new economies.

The raw material resources on planet earth today are large but not unlimited, with the amount and distribution of elements varying substantially from very rare to highly abundant elements. Recycling and re-utilization of elements is therefore not only of interest for very rare elements but also for the abundant elements and their global cycles. In the case of carbon, carbon-based resources can consist of fossil resources formed over long geological times such as coal, gas and oil, biobased resources which are formed on the much shorter timescale of biological organisms such as microbes, algae, and plants, and carbon waste and greenhouse gas emissions produced by anthropogenic activities or by natural biodegradation processes. As carbon is a central element not only for life on earth but also for all kinds of products needed by mankind, decarbonization on a planetary scale is not possible and recycling and re-utilization of the greenhouse gas emissions and carbon waste is needed for closing the carbon cycle [46].

The utilization of the available materials and energy resources in biotransformations of biological organisms, their interactions and metabolic processes, represent key functions of the global ecosystems on planet earth. More than two decades after the publication of the estimated value of the ecosystem services on our planet [47] it has been suggested that these substantial contributions should be at the core of a new economic paradigm in the Anthropocene [48].

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The microbial world thereby plays not only important roles in creating value at micro-levels for higher organisms like plants, animals and humans, but also at macro-levels for driving biogeochemical cycles [49]. At the core of the value creating transformations are enzyme-catalyzed reactions, which constitute the architecture of metabolic processes. It is therefore of much interest to understand their characteristics, evolution, involvement and roles in global and local cycles of chemical elements, (see Figure 1), such as the carbon, oxygen, phosphorus, nitrogen and sulfur cycles [50–54]. The roles of other chemical elements of the periodic system which are present in the environment are also important, from the molecular level of enzyme-catalyzed reactions and the cellular level of living organisms to their interactions in ecosystems and evolution [55]. Beside the key non-metal elements which are occurring at high levels in all living organisms, other non-metal chemical elements such as the halogens, silicon and boron and metal chemical elements such as calcium, potassium, sodium, magnesium, zinc and transition metals are present at lower levels [56,57]. As these and other elements crucial to life need to be efficiently captured, utili-zed and stored, but also released and re-utilized again when needed, the molecular and engineering principles of the underlying biotransformations, as part of biosynthesis and biodegradation pathways utilized by nature, can serve as highly valuable blueprints from nature for building a sustainable bioeconomy. Inspirations can be provided for new value creation architectures, for developing safe and sustainable processes from the beginning, changing linear to circular process design, and for transitioning towards renewable biobased resources [58]. The choice of biobased raw materials, which can originate from one of the traditional carbon-dioxide utilization pathways or from novel enzymatic pathways for the utilization of carbon dioxide waste coming from bur-ning fossil resources, can contribute to negative carbon dioxide emission.

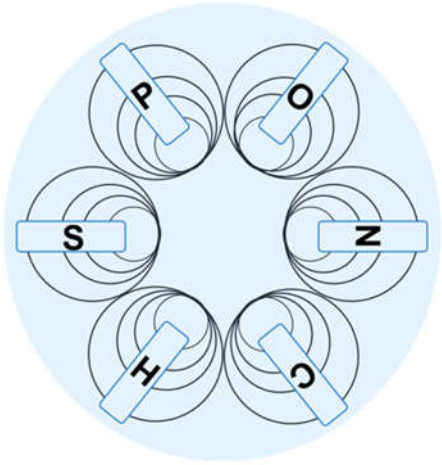

Figure 1. Cycles of key chemical elements occurring at high levels in all living organisms.

3. Enzyme Catalysis for Sustainable Value Creation Using Renewable Biobased Resources

The power and selectivity of enzyme catalysis is not only key to resource-efficient biological processes in healthy living organisms on planet earth, but has also been a driving force and incentive in different areas of synthesis and degradation for developing better processes which are not only providing economic advantages but also benefits to health, safety and environment [13–20,59]. In the synthetic direction enzyme catalysis can, both in nature as well as in research, development and innovation, contribute and create sustainable value towards a variety of goals and concepts of synthesis, as illustrated in figure 2 [60], such as target-oriented synthesis [13,59], linear synthesis [61], convergent synthesis [62], diversity-oriented synthesis [63] and starting material-oriented synthesis [64].

