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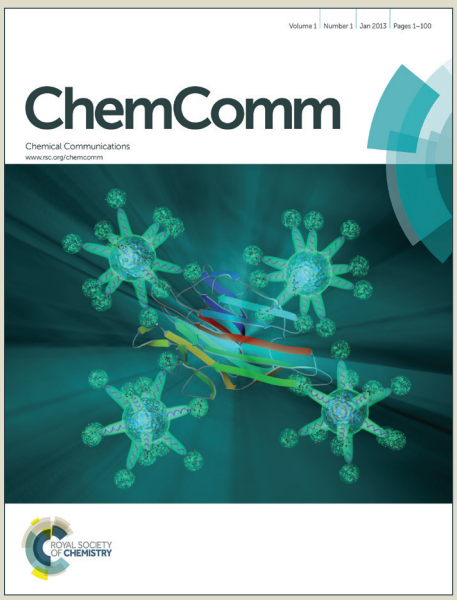

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The taming of oxygen: biocatalytic oxyfunctionalisations

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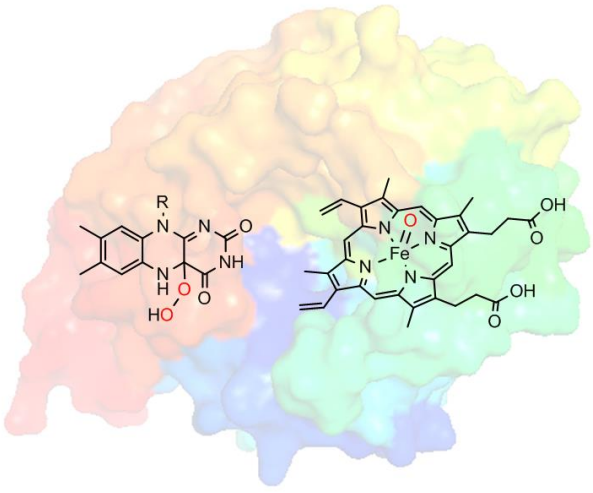
Introduction

Selective oxyfunctionalisation of non-activated hydrocarbons represents a contemporary issue of organic chemistry. The inertness of most C-H bonds requires powerful oxygen transfer agents.[1] High activity, however, is frequently accompanied by poor selectivity, which is in contrast to the demands of modern chemical synthesis.[2]

Nature provides us with a class of catalysts, that comprises both features: activity and selectivity: Oxygenases catalyse the introduction of oxygen atoms from molecular oxygen or hydrogen peroxide into (non-)activated C-H- and C=C-bonds and to heteroatoms. Often, these oxyfunctionalisation reactions occur highly selectively. Many oxygenases are selective for only one position in structurally complex molecules and they introduce the oxygen atoms with high stereocontrol. Furthermore, overoxidation, which is a frequent problem in chemical oxyfunctionalisation, is far less observed in enzymatic oxyfunctionalisations. This unique combination of activity and selectivity stems from the embedding of reactive oxygen transfer reagents such as highly oxidised iron-oxo complexes or organic peroxides in the cavity of an enzyme's active site. The well-defined and chiral environment not only positions the starting material precisely to the 'hot' oxygen atom transferred (accounting for selectivity) but also stabilises transition states thereby leading to, sometimes dramatic, rate accelerations as compared to the biomimetic analogues (Scheme 1).



Scheme 1. Oxygenases comprise highly reactive oxygenation agents such as (formal) Fe^{V}-oxyferryl-heme, or (hydro)peroxo-flavins embedded in the well-defined framework of an enzyme. [3]

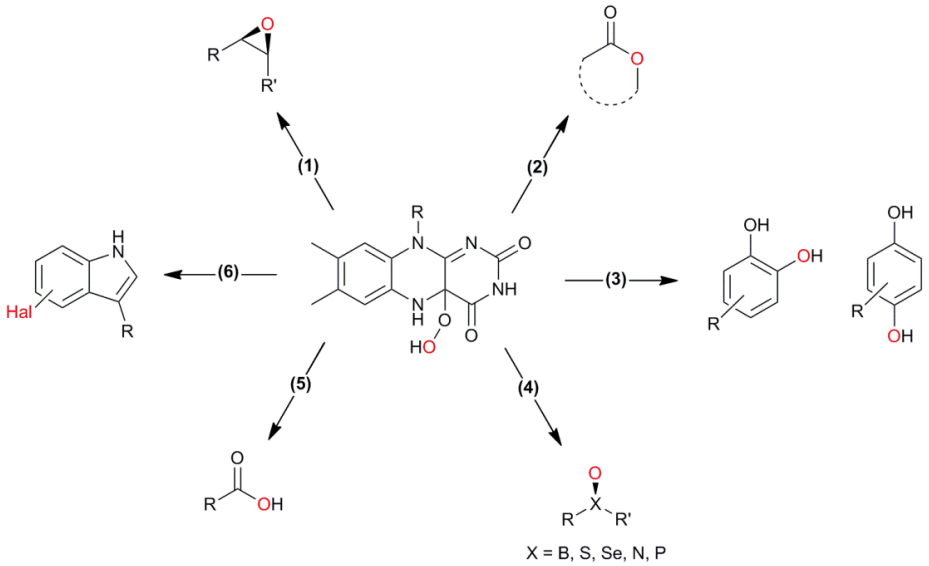
Therefore, it is not very astonishing that the interest in biological oxyfunctionalisation chemistry has been steadily growing over the past decades. We are convinced that oxygenases, following the well-established hydrolases[4-6]and the ever more popular dehydrogenases,[5, 7-10] will represent the next upcoming wave of biocatalysts used in chemical synthesis.[11]

The aim of this perspective is to encourage organic chemists to consider oxygenases in their synthesis planning more often. For this, we will focus on the application of oxygenases for organic synthesis, giving an overview over the rich product spectrum available already today and discussing some recent preparative examples. In particular, we will cover the most-common oxygenases, i.e. flavin-dependent monooxygenases as well as heme-dependent monooxygenases and –peroxygenases. Also some perceived and real limitations *en route* to becoming truly practical catalysts, together with some promising solutions will be discussed. A detailed discussion of the catalytic mechanisms would be beyond the scope of this perspective; the interested reader is referred to some excellent reviews [5, 6, 12-14] exhaustively covering our current mechanistic understanding.

It is also worth mentioning here that continuously new oxygenases are discovered as well as existing ones are improved to match with the requirements of chemical synthesis.[1, 10, 12, 14-35] Again, an in-depth discussion of these approaches, let alone the new enzymes obtained is not possible here; but some excellent recent contributions exhaustively cover this field.

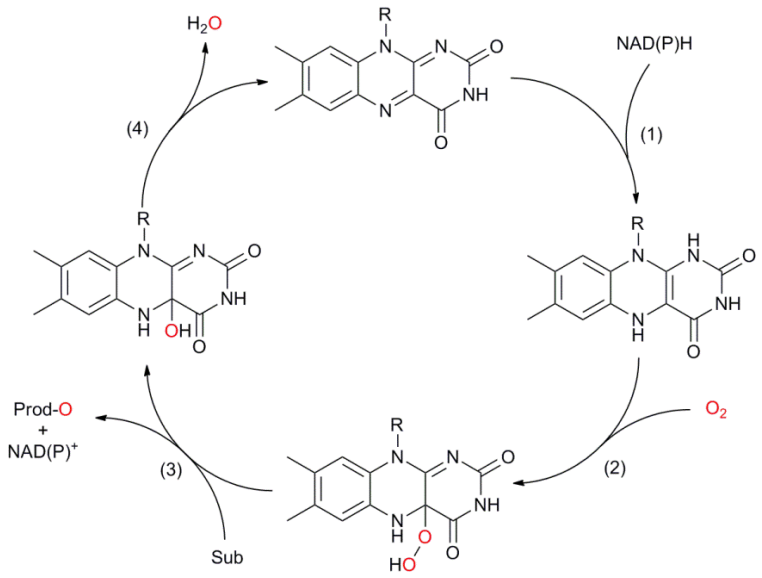
Flavin-dependent monooxygenases

Flavin-dependent monooxygenases represent an extremely diverse class of enzymes catalysing an equally diverse range of synthetically useful oxyfunctionalisation reactions (Scheme 2)[28-30, 33, 36-40].



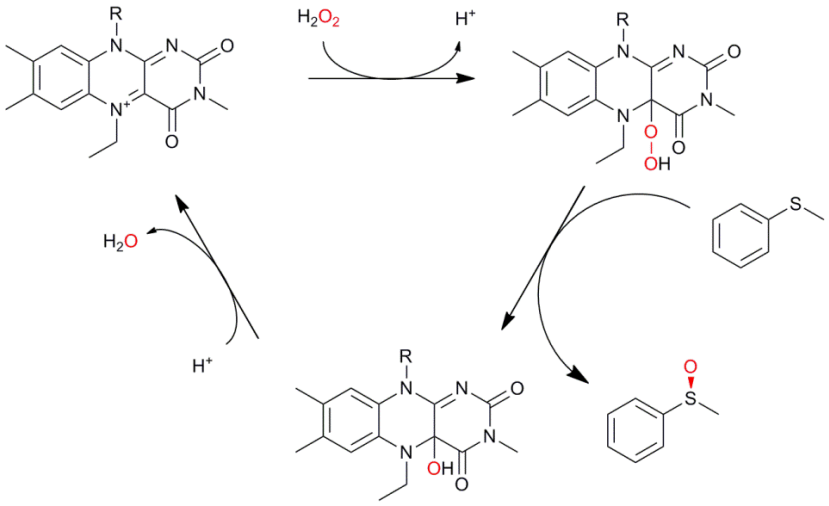
Scheme 2. 4a-(hydro)peroxoflavin as the active species leading to the diverse reactions catalysed by flavin-dependent monooxygenases. (1) Epoxidation of C=C-doube bonds, (2) Baeyer-Villiger oxidation of (cyclic) ketones, (3) *ortho*- and *para*-hydroxylation of phenols, (4) heteroatom oxygenation, (5) oxidation of aldehydes, and (6) halogenation reactions.

