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(51) Neuburger J., Helmholz F., Tiedemann S., Lehmann P., Süss P., Menyes U., Langermann J. Implementation and scale-up of a semi-continuous transaminase-catalyzed reactive crystallization for the preparation of (S)-(3-methoxyphenyl)ethylamine, (2021), doi.org/10.1016/j.cep.2021.108578

Abstract: *Unfavorable equilibrium positions are often a critical factor in the process development of biocatalytic reactions and usually require secondary solutions for efficient synthesis strategies. This explicitly applies to transaminase-catalyzed reactions, which can be used for the synthesis of enantiomerically pure amines. Overcoming the unfavorable equilibrium situation in these biocatalytic reactions, especially with a focus on efficient product isolation, has only been partly studied for preparative applications especially with higher concentration of a product amine. In this study, we present the process development of a transaminase-catalyzed reaction with the specific integration of an in situ- product crystallization, which allows downstream-processing via filtration in addition to the required equilibrium shift. This approach highlights a semi-continuous reaction concept with intermediate substrate addition and product removal in the form of a suspension-to-suspension reaction, supported by a light vacuum to remove the by-product acetone. Using the methodology up to 1.2 mol L-–1 product amine could be obtained by an iterative process development. Thus, the presented method represents a high potential for the preparative application of amine-based biocatalytic reactions at larger scales.*

50) Švarc A., Fekete M., Hernandez K., Clapés P., Findrik Z., Szekrenyi A., Skendrović D., Vasić-Rački D., Charnock S., Presečki A.
An innovative route for the production of atorvastatin side-chain precursor by DERA-catalysed double aldol addition, (2020), doi.org/10.1016/j.ces.2020.116312

Abstract: *A multi-enzyme route for the production of an atorvastatin side-chain was proposed. The approach includes the consecutive double aldol addition of acetaldehyde to the phenylacetamide amino-protected propanal by 2-deoxyribose-5-phosphate aldolase (DERA), the oxidation by ketoreductase, the lipase-catalysed acylation and amino group deprotection by penicillin G-acylase. To explore the feasibility of the process, the DERA reaction was studied into detail. Based on the kinetic and stability studies, a mathematical model was developed and validated in a batch and fed-batch reactor. The highest productivity was obtained in repetitive batch reactor (229.1 g/(L day)). The highest final product concentration of 124 g/L was obtained in fed-batch reactor. The mathematical model-based optimisation provided insight into the possibilities for process metrics improvement. Further, the second step was explored. The results showed that the DERA reaction and the oxidation reaction can be carried out as the multi-enzyme one pot process in the sequential manner.*

(47) Meyer L-E, **Brundiek H.** , Langermann J.
Integration of ion exchange resin materials for a downstream-processing approach of an imine reductase-catalyzed reaction, (2020), doi:10.1002/btpr.3024

Abstract: *In this study, an ion exchange resin-based downstream-processing concept for imine reductase (IRED)-catalyzed reactions was investigated. As a model reaction, 2-methylpyrroline was converted to its corresponding product (S)-2-methylpyrrolidine with >99% of conversion by the (S)-selective IRED from Paenibacillus elgii B69. Under optimized reaction conditions full conversion was achieved using a substrate concentration of 150 and 500 mmol/L of d -glucose. Seven commercially available cation- and anion-exchange resins were studied with respect to their ability to recover the product from the reaction solution. Without any pretreatment, cation-exchange resins Amberlite IR-120(H), IRN-150, Dowex Monosphere 650C, and Dowex Marathon MSC showed high recovery capacities (up to >90%). A 150-ml preparative scale reaction was performed yielding ~1 g hydrochloride salt product with >99% purity. Any further purification steps, for example, by column chromatography or recrystallization, were not required.*

(46) Wunschik D. S., Ingenbosch K. N., **Süss P.**, Liebelt U., Quinte S., Dyllick-Brenzinger M., Zuhse R., **Menyes U.**, Hoffmann-Jacobsen K., Opwis K., Gutmann J .S.; Enzymatic epoxidation of cyclohexene by peroxidase immobilization on a textile and an adapted reactor design, (2020), doi: 10.1016/j.enzmictec.2020.109512

Abstract: *Objective: Regio- and stereoselective hydroxylation of lithocholic acid (LCA) using CYP107D1 (OleP), a cytochrome P450 monooxygenase from the oleandomycin synthesis pathway of Streptomyces antibioticus.* ***Results:*** *Co-expression of CYP107D1 from S. antibioticus and the reductase/ferredoxin system PdR/PdX from Pseudomonas putida was performed in Escherichia coli whole cells. In vivo hydroxylation of LCA exclusively yielded the 6β-OH product murideoxycholic acid (MDCA). In resting cells, 19.5% of LCA was converted to MDCA within 24 h, resulting in a space time yield of 0.04 mmol L-1 h-1. NMR spectroscopy confirmed the identity of MDCA as the sole product.* ***Conclusions:*** *The multifunctional P450 monooxygenase CYP107D1 (OleP) can hydroxylate LCA, forming MDCA as the only product.*

(38) Hülsewede D., Tänzler M., **Süss P.**, Mildner A., **Menyes U.**, v. Langermann J.,
Development of an in situ-Product Crystallization (ISPC)- Concept to Shift the Reaction Equilibria of Selected AmineTransaminase-Catalyzed Reactions, European Journal of Organic Chemistry, 18, 2130-2133 (2018)

