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Review

Mirror, mirror on the wall, which is the greenest of them all? A critical comparison of chemo- and biocatalytic oxyfunctionalisation reactions

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ABSTRACT

This review article critically compares two widely used types of catalysis, chemo- and biocatalysis, and provides insights on their greenness according to specified parameters. A comparative analysis of the environmental impact of chemo- and biocatalytic oxyfunctionalisation reactions based on published experimental data reveals that both methods produce comparable amounts of waste, with the majority stemming from the solvent used. However, it is emphasised that the synthesis of the catalysts themselves, including biocatalysts, should also be considered when assessing their environmental impact. The review underscores the complexity of assessing the environmental impact of catalytic oxyfunctionalisation reactions. The article also discusses the relationship between solvent properties and the energy demands for chemical transformations and downstream processing, underlining that the choice of solvent can significantly influence the environmental impact of a catalytic process. Additionally, the review highlights the importance of considering the recyclability of reagents and the secondary CO_2 emissions caused by the energy requirements of the reaction when evaluating the environmental impact of a catalytic process. Each chemo- and biocatalysis produce a certain environmental impact, the greenness of either method is dependent on several factors, including the type of waste generated, the recyclability of reagents, and secondary CO_2 emissions. This review therefore recommends using consistent metrics and a comprehensive life cycle assessment approach to evaluate this environmental impact, and highlights the importance of considering the synthesis of the catalysts themselves.

1. Introduction

The addition of oxygen atoms into C-H or C-C bonds, as well as C=C bonds, known as catalytic oxyfunctionalisation reactions, is gaining importance in organic synthesis due to their potential for producing highly functionalised and complex molecules. However, these reactions present significant challenges that must be addressed to achieve high yields and selectivity.

One major challenge is controlling selectivity, as oxyfunctionalisation reactions can result in multiple products due to the presence of multiple reaction sites in the substrate. This challenge is compounded by another, generating and controlling highly reactive oxygen species, which can lead to issues with catalyst stability, selectivity, and unwanted byproduct formation. Additionally, traditional oxidants used in these reactions are often toxic or environmentally hazardous.

As a result, most catalysis disciplines are actively developing oxyfunctionalisation catalysts, reactions, and processes. Homogeneous catalysis such as organometallic catalysis and biocatalysis are particularly active in this area, and interdisciplinary interactions could be beneficial. However, these fields do not interact as much as they could, with each often depreciating the other approach. Arguments against biocatalysis often include the high specificity and poor stability of enzymes, their dependence on costly cofactors, and poor scalability. In contrast, biocatalysis publications often disfavour chemocatalysis due to toxic catalysts and solvents and harsh reaction conditions [1-3].

To provide a balanced, objective overview, a comparison of chemo- and biocatalysts for their efficiency and environmental impact is needed. This approach aims to promote a more quantitative discussion and comparison of both fields and potentially initiate productive controversies from which we can all learn.

2. Catalysts available

In the majority of chemical oxyfunctionalisation reactions, catalysis is required to decrease the activation enthalpies and increase selectivity. One common catalytic strategy is to activate molecular

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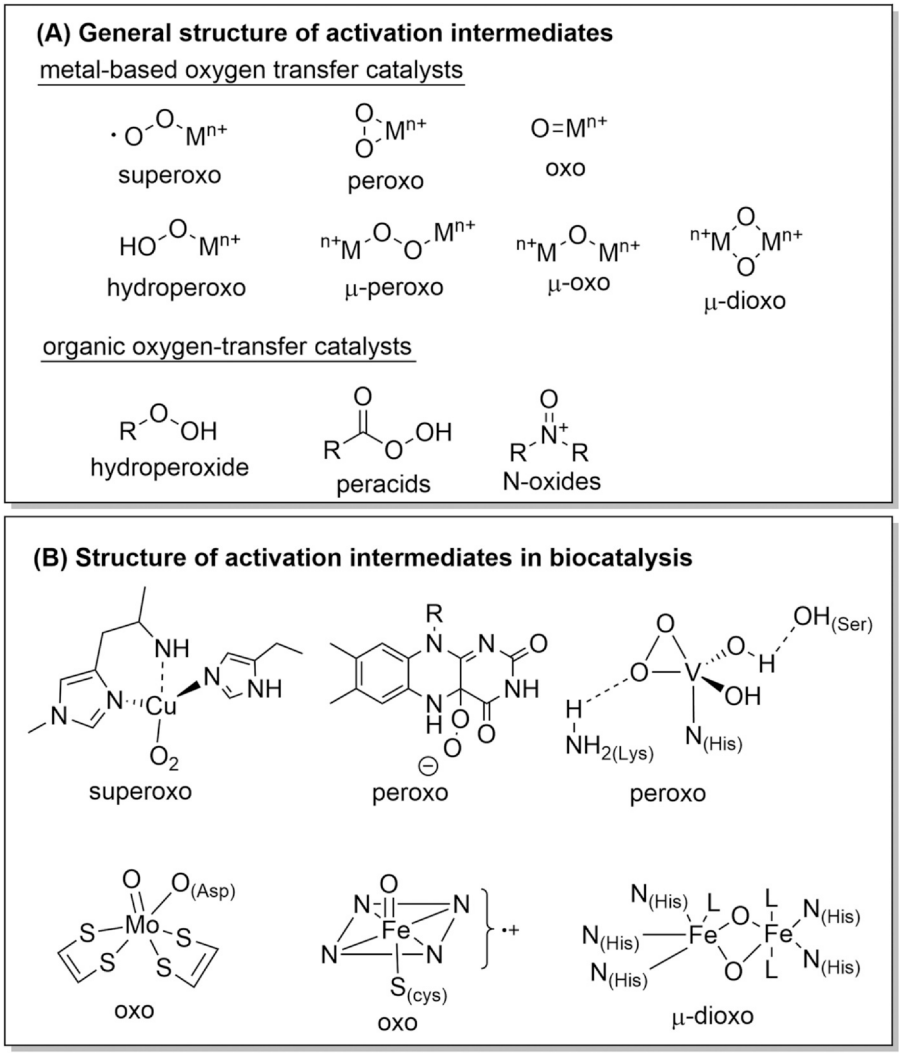


Fig. 1. Selection of (in) organic activated oxygen species for oxyfunctionalisation chemistry.

oxygen or hydrogen peroxide as higher-valent metal oxo species or as (hydro)peroxo species (Fig. 1). Additionally, organic oxidants such as hydroperoxides and peracids are frequently utilised.

Among the catalysts used, various metals such as elements of the platinum group (Ru, Rh, Pd, Os, Ir, and Pt) are prevalent for the activation of molecular oxygen (Fig. 2). For already reduced oxygen species ((hydro)peroxide), salts of V [4,5], Mn [6-8], Fe [9-11], Ni [12,13], Co [14,15], Cu [16], or Pt [17] are commonly used, while photocatalytic systems based on TiO_2 [18-20] or SiO_2 [21] are emerging. Organic catalysts such as BINAP [22], flavins [23-25] or peptides [26] have also been reported, and many of these catalytic systems are applied for different oxyfunctionalisation reactions.

Compared to the wide range of catalysts used in chemical oxyfunctionalisation, biocatalysis relies on a narrower selection of (bioavailable) metals such as Fe, Cu, V, and Mo, and organic catalysts such as flavins and pterins. The most widely known oxyfunctionalisation enzymes are Fe-dependent oxygenases. The haem-dependent P450 monooxygenases [27-31] and peroxygenases [32-36] catalyse a broad range of C–H functionalisation reactions and epoxidation reactions, while Baeyer-Villiger (BV) oxidations are yet unknown. Non-haem Fe oxygenases exhibit an even broader repertoire including *cis*-dihydroxylations of arenes or halogenation of non-activated C–H bonds, but also no BV oxidations [37-39]. Flavin-dependent monooxygenases catalyse BV oxidations, epoxidation reactions, and aromatic hydroxylations [40-42] and some flavin-dependent monooxygenases even catalyse aromaticity-breaking hydroxylations of arenes [43,44] or hydroxylation of sp^3 C–H bonds (which is generally reserved to metal-dependent enzymes) [45]. Flavin-dependent oxidases such as vanillyl alcohol oxidase also catalyse the benzylic oxyfunctionalisation of *p*-alkyl substituted phenols via a desaturation/hydration sequence [46,47]. In contrast to most oxyfunctionalising enzymes, the oxygen inserted does not originate from molecular oxygen but rather from water. Other metals and cofactors such as W or Mo [48], V [49-52] or Cu play a lesser role in biocatalytic oxyfunctionalisation chemistry. A notable exception are the Cu-dependent lytic polysaccharide monooxygenases (LPMOs) [53-55] which are currently experiencing increased interest for the valorisation of recalcitrant polysaccharides.

