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Recent trends in synthetic enzymatic cascades promoted by alcohol dehydrogenases

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Alcohol dehydrogenases have fascinated chemists over the span of a few decades to catalyze oxidation and reduction reactions and have been increasingly incorporated as biocatalysts in scaled-up industrial processes for the production of valuable chiral compounds under mild and environmentally friendly conditions. In this review, we discuss recent advances on alcohol dehydrogenases coupled in cascade reactions with other enzyme classes, chemocatalysts, or organocatalysts to obtain high value–added products. The examples include deracemization processes for the synthesis of chiral diols and amino alcohols, whole-cell and co-expression systems, and chemoenzymatic and organoenzymatic cascades, with a vision for future developments.

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Introduction

Since the 1980s, the application of biological systems, as green catalysts for the synthesis of organic compounds, has experienced a great wave of development. Nowadays, the use of biocatalysis is well established in organic synthesis and represents a valuable and complementary alternative to the classical catalytic methodologies [1]. Biocatalytic procedures can be improved by reaction medium engineering [2], with molecular biology tools to obtain more active and/or selective biocatalysts [3,4], or by different immobilization techniques [5,6]. The integration of several (bio)catalytic transformations in a multienzymatic cascade system has revealed to be particularly beneficial to develop efficient processes [7]. The combination of enzymatic transformations in concurrent one-pot processes presents several advantages, bypassing the need for purification and isolation of intermediates, which leads to a higher E factor [8,9]. The product recovery is easier, and those reversible reactions can be driven to completion. Several examples of cascade reactions have been described by combining several biocatalysts [7,10,11], as well as biocatalysts combined with chemical catalysts [12–14].

Alcohol dehydrogenases (ADHs, KREDs, EC 1.1.1.X) are oxidoreductases that reversibly catalyze the selective reduction of aldehydes and ketones to primary and secondary alcohols [15]. Although their use has been mostly applied for the asymmetric reduction of ketones [16], examples are available for oxidation reactions [17]. ADHs require a nicotinamide adenine dinucleotide cofactor (NAD or NADP) as an oxidant or reductant, efficiently recycled in whole-cell systems, whereas in cell-free biocatalytic reactions, typically coupled enzymes or other chemochemical, electrochemical, photochemical methods [18,19] are implemented.

Previous reviews describe the use of ADHs in various processes to obtain specific valuable chemicals [20,21] and on general biocatalytic cascades [7,10,22]. Here, we aimed at providing a current view on ADH-promoted cascade reactions that lead to relevant products from an application perspective, focusing on bicatalytic and multicatalytic cascades.

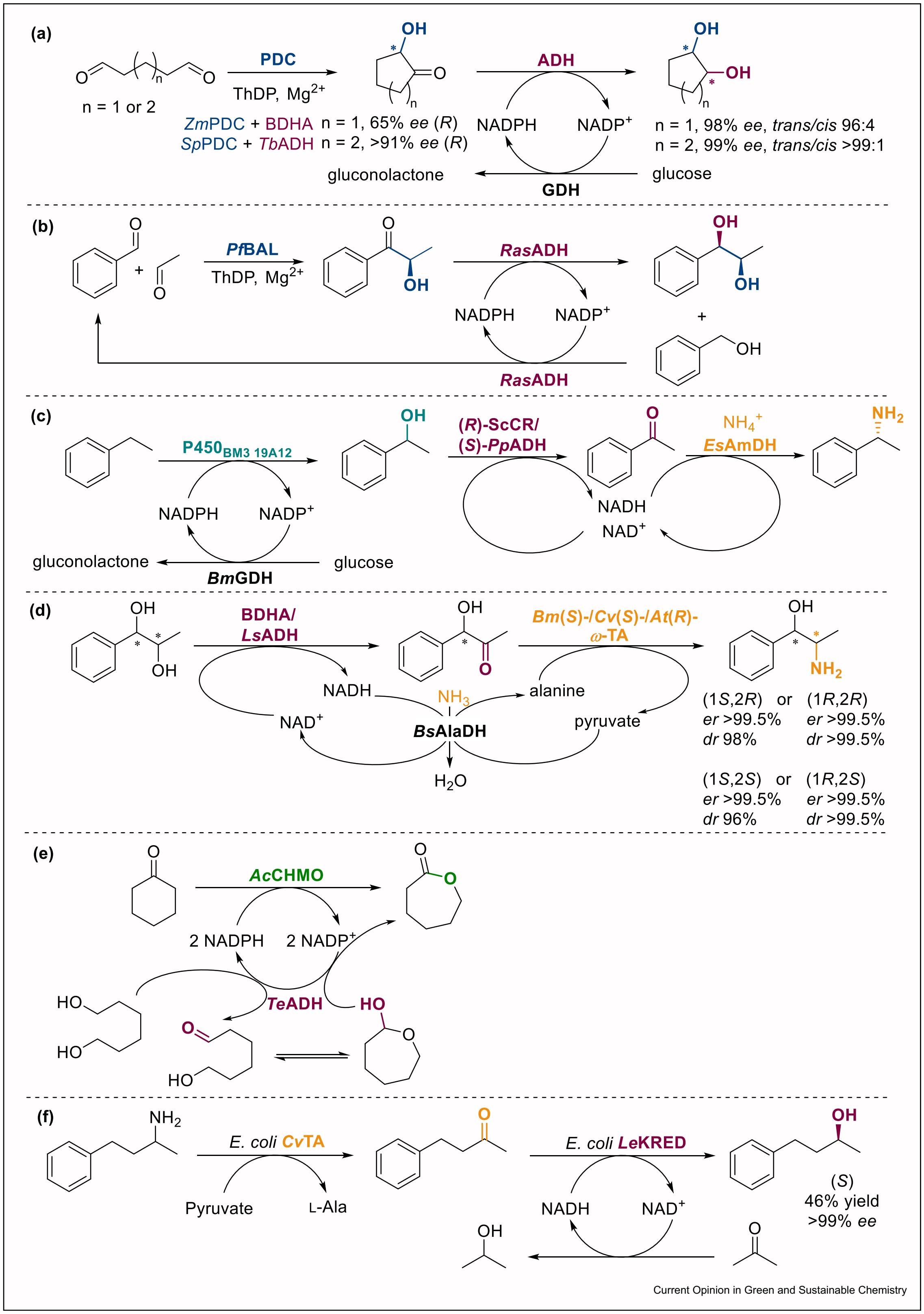
ADH-promoted cascades coupled with other enzyme classes