The catalytic mechanism of the flavin-dependent monooxygenases comprises an oxidative and a reductive half reaction. The catalytic cycles start with the latter by NAD(P)H-mediated reduction of the enzyme-bound flavin group. The reduced flavin interacts with molecular oxygen to form an organic peroxide (C4a-(hydro)peroxoflavin), which acts as the actual oxygen transfer agent (oxidative half reaction). The resulting C4a-hydroxyflavin eliminates water and thereby returns into the oxidized resting form. Only very recently an alternative mechanism for oxygenation by a flavoprotein has been revealed.[41] It was shown that the bacterial enzyme EncM, involved in the biosynthesis of the antibiotic enterocin, performs an coenzyme-independent oxygen insertion via a reactive flavin N5-oxide. In this specific example, the reducing equivalents come from the substrate itself. It remains to be seen whether this is a rare example or whether there are more flavoproteins in nature that employ such a mechanism.



Scheme 3. Simplified catalytic cycle of flavin-dependent monooxygenases. In the resting state of the enzyme the reduced nicotinamide cofactor (NAD(P)H) binds to the enzyme and transfers its hydride to the alloxazine moiety (1). In step (2) the reduced flavin reacts with molecular oxygen yielding the catalytically active (hydro)peroxoflavin, which, in step (3) performs the oxyfunctionalisation reaction. The resting state is regenerated after water extrusion (step (4)). Please note that for reasons of simplicity, protonation steps have been omitted from the scheme.

In principle, the chemical versatility of flavins should also allow for H_2O_2-driven oxyfunctionalisation reactions as frequently demonstrated with N5-alkylated flavins as 'chemical catalysts'.[28] Recently, Fraaije and coworkers have demonstrated that flavoproteins can be engineered to act as peroxygenases by replacing the riboflavin cofactor in riboflavin-binding protein with alkylated flavins. Overall the general feasibility of 'flavoperoxygenases' could be demonstrated (Scheme 4).[42]



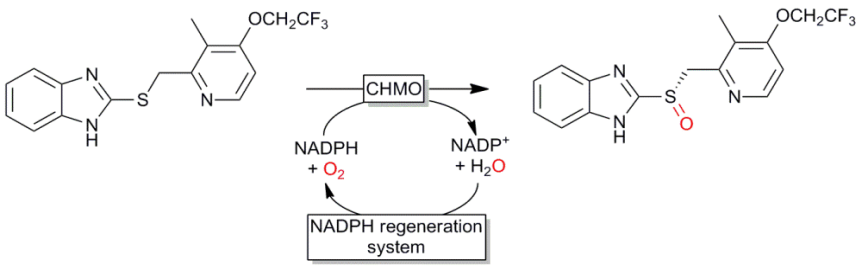
Scheme 4. Simplified scheme of a 'flavoperoxygenase' mechanism.

Organic chemists are probably most acquainted to the enzymatic Baeyer-Villiger oxidation mediated by so-called Baeyer-Villiger monooxygenases (BVMOs, Scheme 2, 2). Since some early contributions from the mid-20th century[43-45] and the pioneering works by Trugdill and coworkers[46, 47] the scope of enzymatic Baeyer-Villiger reactions has been expanded significantly in the last two decades[31, 48-50] and a range of synthetically useful transformations have been reported (**Table 1**). Also, the first crystal structure of a BVMO[51] has significantly contributed to the mechanistic understanding of BVMOs[52, 53] and enabled rational approaches to engineer tailored new BVMOs.[54-64] Today, the enzymatic Baeyer-Villiger oxidation (in form of whole cell biotransformation, *vide infra*) has reached the multi-kg scale[65-68] and further scale-ups and industrial applications may be expected in the nearer future.

A special case of BVMO-catalysed Baeyer-Villiger oxidations is the oxygenation of aldehydes (Scheme 2, 5). In most cases, BVMOs convert aldehydes into the corresponding formyl esters (following the migration rules of the chemical Baeyer-Villiger oxidation). However, recently Bisagni and coworkers reported on a novel BVMO from *Dietzia* sp preferentially catalysing acid formation of e.g. profene aldehydes.[69]

Many of the aforementioned BVMOs are also capable of heteroatom oxygenation (Scheme 2, 4). Enantiospecific sulfoxidation here clearly represents the reaction most frequently investigated.[30, 70-74] Next to the often high enenatioselectivity of this reaction, also its high chemoselectivity is valued as the 'overoxidation product' i.e. the corresponding sulfone is usually not observed in enzymatic sulfoxidation reactions. Next to sulphur also other heteroatoms such as selenium,[75-78] boron,[77, 79] or nitrogen[48] can be oxygenated using flavin-dependent monooxygenases. Recently, Codexis evolved cyclohexanone monooxygenase for the selective sulfoxidation to yield enantiopure (*S*)-pantoprazole (Scheme 5), [74, 80] thereby impressively

demonstrating the potential of protein engineering to tailor a monooxygenase to meet the requirements of industrial-scale synthesis.



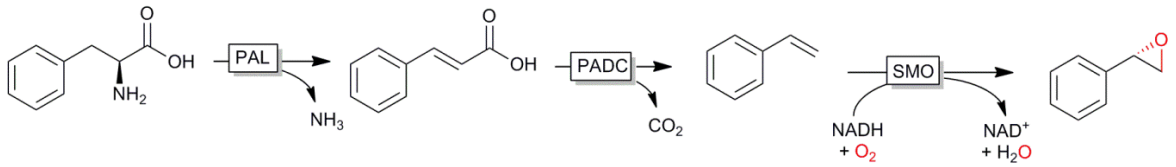
Scheme 5. Cyclohexanone monooxygenase (CHMO)-mediated enantiospecific sulfoxidation for the synthesis of (*S*)-pantoprazole.

Also the regioselective hydroxylation of phenols (Scheme 2, 3) either in *ortho*- or *para*-position represents a principally highly interesting reaction for organic synthesis as the repertoire of chemical aromatic hydroxylations (apart from Dakin-, Sandmeyer- and Baeyer-Villiger-type reactions as well as boronic acid oxidations) is rather limited. However, at present also the number of phenol hydroxylases is rather restricted as well.[81] Nevertheless for example, 2-hydroxy biphenyl-3-monooxygenase (HbpA) has been used at up to kg-scale synthesis of catechols.[82-89] But also phenol hydroxylase (PheA1),[90-93] and the benzoate hydroxylases[94-96] have been reported and might exhibit some synthetic potential.

Stereoselective epoxidation of C=C-double bonds (Scheme 2, 1) is an emerging field in flavoprotein-monooxygenase chemistry. Especially the so-called styrene monooxygenases are enjoying increased popularity. For example the styrene monooxygenase from *Pseudomonas* sp. VLB 120 has been investigate intensively by Schmid and coworkers.[97-114] But also new styrene monooxygenases from other sources are constantly added to the portfolio.[32, 115-121]

Currently, the styrene monooxygenases available appear to have a clear preference for vinyl aromatic substrates even though also aliphatic alkenes have been reported as substrates.[119, 120] The more severe limitation of the present portfolio is that exclusively (*S*)-selective styrene monooxygenases are known. Hopefully, screening of natural diversity and/or protein engineering will close this gap in the nearer future.

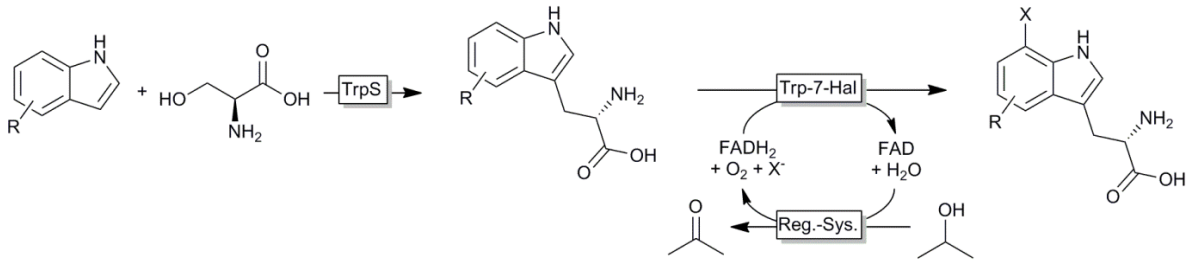
An interesting cascade reaction producing enantiomeriacally pure (*S*)-styrene oxide from (renewable) phenylalanine in a cascade of amino lyase, decarboxylase and styrene monooxygenase was reported recently by Nielsen can coworkers (Scheme 6).[122]



Scheme 6. Cascade from natural phenylalanine to (*S*)-styrene oxide entailing phenylalanine ammonia lyase (PAL), phenoloic acid decarboxylase (PADC) and styrene monooxygenase (SMO).

Also, flavoprotein monooxygenase-catalysed oxidative halogenation reactions (Scheme 2, 6) are worth mentioning here. In the stricter sense, these reactions are not oxyfunctionalisation reactions as a halogen is incorporated instead of an oxygen atom.[123-133] According to our present knowledge, flavin-dependent halogenases primarily catalyse the oxidation of halogenides to hypohalous acids (HOCl, HOBr). These are guided by the protein backbone directly and exclusively to the substrate performing the electrophilic halogenation reaction. Even though, flavin-dependent halogenases seem to be limited to activated (aromatic) substrates, their exclusive regioselectivity should make them highly interesting tools not only for pharmaceutical applications. However, *en route* to preparative application their still comparably poor catalytic activity (k_{cat} being in the range of <1 min^{-1}) needs to be addressed.

