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Batchwise production of chiral building blocks with integrated catalyst recycling

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Introduction

Due to the growing demand for enantiomerically pure compounds in the fine- and pharmaceutical industry there is a strong increase of interest in asymmetric catalysis. In this context, organocatalysts demonstrate certain benefits like low costs, low toxicity and simple handling in comparison to biological or transition metal catalysts, which makes them attractive on an industrial scale.[1] In an industrial application isolation of the product as well as reusability of the precious catalyst is required in terms of economic efficiency. In this study, we present the application of Organic Solvent Nanofiltration (OSN) to a quinine catalyzed Henry reaction. Based on its excellent enantioselectivity and high retention by OSN, benzoylcupreine was selected as a suitable organocatalyst for the Henry reaction.[2]

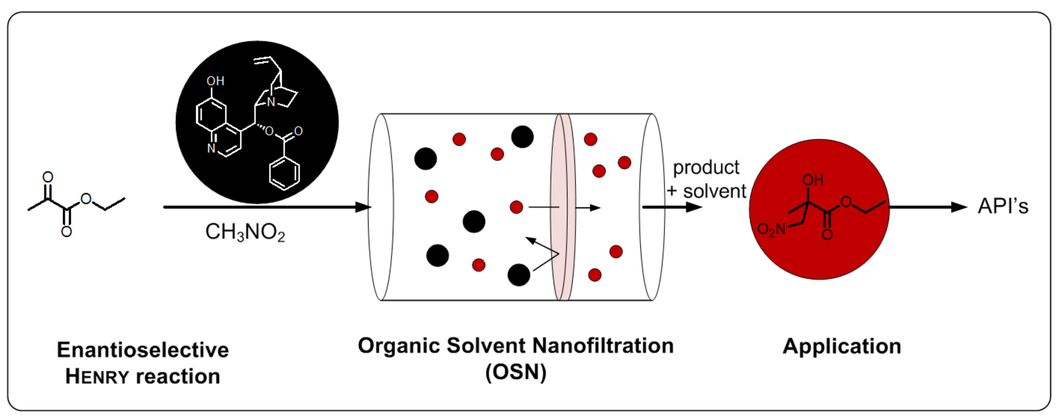

Figure 1. Process scheme, used in this study

Results

Instrumental Setup

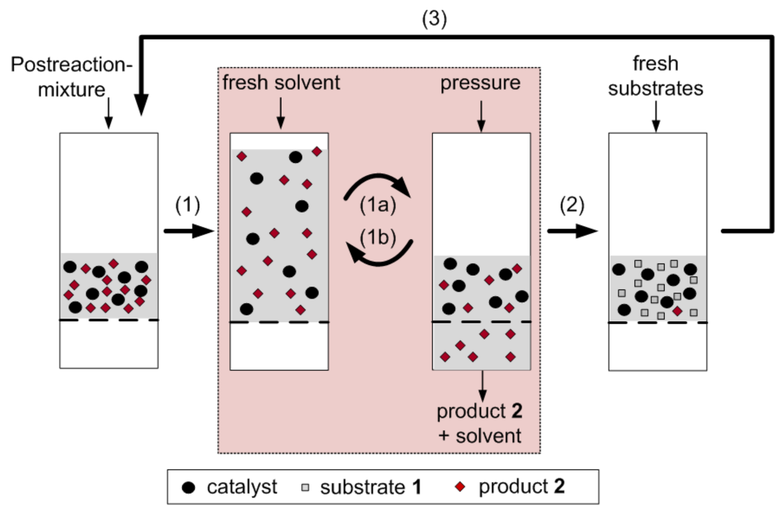

Figure 2. Process scheme for the diafiltration / reaction cycle in the stirred filtration cell: (step 1) discontinuous diafiltration of the diluted postreaction mixture (first batch from reaction vessel); (step 1a) repeated filtration; (step 1b) repeated dilution; (step 2) addition of fresh substrates; (step 3) subsequent reaction.[3]

Filtration Experiments

Rejection of the catalyst BzCPN was obtained with 96.7% (DM 300)[4] and 99.9% (DM 150). The product was rejected with 86.5% and 86.0%, DM 200 and DM 300 respectively, which facilitates a highly selective separation of the catalyst from all reactants.