ADH-promoted *in vitro* enzymatic cascades

Obtaining chiral alcohols and vicinal diols

Access to chiral alcohols by deracemization continues to be developed, with a recent example by Musa et al. [23] using *Thermoanaerobacter ethanolicus* ADH *Te*ADH. A first unselective ADH oxidizes the racemic alcohol to the corresponding ketone, which is then reduced selectively by a second ADH. For access to chiral vicinal diols, a one-pot bienzymatic cascade was developed from aliphatic dialdehydes using a thiamine diphosphate (ThDP)–dependent pyruvate decarboxylase from *Zymomonas mobilis* (*Zm*PDC) or *Streptococcus pneumonia* (*Sp*PDC) and an ADH, from *Bacillus subtilis* (BDHA) or *Thermoethanolicus brockii* (*Tb*ADH) (Figure 1a) [24]. The PDC-catalyzed cyclization of the aliphatic dialdehydes *via* intramolecular C–C bond formation, followed by ADH-catalyzed reduction of the cyclic hydroxyketone, resulted in 1,2-cyclopentanediols in three different

Figure 1



(a) One-pot bienzymatic enantioselective synthesis of chiral cyclic vicinal diols; **(b)** One-pot two-step synthesis of (1*R*,2*R*)-1-phenylpropane-1,2-diol with co-product recycling; **(c)** Multienzymatic cascade to (*R*)-1-phenylethylamine; **(d)** One-pot synthesis of enantio-enriched phenylpropanolamine isomers from chiral 1,2-diols. **(e)** Redox neutral convergent cascade combining CHMO and *Te*ADH using 1,6-hexanediol as the co-substrate, to obtain Ɛ−caprolactone. (**f**) Synthesis of (*S*)-4-phenylbutan-2-ol using *E. coli* cells expressing *Cv*TA and *Le*KRED co-immobilized as sol−gel in silica microspheres.

stereoisomeric forms and 1,2-cyclohexanediols in two different stereoisomeric forms with high conversion and stereoisomeric excess from the initial glutaraldehyde and adipaldehyde substrates. This one-pot bienzymatic cascade represents a promising approach for the synthesis of chiral vicinal diols.