3. Catalyst productivity, performance and loadings

The term chemical productivity is widely used and recognised as crucial, however, it is often ambiguously defined. For the purpose of this discussion, we adopt the definition of chemical productivity as the rate of volumetric product formation (as defined by Eq. 1).

$$\text{Chemical productivity } [\text{mM}\bullet\text{h}^{-1}] = \frac{n_{\text{product}}}{\text{volume}\bullet\text{time}}\left[\frac{\text{mmol}}{\text{L}\bullet\text{h}}\right] \quad (1)$$

Undoubtedly, this parameter is of paramount importance, particularly in terms of the economic viability of any chemical process at an industrial scale. Moreover, from an environmental standpoint, chemical productivity plays a crucial role, as the duration of a reaction is directly

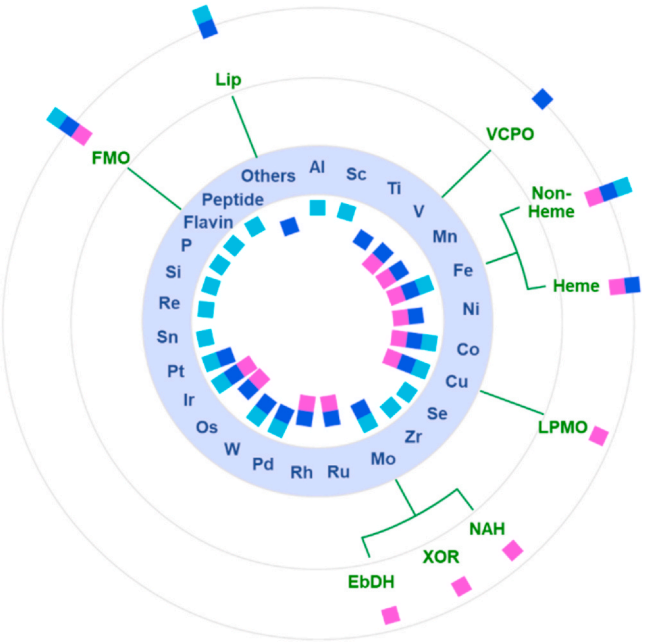


Fig. 2. Classification of chemocatalysts (■) and biocatalysts (–) for hydroxylation (■), epoxidation (■) and Baeyer-Villiger oxidation reactions (■). FMO: flavin-containing monooxygenases, such as styrene monooxygenases; Haem: haem-dependent enzymes, such as cytochrome P450 monooxygenases; Non-haem: non-haem-dependent enzymes, such as ammonia monooxygenases. For more details please refer to Table S2.

proportional to energy consumption (including associated CO_2 emissions) resulting from activities such as stirring, pumping, or thermal control.

Fig. 3A illustrates the notable disparity in chemical productivity between biocatalytic and chemocatalytic oxyfunctionalisation reactions. Specifically, over two-thirds of biocatalytic reactions have a productivity level below 10 mM h^{-1}, whereas only one-third of chemocatalytic reactions fall into this category. Moreover, a considerable portion (20%) of chemocatalytic reactions achieve a chemical productivity of 0.1 M h^{-1} or higher, which is an exceptional achievement in biocatalysis. Part of the reason for this discrepancy can be attributed to the traditionally lower molar catalyst loading used in enzymes as compared to chemocatalysts (as shown in Fig. 3B). Enzymes are usually employed at much lower concentrations, ranging from the lower micromolar to nanomolar range (approximately 90% of the time), while chemical catalysts are typically used at concentrations of 1 mM or higher (> 50%). When we consider the weight of the catalyst, the results may vary. Generally, chemocatalysts consist of a central (transition) metal element surrounded with several simple ligands, with the molecular weight in the range of a few hundred to several thousand Daltons (Da). For enzymes, hundreds of residues are used for the protein structure, forming the 20–120 kDa complex catalyst molecule. It is worth mentioning here that, based on a g L^{-1} basis catalyst concentrations are very comparable in a typical range of 0.1–10 g L^{-1}.

When catalytic productivity is compared in terms of turnover numbers (TON, Eq. 2), the performance of biocatalysts is superior to that of chemocatalysts (Fig. 3C), with over 20 oxyfunctionalisation biocatalysts reaching well above > 10,000 TON. However, when we make the comparison in terms of g g^{-1} (grams of product per gram of catalyst), there is no significant difference between chemocatalysis and biocatalysis.

$$\mathrm{TON} = \frac{n_{\mathrm{product}}}{n_{\mathrm{catalyst}}}\left[\frac{\mathrm{mol}}{\mathrm{mol}}\right] \tag{2}$$

Another parameter relevant in this context is catalyst activity described by turnover frequency (TOF), which refers to the TON per unit of time (Eq. 3). The equivalent term in biochemistry for biocatalyst characterisation is known as the catalytic efficiency described by k_{cat}/K_M. Such comparisons are unfortunately scarcely reported in literature, yet would be valuable to establish catalytic performance. As shown in Fig. 3D, typical TOFs for chemocatalysts range below 100 h^{-1} whereas more than 70% of the enzyme catalysts exhibit TOFs higher than 1000 h^{-1}.

$$\mathrm{TOF}\quad [\mathrm{h}^{-1}] = \frac{n_{\mathrm{product}}}{n_{\mathrm{catalyst}} \bullet \mathrm{time}}\left[\frac{\mathrm{mol}}{\mathrm{mol}\bullet\mathrm{h}}\right] \tag{3}$$

Overall in terms of chemical productivity, chemocatalytic processes currently outperform biocatalytic ones, yet the latter is catalytically more productive, displaying higher TON and TOF. This observation suggests that the productive potential of biocatalysts remains to be explored.

4. Reagent loadings and solvents

High product loadings are crucial for the economic feasibility of chemical processes as they increase the efficiency of infrastructure and operational resources used. Additionally, downstream processing is generally easier, less time-consuming, and requires fewer resources and less energy when the product concentration is high. As mentioned earlier, these economic factors also translate into environmental impacts. In other words, the higher the product concentration, the lower the overall environmental footprint of a transformation. Thus, we compared the substrate loadings reported for both biocatalytic and chemocatalytic oxyfunctionalisation processes (Fig. 4).

A majority of oxyfunctionalisation biocatalysis occurs in dilute reaction media, with over 80% of the reactions being performed in solutions containing less than 100 mM of starting material. In contrast, over 80% of chemocatalytic processes are conducted with starting material concentrations of 100 mM or higher.

There is a clear cultural difference between researchers in the fields of chemocatalysis and biocatalysis when it comes to the choice of solvent for a reaction. Chemists tend to choose the most suitable solvent for the reaction, while biocatalysis researchers predominantly use water. This is understandable as water is often referred to as the "solvent of life" and many enzymes are water-soluble. Moreover, water is perceived as a green solvent, being abundant and renewable in many regions of the world and non-toxic (at least prior to its use as solvent). However, due to its high polarity, water is a poor solvent for hydrophobic reagents such as hydrocarbons, which partially explains the low substrate concentrations used in biocatalysis (Fig. 4). In contrast, chemocatalysis often employs organic solvents such as alcohols (e.g. methanol, ethanol, isopropanol), alkanes, and aromatics (e.g. toluene, xylene), and even halogenated solvents such as CH_2Cl_2 or $CHCl_3$, allowing for high substrate loadings. In the case of liquid starting materials, solvent-free reactions are not uncommon. Today, biocatalysis for oxyfunctionalisation predominantly relies on aqueous reaction media, which presents challenges to scalability and greenness. However, it is worth noting that non-aqueous applications of hydrolases [56] and lyases [57] are quite common. Oxidoreductases, on the other hand, have been slower to adapt. Pioneering work by Klibanov and coworkers [58-60] has recently regained attention from the biocatalysis community [61]. To address the incompatibility of hydrophobic reagents and water-borne catalysts such as enzymes or whole cells, the two-liquid phase system (2LPS) approach has been developed (Scheme 1) [62-66]. This approach not only allows for high overall product concentrations but also enables control over the selectivity of the overall reaction. For example, hydrophobic aldehyde intermediates can be extracted into the hydrophobic organic phase, avoiding their over-oxidation [67]. Additionally, water-labile products such as epoxides can be stabilised using the 2LPS approach [68].

