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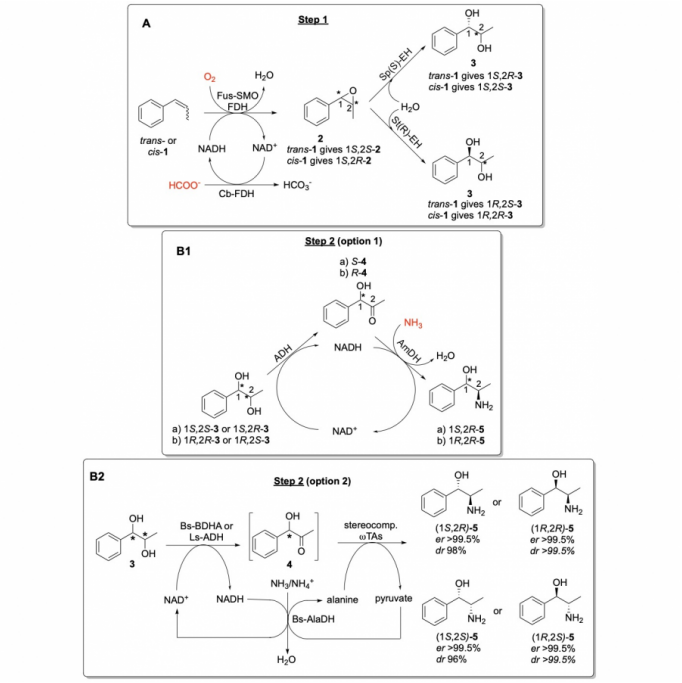
Biocatalytic cascades for the synthesis of amines with two stereogenic centres

AUTHORS
Francesco MUTTI / UNIVERSITY OF AMSTERDAM, SCIENCE PARK 904, AMSTERDAM
Tanja KNAUS / UNIVERSITY OF AMSTERDAM, SCIENCE PARK 904, AMSTERDAM
Maria CORRADO / UNIVERSITY OF AMSTERDAM, SCIENCE PARK 904, AMSTERDAM

PURPOSE OF THE ABSTRACT
Chiral amines are obtained through different enzymatic and chemo-enzymatic methods comprising kinetic resolution, dynamic kinetic resolution and deracemisation of racemic mixture, and asymmetric synthesis from prochiral substrates. These processes are performed using a variety of enzymes, namely hydrolases, transaminases, ammonia lyases, amine oxidases, imine reductases/reductive aminases, amine dehydrogenases, engineered cytochromes P450, etc. Therefore, structurally diverse chiral amines are accessible nowadays using biocatalysis; however, in most cases, only amines possessing one stereogenic centre are generated.
Chiral amines with more than one stereogenic centre are found in many biologically active compounds but are more challenging to synthesise; these amines could be obtained by developing biocatalytic cascades. Early examples are the biocatalytic synthesis of enantioenriched 1,2 amino-alcohols having two stereogenic centers by starting from an aldehyde and pyruvate and combining a carboligase with a transaminase,[1] or by starting from a diketone and combining an alcohol dehydrogenase with a transaminase.[2] Another option is the asymmetric transamination of an α-hydroxy ketone.[3]
In this context, we have recently reported a sequential multi-enzymatic route for the formal chemo-, regio- and stereoselective aminohydroxylation of β-methylstyrene that consumes only dioxygen, ammonia and formate, and generates carbonate as the only by-product.[4] This cascade comprised enantioselective epoxidation and hydrolysis followed by a hydride-borrowing alcohol amination (Fig. 1, A and B1). This was also the first study in which the regioselectivity of the dual-enzyme hydride-borrowing alcohol amination was investigated and exploited in preparative scale. In this way, β-methylstyrene was converted into (1R,2R) and (1S,2R)-phenylpropanolamine in 59–63% isolated yields, and up to >99.5 : <0.5 d.r. and e.r. In another study, we developed a variation of the above-mentioned cascade by combining an alcohol dehydrogenase, a transaminase and an alanine dehydrogenase for the second stereo- and regio-selective alcohol amination step (Fig. 1, A and B2).[5] Thus, again, 1,2-amino alcohols with two stereogenic centres were obtained with e.r. and d.r. up to >99.5 : <0.5 and analytical yields up to 95%. Notably, this was the first report on an enzymatic method that enabled to obtain all the four possible phenylpropanolamine stereoisomers in excellent enantio- and diastereo-selectivity.
With the aim of expanding the accessible chemical space for chiral amines by using biocatalysis, we investigated a cascade that combined ene-reductases with imine reductases/reductive aminases to enable the conversion of α,β-unsaturated ketones into primary, secondary, and tertiary amines containing two stereogenic centres and in very high chemical purity (up to >99%), diastereomeric ratio, and enantiomeric ratio (up to >99.8 : <0.2), (Fig. 2).[6] Compared with previously reported strategies,[7] our strategy could synthesise two, three, or even all four of the possible stereoisomers of the amine products while precluding the formation of side-products. Furthermore, ammonium or alkylammonium formate buffer was used as the only additional reagent since it acted both as an amine donor and as a source of reducing equivalents.

FIGURES



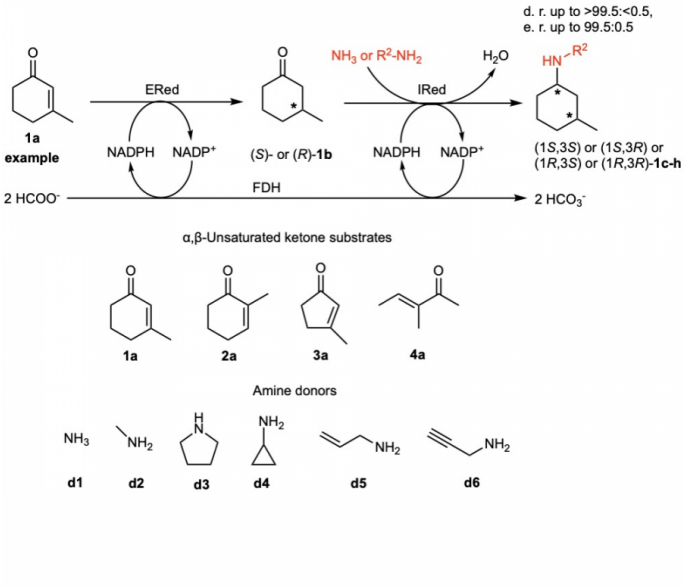


FIGURE 1

Multi-enzymatic synthesis of 1,2 amino alcohols with two stereogenic centres.

Conversion of styrenes into 1,2-amino alcohols possessing two stereogenic centres via biocatalytic cascades comprising monooxygenases, epoxy hydrolases, alcohol dehydrogenases, transaminases, amine dehydrogenases.

FIGURE 2

Multi-enzymatic synthesis of amines with two stereogenic centres.

Conversion of alpha,beta-unsaturated ketones into amines possessing two stereogenic centres via biocatalytic cascades comprising ene reductases, amine dehydrogenases, imine reductases.

KEYWORDS

biocatalytic cascades | chiral amines | oxidoreductases | transferases

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