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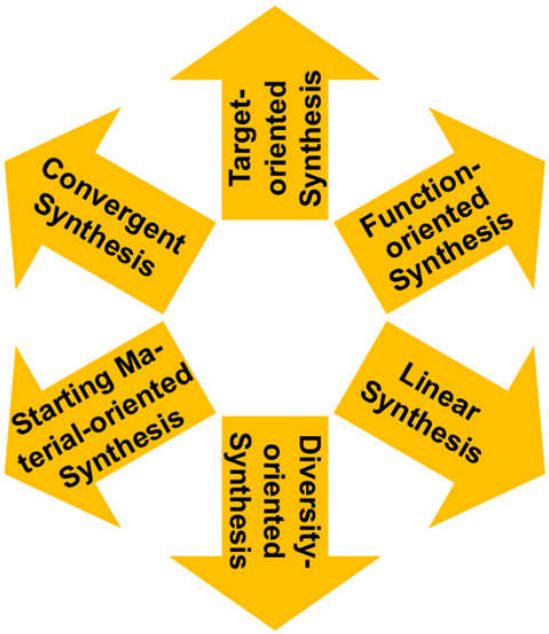

Figure 2. Different concepts of synthesis to which enzyme catalysis can contribute.

The use of enzyme catalysis in target-oriented synthesis can be guided by comprehensive retrosynthetic analysis and considerations, selecting an adequate synthetic strategy with an optimal sequence of reaction steps and by developing suitable chemo-, regio- and stereoselective enzymes which catalyze the formation of covalent bonds in easily available starting materials for synthesizing the desired target molecules of higher value [65–68]. Synthetic routes can be shortened by the use of enzyme-catalyzed reaction steps as the installation and removal of directing or protecting groups can be avoided, and the number of reaction steps can be decreased [69]. Further advantages can be explored by coupling two and more enzyme-catalyzed reactions without isolation and purification of the intermediates [70].

Enzyme catalysis can also be valuable in diversity-oriented synthesis for building complexity from simple starting materials and for expanding the chemical space with a range of diverse molecular structures in the generation of new leads in drug discovery [71]. Analogues, derivatives and libraries of natural products can be obtained by enzymatic diversification of natural products, involving combinatorial biosynthesis, precursor-directed biosynthesis, mutasynthesis and metabolic pathway engineering strategies, for example in natural product glycodiversification [72]. The diversity-oriented biosynthesis of numerous new rapamycin-like polyketide molecules has been achieved in a single experiment by accelerated evolution and rapid recombination with high frequency of polyketide synthase gene clusters [73]. Diverse cyclopropane-containing building blocks have been synthesized by a chemoenzymatic approach, whereby an enzymatic carbene transfer reaction catalyzed by an engineered nitric oxide dioxygenase was followed by a subsequent Suzuki-Miyaura cross-coupling with diverse coupling partners [74].

The concept of a starting material-oriented synthesis is of much interest when a specific starting material is inexpensive, regionally and reliably available in large amounts, and for transitioning starting materials originating from the extraction of non-renewable resources to the continuous and sustainable supply from resources to close the cycle of key chemical elements. In the case of closing the carbon cycle [46] this can involve, as shown in figure 3, various types of starting materials, such as a) waste causing serious consequences to environment and health such as plastic and carbon dioxide, b) a specific side product obtained together with the main product in industrial manufacturing, or c) a starting material originating from renewable biobased resources [64]. The attention to all the starting materials mentioned above and the tremendous capabilities and the power of enzyme catalysis are contributing to solve the challenges of closing the carbon cycle.