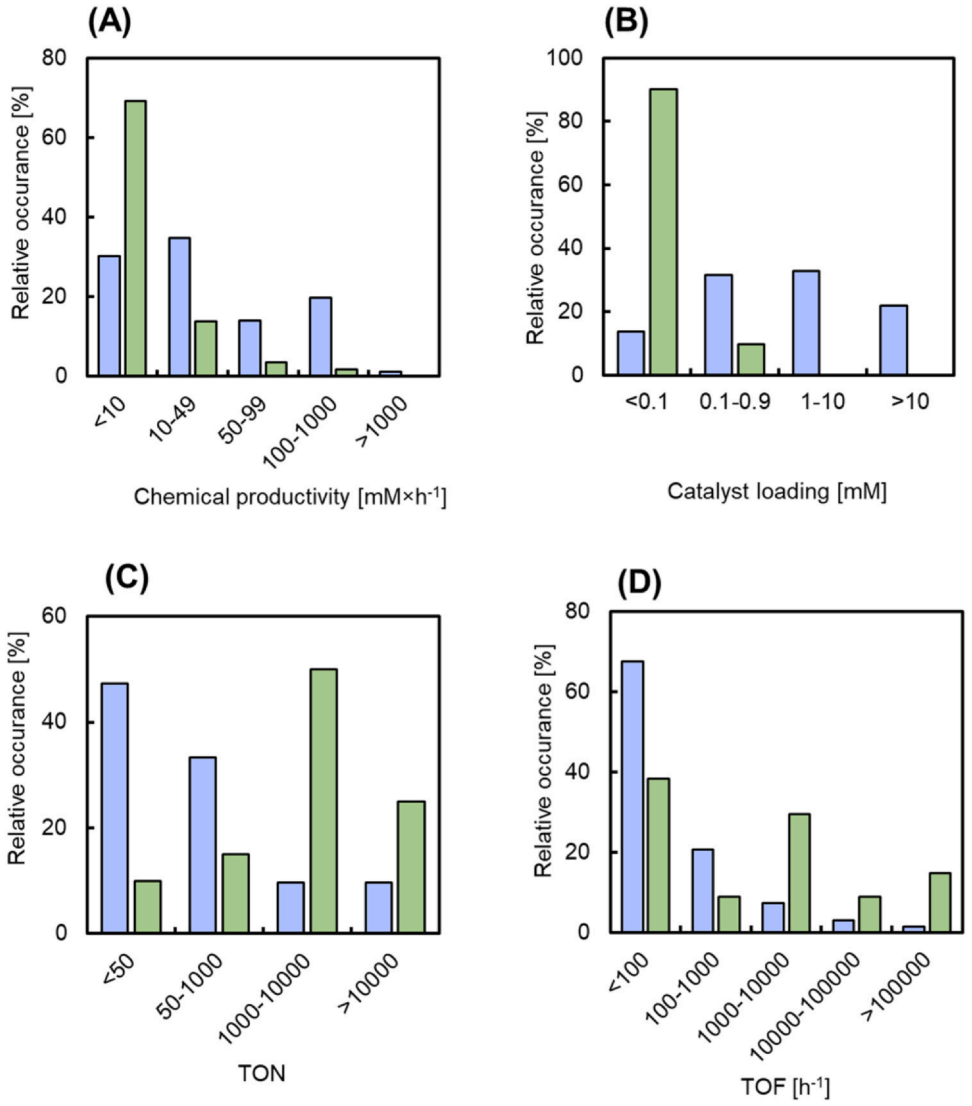


Fig. 3. Comparison of chemical productivities (A), catalyst loadings (B), catalyst turnover numbers TONs (C) and catalyst turnover frequencies TOFs (D) in oxyfunctionalisation reactions catalysed by chemocatalysts (■) and biocatalysts (■). For details please refer to Table S3.

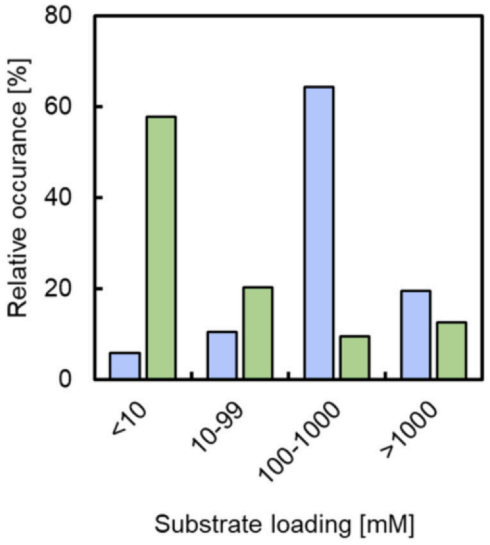
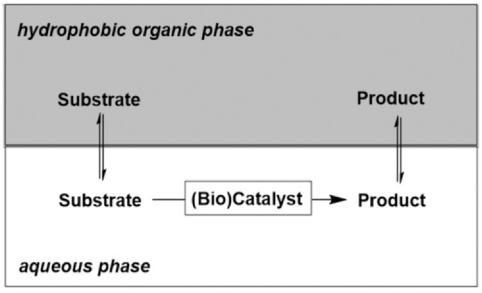


Fig. 4. Comparison of substrate loadings in oxyfunctionalisation reactions catalysed by chemocatalysts (■) and biocatalysts (■). For details please refer to Table S3.

Micro aqueous reaction systems (MARS) can be considered as an extension of the 2LPS approach, but with an even more extreme reduction of water content. The exact residual water content unfortunately varies for different enzymes and no general rules can be given right now [61]. Lipases, for example, generally need far less water than oxidoreductases. Often, buffer-saturated organic solvents provide sufficient water for the biocatalyst to remain active. MARS have shown great potential especially in case of cofactor-independent reactions or in those cases where the cofactor not necessarily diffuses away from the enzyme active site. For reactions requiring a free, diffusible cofactor (e.g., in the case of enzyme-coupled regeneration systems), the extremely low solubility of the ionic cofactors in the hydrophobic liquid media poses a significant challenge for biocatalysis in MARS. Highly polar reagents such as glucose are also not easily applicable in MARS. Therefore, the application of MARS is largely restricted and may not be suitable for the commonly used P450 monooxygenase systems (except for peroxide shunt pathway applications that are cofactor-independent). However, the recently emerging peroxygenase enzymes have shown promising results in both 2LPS and MARS systems, highlighting their potential as versatile catalysts for green and sustainable chemical transformations [69-71].



Scheme 1. The two-liquid phase concept. The hydrophobic organic phase allows for overall high reagent loadings and serves as substrate reservoir and product sink.

5. Oxidants

Stoichiometric oxidants play a crucial role in oxyfunctionalisation reactions. In recent years, a wide range of oxidising agents, which also serve as an O-source, have replaced traditional oxidants such as chromate or permanganate (Table 1). More examples involving further oxidants are listed in Table S1. The oxidant scope of chemocatalytic methods is broader than their biocatalytic counterparts. Chemocatalytic oxyfunctionalisation reactions utilise a diverse range of oxidants, including oxygen (such as O_2 or O_3), peroxides (such as H_2O_2 or (in)organic hydroperoxides), peracids (e.g., mCPBA or peracetic acid), or halogenated oxidants (elementary, hypohalites, or hypervalent iodine species) [72]. In contrast, the oxidant of choice for biocatalytic oxyfunctionalisation reactions is traditionally molecular oxygen. However, hydrogen peroxide and organic hydroperoxides, such as tert-butyl hydroperoxide, have recently gained popularity [73,74].