Very recently, an interesting cascade of tryptophan synthase and tryptophane-7-halogenase was reported giving access to a broad range of tryptophan derivates from simple indole starting materials (**Scheme 7**).[134]

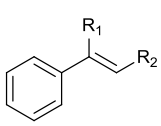
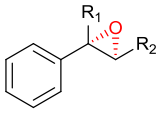
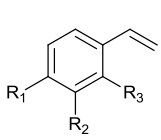
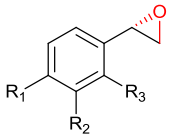
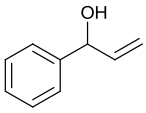
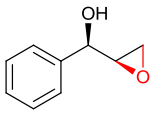
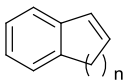
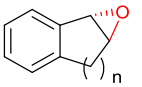
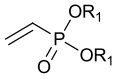
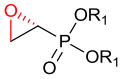
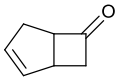
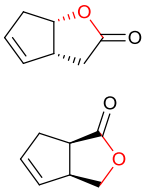


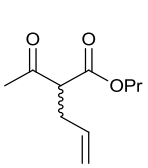
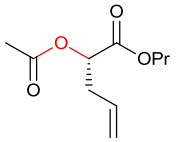
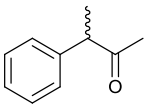
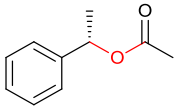
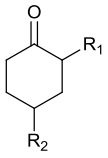
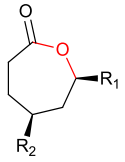
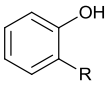
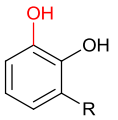
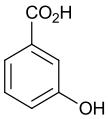
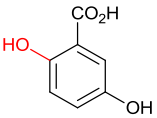
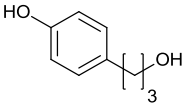
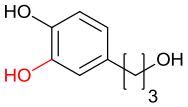
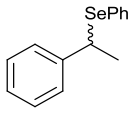
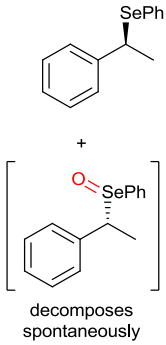
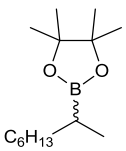
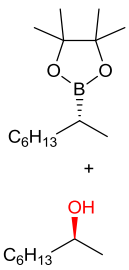
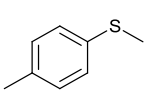
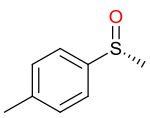
Scheme 7. Cascade for the synthesis of unnatural halogenated tryptophanes from simple indoles. TrpS: tryptophan synthase; Trp7-Hal: tryptophan-7-halogenase; Reg.-Sys.: $FADH_2$-regeneration system comprising a NADH:FAD oxidoreductase, NADH and an alcohol dehydrogenase.

Finally, also a newly discovered long-chain alkane degrading flavoprotein monooxygenase (LadA) should be mentioned here.[135, 136] So far, this is the only flavin-dependent monooxygenase reported capable of hydroxylating non-activated hydrocarbons (being largely the domain of (non)-heme iron monooxygenases, *vide infra*). At present, only few reports deal with this interesting enzyme and future will tell the preparative potential of LadA.

A representative selection of examples ranging from analytical proof-of-concept contributions to (near) industrial scale implementations is shown in **Table 1**.

Table 1. Representative examples of oxyfunctionalisation reactions mediated by flavin-dependent monooxygenases.

Substrate	Product	R	% Conv. (% Yield)	Catalyst	ee (%)	Volumetric scale	Remarks	Ref.
(1) Epoxidation reactions								
		R_1=H, R_2=Me	(87)	SMO (rec in growing *E .coli*)	>99 (*S*)	1 L	$[S]_0$=695 mM; t=8 h;	100
		R_1=H, R_2=Me	95 (87)	SMO (crude cell extract)	99.7 (*S*)	100 mL	$[S]_0$=50 mM; t=10 h; $TON_{(SMO)}$=1844	114
		R_1=R_2= H, R_3=F, Cl, Br, Me	(90, 70, 31, 62)	SMO (rec in resting *E .coli*)	All >99.9 (*S*) except 62.8 (*S*) for Me	1 mL	$[S]_0$=200 mM; t=24h;	119, 120
		R_1=R_3= H, R_2= Cl	91 (73)	SMO (crude cell extract)	>99.9 (*S*)	100 mL	$[S]_0$=50 mM; t=10 h; $TON_{(SMO)}$=2171	114
			(50)	SMO (rec in resting *E .coli*)	>99 epoxide (de=98%)	20 mL	$[S]_0$=4,5 mM; t=2h	137, 138
		n=1	(48)	SMO (rec in growing *E .coli*)	98 (*S*)	1 L	$[S]_0$>150 mM; t=19h	112
		n=2	(53)	SMO (rec in growing *E .coli*)	98.5(*S*)	1 L	$[S]_0$>150 mM; t=45 h	**112**
		R_1=Et, Me	40, 10	CHMO (partially purified enzyme)	≥98 (*R*)	10 mL	$[S]_0$=12 mM; t=48 h;	**139**
(2) Baeyer-Villiger oxidations								
			>99 (58)	CHMO (rec in growing *E .coli*)	99% (1R,5S) 97 (1S,5R)	50 L	900 g; $[S]_0$ >0.1 M; t=20 h	65, 66
						200 L	Fed-batch 4.5 g/L ; ($[S]_{total}$=36 mM); t=7 h	140

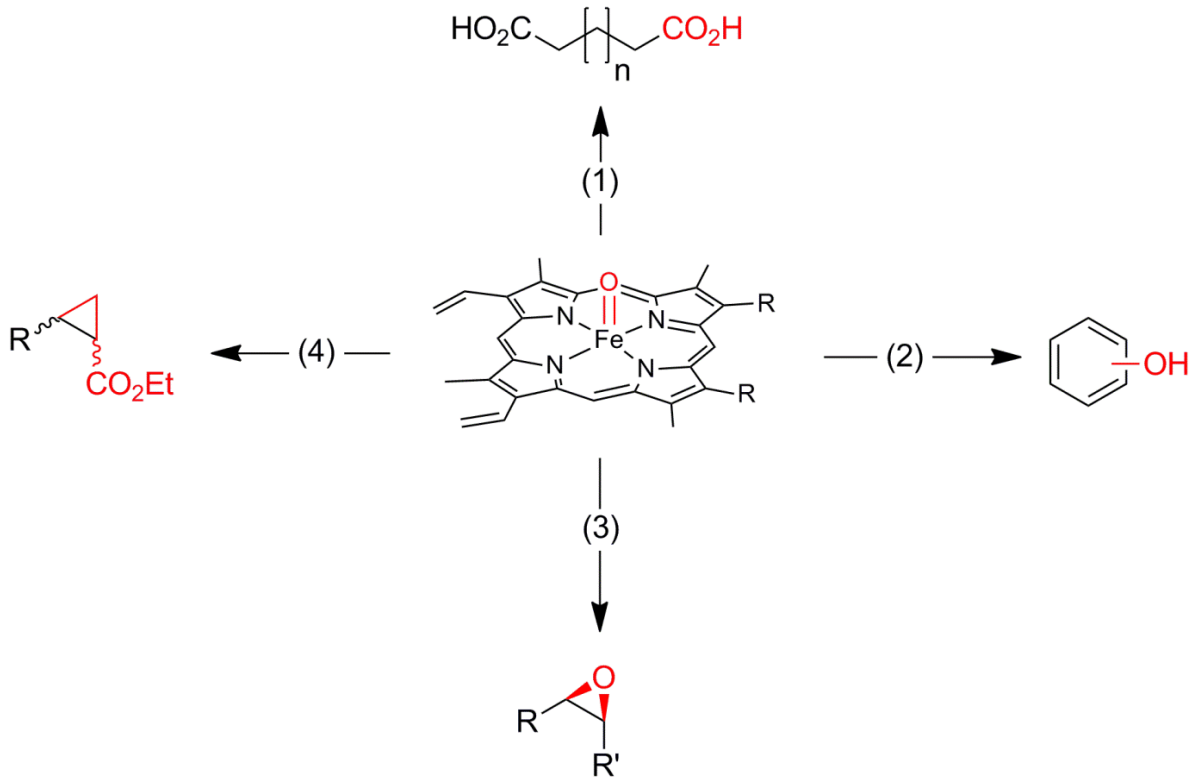
			>99	PAMO (partially purified enzyme)	>99 *(S)*	13 mL	$[S]_0$ >20 mM; t=24 h; DKR	70
			47	HAPMO (partially purified enzyme)	>98 % (Product) E>100	50 mL	KR; $[S]_0$ =5.4 mM	141
		R_1, R_2= Me, Et, *n*Pr, *i*Pr, *n*Bu, allyl (independently)	50	CHMO (partially purified enzyme)	E>200	1 mL	KR or Desymmetrization; $[S]_0$ =2 mM; t=2 h	142
(3) Phenol hydroxylation reactions								
		R=alkyl, aryl	>99	HbpA (partially purified enzyme)		10 mL	$[S]_0$ =160 mM; t=600 h Up to 160 mM	85, 86
			>99	3HB6H (purified enzyme)		1 mL	$[S]_0$=50 mM; t=8 h	92, 143
			>99	PheA1 (rec in growing *E .coli*)		50 mL	$[S]_0$=5 mM; t=10 h	90
(4) Heteroatom oxygenations								
			50%	PAMO (purified enzyme)	99 (unreacted enantiomer)	1 mL	KR; $[S]_0$=10 mM; t=24 h	75, 76
			49	PAMO (purified enzyme)	*E*=23	0.5 mL	KR; $[S]_0$=10 mM; t=24 h	79
			(45)	SMO (rec in resting *E .coli*)	54.5 (*S*)	1 mL	$[S]_0$=200 mM; t=24h	119, 120

SMO: styrene monooxygenase; CHMO: cyclohexanone monooxygenase; BVMO: Baeyer-Villiger monooxygenase; PAMO: phenylacetone monooxygenase; HAPMO: 4-hydroxyacetophenone monooxygenase; HbpA: 2-hydroxy biphenyl-3-monooxygenase; PheA1: phenol hydroxylase; 3HB6H: 3-hydroxy benzoate-6-hydroxylase; (D)KR: (dynamic) kinetic resolution.

Overall, flavin-dependent monooxygenases bear a great potential for organic synthesis. They enable highly selective introduction of molecular oxygen into organic compounds. Very often, a comparable chemical route is yet unknown. Unfortunately, at present time only a few of these promising catalysts are commercially available (e.g. some BVMOs).

