Recent biocatalytic oxidation–reduction cascades
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The combination of an oxidation and a reduction in a cascade allows performing transformations in a very economic and efficient fashion. The challenge is how to combine an oxidation with a reduction in one pot, either by running the two reactions simultaneously or in a stepwise fashion without isolation of intermediates. The broader availability of various redox enzymes nowadays has triggered the recent investigation of various oxidation–reduction cascades.

Introduction
Performing reaction sequences in one pot in a sequential or even simultaneous fashion avoids time-consuming or yield-reducing isolation and purification of the intermediates [1,2]; as a consequence the amount of chemicals/solvents required for extraction/purification of intermediates is minimised leading to an improved E factor [3]. Cascades involving reduction as well as oxidation steps are still a challenge due to the diverging reaction conditions. Since in living cells oxidation and reduction processes are performed simultaneously, enzymes are probably the perfect catalysts to be exploited for synthetic redox cascade applications [4]. In this review, artificial cascades involving an oxidation step followed by a reduction step, or vice versa, will be discussed, whereby at least one redox step is catalysed by an enzyme. The focus is on cascades published during the past 4 years. Cascades employing fermenting cells or involving in vivo metabolism will not be discussed as well as concepts for cofactor/cosubstrate recycling; furthermore, cascades involving the catalase-promoted disproportionation of hydrogen peroxide are out of scope.

The easiest approach to performing such redox cascades is to run the first redox reaction until completion and then start the second step by adding the required reagents; thus, the two steps are separated by time but performed in the same pot. More challenging is to run the two redox reactions at the same time, thus simultaneously in one pot. Here two cases can be distinguished: The simpler case is that the oxidation and the reduction steps are working independently of each other; thus, reagents for the oxidation step as well as for the reduction step are required. The more demanding case is that the oxidation and reduction steps are interconnected: it would be desirable that the formal electrons gained in the oxidation step are consumed in the reduction step. This represents a redox neutral cascade; thus, in an ideal case no additional reducing or oxidising agents are required. Consequently, the review was subdivided into the following subsections (Figure 1): (1a) simultaneous redox neutral oxidation–reduction cascades, (1b) simultaneous independent redox cascades in one pot and (2) subsequent oxidation–reduction cascades performed in one pot but separated by time. The (bio)catalysts working in concert in simultaneous oxidation–reduction cascades can be regarded as an interactive catalyst network. In the special case of redox neutral cascades, it represents an interconnected catalyst network.

(1a) Simultaneous interconnected redox neutral oxidation–reduction cascades
For systematic reasons this approach will be further subdivided into two concepts. In the first concept the substrate is transformed to an intermediate that reacts further (Figure 1, 1a, Concept 1). This is the classical picture of a cascade. In addition, we will also discuss two parallel reactions that are connected via the transfer of the redox equivalents (Concept 2). The scheme of concept 2 is also fitting for classical cofactor regeneration systems; however, these will not be discussed here [5]. Only reactions where both transformations lead to useful products will be considered.

An example for concept 1 is the transformation of D-mandelic acid to L-phenylglycine (Figure 2, a) [6**]. The cascade involved an oxidation catalysed by an alcohol dehydrogenase (ADH, here mandelate dehydrogenase) to the corresponding α-keto acid and reductive amination employing an amino acid dehydrogenase (AADH). The formal electrons subtracted in the oxidation step were transported to the reduction step via the nicotinamide cofactor. When employing racemic mandelic acid as substrate, a racemase ensured that L-mandelic acid was
was required. This strategy to connect two parallel asymmetric transformations was named PIKAT, meaning parallel interconnected kinetic asymmetric transformations. In a similar approach the ADH-catalysed kinetic resolution was coupled with a Baeyer–Villiger monoxygenase (BVMO) to perform asymmetric sulfoxidation (Figure 2, d) [11] or an asymmetric Baeyer–Villiger oxidation [12\(^*\)].

A more equipment-intensive transformation performed in supercritical CO\(_2\) is the combination of a metal-catalysed in situ preparation of hydrogen peroxide for the chloroperoxidase-catalysed asymmetric sulfoxidation (Figure 2, e) [13]. In another recent approach, EDTA was employed as cosubstrate to generate hydrogen peroxide from oxygen via FMN catalysis [14].

