Spatial compartmentalization of chemoenzymatic cascades with heterogeneous (bio)catalysts

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The combination of chemical and biological catalysts allows access to synthetic pathways that would otherwise be inaccessible when using either catalyst type alone. However, most chemo-enzymatic pathways have been constrained by compatibility issues. (1) Catalyst compartmentalization proves to be an effective strategy to address these challenges. In this study, we showcase the immobilization of a gold catalyst and the versatile ketoreductase from *Lactobacillus kefir* (2, 3) for a model three-step chemo-enzymatic cascade, converting 4-pentynoic acid into 4-(R)-hydroxy valeric acid with high enantioselectivity. To achieve this, we employ two packed-bed reactors that physically separate a chemoenzymatic cycloisomerization/hydrolysis step from the self-sufficient biocatalytic asymmetric reduction (Figure 1). Consequently, the chemo-enzymatic system, operating continuously at pH 3.8, maintains a consistent space-time yield (STY) of 0.47 g L-1 h-1 over 24 hours, underscoring the remarkable operational stability of the catalysts. Overall, our results underscore the significance of spatially orchestrating catalysts to develop efficient hybrid chemo-enzymatic cascades.

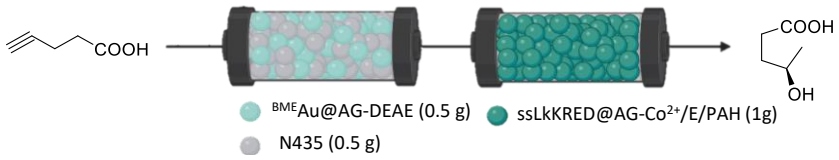

Figure 1. Performance of the optimized hybrid chemo-enzymatic flow-system formed by two telescoped PBRs loading a gold-catalyst (BMEAu@AG-DEAE; cyan), an immobilized lipase (N435; grey), and a self-sufficient immobilized KRED (ssLkKRED@AG-Co2+/E/PAH; tourquise) for the continuous transformation of pentynoic acid into 4-hydroxyvaleric acid.

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