Rother et al. [25] developed an ADH-promoted system to synthesize chiral 1,2-diol building blocks with co-product removal (Figure 1b). This elegant strategy allowed for efficient NADPH cofactor recycling, while removing the co-product formed during the reaction, thereby shifting the equilibrium toward the product formation. In this system, first, a ThDP-dependent benzaldehyde lyase from *Pseudomonas fluorescens* (*Pf*BAL) forms a hydroxyketone intermediate from benzaldehyde and acetaldehyde and then reduced by the ADH from *Ralstonia* sp. (*Ras*ADH) to obtain the desired chiral 1,2-diol, such as (1*R*,2*R*)-1-phenylpropane-1,2-diol. When using benzyl alcohol as a co-substrate to recycle the NADPH, the oxidized co-substrate becomes the benzaldehyde substrate for the carboligase. Without adding benzaldehyde in the first step, the reaction yielded 1,2-diol in >100 mM concentrations with up to 99% *ee* and *de*. Another major advantage is the low benzaldehyde solubility in aqueous medium is no longer a challenge. This cascade combination can be implemented for any system where the co-products of the one-step reaction serve as substrates for the coupled reaction step [25].

In a different approach, Bommarius et al. [26] recently described the deracemization of 1-phenylethanol to yield (*R*)- or (*S*)-1-phenylethanol by combining the (*R*)-ADH from *Lactobacillus brevis* or the (*S*)-ADH from *Bacillus subtilis* with the NADPH-oxidase from *Lactobacillus plantarum*. This bienzymatic system was developed in a bubble column with sparged air, achieving a higher reaction rate in the deracemization than when using a standard solution. Complete conversion of 50 mM 1-phenylethanol was observed in the optimized system.

Obtaining chiral amines and amino alcohols

Chiral amines are highly sought-after, the amino group being present in a plethora of chemical building blocks. The Park group [27] developed enzymatic cascades to obtain long-chain aliphatic amines such as (*Z*)-12-aminooctadec-9-enoic acid, 10- or 12-aminooctadecanoic acid, and 10-amino-12-hydroxyoctadecanoic acid from renewable fatty acids with the combination of a fatty acid double bond hydratase OhyA (from *Stenotrophomonas maltophilia*), a long-chain ADH (from *Micrococcus luteus*), and a variant transaminase (TA, from *Vibrio fluvialis*). Tight control of putative enzyme inhibitors, such as the amino donor and by-products, and the cofactor regeneration system enabled the production of bulky aliphatic amines in high yield. A similar cascade combination has been recently used for the selective synthesis of aromatic fluorinated amino alcohols using panels of ADHs and TAs to find the best complementary enzymes, obtaining the desired stereoisomers in >99% *ee* and *de* [28].

Wang et al. [29] designed a multienzymatic cascade reaction for the selective bioamination of aromatic alkanes, comprising a P450 monooxygenase (mutant $P450_{BM3\ 19A12}$), two stereocomplementary ADHs from *Streptomyces coelicolor* (*Sc*CR) and from *Paracoccus pantotrophus* (*Pp*ADH), and an amine dehydrogenase from *Exiguobacterium sibiricum* (*Es*AmDH) using ammonia as an amino donor (Figure 1c). A series of aromatic alkanes afforded moderate conversions. After reaction optimization, the bioamination cascade of ethylbenzene was implemented on a preparative scale to obtain (*R*)-1-phenylethylamine, achieving a 25% isolated yield with >99% *ee*.

To obtain chiral β-amino alcohols, Zhang et al. [30] developed a multienzymatic cascade coupling an ADH and a TA resulting in 79–99% conversion and 97–99% *ee*, with a self-sufficient cofactor recycling system catalyzed by an ADH. With the same concept, to synthesize enantio-enriched phenylpropanolamines, Mutti et al. [31] used chiral 1-phenylpropane-1,2-diols as key intermediates, obtained from *trans*- or *cis*-β-methylstyrene by combining a styrene monooxygenase with stereocomplementary epoxide hydrolases. The right combination of stereocomplementary-selective NAD^+-dependent ADHs BDHA or *Ls*ADH from *Leifsonia* sp., and ω-TA, *At*TA from *Aspergillus terreus*, *Cv*TA from *Chromobacterium violaceum*, *Bm*TA from *Bacillus megaterium*, together with an alanine dehydrogenase from *Bacillus sphaericus* (*Bs*AlaDH), enabled an impressive redox-neutral process to convert the 1,2-diols into each four possible amino alcohol stereoisomers (Figure 1d).

In 2019, a one-pot enzymatic cascade was developed combining a laccase-catalyzed deoximation with either a KRED for ketone reduction or a ω-TA for reductive amination, to give access to either alcohols or amines, respectively [32]. The selection of each biocatalyst provided conversions in the range from 83 to >99% for alcohols and from 70 to >99% for amines, with excellent *ee*. Of note, the authors discovered that using 1% (w/w) of a polyethoxylated castor oil (Cremophor®) as co-solvent allowed reaching product concentrations of up to 100 mM in the cascade, leading to chiral alcohols.

