Synthetic enzyme cascades - an eco-friendly, selective synthesis strategy

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Enzymatic multi-step reactions offer significant potential to yield industrially relevant chiral building blocks with excellent stereoselectivities. Still, the access to economically feasible product concentrations can be a challenge. By using an integrated engineering approach encompassing enzyme engineering, reaction optimisation and optimal process design, this challenge can be made. This presentation focuses on the development of synthetic enzyme cascades for the production of pharmaceutically active ingredients meeting high selectivities (>98 %) and product concentrations >50 g/L.

By the flexible combination of enzymes with varying selectivities, the access to product platforms is possible. E.g. starting from easily available aldehydes, chiral amino alcohols can be synthesised by a combination of an enzymatically catalysed carbobigation and a transamination step. Depending on the substitution pattern of the starting material, e.g. nor(pseudo)ephedrine[1], methoxamine or metaraminol[2] are accessible. Combining (R)- and (S)-selective catalysts in a modular way, all four stereoisomers of the respective amino alcohol can be gained.

Further, tetrahydroisoquinolines containing three chiral centres can be synthesised by addition of a cyclisation step. This step can be either catalysed by a norcoclaurnine synthase or by phosphate giving stereocomplementary products.[2]

To further increase ecologic and economic efficiency, we investigate the potential in running multi-step biocatalysis in (environmentally benign) organic solvents. Whole cell biotransformations in micro-aqueous reaction systems do not only allow addition of poorly water-soluble substrates in high concentrations, but also facilitate downstream processing. Therewith, the production of several vicinal diols in a 2-step 1-pot cascade with product concentration > 440 mM and space-time-yields > 330 g L⁻¹ d⁻¹ (ee/de >99 %) was possible.[3] Novel set-ups of this system include coproduct recycling and in situ product removal.[4]


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