(1b) Simultaneous independent redox steps in one pot

Although redox neutral cascades as described in concept 1 (Figure 1, 1a) are highly desirable, they are difficult to set up efficiently, since the kinetics and the thermodynamics have to fit. Having two independent redox steps (Figure 1, 1b), the kinetics and the redox equilibrium can be controlled easily. Cascades described in this section are mainly employed for the deracemisation of sec-alcohols [15–17], α-amino acids [7,18–20] or other α-chiral amines [7,20,21]. The cascades may involve either (i) exclusively enzymes or (ii) one chemical step. Focusing first on cascades employing exclusively enzymes, the deracemisation of sec-alcohols was achieved employing two stereo-complementary ADHs possessing opposite cofactor preference (Figure 3, a) [22\(^*\)]. In this system the oxidised cofactor NADP\(^+\) was efficiently recycled by a NADPH oxidase besides a recycling system for the reduced cofactor NADH (formate dehydrogenase FDH). Just by exchanging the ADHs, the stereochemical outcome of the cascade could be easily turned around to produce the other enantiomer in optically pure form. While here four enzymes worked without compartmentalisation, in a related system the oxidation step was separated from the reduction by employing whole cells containing the enzymes for the oxidation step [23]. A related approach is to use intact cells for both the oxidation and the reduction [24]. In other reports a whole organism was used, whereby the cell was considered as a black box without knowing details about cofactor recycling or the involved enzymes [25–28]. Recent reports on the deracemisation of amino acids deal, for instance, with the transformation of racemic naphthylalanine into the L-enantiomer by formal stereoinversion of the α-amino acid (Figure 3, b) [29\(^*\)]. In this study a α-amino acid oxidase from Rhodotorula gracilis was employed for deamination of the α-amino acid and an α-aspartate aminotransferase from E. coli for transamination of the inter-

Figure 1

1. Simultaneous oxidation-reduction reactions in one pot

(a) Redox neutral cascade, interconnected oxidation and reduction

Concept 1: A Oxidation B Reduction C

Concept 2: A Oxidation B Reduction C

(b) Cascade involving independent redox steps

A Oxidation B Reduction C

2. Subsequent one-pot oxidation-reduction cascades*

step 1 step 2

A Oxidation B Reduction C

*steps separated by time

General concepts of oxidation-reduction cascades: The order of the redox reactions can also be inverted; thus, first the reduction is performed, followed by the oxidation.

transformed into d-mandelic acid needed in the cascade. By this concept overall deracemisation [7] was achieved; thus, both substrate enantiomers were transformed into a single product enantiomer. Racemisation of secondary alcohols employing alcohol dehydrogenases represents a further example for concept 1 (Figure 2, b). One alcohol enantiomer is oxidised to the corresponding ketone and then reduced to the other enantiomer by an ADH displaying opposite stereoselectivity. Again the electrons are shuttled via NAD(P)H. Since there is no driving force in the system, all reactions run forward and backward leading overall to racemisation. The concept was applied for sec-alcohols [8] as well as α-hydroxy acids [9].

Turning to concept 2 (Figure 1, 1a), a kinetic resolution of sec-alcohols was combined with the simultaneous asymmetric reduction of ketones bearing an electron-withdrawing substituent in α-position (Figure 2, c) [10]. This approach led to two different optically pure alcohols and avoided the usage of extra reducing or oxidising reagents; thus, it represents an example for combining reactions to optimise atom economy. Another advantage of the approach above is that only a single enzyme (ADH)
Simultaneous interconnected oxidation–reductions: (a) deracemisation of rac-mandelic acid to \( \text{L-phenylglycine} \); (b) racemisation of sec-alcohols; (c) PIKAT employing a single enzyme producing two different optically pure alcohols; (d) PIKAT employing two enzymes and (e) combination of a metal-catalysed reaction with an enzymatic sulfoxidation.

ADH = alcohol dehydrogenase
AADH = amino acid dehydrogenase
BVMO = Baeyer Villiger monooxygenase
CPO = chloroperoxidase
mediate α-keto acid. While the transamination is generally reversible leading to limited conversion, full conversion was achieved here by choosing cysteine sulfinic acid as the amino donor. The latter is transformed into β-keto sulfinic acid as byproduct, which spontaneously decomposed to pyruvate and sulfur dioxide, shifting the equilibrium to the product side.

In the previous example an amino acid oxidase was employed for the oxidation; as an alternative, amino acid dehydrogenases could also be employed. An example for that is the deracemisation of 4-chlorophenylalanine employing a ‘tailored’ whole-cell *E. coli* biocatalyst expressing a D-amino acid dehydrogenase (D-AADH) for the oxidation and a branched-chain amino acid transferase for the oxidation.