Obtaining chiral lactones and lactams

With wide applications in the fragrance industry, chiral butyrolactones are interesting compounds to synthesize. Pietruszka et al. [33] thus developed a one-pot enzymatic cascade for the synthesis of γ-butyrolactone–based fragrances. Starting from α,β-unsaturated γ-ketoesters, a flavin-dependent ene reductase first reduced the double bond, followed by reduction of the ketone catalyzed by an ADH and, in acidic conditions, the hydrolysis of the ester leading to the cyclization to achieve the butyrolactone products with high selectivity. With an efficient NADPH recycling system using glucose dehydrogenase, a preparative scale of 1 g was achieved [33].

An elegant concept to create a redox-neutral cascade system to synthesize lactones was developed through the combination of the NADP-dependent Baeyer-Villiger cyclohexanone monooxygenase from *Acinetobacter* sp. NCIMB 9871 (*Ac*CHMO) and *Te*ADH, using 1,6-hexanediol as the co-substrate (Figure 1e) [34]. The latter is oxidized forming a hemiacetal that is further oxidized, thus affording three molecules of ε-caprolactone from two molecules of cyclohexanone and one of 1,6-hexanediol [34]. The same cascade concept was achieved with an NAD-dependent flavin monooxygenase, thus lowering the cost [35], and otherwise with horse liver ADH coupled to an NADH oxidase starting with amino alcohols, allowing access to lactams [36].

Whole-cell systems with ADHs

Most of the cascade reactions in which isolated biocatalysts are involved present drawbacks, such as a low operational stability and the requirement of usually expensive cofactors for the development of the enzyme activity. For this reason, the use of recombinant whole cells, in different preparations, is an inexpensive and easy alternative for developing multienzymatic procedures [37].

In 2018, *Escherichia coli* whole-cells containing *Cv*TA and *Lodderomyces elongisporus* yeast with ADH activity (*Le*KRED) were co-immobilized as sol−gel using hollow silica microspheres as additive [38] (Figure 1f). This catalyst was used for the kinetic resolution of racemic 4-phenylbutan-2-amine catalyzed by *Cv*TA coupled to the *Le*KRED-catalyzed bioreduction of 4-phenylbutan-2-one. These two steps afforded (*R*)-4-phenylbutan-2-amine and (*S*)-4-phenylbutan-2-ol, valuable chiral synthons for the preparation of pharmaceuticals. When pyridoxal phosphate (PLP) was used as the *Cv*TA cofactor and isopropylalcohol (IPA) as the co-substrate for NADH recycling, an *Le*KRED:*Cv*TA weight ratio of 2:1 was required, in which the final (*S*)-alcohol was obtained enantiopure with 46% conversion, whereas the starting (*R*)-amine was recovered enantiopure after 24 h. The process was carried out under continuous flow conditions. Both enantiopure (*S*)-alcohol and (*R*)-amine were obtained, but ketone accumulation was observed after 4 h, yielding 41% of the alcohol and 30% of the amine after 24 h. Co-immobilized *Cv*TA-*Le*KRED was studied, with enhanced performance after 24 h, with an amine recovery of 44%.

Finally, recently, Borowiecki et al. [39] impressively developed a chemoenzymatic cascade combining whole-cell biocatalysts such as Baker's yeast, microorganisms containing ADH activity, and *E. coli* whole-cells harboring known ADHs to catalyze the reduction of bulky-bulky aromatic γ-ketoesters, toward the synthesis of γ-aryl-γ-butyrolactones.