Heme-iron-monooxygenases and –peroxygenases

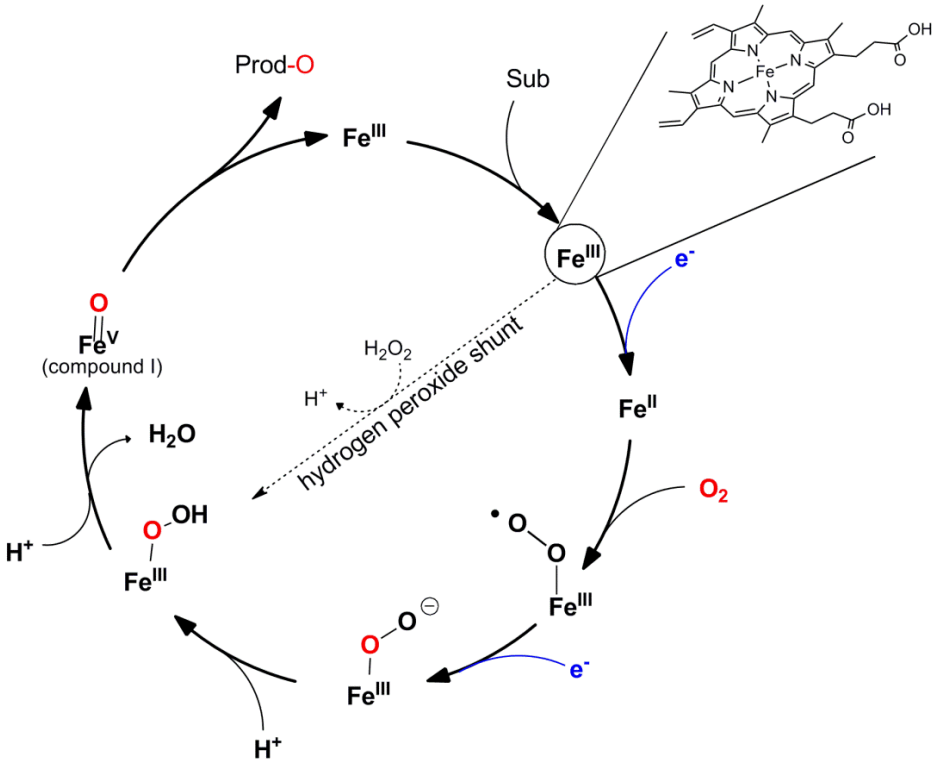
Heme-iron-monooxygenases, also called P450- or CYP- monooxygenases, exhibit an even higher oxyfunctionalisation potency than most of the flavoprotein monooxygenases discussed above. P450 monooxygenases can also abstract non-activated C-H bonds such as in alkanes. Obviously, this has inspired many research groups worldwide to explore the catalytic potential of this enzyme class (Scheme 8).[20, 21, 144-147]



Scheme 8. Compound I as the active species leading to the diverse reactions catalysed by P450-monooxygenases and peroxidases. (1) Hydroxylation of (non)activated C-H-bonds[148-153] even of methane;[154, 155] (2) hydroxylation of aromatics; [156] (3) Epoxidation of C=C-double bonds; (4) Carbene transfer to C=C-double bonds (actually starting from the reduced Fe^{II} stage and not being an oxyfunctionalisation reaction).[157]

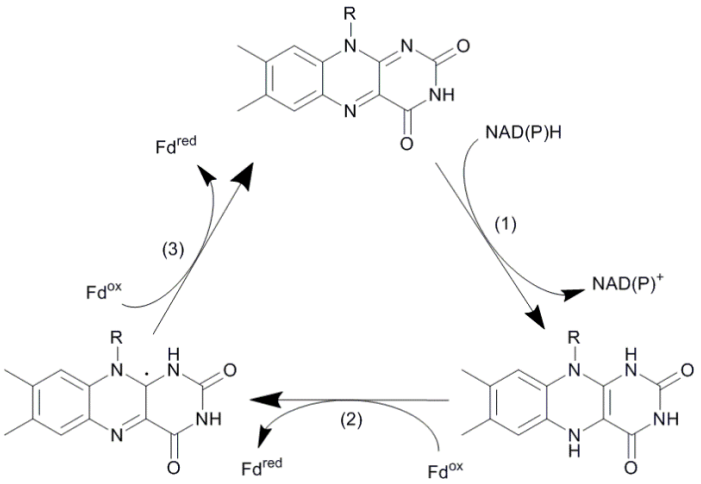
P450 monooxygenases comprise a somewhat more complicated mechanism than flavoprotein monooxygenases. Molecular oxygen is activated by coordination to a highly oxidized (formally

Fe^{V}) iron species enabling electrophilic O-transfer. To achieve this, two additional reducing equivalents are necessary, which are delivered in two individual single electron transfer steps (Scheme 9).



Scheme 9. Simplified catalytic cycle of P450-monooxygenases. The catalytic cycle starts with binding of the substrate to the resting (Fe^{III}) state of the enzyme followed by single electron transfer (from NAD(P)H via the electron transport chain), O_2-binding and the second electron transfer. The resulting hydroperoxo iron is dehydrated after successive protonation resulting in a (formal) Fe^{V}-oxo species (compound I) performing the O-transfer reaction. The intermediate hydroperoxo ironcan also be formed directly from the resting state by addition of H_2O_2 (hydrogen peroxide shunt).

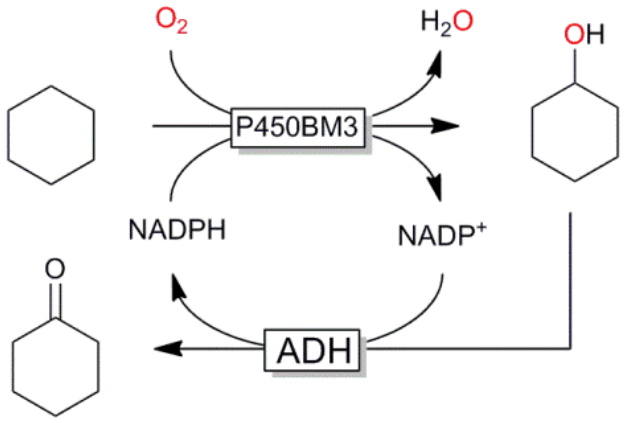
Again, NAD(P)H serves as source for the reducing equivalents needed. However, since NAD(P)H is an obligate hydride donor, it is not capable of interacting directly with the iron centre (being an obligate single electron acceptor). To overcome the mechanistic incompatibility of NAD(P)H and Fe^{3+}, nature uses e.g. NAD(P)H-ferredoxin oxidoreductases as relay systems. These enzymes contain flavins, which due to their mechanistic versatility, can accept a hydride from NAD(P)H and pass on the two electrons in two subsequent steps either to the monooxygenase directly or via electron transport proteins such as Fe_2S_2 ferredoxin (Scheme 10).



Scheme 10. Transformation of a hydride transfer reagent (NAD(P)H) into two single electron transfer reagents (e.g. ferredoxin, Fd). NAD(P)H:Ferredoxine oxidoreductases catalyse the oxidation of NAD(P)H (by hydride transfer to the enzyme-bound flavin cofactor, step (1)). The reduced flavin than successively delivers one electron each to two ferredoxines (Fd).

It is worth mentioning here, that some P450 monooxygenases are capable of forming the catalytically active oxyferryl species from the resting state using hydrogen peroxide (Scheme 9). However, usually, their efficiency with H_2O_2 is relatively poor so that oxidative inactivation of the heme-prosthetic group (and the protein backbone) dominates. In contrast, the so-called peroxygenases utilise this hydrogen peroxide shunt pathway very efficiently enabling H_2O_2-driven P450-oxyfunctionalisation chemistry. In fact, it has been hypothesised that the P450 monooxygenases have evolved from H_2O_2-dependent ancestors.[158]

P450 monooxygenases have received tremendous attention due to their capability to hydroxylate non-activated C-H bonds. For example, the selective and mild hydroxylation of (cyclo)alkanes represents a focus of research. The promise here lies in the high selectivity of the enzymatic hydroxylation avoiding undesired overoxidation of the (more reactive) reaction products as frequently encountered in (industrial) oxidation methods.[159] A very recent contribution by Gröger and coworkers nicely demonstrates the synthetic potential of biocatalytic oxyfunctionalisation (Scheme 11).[160, 161] By combining a P450-monooxygenase with an alcohol dehydrogenase, the authors achieved clean aerobic oxidation of cyclohexane to cyclohexanone with absolute selectivity. The overall low yield of the reaction (<10%) most probably is attributed to the volatility of the reagents and the non-optimised reaction conditions. Nevertheless, the high selectivity of this reaction convinces especially compared to chemical processes, where frequently by-products originating from overoxidation and ring-cleavage are observed.[159]

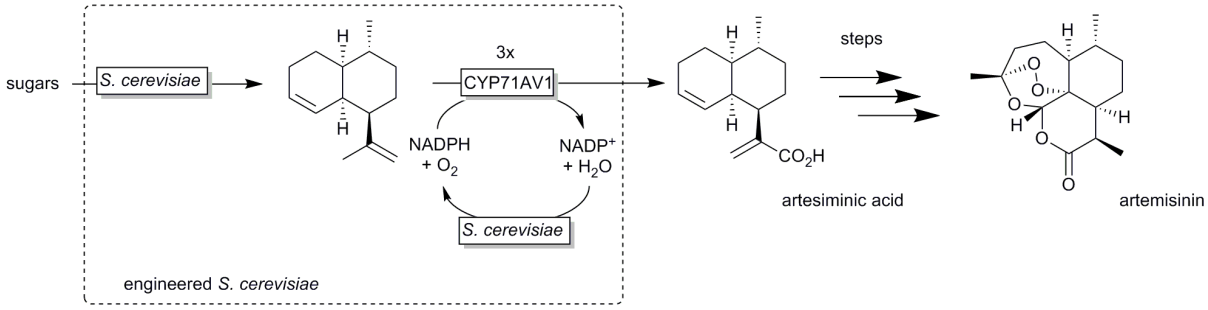


Scheme 11. Bi-enzymatic cascade for the selective aerobic oxidation of (cyclo)alkanes to the corresponding ketones using a sequence of P450 monooxygenase-catalysed hydroxylation (here P450BM3 from Bacillus megaterium) and ADH-catalysed further oxidation to the ketone.

