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Nanofiltration-coupled catalysis to combine the advantages of homogeneous and heterogeneous catalysis

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In a hybrid process that combines nanofiltration with homogeneous catalysis, the best possible reaction rates, chemoselectivities and enantioselectivities are obtained in a continuous operation mode while recycling the catalyst.

In industrial processes, heterogeneous catalysts are generally preferred as they facilitate removal of the catalyst after reaction[1] and allow a continuous operation mode. On the other hand, preparing a heterogeneous catalyst can be tedious and might demand a high preparative effort. In certain cases, mass or heat transfer limitations in the solid state catalyst may lead to decreased activities, and homogeneous reactions generally show higher chemo- and enantio-selectivities.[2]

In the reported hybrid process (Fig. 1), a reaction takes place in a continuously stirred tank reactor, thus reaching activities and selectivities as in homogeneous reactions. The liquid is contacted with a nanofiltration (NF) membrane that allows products to permeate but rejects the dissolved catalyst. This set-up is made possible by the recent development of solvent resistant NF membranes.[3] They have a molecular weight cut-off (MWCO) in the range of 200–700 Da and working conditions below 40 °C and 35 bar.

In related work by Giffels *et al.*,[4] the same membranes are used but they behave only like ultrafiltration membranes under the reaction conditions applied. This implies that an enlargement of their oxazaborolidines is still necessary to have them rejected by the membrane. Derivatisation of the catalyst in order to enlarge it—*e.g.* by linking it to polymers or by forming dendrimers—is avoided in our experiments by operating the membrane filtration under true nanofiltration conditions. The catalysts are thus retained by the membrane without the need to derivatise them first, and they can be used off the shelf in the form in which they are readily available.

In particular, chiral catalysts are among the preferred systems for this hybrid membrane/catalysis process due to their extremely high cost and their sensitivity towards traditional heterogenisation methods. Furthermore, most of these catalysts contain transition metal complexes with a molecular weight above 500 Da and high activities and selectivities under moderate reaction conditions. In the reported set-up, the hydrogen pressure needed for the hydrogenation of the substrates, forms—without any additional cost or equipment—the driving force for the membrane permeation. The whole hybrid process is operated in such a way that a sufficient amount of product with high purity is yielded in the catalytic process, while a good rejection of the the catalyst and reasonable fluxes are preserved in the NF.

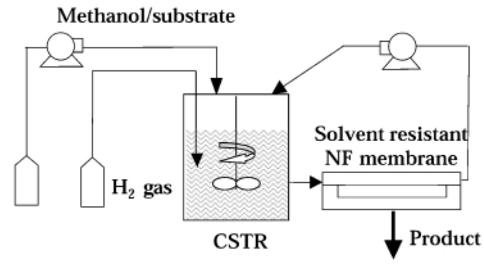

Fig. 1 Reactor set-up for NF-coupled catalysis.

The continuous enantioselective hydrogenation of dimethyl itaconate (DMI) with Ru–BINAP (MW 929 Da) and of methyl 2-acetamidoacrylate (MAA) with Rh–EtDUPHOS (MW 723 Da) (Fig. 2) were selected because of the excellent performance[5] of these catalysts and their industrial relevance.[6] Several ways to heterogenise these complexes have been reported already[7–9] but most did not equal the performance of the homogeneous catalyst, either in ee, activity or in the range of possible substrates.

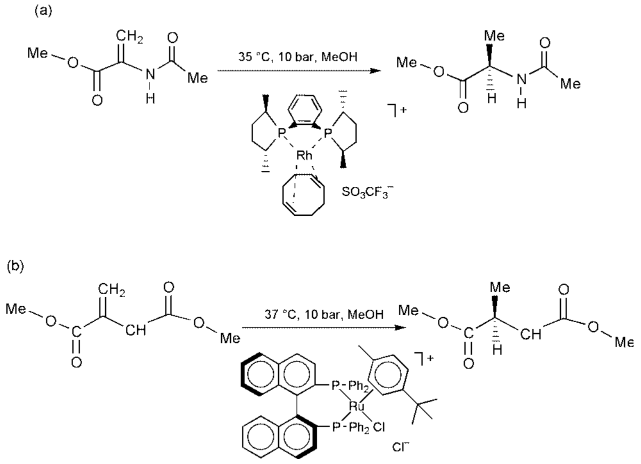

Fig. 2 Reactions with (a) Rh–EtDUPHOS and (b) Ru–BINAP.

Because the membrane fluxes in the NF part of the process are coupled *via* the hydrogen pressure to the reaction rates during catalysis, the reaction rate and enantiomer excess were determined first in a batch-wise reference reaction at pressures that fall within the range for nanofiltration (Table 1).