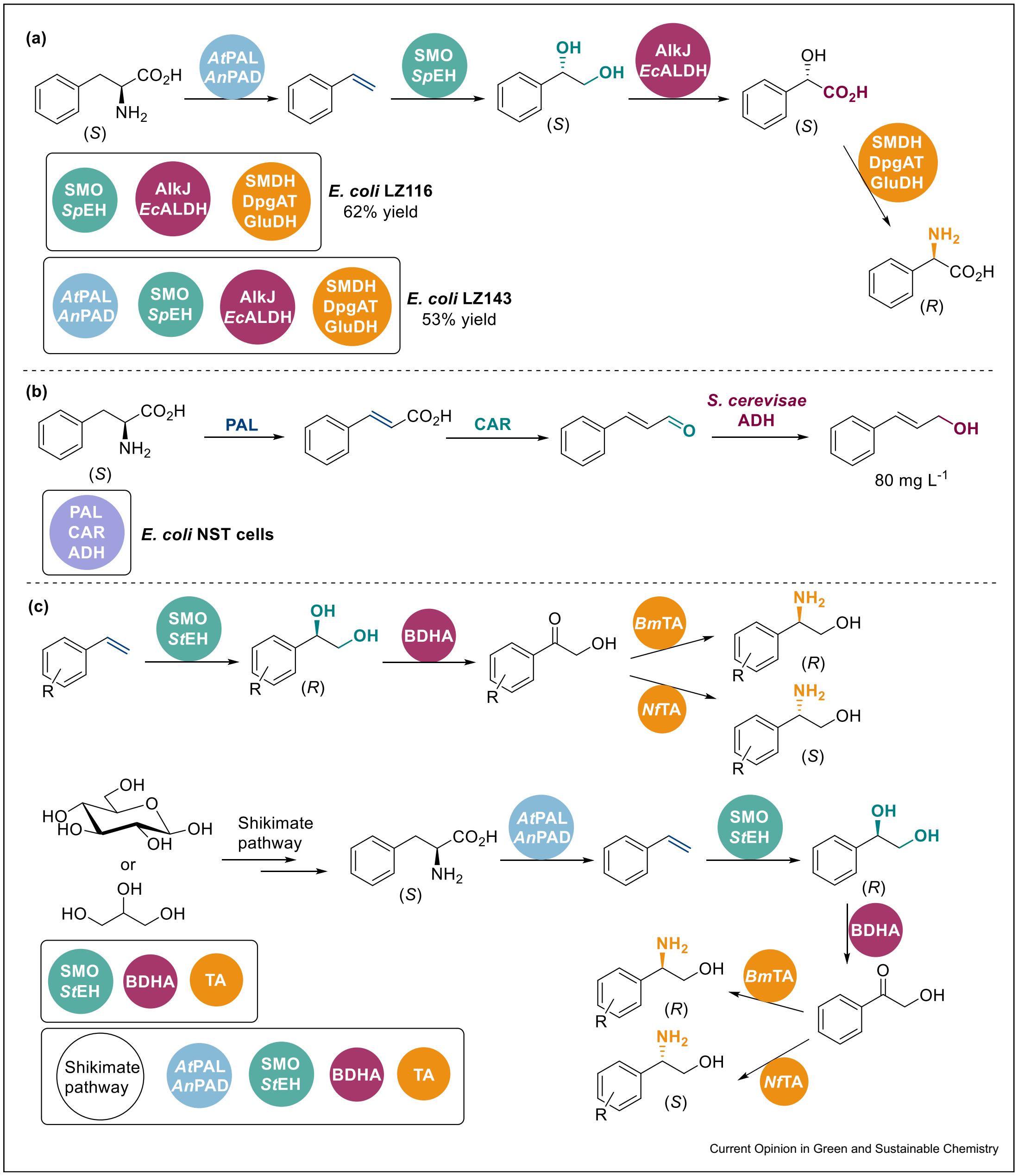
Co-expression systems with ADHs

The application of multienzymatic biosynthesis has allowed performing complex preparations, avoiding the separation and purification of intermediates. Thus, the use of biocatalytic cascades for the synthesis of chemical compounds is becoming one efficient approach in organic synthesis.

Optically pure D-phenylglycine was obtained by engineering a recombinant *E. coli* (LZ110) starting from cheap and easily available starting materials [40]. One of the synthetic procedures consists in a cascade biotransformation from styrene using six enzymes (Figure 2a). Thus, styrene monooxygenase (SMO), epoxide hydrolase (*Sp*EH), ADH (AlkJ), and aldehyde dehydrogenase (*Ec*ALDH) were used to obtain (*S*)-mandelic acid and then combined with an FMN-(*S*)-mandelate dehydrogenase (SMDH) and a D-phenylglycine aminotransferase (DpgAT) to afford the desired D-phenylglycine. Glutamate dehydrogenase (GluDH) was used to enhance the productivity, regenerating L-glutamate in the amino transfer process. The seven enzymes of the reaction were divided into three enzyme modules to achieve a better enzyme expression. SMO-*Sp*EH, AlkJ-EcALDH, and DpgAT-GluDH-SMDH were prepared, and each enzyme module was constructed on four plasmids. Combination of these plasmids afforded 24 *E. coli* strains, each one co-expressing the seven enzymes. The cascade transformation of styrene was tested with resting cells of *E. coli* in a two-phase system (phosphate buffer/ethyl oleate) containing ammonia and glucose for NADPH regeneration. D-Phenylglycine acid was obtained from all the strains after 24 h, with 80% conversion in the presence of *E. coli* LZ116, with only very small concentrations of some of the intermediate compounds. This strain was tested in the reaction of twelve substituted styrenes, affording the corresponding D-phenylglycines with excellent optical purities and high conversions.