Similar examples comprise the selective transformation of (cyclo)alkanols into the corresponding esters (e.g. cyclohexanol to ε-caprolactone). [162, 163]

Industrial interest in P450 monooxygenases today mainly stems from the pharmaceutical industry for the generation of drug metabolites and the production of active pharmaceutical ingredients (APIs) such as steroids.[26, 146, 147, 164, 165] But also selective oxyfunctionalisation of terpenes is of great interest.[152, 166-173]

A very elegant approach was reported by Keasling and coworkers who used an engineered *Saccharomyces cerevisiae* overexpressing a P450 monooxygenase to produce Artemisinic acid (basically from sugar) (Scheme 12).[174, 175]



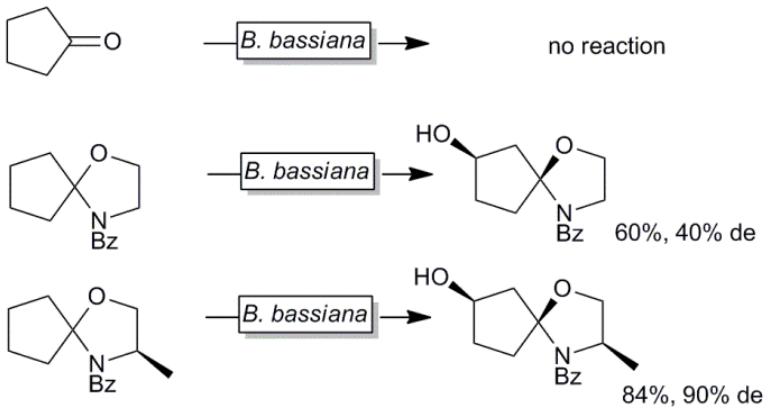
Scheme 12. Engineered *Saccharomyces cerevisiae* overexpressing a P450 monooxygenase (CPY71AV1) for the selective (triple) oxygenation of amorpha-3,11-diene to artemisinic acid, a precursor for the anti-malaria drug artemisin.

Often, P450 monooxygenase-catalysed reactions still are somewhat too slow and yield too low product titers (*vide infra*)[26] to meet the economic requirements for bulk chemicals.[176]

Nevertheless, oxyfunctionalisation of fatty acids to yield α,ω-dicarboxylic acids (as polymer building blocks) has been demonstrated at appreciable product titres of more than 100 gL^{-1}[177-180] pointing towards large-scale applicability of these biocatalysts.

For a long time, methane hydroxylations was believed to be limited to non-heme iron monooxygenases and out of scope for P450-monooxygenases. Especially the higher bond-strength of the methane C-H bond as compared to higher homologues was thought to be the mayor reason for this.[154] However, recently Reetz and coworkers have demonstrated that inert decoy molecules such as perflourinated acids enable the P450BM3-catalysed hydroxylation of even methane.[155] It is thought that the perfluorinated alkyl chain 'fills up' the large cavity around the active site and thereby facilitates methane binding. The same approach (decoy molecules) was also successful in enhancing P450BM3-catalysed hydroxylation of e.g. benzene. [156, 181] It is also interesting to note that such decoy molecules may have an influence on the stereoselectivity of P450-catalysed oxyfunctionalisation reactions.[182]

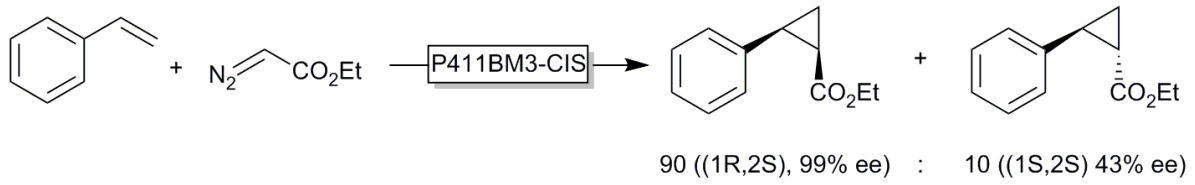
Next to protein engineering [20, 158, 164, 183-189] also substrate engineering may be a promising approach to improve P450-monooxygenase-catalysis as demonstrated by Griengl and coworkers.[190-193] For example *Beauveria bassiana* cannot convert cyclopentanone whereas the corresponding N-benzoylspirooxazolidine was converted smoothly by the same organism (Scheme 13).



Scheme 13. Effect of temporary attachment of an oxazolizine protection group to cyclopentanone on the biohydroxylation by *B. bassiana*.

It was suggested that the starting material itself was not efficiently recognised by the monooxygenase. Also the nature of the temporary protecting group had an influence on the stereoselectivity of the hydroxylation reaction. So far, this approach has not found widespread and systematic investigation.

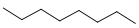
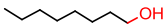
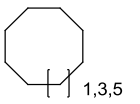
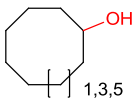
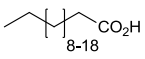
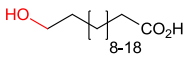
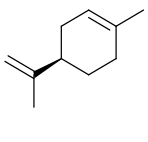
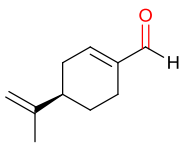
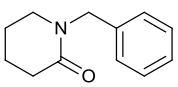
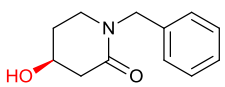
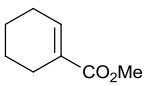
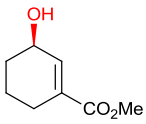
Another exciting new development in P450-chemistry is the recent finding by Arnold and coworkers that reduced (Fe^{II}) P450 monooxygenases are efficient cyclopropanation catalysts (Scheme 14) opening up new avenues for P450-chemistry.[157]

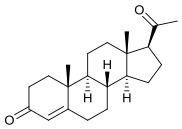
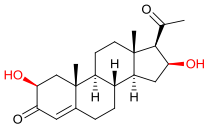
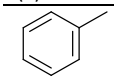
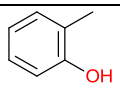
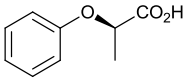
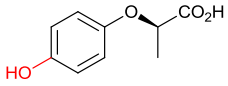
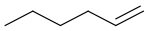
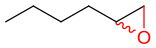
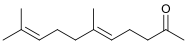
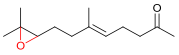


Scheme 14. Enzymatic cyclopropanation of styrene using a serine-mutant of P450BM3 (P411BM3-CIS).

Table 2 gives a representative, yet naturally incomplete, overview over the diversity of P450 monooxygenase-catalysed oxyfunctionalisation reactions.

Table 2. Representative examples of P450-catalysed oxyfunctionalisation reactions.

Substrate	Product	Yield	Catalyst	ee (%)	Volumetric scale (Aq only)	Remarks	Ref.
(1) CH bonds							
		n.d. (up to 3.3 mM product)	P450BM3 (purified enzyme)	-	1 mL	Perfluoro carboxylic acids as 'decoy' molecules	[155, 181]
		n.d. (up to 67 mM product)	CYP153A6 (recombinant in *E. coli*)	Selectivity for 1-octanol = 94%	1 ml	t=24h	[167]
		Up to 90%	BM3 Variants (purified enzymes)	-	1ml	$[S]_0$=200uM ; t=1h	[194]
		86% (up to 174 gL^{-1})	*Candida tropicalis*	-	1 L	100-200 gL^{-1}	[177]
		30%	CYP153A6 (rec. in *E. coli*)	-	1L	T=26h; Whole-cell biocatalysts	[166]
		73%	P450pyrvariant (rec. in *E. coli*)	94% (*S*) Exclusive regioselectivity	0.5 mL	$[S]_0$=4.5 mM; t=9h	[149]
		86%	P450 BM3 variants (rec. in *E. coli*)	>99% (*R*) regioselectivity >93%	50 mL	t=8 h	[195]

		90%	P450 BM3 variants (rec. in *E. coli*)	96–97% up to exclusive regioselectivity	100 mL	$[S]_0$=1 mM ; t=24 h [164]
(2) aromatic hydroxylations						
		n.d.	P450 BM3 variants (purified enzymes)	Up to 90% selectivity (p- and benzyl-products)	1 mL	$[S]_0$=5 mM ; t=24 h use of decoy molecules [156]
		n.d.	*Beauveria bassina*			
(3) epoxidations						
		42%	P450 BM3 variants (rec in in *B. subtilis* 3C5N)	27.8 (R)	10 mL	[196]
		90%	P450 BM3 variants	97% ee (n.d.)exclusive regioselectivity	1 mL	$[S]_0$=0.2 mM [172]

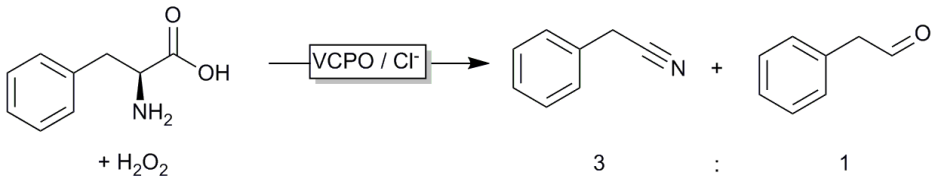
P450BM3: Cyp102A1 from *Bacillus megaterium*; P450cam: Cyp101 from *Pseudomonas putida*; P450pyr: from *Sphingomonas* sp. HXN-200; CYP152A1: from *Bacillus subtilis*; CYP152A2: from *Clostridium acetobutylicum.*

Peroxygenases entail the chemical versatility of P450 monooxygenases without being dependent on the complicated electron transport chains (*vide infra*). Instead of relying on reductive activation of molecular oxygen, peroxygenases utilise H_2O_2 to form the catalytically active oxyferryl species (hydrogen peroxide shunt in Scheme 9). [197]

For many decades chloroperoxidase from *Caldariomyces fumago* (CPO) has been the role model and only representative of this highly interesting enzyme class. [198-227] However, more recently a range of new (and potentially more useful) members of this enzyme class have gained interest.[228-244] For example a peroxygenase from the basidomycetous fungus *Agrocybe aegerita* is capable of cyclohexane hydroxylation, a reaction that has never been observed for CPO.[228] If developed further, this reaction might become a viable alternative to the existing, selectivity-wise highly challenging chemical cyclohexane oxygenation reactions.[159]

