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Continuous Homogeneous Asymmetric Transfer Hydrogenation of Ketones: Lessons from Kinetics

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Abstract: Is polymer enlargement of homogeneous catalysts a tedious task? Is not batch operation with homogeneous catalysts the optimum performance point for homogeneous catalysis? Is kinetic modelling relevant to more than academic questions in homogeneous catalysis? Can all answers for a given system be answered satisfactory? In the authors' view, answers to these questions are no, no, yes, and depends. Polymer enlargement allowed the continuous operation of transfer hydrogenation in a chemical membrane reactor with total turnover numbers of up to 2.6×10^3 and a space–time yield of $0.58\,kg\,L^{-1}\,d^{-1}$ with an enantiomeric ratio of 26.8 (enantiomeric excess 92.8%) for a conversion level of 80%. This was predicted from simulation conducted with a model from kinetic batch experiments adopted for continuous application. These simulations for the polymer-enlarged and the unmodified catalyst show that achieving comparable performance cannot be obtained by batch operation.

Keywords: alcohols · asymmetric catalysis · hydrogenation · kinetics · membranes

Introduction

Selective retention of macromolecular catalysts is possible by membrane filtration.[1,2] By using ultra- or nanofiltration membranes, the high-molecular-weight catalysts are separated from low-molecular-weight reactants and the residence times are effectively decoupled. This is an alternative to heterogeneous immobilisation of homogeneous catalysts.[3] For the large class of natural homogeneous catalysts, enzymes, this has proven to be a successful concept and the enzyme membrane reactor (EMR) has been used for the production of fine chemicals for more than two decades.[4–6]

Application of an analogous concept to polymer-enlarged, chemical, homogeneous catalysts is attractive for both recycling and continuous operation.[7] Reactor concepts for continuous operation are denoted as chemical or "chemzyme"[7] membrane reactor (CMR), in close analogy to the enzymatic idol. The scope of feasible reactions in the CMR and suitable man-made macromolecular catalysts are reported in a number of accounts and reviews.[7–12] Feasible reactions include diethylzinc addition,[11] Corey–Bakshi–Shibata (CBS) reduction,[13,14] Sharpless dihydroxylation,[15] allylic substitution,[16] hydrovinylation,[17] and transfer hydrogenation with formate[18] and, most recently, 2-propanol[19] as reducing agents.

The synthesis of macromolecular catalysts is generally more labour-intensive than that of its low-molecular-weight pendant and usually involves more synthetic steps. Furthermore, the macromolecular catalyst is often less active in terms of turnover frequency (TOF) per active site. Consequently, the question of whether the extra effort pays off is valid and important. In our opinion, there is no general answer to this question. Reaction viability is best determined by comparing space–time yield (STY) and total turnover number (TTN). Under reaction conditions, these properties are governed mainly by catalyst robustness and apparent deactivation, respectively. In a CMR, catalyst loading can be chosen to be much higher than for batch reactions to

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compensate for lower activity under the reaction conditions. Lower activity is due mainly to the overall lower catalytic activity and the high conversion level in the CMR, which is operated as a continuously stirred tank reactor. The upper limit for TTN is a direct result of apparent stability.[19] Thorough kinetic investigation and modelling are a powerful tool to judge whether a catalyst is suitable for continuous applications or should be disqualified due to low stability.[20] Furthermore, it is not always possible to account for continuous conditions by kinetic investigations.[19,21] Catalysts suitable for continuous operation are chosen for stability reasons rather than for short-lived activity.

Transfer hydrogenation with 2-propanol as reducing agent is an equilibrium reaction with coupled equilibria between possible enantiomeric products (Figure 1). To optimise reaction conditions, it is necessary to derive a kinetic model. A kinetic model can also suggest whether a modified or extended reactor setup is likely to yield better results for the reaction system. Even though the coupled equilibrium with two parallel reactions is among textbook examples,[22] a satisfactory description for the homogeneous catalytic system was not available. Previous work on the topic showed that reverse reactions and thermodynamic boundaries could be disregarded.[23,24] A kinetic description following this approach is, therefore, not appropriate for our experimental outcomes, especially thermodynamically limited conversion and decrease of enantiomeric excess (*ee*) at semi-equilibrium conversion.