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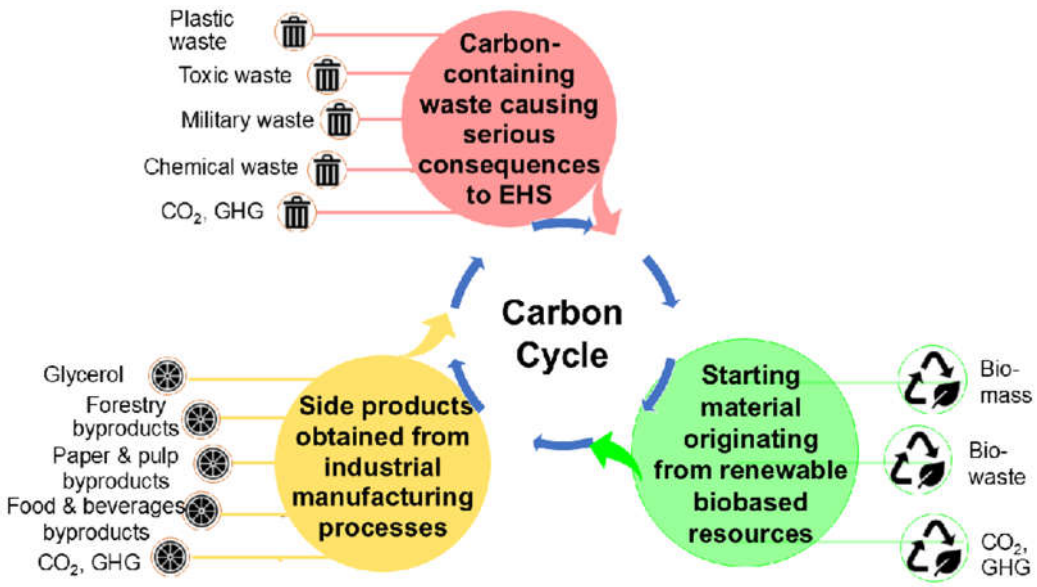

Figure 3. Starting material-oriented synthesis towards closing the carbon cycle.

Enzyme catalysis has been essential in the history of the carbon dioxide content of our planetary atmosphere and ribulose-1,5-bisphosphate carboxylase/oxygenase (RubisCO) has evolved to a key enzyme in the global carbon cycle, catalyzing not only the conversion of inorganic carbon into biomass but also providing oxygen needed for aerobic life [75]. Improved or novel RubisCO-enzymes and other natural or engineered enzymes are therefore attractive for catalyzing *in vivo* the conversion of carbon dioxide to biomass or to different biochemical building blocks using the THETA cycle [76]. Exploring completely novel synthetic enzyme systems is of major interest for carbon recycling [77] and catalyzing *in vitro* the conversion of carbon dioxide to valuable biochemical products, such as glycolate [78], the carboxylation of glycolate to (*R*)-glycerate [79] the use of the CETCH cycle to malate [80] or 6-deoxyerythronolide B [81], and the chemoenzymatic conversion of carbon dioxide and hydrogen to starch [82].

The discovery of synthetic polymers more than a century ago has lead to an ever increasing consumption and production at large scale of high performance materials and their accumulation as waste, which requires that the many challenges are addressed and overcome by new approaches and bold changes, for closing the carbon cycle and for avoiding to undermine UN Sustainable Development Goals [83]. One challenge to which enzyme catalysis can contribute is the use of synthetic polymer waste as starting material, which requires however the type-specific polymer collection to make them suitable as starting materials. The power of enzyme catalysis provides great opportunities to develop suitable bioprocesses using novel enzymes for catalyzing the depolymerization into the corresponding building blocks, thus contributing to a change in perception, from waste to suitable starting materials, of the corresponding synthetic polymers [84]. A highly efficient depolymerization of poly(ethylene terephthalate) (PET) into its monomers has been developed using an engineered PET hydrolase at 3 mg enzyme per gram PET, whereby a space-time yield of 16.7 g L^{-1} h^{-1} has been achieved for terephthalate [85]. It is of much interest to expand this success with using PET as starting material to other synthetic polymers such as polyamides and polyurethanes by searching and engineering suitable depolymerizing enzymes, such as nylonases [86] and urethanases [87] for catalyzing the depolymerization of nylon PA6 and polyurethan, respectively.