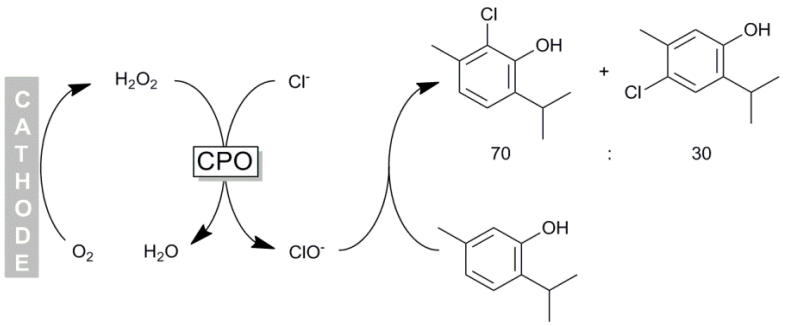
Even though peroxygenases are most valuable for the organic chemist due to their oxygen transfer capability (yielding e.g. enantiomerically pure epoxides or sulfoxides), some other – potentially very useful– applications have been reported recently. Haloperoxidases, for example, catalyse the oxidation of halogenides and release of the corresponding hypohalogenide into the reaction medium. Recently, Le Notre, Scott and coworkers reported a 'biocatalytic' oxidative decarboxylation of natural amino acids such as phenyl alanine yielding the corresponding

nitriles as major product (Scheme 15).[245] The role of the vanadium peroxidase was restricted to *in situ* formation of hypochloride, which mediated the oxidative decarboxylation of the α-amino acid. Compared to a stoichiometric use of bleach, this catalytic method excels by its catalytic use of chloride thereby significantly reducing salt wastes.



Scheme 15. Vanadium-Haloperoxidase catalysed oxidative decarboxylation of phenylalanine.

Some of us have applied CPO recently for the chemoenzymatic halogenation of thymol. The hydrogen peroxide needed for the enzymatic reaction was generated by electrochemical reduction of molecular oxygen (Scheme 16) thereby providing H_2O_2 in sufficient amount to sustain the catalytic cycle while minimising H_2O_2-related inactivation of the enzyme.



Scheme 16. Chemoenzymatic halogenation of phenols (e.g. thymol) using CPO-generated hypochloride. H_2O_2 was obtained *in situ* from electrochemical O_2 reduction.

Overall, P450-enzymes (monooxygenases and peroxygenases) exhibit an enormous potential for preparative organic synthesis.

Regeneration strategies

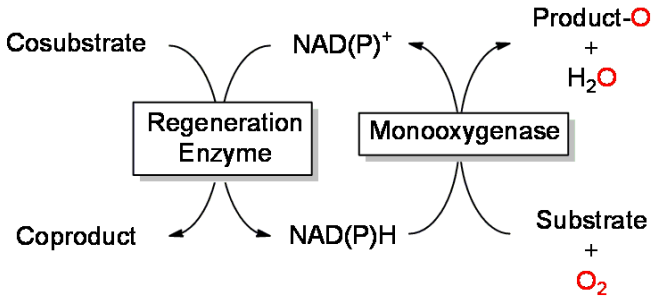
As mentioned above, reduced nicotinamides serve as universal electron donors for the reductive activation of molecular oxygen. Therefore, it is not very astonishing that the majority of published applications include NAD(P)H. Due to its fairly high costs, NAD(P)H cannot be applied in stoichiometric amounts but rather in catalytic amounts together with a suitable cofactor

regeneration system (Table 3). Overall, oxidation of a simple sacrificial cosubstrate is utilised to promote monooxygenase catalysis.

One obvious approach is to utilise the microbial metabolism to provide the reducing equivalents needed.[65, 97, 98, 100, 103-105, 111-113, 137, 138, 140, 246-250] The advantages of this approach are: (1) the enzyme(s) are not isolated thereby significantly reducing the catalyst preparation costs[176] the same is true for the nicotinamide cofactor, which is supplied by the microbial cell; (2) generally, enzymes within their natural environment (the microbial cell) are more stable than as isolated preparations, also the microbes can constantly replace inactivated enzymes; (3) the growth substrate (e.g. glucose) for the microorganism also serves as sacrificial electron donor for the biotransformation reaction thereby theoretically providing the maximal amount of reducing equivalents available from complete mineralisation. These advantages explain, why fermentative processes still dominate the field of biocatalytic oxyfunctionalisation chemistry. There are, however, also a range of challenges that have fostered research on the use of isolated enzymes. Amongst them are the frequently observed toxicity of the reagents to the microbial cells, transport limitations of reagents over the cell membranes, as well as issues related to undesired side reactions catalysed by the many other enzymes present in the microbial cells. Also, it is not always easy to balance the microorganism's redox needs with the demands of the desired biotransformation.

Using isolated monooxygenases circumvents some of the aforementioned challenges: by utilising isolated enzymes, the biotransformation is uncoupled from the fermentation step and therefore can be controlled more easily. Also, undesired side reactions are generally observed to a lesser extent than in whole-cell systems. The major challenge of using isolated enzymes is that the supply of the monooxygenase with reducing equivalents does not anymore come along with the microbial metabolism. Hence, the nicotinamide cofactor (in substoichiometric amounts) has to be applied together with a *suitable in situ* regeneration system. Table 3 gives an overview on common enzymatic NAD(P)H regeneration systems used to promote monooxygenase reactions. To estimate the efficiency of a given regeneration system the total turnover number (TTN) of the nicotinamide cofactor can be used. As a rule of thumb, TTN of greater than 1000 are generally considered to be sufficient for an economically reasonable process (even though it must be mentioned here that this very much depends on the price of the product amongst others).

Table 3. Examples for enzymatic NAD(P)H regeneration systems used for monooxygenase reactions.

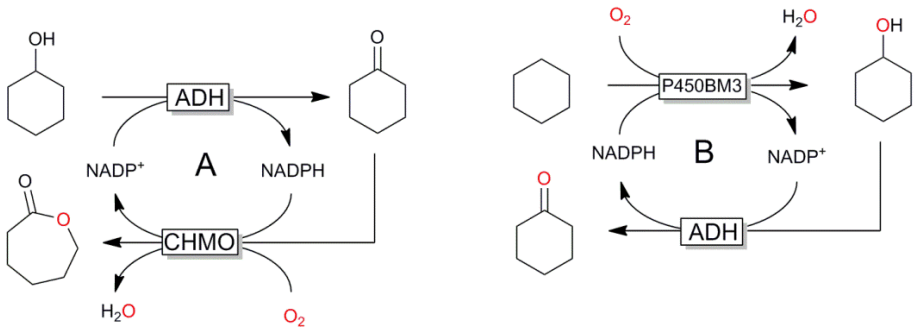


Regeneration enzyme	Cosubstrate	Coproduct	Cofactor	Reference
FDH	Formate	CO_2	NADH	86, 114, 173, 251
ADH	Isopropanol	Acetone	NADPH	62, 120
PDH	Phosphite	Phosphate	NAD(P)H	148, 252, 253
G6PDH	Glucose-6-phosphate	Glucono-6-phosphate lactone	NAD(P)H	40, 254-256

FDH: formate dehydrogenase; ADH: alcohol dehydrogenase; PDH: phosphite dehydrogenase; G6PDH: glucose-6-phosphate dehydrogenase.

Recently, so-called designer cells have gained significant attention. This approach combines the advantages of whole cell biocatalysis and the regeneration approaches outlined in Table 3 by coexpressing the production enzyme together with a suitable regeneration system and using the whole cells as catalysts.[120, 252] On the one hand the enzymes are protected in their natural environment and also protein-isolation and –purification is not applied. On the other hand, the cells are usually not metabolically active thereby largely eliminating toxicity issues as well as undesired side reactions. Overall, the designer-cell approach appears to be a very promising catalyst concept for future biocatalytic oxyfunctionalisation reactions.

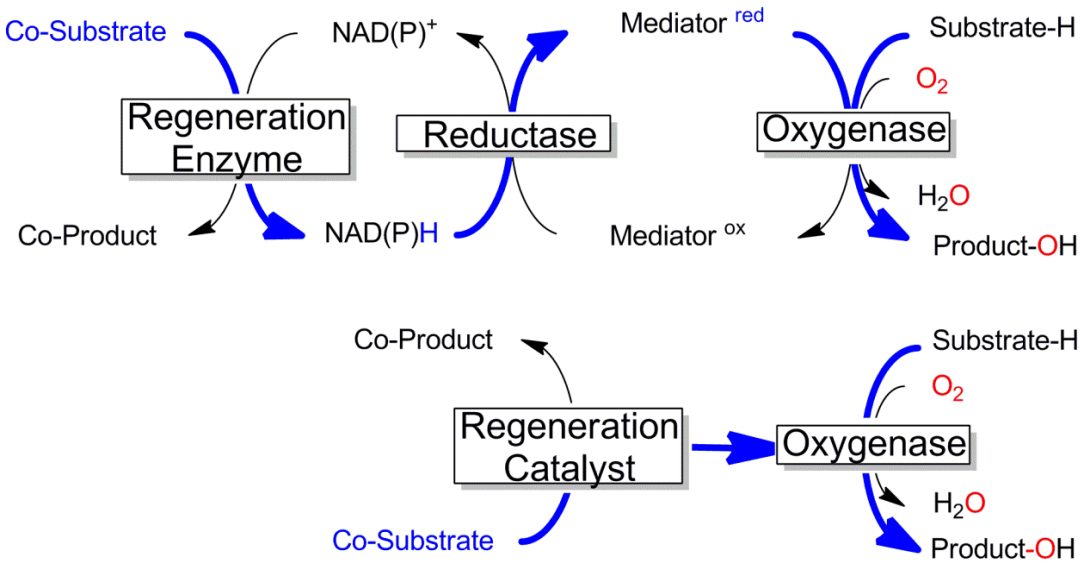
The regeneration approaches outlined before all are based on the enzyme-coupled regeneration concept: regeneration reaction and production reaction are linked via the nicotinamide cofactor only. Hence, the cofactor regeneration consumes another substrate (cosubstrate) and produces a stoichiometric coproduct. Another interesting approach is the so-called intrasequential cascade, wherein the NAD(P)H-consuming (oxyfunctionalisation) reaction is also productively coupled to the NAD(P)H-regenerating reaction via an intermediate product (Scheme 17). Their use elegantly circumvents the need for the additional cosubstrate/coproduct couple by double transformation of only one substrate but naturally are rather limited in scope. However, the self-sufficient nature of these reactions as well as the apparent non-generation of wastes might point towards bulk-scale application such as ε-caprolactone or cyclohexanone from simple starting materials.