En route to the 'ultimately green oxidant' several aspects should be taken into account. Waste formation is certainly one of the most relevant features. Oxidants such as mCPBA or iodosyl benzene are very popular on the lab scale but also yield very significant amounts of byproducts reducing their environmental and economic attractiveness at preparative applications. In this respect, O_2 or H_2O_2 appear most attractive as (eventually) only water is formed as by-product. But also here, safety considerations (explosion hazards, corrosion issues) should be taken into account especially if volatile and flammable organic compounds (such as solvents) are involved. This issue is of lesser importance in case of aqueous reaction media, but the low solubility of O_2 (approx. 0.25 mM, depending on temperature, pressure and buffer composition) presents challenges for biocatalysis. The amount of oxygen available may lie below the enzyme's K_M value, leading to sub-optimal enzyme activities. Enzyme engineering can generate mutants with higher O_2 affinity [94], but O_2 diffusion rate into the aqueous reaction mixture remains a limiting factor. Process engineering can address this issue [95]. Enzyme stability under aeration reaction conditions is another consideration. Exposure to the gas-liquid interface can cause denaturation of enzymes, and oxidation of labile amino acids such as methionine and cysteine can impair enzyme activity or stability [94].

One challenge faced by monooxygenase reactions is uncoupling [96]. Monooxygenases first activate molecular oxygen through a reductive process to produce an activated, enzyme-bound oxygen species that then performs oxygen insertion [37]. The reducing equivalents required for this reaction are typically obtained from reduced nicotinamide cofactors and delivered to the monooxygenase through complex electron transport chains. However, a significant portion of the reducing equivalents provided by the sacrificial electron donor can also be wasted in a futile uncoupling reaction, which involves the direct aerobic oxidation of radical intermediates. This loss of reducing equivalents hinders the large-scale application of biocatalytic oxyfunctionalisation, as the cost contribution of the sacrificial electron donor exceeds the economically feasible range and results in additional consumption of feedstock [96]. In addition, the reactive oxygen species formed in the uncoupling process can impair the stability of biocatalysts.

Peroxygenases, in contrast to monooxygenases, do not suffer from uncoupling issues, as they utilise already reduced oxygen in the form of H_2O_2 as a stoichiometric oxidant, resulting in highly simplified reaction schemes. This advantage makes peroxygenases an attractive option for industrial oxyfunctionalisation processes, as the cost contribution of a sacrificial electron donor, which is often necessary in monooxygenase-catalysed reactions, can be eliminated. However, like all haem-containing enzymes, peroxygenases are susceptible to irreversible haem degradation in the presence of high concentrations of H_2O_2, but this can be easily controlled by adjusting the in situ H_2O_2 concentration [74]. Despite the somewhat limited substrate scope of peroxygenases, recent research efforts have successfully expanded the range of substrates that these enzymes can act on [35,97-104], demonstrating their potential for future applications.

6. Selectivity

Selectivity represents a key performance indicator for (catalytic) reactions. The higher the conversion of a given starting material into the desired product and the lower the formation of undesired side-products, the more efficiently resources are utilised.

It should also be noted that downstream processing and product purification often very significantly contribute to the overall waste formation of a given chemical process. For example, Schrittwieser et al. compared various synthetic routes of Tembamide synthesis finding that up to 90% of all waste generated (depending on the synthetic route) is caused by product isolation and -purification [105]. These numbers underline the potential impact of product purity and consequently the selectivity of a catalyst.

Furthermore, the separation of undesired by-products from the desired one consume further resources (reagents, time and CAPEX) and generate additional wastes. Therefore, highly selective catalytic transformations are desirable from an economic and an environmental point-of-view. Generally, regio-, chemo- and enantioselectivity are differentiated. The selectivity of catalytic oxyfunctionalisation reactions depends on two factors: (1) the reactivity of the C–H bond to be converted (mainly affecting the regioselectivity of a given reaction) and (2) the positioning of the starting material relative to the catalytically active species (affecting regio- and stereoselectivity). The selectivity of a catalyst is determined by the relative stabilisation of transition states leading to the competing products. According to the Arrhenius equation, the relative reaction rate (and therewith the product distribution) directly correlates with the activation energy of the different transition states. This can be achieved by introducing attracting and repulsive interactions of the starting material with the catalyst (i.e., the ligands in case of chemical catalysts and amino acid residues in the active site in case of enzymes).

However, as low-molecular weight compounds, chiral ligands have limited possibilities to interact with the catalyst-bound starting material and thereby to control substrate binding (Fig. 5) [106]. In contrast, an enzyme active site offers various attractive and repulsive interactions with the starting material, providing the enzyme with more opportunities to control substrate binding relative to the catalytically active group (Fig. 5).

The difference in control of binding interactions can be exemplified in the hydroxylation of non-functionalized alkanes. In chemical hydroxylation reactions, the reactivity of a given C-H bond and the steric hindrance around it determine the regioselectivity of the reaction. While these factors also play a role in enzymatic hydroxylations, they are complemented by the interaction of the starting material with the enzyme active site. This interaction favours the binding of the starting material to the hydroxylation catalyst in an orientation leading to a kinetically favourable product. An illustrative example is the oxyfunctionalisation of octane catalysed by cobalt aminodiphosphine complexes, yielding a statistical mixture of regio- and stereoisomeric 1- to 4-octanols (Fig. 6, upper reaction) [107-109]. However, the cytochrome P450 monooxygenase from *Mycobacterium* sp. HXN-1500 produces 1-octanol in greater than 95% selectivity [110]. Similarly, alkane

Table 1
Selection of commonly used oxidants in catalytic oxyfunctionalisation.

Substrate-H + Oxidant —Catalyst→ Product-O + By-product

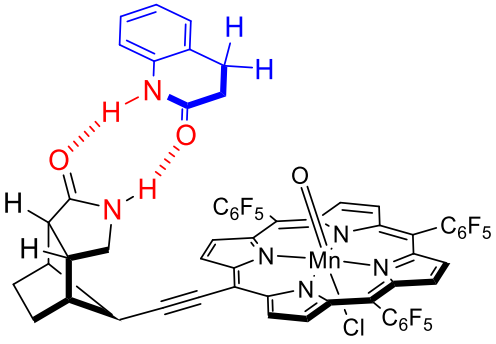
Oxidant	By-product	Waste [g $mol_{product}^{-1}$]	Hydroxylation(O-activation)		Epoxidation(O-activation)		BV-oxidation(O-activation)	
			Chemo	Bio	Chemo	Bio	Chemo	Bio
O_2	H_2O_2 / H_2O	34 / 18	Mn[a]	P450[b] VAO[c]	Mn[d]	FMO[e] P450[b]	SiO_2[f]	BVMO[g]
H_2O_2	H_2O	18	Co/Fe[h] Fe[i]	UPO[j] P450[k]	Ti[l] Mn[m]	UPO[j] P450[k] Lipase/acid[l]	Co[m] Pd[n]	Lipase/acid[l]
Ph-I=O	Ph-I	200	Fe[o]	P450[p]	Mn[q]	-	Fe[r]	-
mCPBA	acid	156	Fe[s]	-	Ni[t]	-	Sc (**14**)[u]	-