Abstract: *The synthesis of enantiopure amines via amine transaminases involves several challenges including unfavorable reaction equilibria and product inhibition. Described here is a non-catalytic approach to overcome such problems by using an in situ-product crystallization (ISPC) to selectively remove a targeted product amine from an amine transaminase-catalyzed reaction. The continuous removal of the product amine from its reaction solution as a barely soluble salt effectively yields a displacement of the reaction equilibrium towards the products and facilitates a simple downstream processing approach via filtration. The targeted product amine is eventually obtained from the salt, while the counterion compound can be easily recycled.*

(35) Hülsewede D., Tänzler M., Süss P., Mildner M., **Menyes U.**, v. Langermann J. (2018),
Development of an in situ-Product Crystallization (ISPC)-Concept to Shift the Reaction Equilibria of Selected Amine Transaminase-Catalyzed Reactions, Eur. J. Org. Chem. 10.1002/ejoc.201800323

Abstract: *The synthesis of enantiopure amines via amine transaminases involves several challenges including unfavorable reaction equilibria and product inhibition. Described here is a non-catalytic approach to overcome such problems by using an in situ-product crystallization (ISPC) to selectively remove a targeted product amine from an amine transaminase-catalyzed reaction. The continuous removal of the product amine from its reaction solution as a barely soluble salt effectively yields a displacement of the reaction equilibrium towards the products and facilitates a simple downstream processing approach via filtration. The targeted product amine is eventually obtained from the salt, while the counter ion compound can be easily recycled.*

(31) Wardenga R., Rother D. (2017)
Efficient Chiral Chemistry by Application of Stereoselective Biocatalysts in Micro-Aqueous Reaction Systems, Speciality Chemicals Magazine, volume 31, issue 01, February 2017, pages 16-17

Abstract: *Dr Rainer Wardenga of Enzymicals and Dr Dörte Rother of Forschungszentrum Jülich discuss the applicability of diverse enzymes in micro-aqueous reaction systems, enabling the conversion of hydrophobic or water-unstable substrates while maintaining the stereoselectivity of the biocatalysts.*

(28) Hinze J., **Süss P.**, Strohmaier S., Bornscheuer U. T., **Wardenga R.**, v. Langermann J. (2016)
Recombinant Pig Liver Esterase-Catalyzed Synthesis of (1S,4R)-4-Hydroxy-2-cyclopentenyl Acetate Combined with Subsequent Enantioselective Crystallization, DOI: 10.1021/acs.oprd.6b00093, Org. Process Res. Dev. 2016, 20, 1258–1264

Abstract: *The recombinant pig liver esterase catalyzed hydrolysis of cis-1,4-diacetoxy-2-cyclopentene forming (1S,4R)-4-hydroxy-2-cyclopentenyl acetate was investigated and realized at preparative scale. Relevant reaction conditions were examined and optimized to achieve full conversion with an enantiomeric excess of about 86% ee. Enantiopure product was then obtained after enantioselective crystallization, which required further studies of the solid phase behavior, including its binary melting point phase diagram.*

(21) Schmidt S., Scherkus C., Muschiol J., **Menyes U.**, Winkler T., Hummel W., Gröger H., Liese A., Herz H.G., Bornscheuer U.T.,
An Enzyme Cascade Synthesis of ε-Caprolactone and its Oligomers, Angew. Chem. Int. Ed. 2015, 54, 2784-2787

Abstract: *Poly-ε-caprolactone (PCL) is currently produced only chemically on industrial scale in spite of the need for hazardous peracetic acid as oxidation reagent. Although Baeyer-Villiger monooxygenases (BVMO) allow in principle the enzymatic synthesis of ε-caprolactone (ε-CL) directly from cyclohexanone with molecular oxygen, current systems suffer from low productivity and entail substrate and product inhibition. In this work, we overcame major limitations for such a biocatalytic route to produce this bulk chemical by combining an alcohol dehydrogenase with a BVMO to enable an efficient oxidation of cyclohexanol to ε-CL. Key to success was a subsequent direct ring-opening oligomerization of in situ-formed ε-CL in an aqueous phase using lipase A from Candida antarctica, thus solving efficiently the product inhibition problem and leading to formation of oligo-ε-CL at >20 g/L when starting from 200 mm cyclohexanol. This oligomer could easily be polymerized chemically to PCL.*

(20) Scherkus C., Liese A., Gröger H., Kragl U., Bornscheuer U. T., **Menyes U.**, (2014)
Prozessentwicklung zur enzymatischen Synthese eines biologisch abbaubaren Polymers, Chemie Ingenieur Technik, 86 (9), 1424–1425

Abstract: *No abstract available*

(17) Süss, P., Illner, S., v. Langermann, J., **Borchert, S.**, Bornscheuer, U.T., **Wardenga, R.**, Kragl, U. (2014)
Scale-Up of a Recombinant Pig Liver Esterase-Catalyzed Desymmetrization of Dimethyl Cyclohex-4-ene-cis-1,2-dicarboxylate. Org. Process Res. Dev., 18, 897-903

Abstract: *A recombinant isoenzyme of pig liver esterase was used for the highly enantioselective desymmetrization of dimethyl cyclohex-4-ene-cis-1,2-dicarboxylate. The selected recombinant esterase showed a significant advantage in enantioselectivity over the commonly used esterase from the mammalian source. The process was scaled up to yield 265 g of product with a simplified pH control, and the target molecule was obtained with an enantiopurity of >99.5% ee.*