The biosynthesis of D-phenylglycine was also tested starting from L-phenylalanine. A cascade biotransformation was proposed including nine enzymes, the seven used in the previous synthesis plus phenylalanine ammonia lyase (PAL) and phenylacrylic acid decarboxylase (PAD). The PAL−PAD was also prepared in four plasmids, leading to 24 strains of *E. coli*, which were tested in the biotransformation of (*S*)-phenylalanine in the biphasic system containing glucose. The *E. coli* LZ143 strain was able to perform the transformation to enantiopure D-phenylglycine.

Figure 2



(a) Synthesis of D-phenylglycine using an engineered recombinant *E. coli* (LZ110) in two multienzymatic approaches including the ADH-catalyzed process, starting from styrene or from L-phenylalanine. **(b)** Preparation of cinnamyl alcohol in a three-step cascade using an engineered *E. coli* NST strain. **(c)** Artificial multienzymatic cascades to obtain (*R*)- and (*S*)-2-phenylglycinols.

Preparative cascades were performed for the conversion of styrene and L-phenylalanine into D-phenylglycine at the optimized conditions, achieving 62% and 53% yield, respectively, after 24 h, demonstrating the potential of these one-pot cascades.

(*R*)- and (*S*)-2-phenylglycinols are building blocks in pharmaceutical chemistry which have been recently prepared in a multienzymatic method [41]. Thus, starting from styrene, a cascade process including four enzymes, with a styrene monooxygenase from *Pseudomonas* sp. (SMO), an epoxide hydrolase *Solanum tuberosum* (*St*EH), butanediol dehydrogenase BDHA, and a TA, was conducted by co-expressing these enzymes from three plasmids into the strain *E. coli*-SSBB-1. After optimizing the reaction conditions, the one-pot biotransformation was carried out with good yields and complete selectivity. This biosynthesis was also performed from L-phenylalanine, by converting this compound into styrene in a two-step process catalyzed by a PAL and a PAD, which were expressed together and combined with the rest of biocatalysts into the strains *E. coli*-PPSSBB and *E. coli*-PPSSBN. The process was finally developed from renewable feedstocks as glucose and glycerol, which were converted into L-phenylalanine by the Shikimate pathway. Two strains, *E. coli* NST-PPSSBB and *E. coli* NST-PPSSBN, were engineered, leading to good results in the preparation of chiral 2-phenylglycinols.

The preparation of cinnamyl alcohol has been performed in a three-step cascade from L-phenylalanine [42], combining a PAL from *Anabaena variabilis* with the carboxylic acid reductase from *Mycobacterium marinum* (*Mm*CAR) and the ADH from *Saccharomyces cerevisiae* by metabolic engineering (Figure 2b). L-Phenylalanine was produced by the *E. coli* NST strain using a mixture of glycerol and glucose as the carbon source. *E. coli* NST cells were then transformed with the pZZ-Eva2 vector, which allows the formation of cinnamyl alcohol. When the biotransformation was carried out in Terrific broth (TB) medium, a maximum of 300 mg of the final product per liter of culture was produced after 24 h. In mineral media M9, starting from the glycerol/glucose mixture, the production of cinnamyl alcohol rises up to 80 mg L^{-1}, with no side-product formation in this reaction medium.

Chemoenzymatic cascades with ADHs

The combination of chemocatalytic reactions with biotransformations catalyzed by ADHs toward chemoenzymatic cascade-type one-pot processes has gained a great interest in the last few years. The application of catalysts of different nature allows complementing their different reactivity. Thus, most of the examples developed until nowadays include metal- and organo-catalyzed carbon-carbon bond formation, combined with a biocatalyzed reaction. In general, chemical catalysis has shown high versatility and efficiency, whereas enzymes are usually more selective. In these chemoenzymatic methodologies, the compatibility between the chemical catalyst and the biocatalyst is a key parameter that has to be precisely controlled [43].

Metal catalysts combined with ADHs

In 2019, the preparation of the odanacatib precursor, (*R*)-2,2,2-trifluoro-1-(4'-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)ethanol, was developed [44]; starting from 1-(4-bromophenyl)-2,2,2-trifluoroethanone, the Suzuki−Miyaura coupling of the ketone with boronic acids, followed by ADH-catalyzed bioreduction led to the desired alcohol (Figure 3a), with quantitative conversion using ADH-A, ADH-T, *Ras*ADH, or evo-1.1.200. The cross-coupling reaction was studied, using both reagents in stoichiometric amounts with 2 mol% of $PdCl_2(PPh_3)_2$ in the presence of Na_2CO_3 and water. When the process was carried out in a one-pot procedure, 500 mM of the starting ketone gave enantiopure (*R*)-alcohol with 85% yield.