Another material stream for closing the carbon cycle can come from utilizing as starting materials instead of the waste disposal of specific side products obtained together with the main product in industrial manufacturing. The large surplus of the annual glycerol production, which results from the difference between the much larger amount of glycerol generated as a byproduct in biofuel manufacturing and the demand of glycerol, makes glycerol an attractive starting material for

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its sustainable conversion using enzyme catalysis to various value-added products, such as acrolein, 1,3-dihydroxyacetone, 1,3-propanediol, propionic acid, 3-hydroxypropionic acid, D- and L-lactic acid, mono-, di- and triacylglycerols, L-serine, L-tyrosine [88–90]. The key advantage of the inherent stereoselectivity of enzyme catalysis enables the enantioselective desymmetrization of glycerol and the synthesis of enantiomerically pure compounds. (*R*)-*α*-monobenzoate glycerol has been obtained in 99% enantiomeric excess by enantioselective glycerol esterification with benzoic acid in 1,4-dioxane using lipase B from *Candida antarctica*, immobilized on silica [91]. The high enantioselectivity of a glycerol dehydrogenase from *Gluconobacter oxydans* was used in the reductive direction for synthesizing L-glyceraldehyde [92,93]. From screening acetic acid bacteria for microbial glycerol oxidation to D-glycerate an *Acetobacter tropicalis* strain was identified which produced 101.8 g L^{-1} D-glycerate in 99% enantiomeric excess [94], while glycerol oxidation catalyzed by an evolved alditol oxidase yielded 30 g L^{-1} D-glycerate [95]. Enantioselective glycerol desymmetrization by phosphorylation has already been demonstrated long ago by the preparation of L-glycerol-3-phosphate using glycerol kinase, ATP and enzymatic regeneration of ATP [96].

Enzyme catalysis is not only highly valuable for improving the manufacturing processes by using isolated enzymes, cell-free systems or whole cells for catalyzing the transformation of raw materials to products but also for the preceding manufacturing processes of the starting materials from renewable biobased resources, which are strategically preferred carbon sources towards circular processes with net zero carbon emission [58,97–99]. Considering synthetic routes to products from the biogenic carbon origin of starting materials can not only inspire the design of completely novel products with desired properties but can also address climate, health, safety and environment issues and support the complex transition from fossil-based raw materials used in numerous industries to starting materials originating from renewable biobased resources. Manufacturing processes using enzyme catalysis in microbial cell factories and biobased starting materials have long ago been attractive for the chemical industry. The early application of a regioselective microbial D-sorbitol oxidation at C5 to L-sorbose in the sequence of reactions for the synthesis of L-ascorbic acid from readily available biobased starting material enabled the demonstration of its identity with natural vitamin C [100,101]. This has been a key reaction for vitamin C production for decades [102]. The benefits of using biobased starting materials and the application of more and more enzymatic reaction steps in vitamin production [103] have been clearly demonstrated. The milestone of vitamin B_{12} production from D-glucose using recombinant strains expressing highly productive biosynthetic enzymes demonstrates that the greatest synthetic challenges can be solved by characterizing the biosynthetic enzymes and utilizing them a) in a cell-free system for vitamin B_{12} synthesis [104,105], or b) in whole-cell systems for developing an industrial process for making the global vitamin B_{12} supply possible [106]. Carefully controlled enzyme catalysis in microbial cell factories can replace lengthy chemical synthesis [107], facilitate and widen synthetic access to natural products [108] and are becoming more important in the chemical industry for replacing fossil-derived chemicals by biobased chemicals [109,110]. The diverse composition of underutilized carbon sources such as agricultural, forestry, food and other residues can thereby provide a selection of suitable biobased raw materials for which improved feedstock utilization can be developed towards manufacturing a broad range of valuable biobased chemicals [111–113]. Enzyme catalysis can thereby reduce complexity and simplify manufacturing processes [114], but whether a particular synthetic challenge is best addressed by using enzymes in whole cell or cell-free forms depends on factors such as involved enzyme types, substrates and products, or the research stage of screening, process development or production.