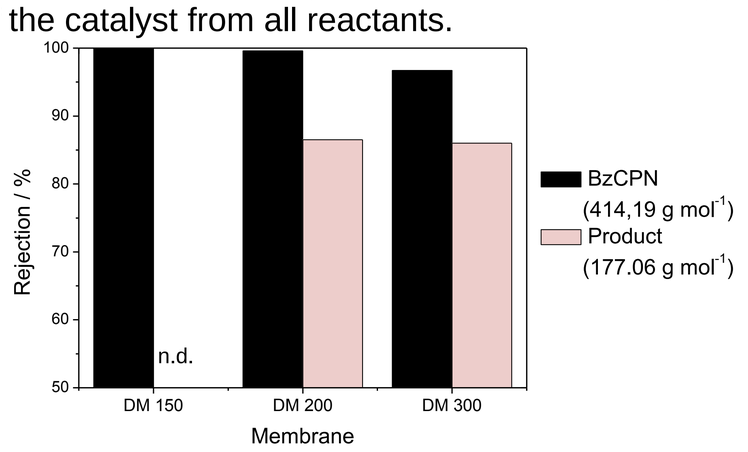

Figure 3. Filtration results for different membranes.[4] Conditions: 0.01 M BzCPN in THF, 30 bar pressure, stirred cell, 20 °C, n.d. = not determined.[3]

Catalyst and Product Separation from Postreaction Mixture

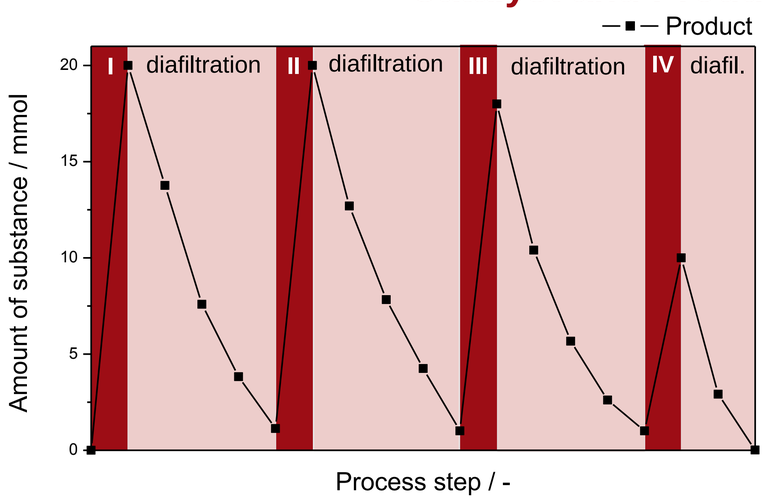

Figure 4. Amounts of product in the filtration cell during different reaction batches and diafiltration steps (I-IV denote the reaction batches).[3]

Table 1. Separation results for the Henry Reaction

		HPLC[a]	isolated[b]			
batch	ee (%)[a]	yield (%)		R_P (%)[c]	R_C (%)[d]	c_C (mol L^{-1})[e]
I	87	81	76	61.2	99.6	0.048
II	88	80	76	56.0	98.9	0.037
III	88	71	66	64.3	98.4	0.022
IV	89	38	37	25.0	96.4	0.009

[a]Determined by HPLC measurements. [b]Isolated yield after diafiltration steps and solvent removal under reduced pressure, as determined by weighing. [c]Rejection of product. [d]Rejection of BzCPN catalyst. [e]Concentration of BzCPN catalyst in the repeated batch reactions, as determined by UV/Vis.[3]

The reaction mixture consisting of ethyl pyruvate (25 mmol), BzCPN (10 mol%) and nitromethane in THF was allowed to react for 12 h. Prior dilution with 150 mL THF (batch I), ee and yield were determined (Tab. 1). Up to four discontinuous diafiltration steps were performed. Fig. 3 presents the amount of product during the reaction/filtration cycles.

The product was isolated with a purity of 94% after each batch. To investigate the catalysts activity after the filtration steps, fresh substrates were added to the solution and stirred again for 12 h. The yields and ee‘s measured for subsequent batches showed that the catalyst was still fully active and could be easily reused.[3]

Summary and Outlook

With this study we illustrate OSN as an eco-friendly alternative separation technology to existing methods for product and catalyst separation. The membrane screenings show high rejection rates with over 99.9% for the catalyst. With the separation experiments we isolated the product in high purity without further purification steps. At the same time the catalyst was reused without any loss of activity. OSN will open a new window in the fine- and pharmaceutical industry for the production of chiral building blocks on an industrial scale. Separation experiments by continuous process steps in kg-scale and kinetic investigations for reaction time optimization will follow.

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References: [1] Dalko, P. I. and L. Moisan (2004). *Angewandte Chemie-International Edition* **43(39): 5138-5175.**
[2] Li, H. M., Y. Wang, L. Tang and L. Deng (2004). *Journal of the American Chemical Society* **126(32):9906–9907.**
[3] Fahrenwaldt, T., Großeheilmann; J., Erben, F., Kragl,U. (2013). *Organic Process Research & Development* **DOI: 10.1021/op400037h**, in press.
[4] EVONIK membranes. DuraMem®150; DuraMem®200; DuraMem®300.

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