“SYNTHETIC ENZYME CASCADES –
FROM TARGETED REGULATION TO SUSTAINABLE PROCESS CHAINS”

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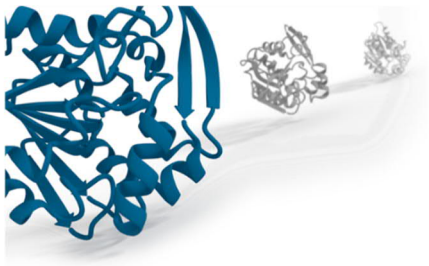

Enzymatic multi-step reactions offer significant potential to yield chiral building blocks with excellent stereoselectivities. But the access to economically feasible product concentrations can be a challenge. This challenge can be met using an integrated engineering approach that includes enzyme engineering, reaction optimisation and optimal process design. Examples of synthetic enzyme cascades for the production of pharmaceutically active ingredients meeting selectivities >98 % and product concentrations >50 g/L will be presented.

By the flexible combination of enzymes with varying substrate specificities and stereo-/ regioselectivities, the access to whole product platforms is possible. Combining (R)- and (S)-selective transaminases and carboligases in a modular way, all four stereoisomers of e.g. amino alcohols like nor(pseudo)ephedrine1, methoxamine or metaraminol2 are gained from differently substituted starting aldehydes. On top, tetrahydroisoquinolines (THIQ) containing three chiral centres can be synthesised by an additional cyclisation step. This step is either catalysed by a norcoclaurine synthase or simply by phosphate giving stereocomplementary products.2 This example shows the power of hybrid systems, where optimal catalysts are selected, no matter from which origin they are. Since recently, we even combine enzymes and chemical with (living) microbial cell factories in process chains. In this way, renewable raw materials are converted into valuable chiral compounds in a sustainable way. The entire process chain, including downstream processing3, is evaluated in terms of ecological and economic efficiency.

With the latest developments in the field of (modular) multi-stage biocatalysis, the range of complex products is constantly increasing. With new opportunities, new challenges arise. The more enzyme steps are combined in one pot, the higher is the risk of undesired cross-reactivity4. Therefore, many reaction steps must be separated in space or time. In addition to separation in space, e.g. by modules, we have recently begun to investigate techniques that regulate the activity of the individual enzymes in one-pot systems. External stimuli such as light and temperature are used.

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4 C. Claaßen, T, Gerlach, D. Rother (2019), Adv. Synth. Catal. 361(11): 2387–2401