[a] Mn^{II}-Met@MMNPs [75]
[b] P450 monooxygenases [29]
[c] Vanillyl alcohol oxidase (VAO) and related enzymes activating *p*-hydroxy alkyl benzenes a quinone methides for H_2O attack [46]
[d] Fe_3O_4-[Mn(TCPP-Ind)Cl] [76]
[e] FMO: Flavin-dependent monooxygenases [40]
[f] SiO_2-mediated aerobic oxidation of benzaldehyde to perbenzoic acid [21]
[g] Baeyer-Villiger monooxygenases (BVMO, flavin-dependent) [41]
[h] $[Co_4^{III}\ Fe_2^{III}\ O(L^{10})_8]$ 4DMF·H_2O [77]
[i] $[((R)\text{-}(-)\text{-N4Py*})Fe^{II}(CH_3CN)]^{2+}$ [10]
[j] UPO: unspecific peroxygenase [34]
[k] P450 monooxygenases using decoy molecules [78]
[l] titanium(salan) complexes [79]
[m] Mn porphyrin complexes [80] or MnO_2 NP/g-C_3N_4 [81] [l] lipase-catalysed *in situ* generation of peracids [82-85] [m] Co-salen complex [15]
[n] $(PhCN)_2PdCl$ [86]
[o] porphyrin complexes [87]
[p] [88]
[q] $[Mn^{III}(TDCPP)Cl]$ [89]
[r] $[Fe^{II}(CH_3CN)(N,N\text{-bis(2-pyridylmethyl)-}N\text{-bis(2-pyridyl)methyl-amine})(ClO_4)]ClO_4$ [90]
[s] $Fe_2^{III}(O)(L)(OBz)](ClO_4)$ [91]
[t] $[Ni^{II}(L)Cl]$, L=(2-[bis(pyridin-2-ylmethyl)amino]-N-(quinolin-8-yl)acetamide) [92]
[u] L-RaPr$_2$-*t*Bu/Sc(OTf)$_3$ [93]. For the activation mode, please refer to Figure 1, for details of abbreviations please refer to Table S2.

hydroxylases (i.e. non-haem Fe monooxygenases) [111] generally exhibit a preference for terminal hydroxylation, while hydroxylases from different organisms exhibit other selectivities [112-115] While the majority of wild type hydroxylases exhibit poor selectivity towards non-natural starting materials such as octane, modern enzyme design enables the modification and fine-tuning of hydroxylase selectivity towards these substrates. Recent studies have shown the success of enzyme design in modifying the selectivity of hydroxylases towards various substrates [27,35,99,116-125].

Enzymes are also superior to chemical catalysts in terms of stereoselectivity. As mentioned earlier, enzymes have more control over the orientation of the substrate with respect to the catalytic site, and this is crucial for achieving high stereoselectivity. For instance, chiral transition metal catalysts typically give enantiomeric excess (ee) in the range of 40%–80% for the stereoselective benzylic hydroxylation of ethyl benzene [8,11,126], and low reaction temperatures are often required to achieve high stereoselectivity, resulting in significant energy input for the transformations. In contrast, a wide range of highly (*R*)- or (*S*)-selective oxygenases are available, including haem-dependent monooxygenases [127,128] and peroxygenases [129], which have been reported to achieve high selectivity. In addition, more "exotic enzymes" such as Mo-dependent dehydrogenases and flavin-dependent oxidases, which follow a desaturation-hydration mechanism, have also been reported to exhibit high stereoselectivity [130,131].

Both chemical and enzymatic catalysts face the challenge of overoxidation in hydroxylation reactions, where the hydroxylated product is more reactive than the starting material and can be further converted. One approach to mitigate overoxidation is in situ removal of the alcohol product from the reaction mixture, which prevents further conversion



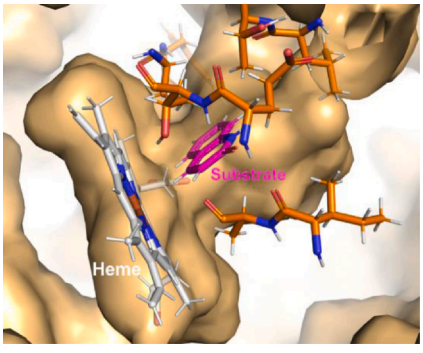


Fig. 5. Comparison of binding interactions between catalysts and starting materials at the examples of the chemo (left) [106] and biocatalytic (right) hydroxylation of 3,4-dihydroquinolin-2(1 H)-one. While in the first case essentially only two H-bond with a conformationally flexible ligand influence substrate binding, the enzyme active site offers various amino acid residues to position the starting material (the staring material was docked into the active site of P450 monooxygenase BM3 mutant using YASARA.

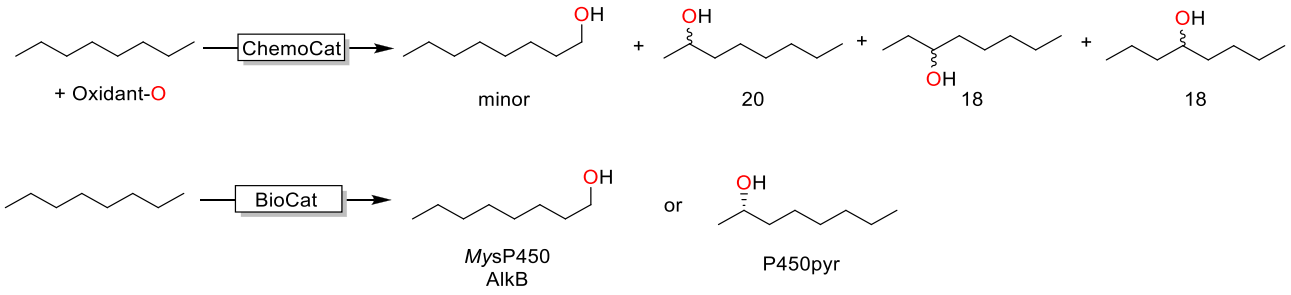


Fig. 6. Comparison of the selectivity of chemo- and biocatalytic hydroxylation. For reasons of simplicity overoxidation products have been omitted.

[132,133]. Another strategy is medium engineering, where the reaction conditions are adjusted to favour alcohol accumulation [134,135]. For enzyme catalysts, modulation of the hydrophobicity of the active site can also help to reduce the overoxidation rate [136].

Compared to hydroxylation, there are a broad range of highly enantioselective epoxidation catalysts available, including those reported by Jacobsen and Katsuki [137], Sharpless [138], Shi [139] and more (Fig. 7) [76,79]. In addition, a variety of suitable oxidoreductases are also available. For example, flavin-dependent styrene monooxygenases are proven epoxidation catalysts [40,140-146], but haem- and non-haem-dependent monooxygenases and peroxygenases can also catalyse a wide range of enantioselective epoxidation reactions. However, it should be noted that haem-dependent oxygenases may suffer from limited selectivity, as allylic hydroxylation frequently competes with epoxidation [147,148].

BV oxidation reactions also face selectivity challenges, especially with unsymmetrically substituted ketones that can yield two ester isomers, normal (NP) and abnormal (AP). In chemical BV-oxidations, stereoelectronic effects dominate the migration tendency of carbonyl substituents within the Criegee intermediate, favouring the formation of NP and yielding a product mix that reflects the starting material's regioselectivity. However, when the substituents' carbocation stabilising tendencies are similar, such as in 3-methyl cyclohexanone, the product mixture can become more complex. In contrast, some enzymatic BV-oxidation catalysts, such as the BVMO from *Aspergillus flavus*, show excellent regioselectivity by favouring the migration of the less stabilising substituent and yielding the AP. Moreover, protein engineering can further modulate the selectivity of BVMOs for either NP or AP, enabling the efficient synthesis of a specific isomer [93,149-152].

Enantioselectivity has been extensively studied in both chemical and biocatalytic Baeyer-Villiger oxidations. In the case of chemical catalysis, a number of investigations have focused on the development of enantioselective catalysts [25,26,93,153,154].

Similarly, significant efforts have been devoted to the development of biocatalytic BV-oxidation processes with high enantioselectivity [149,155-169]. These investigations have led to the development of highly enantioselective [26] in both chemical and biocatalytic BV-oxidations.

Overall, it can be concluded that selectivity is a clear strength of biocatalysis, with enzymes able to offer high selectivity for a wide range of reactions (Fig. 8). While some highly selective chemical catalysts have been developed in recent decades, biocatalysts remain unparalleled in terms of selectivity. Furthermore, enzyme selectivity can often be improved through protein engineering, making them even more attractive for use in industrial processes.