The homogeneous reactions were carried out in magnetically stirred 10 ml autoclaves. 0.35 g (2.5 mM) MAA was dissolved in 9 ml MeOH and flushed with N_2 before adding 1.7 mg Rh–EtDUPHOS (2.35 μM). For the homogeneous reaction with Ru–BINAP, 0.6 g (4 mM) DMI was dissolved in 9 ml MeOH, flushed with N_2 and subsequently mixed with 4.3 mg (4.6 μM) catalyst. The results[10] are shown in Fig. 1. For the hydrogenation of DMI with Ru–BINAP, no literature data could be found. The enantiomer excess and the activity for reactions with Rh–EtDUPHOS were lower than reported in the literature.[11]

Table 1 Hydrogenations of MAA and DMI with, respectively, Rh–EtDUPHOS and Ru–BINAP

	Substrate/ catalyst	Pressure/ bar	*T*/°C	TOF/ h^{-1}	Ee (%)
Rh–EtDUPHOS[a]	2000	2	22	> 2000	99.4
Rh–EtDUPHOS	1050	4	30	703	95
Ru–BINAP	850	10	37	330	93

[a] Burk *et al.*[11]

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Table 2 Methanol fluxes at different temperatures and pressures for MPF-60 membranes (KOCH)

Pressure/bar	T/°C	Flux/kg m^{-2} h^{-1}
10	30	1.2
	40	1.6
	50	2.6
	60	3.2
15	30	1.7

This is believed to be due to a less thorough pre-treatment of solvents and reagents as compared with literature.

A NF membrane generally does not discriminate between reactants and hydrogenated products, given their negligible difference in MW, shape or polarity. This means that the conditions that determine the membrane flux—such as membrane type, membrane area, applied pressure gradient, temperature and type of solvent[12]—can be adjusted to the catalytic conditions that determine the conversion of the reactant. Methanol fluxes through the NF membrane (KOCH, MPF-60), are given in Table 2 for different temperatures and pressures: as expected, higher temperature and pressure are tools used to increase the flux through the membrane and thus realise a shorter residence time (τ) for a given reactor volume.

The continuous reactions were carried out in a stirred 100 ml autoclave containing an MPF-60 membrane at the bottom. The permeate was collected in a cooled flask (−78 °C). Both feed and permeate were analysed by GC and AAS to determine retention (retained concentration/feed concentration) of reactants, products and catalyst. For the hydrogenation of DMI with Ru–BINAP at 37 °C and 10 bar, the feed solution (C_0 = 0.4 μM) was pumped at a rate of 3.6 ml h^{-1} to the reaction mixture (V = 14 ml, C_0 = 0.4 μM and 33.7 mg Ru–BINAP). The hydrogenation of MAA was performed at 35 °C and 10 bar (V = 16 ml, C_0 = 0.13 μM and 8.5 mg Rh–EtDUPHOS) with the feed solution (C_0 = 0.13 μM) added at a rate of 3.5 ml h^{-1}.

To fully prove the concept, activities should remain unchanged after several refreshments of the reactor volume and the complex should be retained sufficiently. The hydrogenation of DMI shows a constant enantiomer excess as a function of time (Fig. 3). The very small decrease in conversion, becoming apparent after several hours, can be ascribed to the incomplete rejection of Ru–BINAP (> 98%). Nevertheless, this nanofiltration-coupled catalysis allowed the continuous hydrogenation of ten reactor volumes—as indicated by the vertical lines on the graph—with an enantiomer excess of 93%, which equals those reached under homogeneous conditions. For the hydrogenation of MAA with Rh–EtDUPHOS (Fig. 4), the decrease in enantiomer excess and conversion in the long term is slightly more significant. Since the 97% retention of this complex cannot alone account for this effect, a slow deactivation of the catalyst—possibly due to oxidation of the phosphine ligand—is assumed but still needs further investigation. The total TONs for the hydrogenation with Ru–BINAP and Rh–EtDUPHOS are, respectively, 1950 and 930.

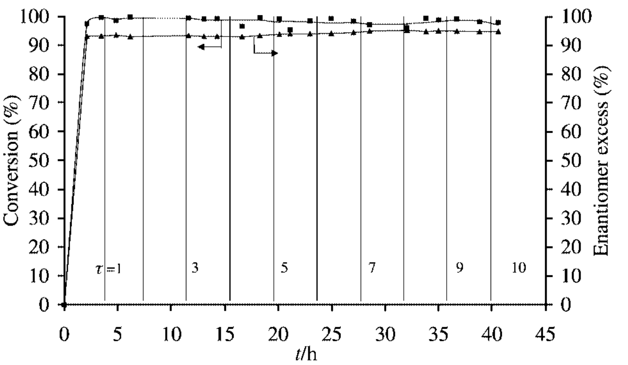

Fig. 3 Conversion and enantiomer excess as a function of time for the continuous NF-coupled hydrogenation with Ru–BINAP.

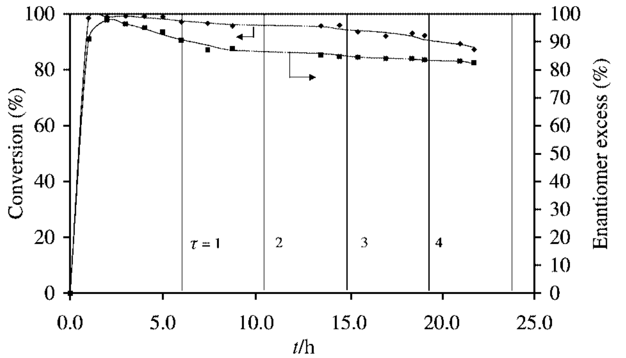

Fig. 4 Conversion and enantiomer excess as a function of time for the continuous NF-coupled hydrogenation with Rh–EtDUPHOS.

These two continuous reactions demonstrate the general concept of this hybrid process to perform homogeneous reactions in a continuous mode whenever the membrane is able to retain the catalyst and does not retain the products. Even though the system is limited by working conditions—like solvent, temperature and pressure—it is believed that the concept can be applied in many different types of reaction and for a wide range of catalysts and substrates, especially in the field of fine chemical synthesis.

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