Scheme 17. Examples of intrasequential oxyfunctionalisation sequences with the monooxygenase catalysing the second (A) [162, 163] or the first step (B) [160, 161] of the sequence.

Direct regeneration approaches

Many monooxygenases rely on rather complicated, multi-enzyme electron transport chains to deliver the reducing equivalents from NAD(P)H to the flavin- or heme-prosthetic group. While this architecture makes sense for the (microbial) cell as it adds further levels of control over the cellular redox metabolism, it adds further complexity to the application of monooxygenases for chemical synthesis. Often, only the reducing equivalents are needed to sustain the monooxygenases' catalytic cycles; therefore in recent years a growing number of research efforts have been dedicated to delivering the reducing equivalents directly to the monooxygenases and circumventing the electron transport chains (Scheme 18).



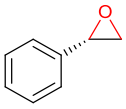
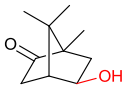
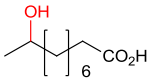
Scheme 18. Comparison of the 'traditional' regeneration of multi-component monooxygenases (upper) with the direct regeneration approach (lower). The flow of reducing equivalents is shown in bold blue. [11, 257, 258]

The potential benefit of such direct regeneration approaches is that complicated electron transport chains comprising up to 2 additional enzymes and 2 additional cofactors can be

substituted by only one regeneration catalyst, resulting in highly simplified (and more easily controllable) reaction schemes.

Table 4 summarises some representative examples of oxyfunctionalisation reactions performed by direct regeneration.

415 **Table 4. Examples for direct regeneration of monooxygenases.**

Product	Monooxygenase	Regeneration catalyst	Source of reducing equivalents	TTN (Regeneration catalyst)	Reference
	P450 cam	Pdx	Cathode	0.06	259
	StyA	FAD	Cathode	Up to 700	101, 108, 260
	StyA	[Cp*Rh(bpy)(H_2O)]$^{2+}$	$NaHCO_2$	10	110
	Myoglobin	None	Cathode	-	261, 262
	P450 cam	Pdx	Cathode	0.51	263
	P450rFP450 04A1	Co(sep)	Cathode	0.016	264
	P450BM3	Co(sep)	Zn	<1	265, 266
	P450BM3	[Cp_2Co]$^+$	Cathode	0.05	267
	P450BM3	Co(sep)	Zn	0.15	266
	P450 BM3 – Ru-hybrid catalyst		sodium diethyldithiocarbamate	140	153 268
	P450 BM3	Deazaflavin	EDTA	7	269
	P450 BM3	Co(sep)	n.d.	Cathode	168, 270-272
	P450 cin	Co(sep), phenosafranine T, neutral red, flavins	n.d.	Cathode	273

It becomes clear from Table 4 that the immense potential of direct regeneration of monooxygenases still remains to be exploited. The major limitation are the regeneration catalysts, which in most cases do not appear to act as true catalysts. We believe that the reason

lies in the high reactivity of most mediators with molecular oxygen. Hence, futile reoxidation of the reduced regeneration catalysts by molecular oxygen competes with the desired monooxygenase regeneration thereby lowering the productive catalytic turnover of the regeneration catalysts. Furthermore, the futile cycle leads to the generation of reactive (partially reduced) oxygen species (ROS), which impair enzyme stability and lead to undesired side reactions.

The molecular reason for this undesired side reaction probably lies in the redox properties of the regeneration catalysts used. With the exception of $[Cp^*Rh(bpy)(H_2O)]^{2+}$ and deaza-flavin, all regeneration catalysts are obligate one electron donors; hence their reaction with the predominant tripett oxygen ($^3O_2$) is spin-allowed (and fast) whereas the reactions of the two-electron donors ($[Cp^*Rh(bpy)H]^+$ and deaza-flavin^{red}) with $^3O_2$ are spin-forbidden (and therefore slow). Also the natural redox mediators such as putida redoxin (Pdx) are single electron mediators and therefore prone to fast aerobic reoxidation. The same is true to some extent for reduced flavins. Even though they are traditionally denoted as two-electron donors (in the classical mechanisms) they are also able to form semiquinones e.g. during sequential reduction of FeS-redoxproteins or during fast synproportionation with oxidised flavins.[274] This also explains the exceptionally high turnover numbers observed by Schmid and coworkers (Table 4).[101] By using very low flavin concentrations they could efficiently shift the flavin synproportionation equilibrium away from the reactive flavin semiquinones. Furthermore the advanced electrochemical reactor setup enabled minimising the contact time of reduced flavins and molecular oxygen.

Unfortunately, so far this undesired uncoupling reaction (also observed quite frequently with the 'traditional' regeneration approaches) has not been addressed very much and a general awareness of this oxygen dilemma is missing.

Overall, it can be asserted that on the one hand undesired, spontaneous reduction of molecular oxygen leads to a waste of reducing equivalents and concomitant of toxic ROS. On the other hand, molecular oxygen, as an integral part of the monooxygenases' catalytic cycle, cannot be omitted form the reaction schemes, resulting in the 'oxygen dilemma'. Practical solutions to the oxygen dilemma are urgently needed in order to make monooxygenase-catalysis truly practical for organic synthesis.

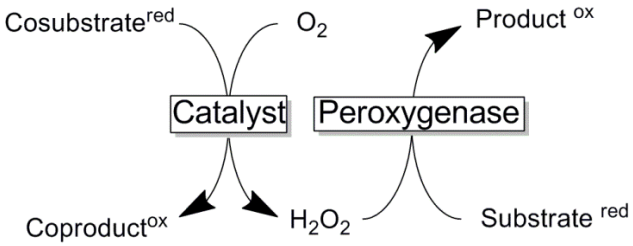
Supply with H_2O_2 to promote peroxygenase catalysis

The dependence of peroxygenases on simple peroxides only at first sight offers a trouble-free catalyst system to be used in organic synthesis. The major challenge of using peroxides as source of oxygen lies in their reactivity, especially with the prosthetic heme group itself. The exact

inactivation mechanism is still under debate but it is clear by now that already small concentrations of hydrogen peroxide irreversibly inactivate the heme group (most probably oxidatively). [275]

The simplest approach to circumvent the undesired oxidative inactivation of peroxygenases is to supply H_2O_2 in various, small portions. This approach is, however, work-intensive and also leads to significant volume increases which will complicate downstream processing. Alternatively, organic hydroperoxides have received some attention as milder alternatives to H_2O_2.[197] More recently, various *in situ* O_2 reduction methods have been evaluated to generate H_2O_2. The principle behind is that these methods enable to generate H_2O_2 *in situ* in just the right amounts to sustain peroxygenase catalysis while minimising the H_2O_2 related inactivation. Table 5 gives an overview over the different sources of reducing equivalents needed for O_2 reduction and catalysts used.

Table 5. *In situ* H_2O_2 generation methods to promote peroxygenase reactions.



Catalyst	Cosubstrate	Coproduct	Ref
GOx	Glucose	Gluconolactone	197, 211, 276-279
Cathode	-	-	201, 280-284
Pd	H_2	-	285
Flavin/hν	EDTA	Ethylene diamine, CO2, formaldehyde	228, 286, 287

GOx: Glucose oxidase

Each H_2O_2 generation method exhibits specific advantages and disadvantages. For example, cathodic reduction of molecular oxygen represents a potentially very simple and environmentally benign approach, but also requires specialised equipment. Glucose oxidase mediated reduction of O_2 is simple and easy to apply, however gluconic acid accumulates in stoichiometric amounts leading to challenges in pH control. Overall, 'the ideal' *in situ* H_2O_2 generation does not exist and a suitable method has to be established for every peroxygenase reaction.

How green / environmentally friendly are biocatalytic oxyfunctionalisation reactions?

Today, biocatalysis is generally accepted as a 'green technology'. Often, one or a few of the famous Twelve Principles of Green Chemistry[288] are used to substantiate the green touch of a given biocatalytic reaction. However, we are convinced that authors should be more careful with green claims as a critical evaluation of the environmental impact might actually result in nasty surprises. The Twelve Principles of Green Chemistry are a wonderful framework for design of environmentally more friendly processes but simple adherence to some of these principles does not make a given reaction/process 'green'. Therefore, a more quantitative (and critical) evaluation is a prerequisite *en route* to truly Green Chemistry. Today, full life cycle assessment, taking into account as many parameters as possible, represents the 'golden standard' of environmental evaluation. However, the data basis required for LCAs is enormous, making LCAs time-consuming and too expensive for academics to perform.

We believe that simple, mass-based metrics such as the E-factor (E being the amount of waste generated per kg of product)[289] may be a valuable tool especially for academic researchers to estimate the 'greenness' of a given reaction.[290-293] The E-factor concept is easily understood and the calculations easily and quickly done. Of course, such a simple mass-based tool neglects important contributors to the environmental impact such as energy consumption and does not weigh the quality of the different mass flows (scarce starting materials, hazardous wastes).[294, 295] Nevertheless, the E-factor frequently qualitatively points into the same direction as more advanced analyses and thereby can give valuable hints to optimise a reaction.[100, 290, 296] Therefore, we would like to encourage especially academic researchers to use this simple tool more often to critically assess the environmental impact of their reactions.

In the following, we highlight and discuss two Green Chemistry issues that – to our mind –are notoriously underestimated in the scientific literature dealing with (bio)catalytic oxyfunctionalisation chemistry: substrate loading and downstream processing.

Substrate loading has a very significant impact on the economic feasibility and environmental impact of a reaction. However, the majority of reactants of interest is poorly water soluble. Unfortunately, the general solution to this challenge is to apply the starting material in low concentrations (often in the lower millimolar range). A simple, E-factor estimation however demonstrates the dimensions of the water ballast resulting from this (Figure 1). Producing tons of contaminated waste water per kg of product cannot be the ultimate green (not to mention economical) solution.