Cascades involving simultaneous independent redox steps employing either (i) exclusively enzymes or (ii) enzymes in combination with a chemical redox step.
amination (BC-AAT) [30]. In a related study the deracemisation of 4-chlorophenylalanine by resting cells of *Nocardia diaphanozonaria* JCM 3208 was reported [31].

Switching to cascades involving enzymes and chemical redox steps, a well-known concept for the deracemisation of amino acids and amines involves amino acid oxidases in combination with a chemical reducing agent (Figure 3, c). The oxidases perform an enantioselective oxidation of one substrate enantiomer. The reducing agents are achiral, like NaBH₄/NaB(CN)H₃ amine-boranes (NH₃/CH₃BH₃, t-BuNH₂/BH₃, BH₃-Pyridine) or palladium catalysts (H₂COONH₄/Pd/C) [19,32,33]. The combination of an enantioselective oxidation combined with a non-stereo-selective reduction finally
led to deracemisation. The concept was successfully extended for the deracemisation of cyclic secondary amines [34], cyclic tertiary amines [35] and the alkaloid crispine A [36] (Figure 3, c). Instead of using a chemical reducing agent, a graphite electrode may also be used. This was shown in combination with a D-amino acid oxidase for the preparation of L-leucine [37]. A related approach was followed for sec-alcohols employing NaBH4 as reducing agent in combination with cells of Geotrichum candidum performing the enantioselective oxidation in a mixture of buffer and ionic liquid [38].

In a very recent study a metal-catalysed oxidation step was performed in the presence of an enzyme-catalysed asymmetric reduction [39] (Figure 3, d). Thus, in contrast to the previous examples the reduction was now catalysed by an enzyme, while the oxidation was metal catalysed. The concept was exemplified for the deracemisation of chlorohydrins. The main challenge in this approach was to identify suitable compatible reaction conditions for the oxidation and the reduction to circumvent any cross-reactions. This could be achieved by choosing a specific sterically hindered chloroketone as hydrogen acceptor for the oxidation, while formate was employed as reducing agent for the reduction.

(2) Subsequent oxidation–reduction steps performed in one pot

The divergent reaction conditions that characterise an oxidation–reduction cascade often prohibit a one-pot concurrent process, for instance if dioxygen required in the oxidative step inactivates the enzyme involved in the reductive step [40,41]. In a more recent example a double regio-selective and stereo-selective oxidation at positions 7 and 12 of cholic acid was followed by another regio/stereo-selective reduction (Figure 4, a) [42]. Although first experiments headed towards a simultaneous process, the reductase had to be performed in a stepwise fashion, due to a low cofactor preference of the NADPH-glucose dehydrogenase. In a simultaneous reaction the GDH recycled NADPH as well as, to some extent, NADH, which interfered with the oxidation cycle.

In another example a dehydrogenase (NDDH) had to be added after enzymatic epoxidation for the oxidation of a benzyl alcohol to the corresponding acid (Figure 4, b). The oxidation to the acid could not be performed simultaneously, since the formed acid inhibited the epoxidation reaction catalysed by styrene monoxygenase (SMO) [43]. In a related sequence transforming phenylglyoxal to mandelic acid (Figure 4, c), the oxidation to the acid had also to be the last reaction to avoid inhibition by the acid [44].

A stepwise reaction sequence was also needed for the deracemisation of α-chiral primary amines by ω-transaminases (ω-TA) [45], since two enzymes of the same type, just possessing opposite stereo-preference but possessing a similar cosubstrate preference, were applied [46,47]. The ω-TA employed in the first step performed the kinetic resolution of the racemate, yielding the remaining optically pure amine and the ketone intermediate (Figure 4, d) [48]; the latter was aminated by a stereo-complementary ω-TA in a second step to achieve overall deracemisation. Just by inverting the order of the two ω-TAs, the other enantiomer could be obtained.

Besides these oxidation/reduction cascades, stepwise transformations performed in one pot involving biocatalysts and organo-catalysts as well as metal-catalysts (e.g. for C–C bond formation) have also gained significant attention recently [49,50].

Conclusions

Enzymatic cascades offer the possibility to perform several reactions in one pot without the need for isolating intermediates. Especially cascades involving redox steps allow to perform transformations that are not easily achievable by classical chemistry methods in one pot. The enzymes can be regarded as modules that can be combined in creative ways to set up novel cascade networks solving ‘impossible’ chemical problems. Since more enzymes become available from commercial sources or get described in literature, it can be expected that many new cascades will be developed in the future. Such cascades will lay the base to construct artificial metabolisms and create (interacting/interconnected) catalyst networks.

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