Key factors influencing the economic success and viability of a bioprocess from a biobased raw material to a biobased chemical and its competitiveness with the corresponding fossil-derived chemical are the product value, process metrics, process complexity, quality, application and customer benefits.

Biobased starting materials and enzyme catalysis have become well established in manufacturing high quality pharmaceuticals and pharmaceutical intermediates [15,18,20,65,69,115–117]. An environmental impact analysis of pharmaceutical processes according to non-renewable and

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renewable feedstock types and processing routes has shown the sustainability potential of the rapidly growing global pharmaceutical market [118]. Selected examples of enzyme catalysis using starting materials from biobased resources for the production of pharmaceuticals and biomaterials are provided in the following. Enzymatic synthesis of β-lactam nuclei from biobased stating materials, side chains and their enzymatic coupling have due to their shorter and cleaner routes replaced traditional chemical routes leading to more economic and sustainable manufacturing [119]. Enzyme-catalyzed reactions are widespread in the manufacturing of antivirals, such as the enzymatic synthesis of islatravir, a nucleoside analog for investigational HIV treatment [120]. The enzymatic synthesis of islatravir as a single stereoisomer has been achieved with 51% overall yield in a reaction cascade using five engineered enzymes and four auxiliary enzymes, whereby also biobased starting materials such as dihydroxyacetone [121] and acetyl phosphate have been used (see figure 4A) and the number of reaction steps has been shortened compared with previous routes [120]. Further improvements have been achieved by inverting the enzymatic oxidation and phosphorylation steps and to evolve the galactose oxidase for the oxidation of the phosphorylated triol, which together with process development and improved gas-liquid mass transfer oxygen have resulted in a more sustainable aerobic oxidation with excellent yield at multi-kilogram scale [122]. The importance of fast process design has become clearly evident with the urgency and high demand for antiviral drugs against SARS-CoV-2 [16]. The design and optimization of an efficient and scalable enzymatic synthesis of molnupiravir from easily available biobased D-ribose and uracil (see figure 4B), which shortened the original chemical synthesis to 3 steps and improved the overall yield, enabled the rapid large scale supply of the antiviral agent molnupiravir [123]. Enzyme catalysis in a novel reaction cascade, involving a lipase, engineered ribosyl-1-kinase and uridine phosphorylase, pyruvate oxidase and acetate kinase for recycling phosphate, has been key for rapidly reaching manufacturing scale [123].

Biomaterials for medical as well as cosmetic applications can be produced with good control of the required high quality from biobased starting materials using multi-step enzymatic synthesis of well-defined biopolymers. The advantages of selective enzyme catalysis are clearly evident in the precise and protecting group free polymerization of monosaccharides to homopolysaccharides and complex heteropolysaccharides such as glycosaminoglycans [124–126]. The coupling of the two enzymatic reaction modules for synthesizing the two building blocks UDP-*α*-*N*-acetyl-D-glucosamine and UDP-D-glucuronic acid from biobased D-glucuronic acid and *N*-acetyl-D-glucosamine and including ATP regeneration, with their controlled hyaluronan synthase-catalyzed polymerization enabled the synthesis of hyaluronic acids of high quality [127].

Enzyme catalysis has traditionally provided benefits for the conversion of biobased raw materials to food and food ingredients and is attractive for the preparation of health promoting food ingredients and metabolites, such as the enzymatic production of prebiotic oligosaccharides [128], bioactive lipids containing omega-3 fatty acids [129] or urolithins [130].