7. Environmental impact

The literature on biocatalysis often highlights the environmental benefits of using enzyme-catalysed reactions, such as the renewable nature of the catalysts, mild reaction conditions, high selectivity, and the use of water as a benign solvent [3]. However, these claims are often oversimplified, and more quantitative comparisons are necessary to accurately assess potential environmental advantages [172,173]. One useful tool for estimating the environmental impact of a reaction is Sheldon's E-factor (Eq. 4), which calculates the ratio of mass of wastes generated to mass of product produced [174].

$$E = \frac{\sum m_{\text{Waste}}}{m_{\text{Product}}} \left[\frac{\text{kg}}{\text{kg}}\right] \tag{4}$$

We conducted a comparison between a chemo- [7,8] and a biocatalytic [175] hydroxylation of ethyl benzene, based on published experimental data (Table 2). We found that both methods produced comparable amounts of waste (28.1 and 36.5 kg_{waste} $kg_{product}^{-1}$). Furthermore, in both cases, the majority of waste generated was due to the use of solvent (approximately 95%), and the contribution of the catalysts to waste generation was negligible (< 0.1%). Hence, the E-factor analysis suggests to focus on more efficient solvent use (e.g., by increasing product concentrations and/or recycling of the solvent) to reduce the amount of waste. Also, this comparison may cast some doubt on the environmental superiority claims of biocatalysis.

Although an E-factor analysis is simple and can be conducted quickly and with readily available information (from the literature or one's own labjournal), it by far does not represent the environmental impact of a given transformation. For example, the hazardousness of wastes are not taken into account by the classical E-factor, also secondary emissions caused by a reaction due to its energy requirements (e.g. electricity) are not included. Finally, also the 'history' of the reagents used is generally not taken into account for an E-factor calculation.

7.1. Hazardousness of reagents

It is self-evident that next to the sheer amount of waste, its 'quality' also determines environmental impact. For example, a highly volatile and toxic waste product will have a proportionally bigger environmental impact compared to e.g., H_2O or N_2 as by-product. To account for this, Sheldon proposed a refinement of his E-factor, the so-called EI-factor (environmental impact, Eq. 5) [176].

$$\text{EI} = \frac{\sum m_{\text{Waste},x} \bullet Q_{\text{Waste},x}}{m_{\text{Product}}} \tag{5}$$

Q is a measure for the 'environmental unfriendliness' of a given waste component and weights its overall contribution. While Sheldon remained vague about the definition of Q, Eissen and Metzger [177] proposed using semi-quantitative data such as Greenhouse effect, Ozone depletion / Ozone creation, Nutrification, Acidification, Ecotoxicology, Smog formation, Bioaccumulation, Degradability, Risk or Acute and Chronic toxicity. Bühler and coworkers performed an EI-factor comparison between a biocatalytic enantioselective epoxidation reaction and some chemocatalytic equivalents [178]. The absolute E-factor value of the biocatalytic process (ca. 20 kg kg^{-1}) was significantly higher than the E-factors of the chemical

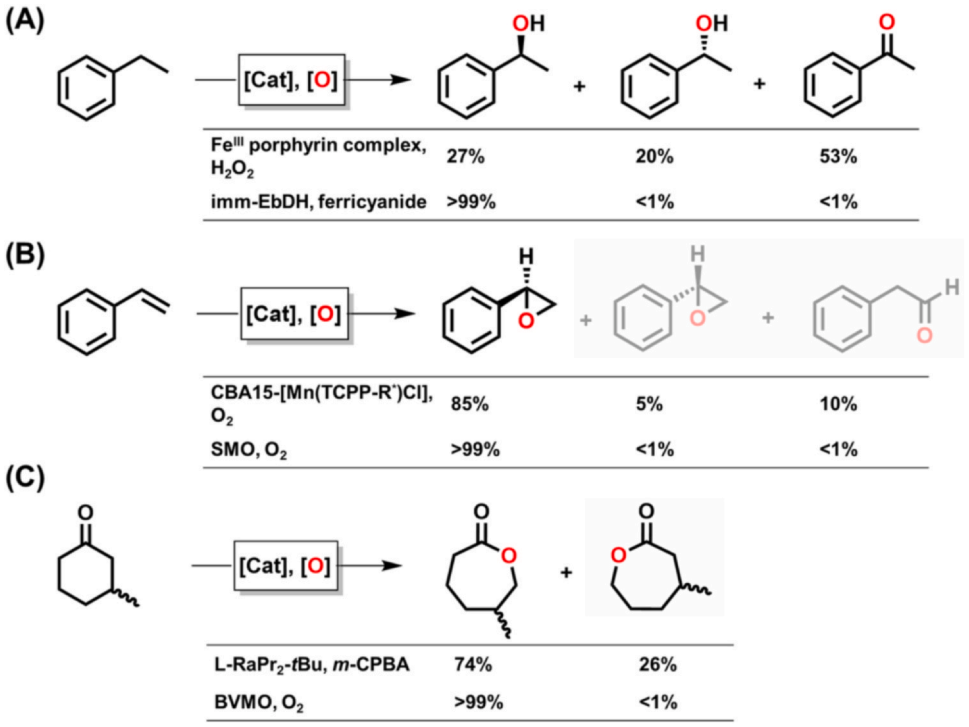


Fig. 7. Representative examples of (non)selective hydroxylation (A) [134,170], epoxidation (B) [76,171] and Baeyer-Villiger oxidation reactions, please note that racemic products were formed (C) [93,151] catalysed by chemocatalysts and biocatalysts. Details of abbreviations could be found in Table S2.

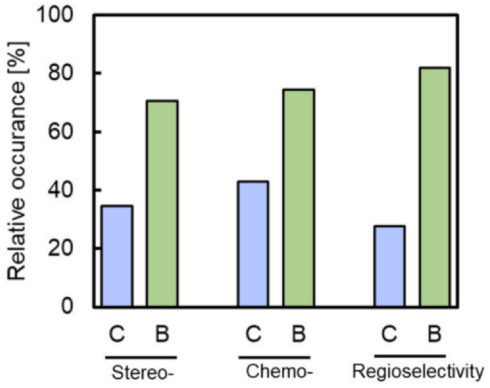


Fig. 8. Relative occurrences of the high stereo-, chemo- and regioselectivity (> 90%) in oxyfunctionalisation reactions catalysed by chemocatalysts (C, ■) and biocatalysts (B, ■). Details of abbreviations can be found in Table S3.

counterparts (2–15 kg kg^{-1}). Taking the environmental unfriendliness into account, the final result was somewhat more balanced.

Overall, the EI factor appears to provide a more realistic representation, closely resembling a life cycle assessment (LCA), of a chemical process. However, the question of transparency regarding individual weighting factors remains. Since these factors significantly influence the final result, readily accessible and transparently determined Q-values for a large number of reagents are necessary. For instance, the Q-value for water as a solvent is often set to zero (thus eliminating water as waste). However, it should be noted that contaminated reaction water should indeed be considered as waste.

Toxicity issues have been investigated widely in the case of solvents [179,180]. The GSK Solvent Guide in which solvent alternatives have been ranked according to environmental impact, toxicological and safety issues has gained a certain level of recognition [181,182].

7.2. Energy requirements

Currently, the majority of energy used in the chemical industry still comes from fossil fuels, which is responsible for significant CO_2 emissions. Since the E-factor does not take this into account, we proposed the E^+-factor to address this issue (Eq. 6) [183].