Recently, a two-step approach combining gold catalysis and ADH-catalyzed bioreduction was developed for the preparation of optically active β,β-disubstituted allylic alcohols [45], starting from propargylic alcohols (Figure 3b). These compounds were subjected to the Meyer−Schuster rearrangement to yield the corresponding α,β-unsaturated ketones in the presence of *N*-heterocyclic carbene gold (I) catalysts. Best results were achieved in the presence of $IPrAuNTf_2$ in a mixture of water/IPA (4:1 v/v). The bioreduction of (*E*)-4-phenylpent-3-en-2-one led to the formation of (*R*)- or (*S*)-allylic alcohols with *E. coli Lb*ADH or KRED-P1-A12. This methodology was extended to other propargylic alcohols to achieve the (*R*)- or the (*S*)-allylic alcohols with high yields and optical purities, even allowing a 100 mg scale to (*R*,*E*)- or (*S*,*E*)-enantiomers.

Nanoparticles were combined with ADHs in chemoenzymatic cascades in the synthesis of (1*S*,3*S*)-3-methylcyclohexanol from 3-methyl-2-cyclohexenone [46]. The initial step was the metal-catalyzed hydrogenation of the starting material to 3-methyl-2-cyclohexanone in the presence of Pd or Pt nanoparticles (NPs), followed by the addition of the ADH from *Thermus* sp. ATN1 (TADH). Pt-based NPs led to quantitative conversion albeit with lower selectivity. In contrast, the use of the Pd-NPs afforded lower conversions, but the (1*S*,3*S*)-product had 95% *de*.