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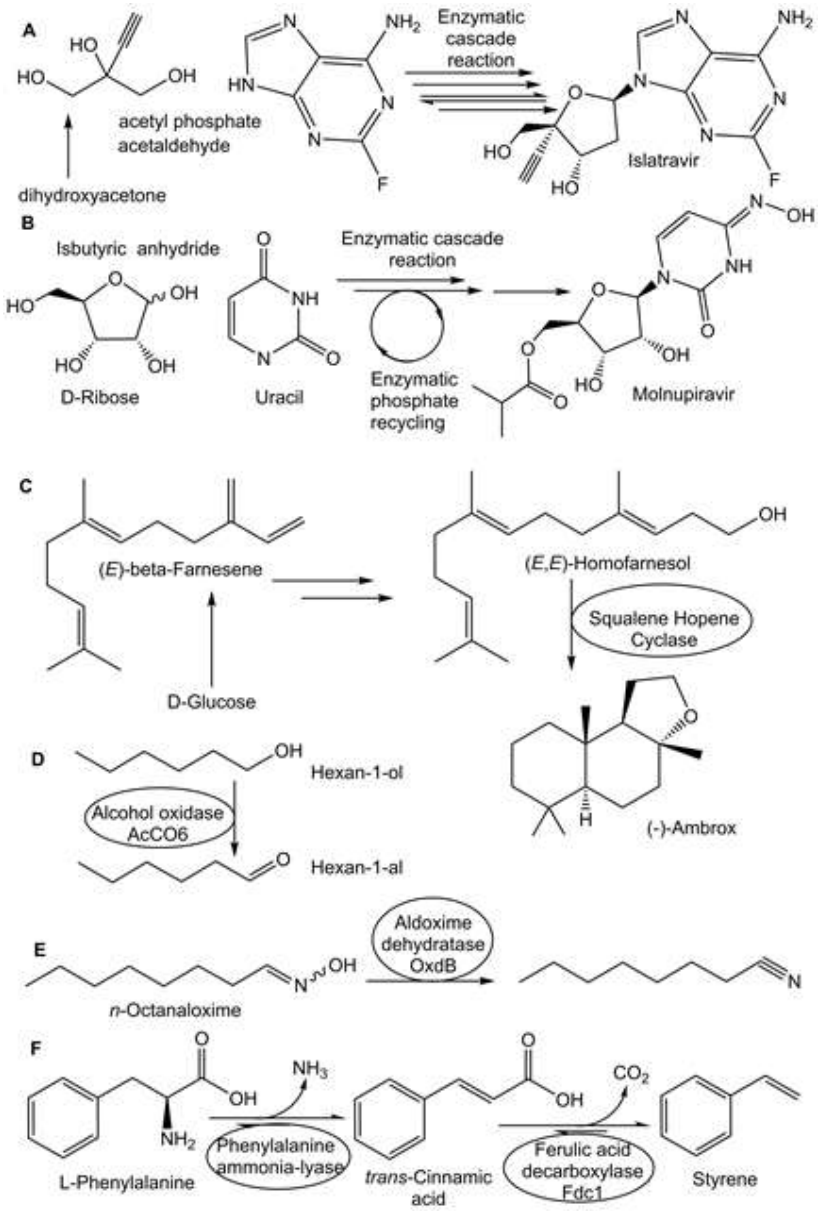

Figure 4. Selected enzyme-catalyzed reactions to valuable biochemical products utilizing starting materials from renewable biobased resources.

The use of enzyme catalysis provides also great benefits in manufacturing naturally-derived fragrance ingredients when all carbon atoms of the biobased starting material end up in the product, as demonstrated in the biomanufacturing of (-)-ambrox by a squalene hopene cyclase-catalyzed bioconversion (see figure 4C) of (*E*,*E*)-homofarnesol [131,132]. The starting material (*E*,*E*)-homofarnesol was thereby obtained from the biobased (*E*)-β-farnesene, which was produced by fermentation [131,132]. Excellent process metrics with complete conversion up to 300 g L^{-1} substrate concentration has been achieved [132]. An engineered alcohol oxidase enabled the enzymatic synthesis of a broad range of aldehydes (see figure 4D) by the selective oxidation of the corresponding primary alcohols [133].