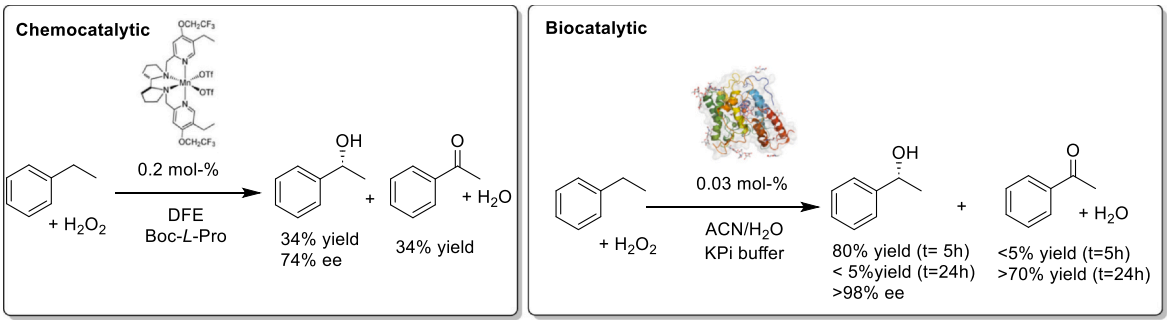
$$E^+ = \frac{\sum m(\text{wastes})}{m(\text{product})}\left[\frac{\text{kg}}{\text{kg}}\right] + \left[\frac{\text{kWh} \times \frac{\text{kg}(CO_2)}{\text{kWh}}}{\text{kg}}\right] \quad (6)$$

In essence, the E^+-factor extends the E-factor by CO_2 emissions caused indirectly due to the energy consumed for the transformation (stirring, heating, cooling, pumping, etc.). Practically, this is done by measuring the energy consumed (e.g. electricity) and multiplying this with the local carbon intensity (CI) of the energy source used.

It is important to emphasise the relationship between solvent properties and the resulting energy demands for the chemical transformation as well as downstream processing. It should be noted that distillation is a commonly used method for solvent recycling and purification, but it is an energy-intensive process. Unless powered by off-heat from other exothermic processes, it necessitates the consumption of primary energy and causes greenhouse gas emissions. Table 3 provides examples of the theoretical energy consumption for the distillative purification of some commonly used solvents. It also gives an indication of the energy consumption required for temperature adjustment during a reaction. The higher the specific heat capacity (C_p) and boiling point (b.p.) of a solvent, the higher the energy required. Based on these numbers, water may not necessarily be among the 'greenest solvents'. Also the viscosity of the reaction medium directly correlates with the energy demands for stirring and pumping.

In this regard, the biocatalytic reaction, performed at ambient temperature, appears to be more energy demanding than its chemocatalytic counterpart, which requires temperature control at –30 °C

Table 2
E-factor contribution comparison of a chemocatalytic and a biocatalytic oxyfunctionalisation of ethyl benzene.



	Chemocatalytic		Biocatalytic	
	[g g^{-1}]	[%]	[g g^{-1}]	[%]
Catalyst	0.021	<0.1	<0.02	<0.1
Additives[a]	0.76	2.7	1	2.7
Solvents[b]	27.0	95.9	34.5	94.5
Unreacted substrate and byproducts	0.37	1.3	1	2.7
Sum	**28.1**	**100**	**36.5**	**100**

[a] Chemocatalytic: Boc-L-proline (Boc-L-Pro); Biocatalytic: KPi buffer;
[b] Chemocatalytic: difluoroethanol (DFE) including H_2O from H_2O_2 addition; Biocatalytic: H_2O/MeCN (1/1).

(Table 4). Especially the significantly higher heat capacity of water compared to DFE results in a higher energy demand of temperature control in case of the biocatalytic process.

7.3. 'History' of reagents

A simple E-factor does not account for the synthetic history of the components used, i.e., the energy- and resource-consuming synthesis and waste generated during the production of the starting materials. For instance, an E-factor of 209,000 kg_{waste} kg_{AaeUPO}^{-1} has been estimated for the biocatalyst [183]. Taking this prehistory into account increases the catalyst E-factor contribution of the biocatalyst in Table 2 from < 0.02 to 4180! A similar consideration for the chemocatalyst based on the synthesis information given in Ref.[8] suggest an E-factor of only ca. 34 kg_{waste} kg_{Cat}^{-1} for the Mn-catalyst, suggesting a much lower overall contribution to the final product. However, it is important to note that, in contrast to the enzyme calculation, no CO_2 emissions due to energy consumptions have been taken into account. Therefore, both numbers are not comparable.

Jessop proposed building synthesis trees for chemicals tracing back their synthesis to the original compounds (extracted from the ground, air, or sea) [179]. A comparison of the synthesis trees for the chemo- and the biocatalyst reveals the significantly more complex prehistory of the former, indicating a much higher E-factor prehistory (Fig. 9). Therefore, a more detailed and comprehensive analysis is required to assess the true environmental impact of a reaction.

The synthesis tree also reveals that the production of enzymes is not entirely renewable. Although enzymes are biocatalysts and have renewable sources such as microorganisms, the mineral components used for their growth media are often mined from finite resources. For example, phosphate is a well-known example of a non-renewable resource. Additionally, other fermentation components such as NH_3 or MeOH, which are synthesised using natural gas as feedstock, are still dependent on fossil resources. Thus, the sustainability of biocatalysis should also consider the renewable and non-renewable resources used in the synthesis of the fermentation components and the growth media.

In terms of productivity and economic viability, it is important to note that a high E-factor for the preparation of a given catalyst does not necessarily correspond to a large impact on the production of the final product. As the performance of the catalyst increases in terms of TTN, its contribution to the overall E-factor decreases. This means that the cost contribution of the catalyst to the final product also decreases (Fig. 10).

Overall, assessing the environmental impact of a catalyst is a complex task that cannot be trivialised, and simple arguments in favour or against a particular type of catalyst may not be appropriate. It requires a comprehensive evaluation of various factors, including recyclability

Table 3
Exemplary calculation of the energy consumption (and coupled CO_2 releases) for the distillative purification of some common solvents.

Solvent	C_p [J g^{-1} K^{-1}]	b.p. [°C]	Energy consumption for distillation [kJ L^{-1}][a]	CO_2 emission produced [g (CO_2) L^{-1}][b]
Water	4.18	100	334	27.8
Toluene	1.51	110	117	9.8
Ethanol	2.4	78	110	9.2
Acetonitrile	2.25	82	110	9.2
Acetone	2.14	56	60	5

[a] assuming ambient pressure and starting from 20 °C;
[b] assuming a CO_2 intensity of 300 g(CO_2) kWh^{-1} (https://www.eea.europa.eu/ims/greenhouse-gas-emission-intensity-of-1)

Table 4
Estimated energy demand for temperature control of the reactions shown in Table 2.

	Chemocatalytic	Biocatalytic
Reaction volume [mL]	0.2	100
Product [mM]	126	188
Reaction temperature [°C]	-30	25
Reaction time [h]	0.5	6
C_p of solvent [J g^{-1} K^{-1}][a]	0.06	4.18
Q [kJ $g_{product}^{-1}$]	0.22	0.91
CO_2 [g $g_{product}^{-1}$] [b]	**0.02**	**0.08**

[a] assuming ambient pressure and starting from 20 °C;
[b] assuming a CO_2 intensity of 300 g(CO_2) kWh^{-1} (https://www.eea.europa.eu/ims/greenhouse-gas-emission-intensity-of-1)