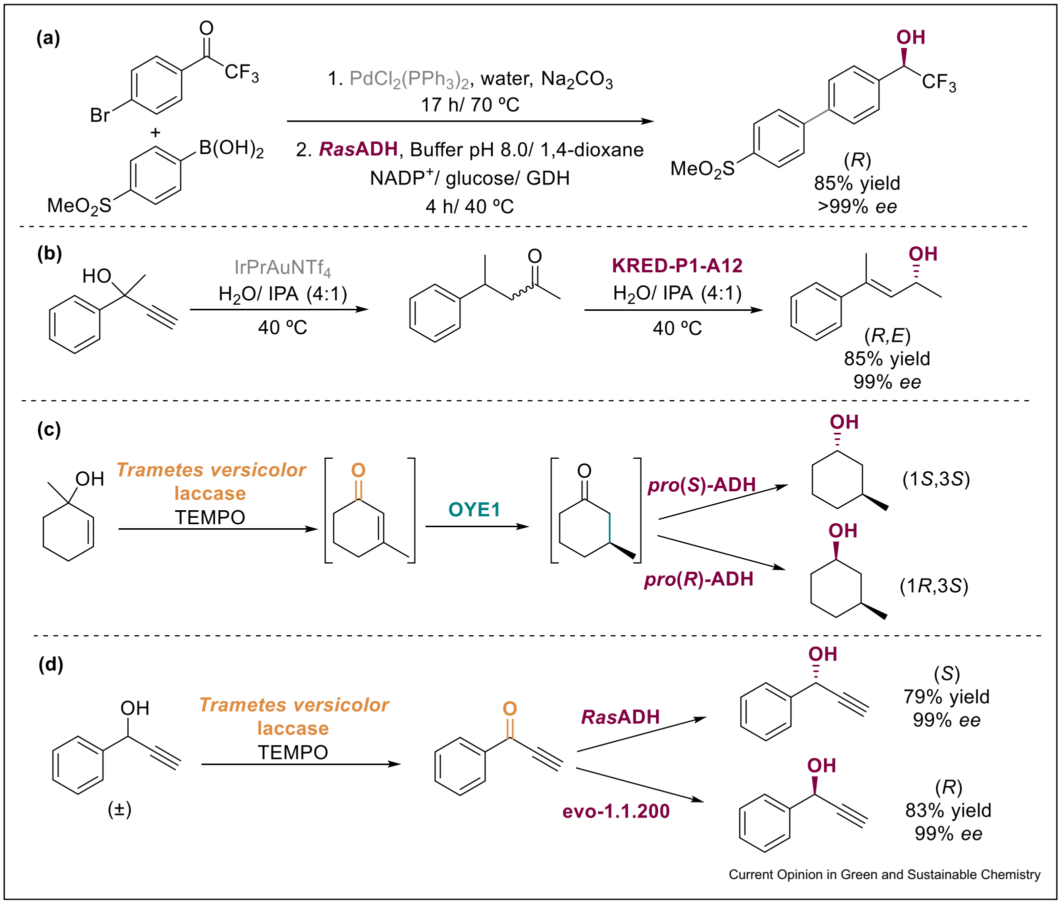
Chemocatalysts combined with ADHs

Apart from metal catalysts, some other examples of the use of chemocatalysts and ADHs for the synthesis of valuable compounds have been reviewed [12]. In 2020, the preparation of optically active vicinal fluoro alcohols, valuable building blocks of natural products, has been developed in a three-step one-pot procedure starting from β-ketoesters [47]. These esters were treated with the lipase CAL-B and Selectfluor in water in a process of hydrolysis and decarboxylative fluorination to yield the vicinal fluoroketones that were selectively reduced to the (*S*)-fluoro alcohols by the ADH from *Kluyveromyces thermotolerans* (*Kt*CR) and to the (*R*)-products by the *Bacillus* sp. ECU0013 ketoreductase (YtbE) with moderate to good yields and high enantioselectivity.

Deracemizations combining chemocatalysts and ADHs

Chemical catalysts have been combined with ADHs in deracemization procedures [48]. Synthesis of *cis*- and *trans*-3-methylcyclohexanol and other fragrance products has been performed with ADHs in combination with TEMPO [49]. The starting 1-methylcyclohex-2-enol undergoes an oxidative 1,3-rearrangement

Figure 3



(a) One-pot ADH-promoted cascade to synthesize an odanacatib precursor by combining Suzuki–Miyaura coupling with *Ras*ADH-catalyzed bio-reduction; **(b)** One-pot synthesis of optically pure allylic alcohols using a *N*-heterocyclic gold catalyst and an ADH; **(c)** Multienzymatic cascade to obtain *cis*- and *trans*-3-methylcyclohexanol; **(d)** Procedure for the deracemization of propargyl alcohols combining laccases and ADHs.

catalyzed by the laccase of *Trametes versicolor* in the presence of $TEMPO^+BF_4^-$ as an organic mediator (Figure 3c). The resulting enone was reduced by ene reductase OYE1 or OYE2 to (*S*)-3-methylcyclohexanone with good yields and excellent selectivity. The cascade was completed by adding different commercial ADHs to obtain the final (1*S*,3*S*)-*trans*-product (*de* >98%) or (1*R*,3*S*)-*cis* configuration (>90% *de*).

In 2020, the laccase from *T. versicolor* coupled with TEMPO [50] was combined with different ADHs to synthesize optically active propargylic alcohols starting from a racemic mixture (Figure 3d). The laccase/TEMPO system performed the oxidation to the propargylic ketones with high yield and selectivity, followed by the bioreduction using either (*S*)- or (*R*)-selective ADHs giving high to excellent selectivity for the (*S*)-selective ADHs. The sequential process was studied in the deracemization of 50 mM 1-phenylprop-2-yn-1-ol; a scale-up yielded the enantio-enriched (*S*)- and (*R*)-alcohols with 79% and 83% yield, respectively. This methodology was successfully extended to other propargylic alcohols.

Similarly, 2-azaadamantane *N*-oxyl, combined with stoichiometric amounts of NaOCl, has been used as an organocatalyst for the oxidation of racemic secondary alcohols to the corresponding ketones, which were then reduced by isolated commercial ADHs [51]. Thus, 250 mM of 1-(4-trifluoromethyl)-phenylpropan-2-ol was oxidized to the ketone, further reduced by an ADH to obtain the desired (*S*)-alcohol with complete conversion. This method was successfully extended to other aromatic or aliphatic alcohols.

Conclusions

ADHs have been shown to be compatible with a wide variety of biocatalysts and chemocatalysts, being used in concurrent or sequential multistep processes for the preparation of different chiral compounds including vicinal diols, amines, amino alcohols, and lactones, among others. In the present review, we have given an overview of the current use of ADHs in various multicatalytic processes, using *in vitro* artificial cascades as well as whole-cell systems, to give access to enantioenriched valuable products.

The future use of ADHs as valuable synthetic catalysts in cascades will certainly continue to evolve not only with the discovery of new ADH libraries [52], protein and cofactor engineering, and metalloprotein modifications [53] but also with novel combinations of biocatalysts/chemocatalysts/organocatalysts, thus expanding the (bio)catalytic toolbox to access new synthetic routes [54].

Declaration of competing interest

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 article.

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