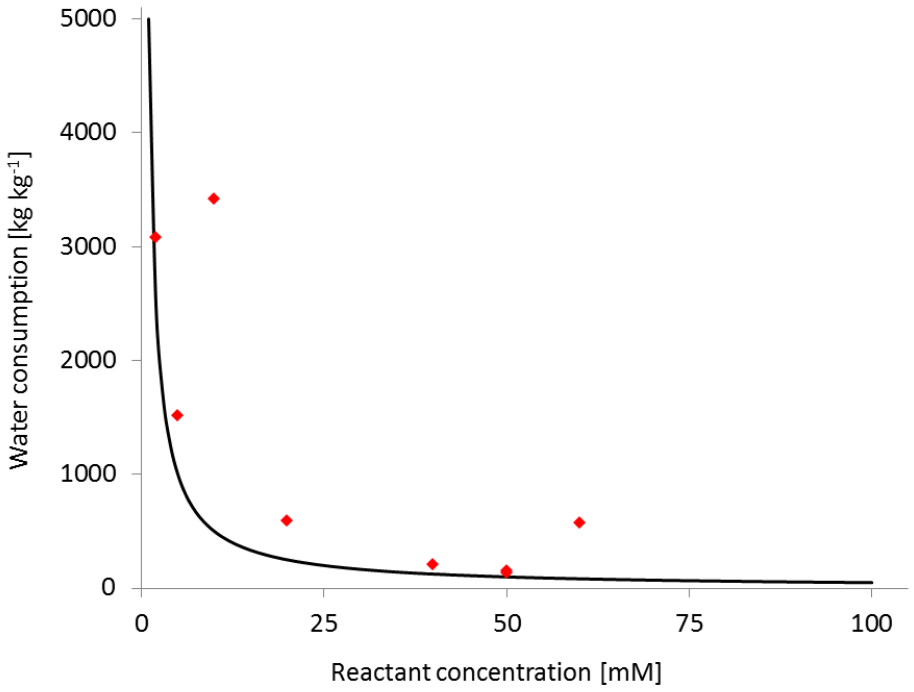
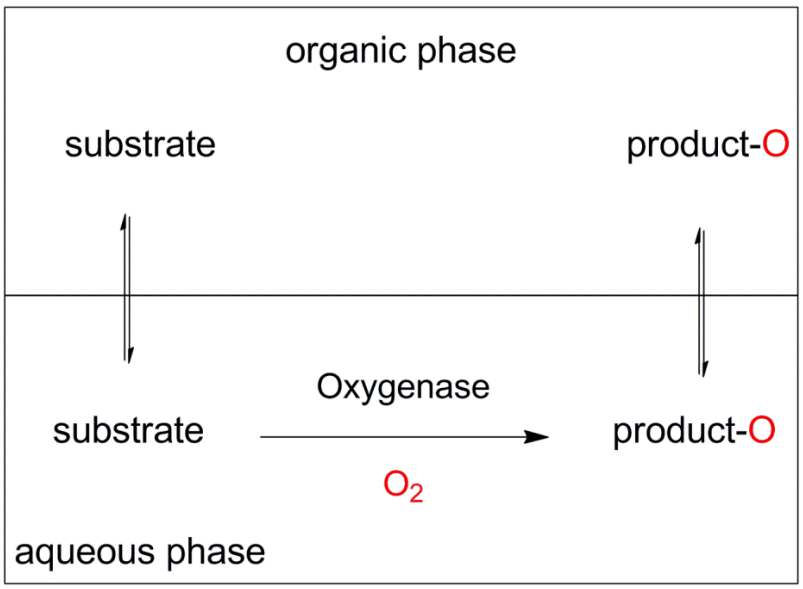


Figure 1. Water consumption at different reactant concentrations (expressed as kg(wastewater) per kg(product)). Black line: theoretical Water-E-factor (assumption M(product)=200 g mol^{-1}, full conversion); red diamonds: experimental Water-E-factors from published monooxygenase reactions,[290] the examples with higher than expected E-factors are those with incomplete conversion.

Increasing the overall substrate concentration can significantly reduce the water ballast of any given reaction and therefore should be more often be strived for. To cope with the poor substrate solubility, the two-liquid-phase-system (2LPS) approach seems one viable solution. Here, a water-inmixible apolar organic phase serves as substrate reservoir and product sink enabling overall high payloads.

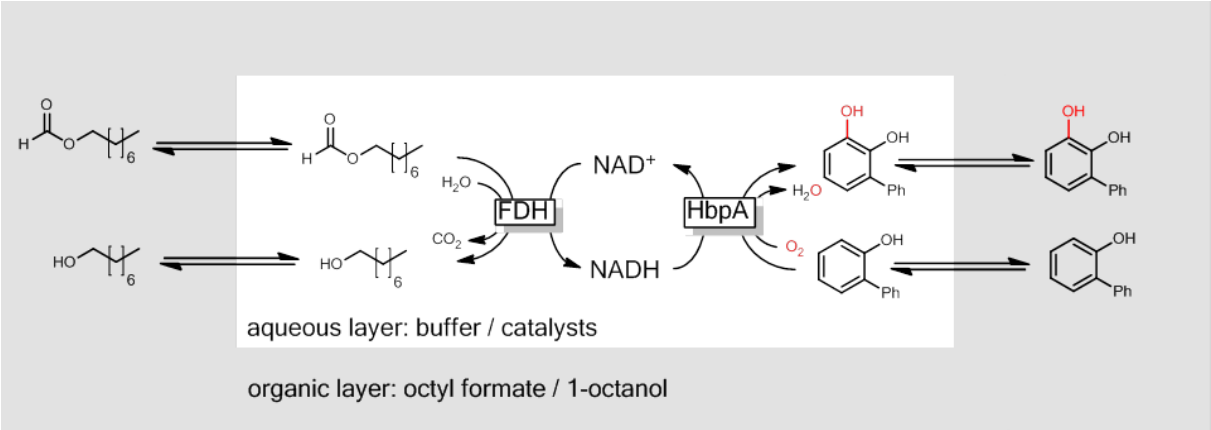


Scheme 19. The two-liquid phase system (2LPS) approach. A hydrophobic organic phase solubilises overall high amounts of the hydrophobic reactants. From there, the substrate partitions into the aqueous, oxygenase-containing aqueous phase to be converted. The product, again, partitions between both phases and thereby is largely extracted into the organic layer.

Additional benefits from the 2LPS concept may be alleviation of reactant toxicities and inhibitory effects (especially for whole cell biocatalysts),[100, 297] prevention of over-oxidation (e.g. of aldehydes into carboxylic acids),[11, 100, 246, 297-303] and prevention of hydrolytic degradation of e.g. epoxide or lactone products.[14, 111, 112, 114, 304-306] Furthermore, high product concentrations in easily water separable organic phases will also facilitate DSP (*vide infra*).

Of course, the selection of the organic solvent should –next to practical issues such as partitioning coefficients and biocatalyst stability- also take its potential environmental impact into account.[307-309]

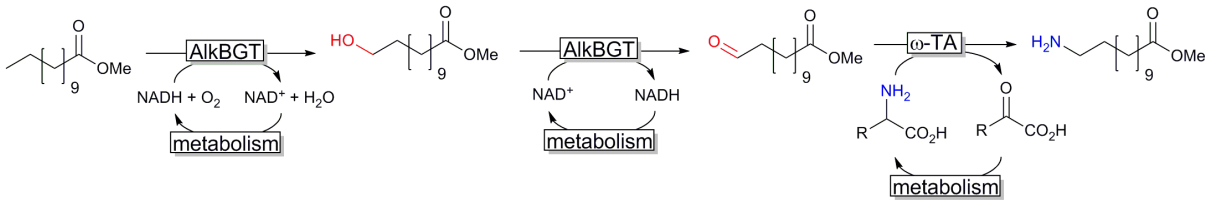
One issue of 2LPS arises from the rather hydrophilic character of many sacrificial electron donors used such as formates, phosphites or glucose making them incompatible with 2LPSs exhibiting high volumetric ratios of organic to aqueous phase. To solve this challenge, some of us have recently proposed using hydrophobised formates as organic phase for biocatalytic oxyfunctionalisation reactions (Scheme 20).[251]



Scheme 20. Hydrophobic formic acid esters as reactive organic phase serving as substrate reservoir/product sink and source of reducing equivalents for FDH-catalysed NADH regeneration.

Downstream processing (DSP) is an issue that is not very frequently addressed in typical publications dealing with (bio)catalysis. However, DSP is an integral part of the production system as 'it is no product unless it is in a bottle' (C. Wandrey). From an environmental point-of-view, DSP can contribute very significantly to the overall environmental impact of a production system.[290, 310] Therefore, an increased focus on DSP issues also at an early stage of development is highly desirable. This should include, 'smart by design' reaction systems enabling facile product isolation e.g. by filtration or 2LPSs enabling low-energy distillation DSP.

Another, very promising line of research comprises so-called cascade reactions, [311, 312] wherein complex reaction sequences are performed without isolation of the intermediate reaction products. A very elegant cascade was reported recently by Bühler and coworkers reporting a formal terminal amination of fatty acids by combining a sequence of two hydroxylase- and one transaminase-reaction (together with the corresponding cofactor regeneration reactions) in one engineered *E. coli* production strain (Scheme 21).[313, 314]



Scheme 21. Cascade combining AlkB and ω-TA in recombinant *E. coli*.[313, 314]

Today, still too many research projects on biocatalytic oxyfunctionalisation focus on the biocatalyst only while accepting low substrate loadings and completely neglecting the DSP part.

Conclusions

Biocatalysis has a lot to offer for the organic chemist. Simple and robust catalysts such as lipases for chirotechnology applications are well-established already. Oxygenases are on the go to follow them. This will significantly broaden the chemist's toolbox for selective oxidation/oxyfunctionalisation reactions. Especially the high selectivity of enzymes will enable shorter synthesis routes and yield higher quality products. Another interesting feature of biocatalysis (in general) is its potential for environmentally more benign syntheses. However, being biobased alone does not make an enzymatic route green; a more self-critical evaluation of contributors is highly desirable. In this respect, already simple metrics such as the E-factor may be valuable and simple tools.

Acknowledgements

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