MODULAR SYNTHETIC ENZYME CASCADES – FROM CATALYST SELECTION TO REACTION DESIGN

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Enzymatic multi-step reactions offer significant potential to yield industrially relevant chiral intermediates and building blocks with excellent stereoselectivities. This presentation focuses on the development of synthetic enzyme cascades for the production of pharmaceutically active ingredients with multi-chiral centres in a modular approach. Strategies to increase ecologic and economic efficiency of such processes are highlighted.

By flexible combination of enzymes with varying substrate preferences or stereoselectivities to cascades, the access to broad product platforms is possible. Starting from easily available aldehydes or keto acids, chiral amino alcohols can be synthesised by the combination of an enzymatically catalysed carboligation 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. By the flexible combination of (*R*)- and (*S*)-selective catalysts, in many cases all four stereoisomers of the amino alcohol are gained in a highly selective manner. Enzyme engineering, reaction- and process engineering enables the access to industrially feasible product concentrations.
In a recent project the building bock 1-amino-1-phenylpropan-2-ol could be synthesised after screening a range of wild type transaminases. This represents a more challenging synthesis, as due to the formation of 2-hydroxypropiophenone as intermediate, a more bulky ethan-1-ol end group has to be optimally arranged in the active side of the transaminases to enable transformation. Here, the use of catalysts immobilised with novel techniques[3] proofed to be an effective strategy for optimal process design.
Finally, tetrahydroisoquinolines are accessible with high selectivity by addition of a cyclisation step. This additional step can be catalysed enzymatically (by a norcoclaurine synthase) or chemically (mediated by phosphate) to obtain stereocomplementary products.[2] Also the combination of enzymes and photocatalysts is feasible[4], expanding the diversity of catalyst combinations to cascades.

To further increase ecologic and economic efficiency, we also intensively investigate the applicability of whole cell cascade approaches in (environmentally benign) unconventional media and neat substrate systems. E.g. micro-aqueous reaction systems do not only allow addition of high amounts of poorly water-soluble substrates, but also facilitated downstream processing. The implementation of lyophilised whole cells cuts on production costs and circumvents the need of cofactor addition.[5]

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