Enzyme catalysis has from its beginnings been of fundamental importance in bringing forward novel and sustainable approaches for asymmetric synthesis of valuable chiral compounds [13,14,134], which have found broad applications in various industrial sectors [15–18,135]. The discovery or engineering of enantiocomplementary enzymes opens the opportunity of synthetic access to both enantiomers of a chiral compound [136]. Enzyme catalysis continues to be very attractive also for the asymmetric isotopic labelling of molecules of biobased or synthetic origin, such as the highly selective single step asymmetric reductive deuteration using NADH-dependent

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reductases [137]. Enzyme catalysis using biobased starting materials has become well established for manufacturing high value chiral compounds and intensification of enzymatic processes towards medium value type products and commodity products is moving forward. An enzymatic manufacturing strategy for the fossil-derived commodity chemical styrene, which is used for numerous syntheses of polymers and chemicals, has been developed at laboratory scale by using an efficient two-step whole cell biotransformation from L-phenylalanine via *trans*-cinnamate to yield a concentration of about 25 g L^{-1} styrene (see figure 4F) despite the toxicity of styrene to cells [138]. Excellent conversion and productivity has been achieved in the synthesis of aliphatic nitriles by aldoxime dehydratase-catalyzed water elimination from aldoximes (see figure 4E), which can be derived from renewable biobased alcohols [139]. The aldoxime solubility could be increased by 10 % (v/v) ethanol and extremely high substrate concentrations of *n*-octanaloxime up to 1.4 kg L^{-1} could be converted to *n*-octanenitrile in 24 hours [140]. Although multiple requirements and several criteria need to be met for commodity products to be competitive with traditional routes, the increasing number of biotransformations of biomass to commodity products by the use of enzymes and cells and the improvements and strategies in the utilization of waste feedstock look promising for sustainable biomanufacturing [112,141].

These benefits and favourable safety, health and environment aspects of enzyme catalysis have made this technology highly attractive for sustainable manufacturing of products by SDG-fit novel processes from laboratory scale to industrial large scale [15–20].

4. Discussion

The increasing use of biobased resources and enzyme catalysis for manufacturing valuable products in various industrial sectors across planet earth contributes towards more than half a dozen UN Sustainable Developments Goals and to the transformations which have been introduced as operationalized modules how to achieve the Sustainable Development Goals [142]. The dimensions of biobased resources and the advances in enzyme catalysis provide hope and support for accelerating these encouraging developments to produce biobased starting materials by industrially viable routes to utilize carbon dioxide over different time scale [97,143]. As many platform chemicals which are used in numerous applications are manufactured from fossil-based resources, it is of special interest that carbon-negative bioproduction of the common solvents acetone and isopropanol with a productivity of about 3 g L^{-1} h^{-1} has been demonstrated at industrial pilot scale [144].

In order to provide transparency about the origin of the starting materials, a globally harmonized system of labelling would be desirable for clear communication along the entire value chain and the progress in transitioning from fossil resources. It would also support decision-making on whether to use a starting material originating from carbondioxide-utilizing, bio-based or fossil resources. Standardization is also desirable in the description of enzyme catalysis and the STRENDA guidelines [145], which are recommended by more the 50 journals, provide a global framework for describing experimen-tal enzyme function data and building the STRENDA database [146] as functional counterpart to the PDB structure database.

5. Conclusions

The scientific and technological advances in enzyme catalysis have not only lead to a tremendous growth of fundamental knowledge and understanding of life on our planetbut also to such a large and rapidly increasing number of applications that the present time can be considered a golden age for enzyme catalysis. As transformations catalyzed by enzymes have contributed to shape at scale the planet earth up to the present time periods, the power of enzyme catalysis can also contribute to stabilize the Anthropocene within planetary boundaries. The dimensions of the global challenges in space and time require however bold and consistent actions by all stakeholders across multiple scales.

6. Future Directions

Whether already known to exist in nature, being modified, engineered of synthesized de novo, novel enzyme functions able to selectively catalyze desirable transformations from renewable biobased resources or directly utilizing carbon dioxide are of fundamental interest deserving bold investments into research, development and innovation. The whole innovation pipeline from idea to discovery, rapid prototyping, reaction and process development to intensification and scaling depends on successful cooperation between people from all the involved areas in order to deliver sustainable value in time and at scale. Enzyme catalysis is in an excellent position to make contributions step by step towards bioeconomy [147,148] and the UN Sustainable Developments Goals.

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