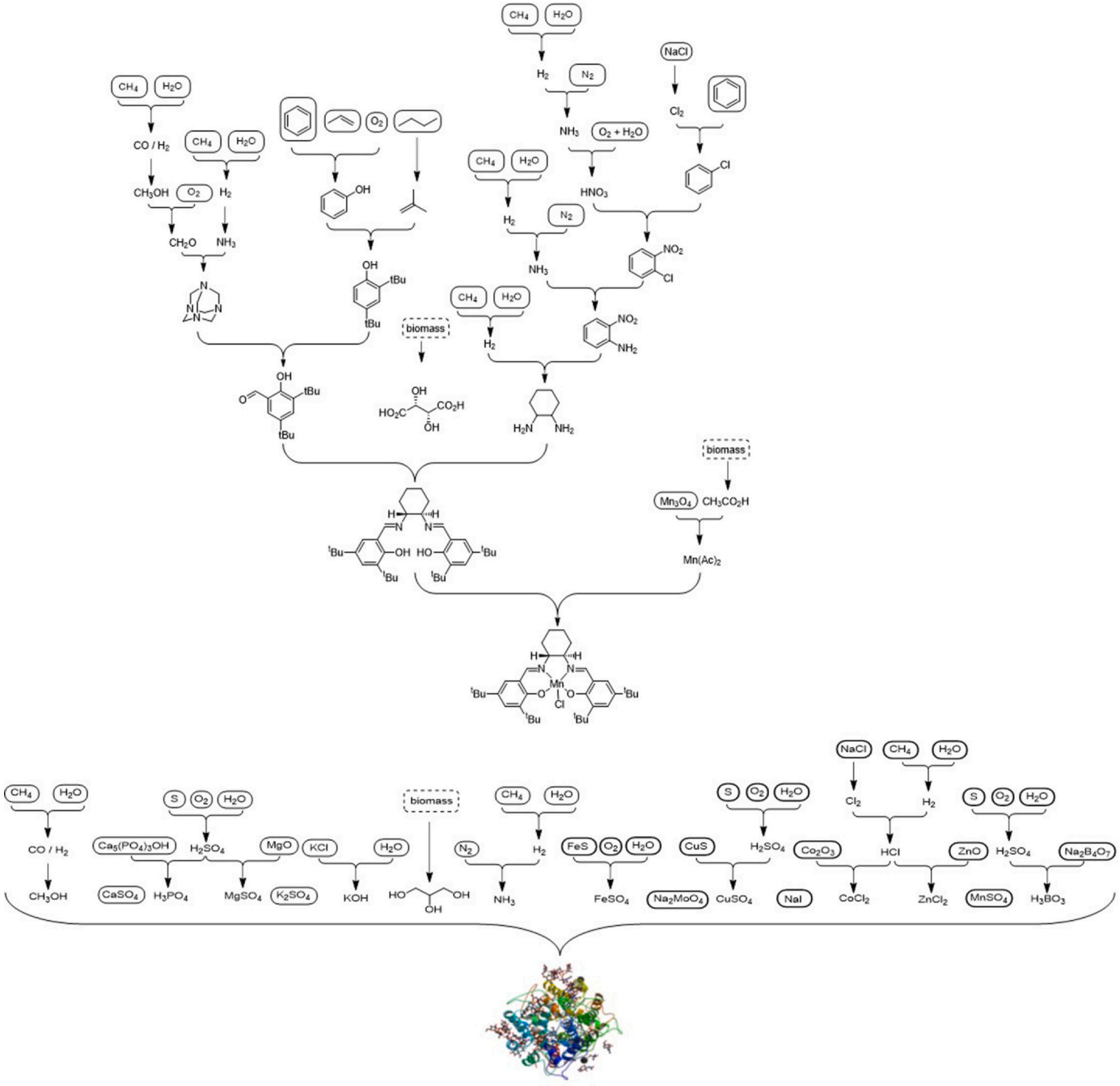


Fig. 9. Synthesis trees for the catalysts compared in Table 2 [7,132,184].

of reagents, harmfulness of wastes, energy requirements, and prehistory of the components used. In addition, it is essential to consider the relationship between solvent properties and the resulting energy demands for chemical transformation, as well as downstream processing. Therefore, a detailed analysis and life cycle assessment is necessary to make informed decisions regarding the use of a particular catalyst.

7.4. Scale-up

The term *Economy of Scale* primarily refers to the cost advantages that a company or process can achieve as production or scale increases. It often leads to lower per-unit costs as production volumes increase. In addition to the factors discussed above, including the choice of reactants, the efficiency of the catalyst, energy consumption and waste generation, scaling up production may lead to increased efficiency. In many cases, larger-scale chemical processes are more energy-efficient than smaller-scale ones. This is because heat transfer and other energy-related processes can be optimised at a larger scale, reducing overall energy consumption. In larger production sites also process integration e.g., by utilising waste heat from one process to fuel other, heat-consuming processes can reduce the overall energy demands significantly. Scaling up can lead to changes in waste generation patterns. Larger-scale

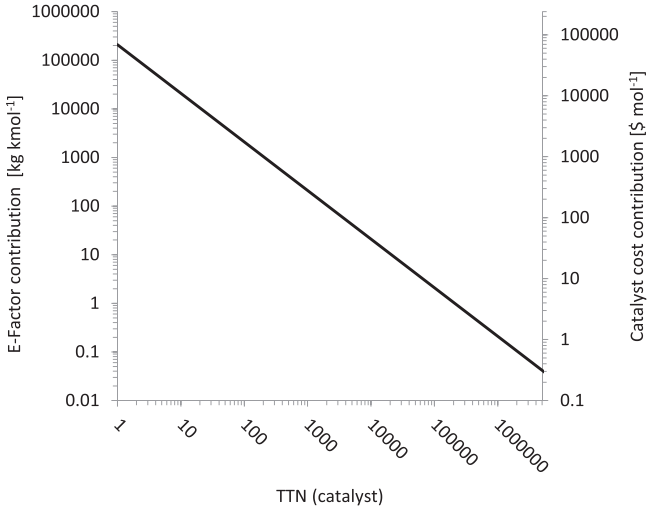


Fig. 10. Model calculation for the E-factor contribution and cost contribution for a catalyst exhibiting a prehistory E-factor of 200,000 g g^{-1} and costing 2000 \$ kg^{-1}.

processes may provide opportunities for more efficient waste management and recycling. Effective waste management strategies can mitigate the environmental impact of increased waste production. On the other hand, larger processes may locally challenge the environment, e.g., excessive water usage. Hence, the impact of scaling up can be both positive and negative, depending on various factors and how the scale-up is managed.

8. Conclusions

The environmental impact of a catalytic reaction is a complex and multi-faceted issue that cannot be adequately captured by a single metric such as the E-factor. While the E-factor provides a useful starting point for assessing the environmental impact of a reaction, it has limitations, such as not accounting for the recyclability of reagents, the toxicity of waste products, and the resource- and energy requirements of the reaction. Therefore, it is important to use a combination of metrics and approaches, including a life cycle assessment, to comprehensively evaluate, and look into the mirror, which of the chemo- or biocatalyst is the greenest for oxyfunctionalisation reactions.

It is difficult to make a definitive conclusion on which type of catalysis is greener based on the arguments above. Both chemocatalysis and biocatalysis have advantages and disadvantages in terms of environmental impact. Biocatalysis offers more selectivity and operates at ambient temperatures, yet still has the current aqueous media limitation. On the other hand, chemocatalysis is more versatile and operates under shorter reaction time, but may require harsher reaction conditions, leading to higher energy consumption and waste generation. Additionally, the environmental impact of the starting materials, catalyst synthesis, solvent properties, and downstream processing should also be taken into account (Fig. 11). Therefore, a case-by-case analysis is needed to determine which catalysis type is greener for a specific reaction.

Overall, assessing and minimising the environmental impact of catalysts is an important goal for achieving sustainable chemistry and mitigating the impact of chemical processes on the environment. By using a multi-faceted approach to evaluate catalysts and focusing on sustainable design principles, we can move towards a more sustainable future for the chemical industry. Moreover, it is indeed interesting to extend this line of thinking to other chemical reactions as well. This broader perspective allows for a comprehensive and holistic approach to reduce the environmental footprint of chemical processes.

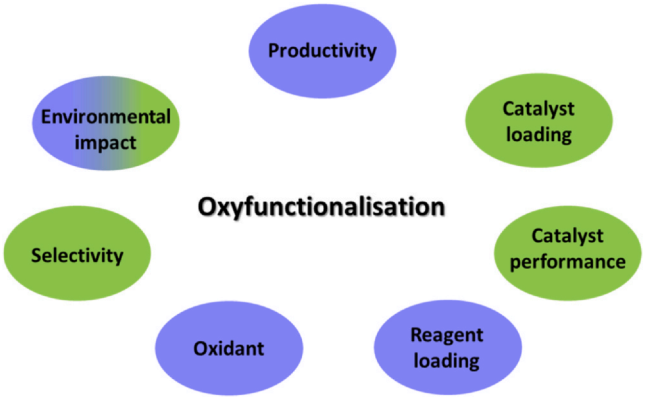


Fig. 11. The advantage of chemocatalysis (●); the advantage of biocatalysis (●).

Declaration of Competing Interest

Frank Hollmann is an editorial board member for Green Carbon and was not involved in the editorial review or the decision to publish this article. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.greenca.2023.10.004.

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