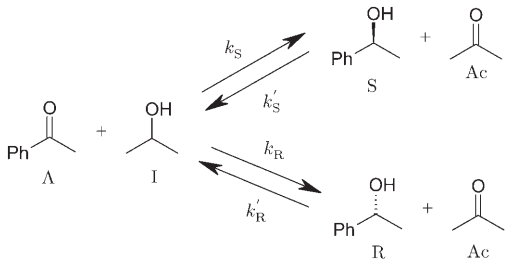
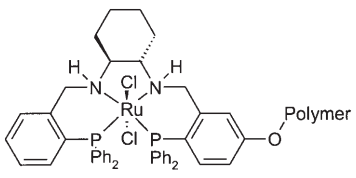


Figure 1. Reaction system for asymmetric-transfer hydrogenation.

Here, we report on how mechanistic and thermodynamic considerations were included in deriving a model for asymmetric-transfer hydrogenation with polymer-bound catalyst C, which was successfully employed continuously in the CMR.[19,25] Simulation led to an isoconversion maximum of STY. Furthermore, the catalyst performance of classical batch operation and continuous operation was compared for a given STY and verified experimentally.



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Results and Discussion

Transfer hydrogenation of acetophenone (A) with 2-propanol (I) is best described as a reversible parallel reaction that yields the two phenyl ethanol enantiomers (*S*) and (*R*) and acetone (Ac).

Equilibrium thermodynamics: The overall equilibrium of the reaction is given by the difference in redox potentials, ΔE^0. For the system acetophenone (A) and 2-propanol (I), this value is $\Delta E^0 = -11$ mV.[26] This results in an equilibrium constant $K = 0.4482$ at 45 °C. For the reaction system, equilibrium conversion is determined by the concentration ratio of I and A [Eq. (1)],

$$r_0 = \frac{[\mathrm{I}]_0}{[\mathrm{A}]_0} \geq 1 \tag{1}$$

in which initial concentrations of both reactants are used, assuming no product is present at $t = 0$. Equilibrium conversion $X_{\mathrm{eq,A}}$ is given by the physically meaningful solution shown in Equation (2).[27]

$$X_{\mathrm{eq,A}} = K\frac{r_0 + 1 - \sqrt{(1-r_0)^2 + 4K^{-1}r_0}}{2(K-1)} \tag{2}$$

From the fact that the standard potential is negative and $K \leq 0$, it is clear that an excess of 2-propanol must be employed for synthetically useful conversion levels. Commonly, this is achieved by using 2-propanol as the solvent. For pure solvent, an equilibrium conversion of $X_{\mathrm{eq,A}} = 0.96$ is possible. For 80% 2-propanol content, equilibrium conversion is slightly decreased to 0.95. It is evident that a thermodynamic equilibrium implies $[R]_{\mathrm{eq}} = [S]_{\mathrm{eq}}$ in accordance with the second law of thermodynamics.

Model

Mechanistic implications: Activation of catalytic activity and catalytic cycle have been targets of investigations. Activation of catalyst is assumed to occur via base-induced formal hydrogen chloride abstraction from the catalyst.[28] Both enantioselectivity and TOF are dependent on base concentration. In continuous experiments, base dosage after initial activation was proved necessary.[19] This is most likely due to catalyst deactivation by trace amounts of water in the solvent. This deactivation is reversible and the catalyst is maintained in an active state by the addition of base.

Among the various mechanistic routes for transfer hydrogenation,[29] the mechanism proposed by Noyori and co-workers[30] is the most likely for the catalyst used in this study. It was shown that the imine analogue of catalyst shows no catalytic activity[25] and a hydride species was confirmed.[31] Our own attempts to elucidate the mechanism with non-polymer-bound catalyst analogous to the work of Wills and co-workers[32] were unsuccessful. Probably only a minor fraction of catalyst is activated. This would explain

the comparably[33] low turnover frequencies achieved for this catalyst.

Deriving the kinetic model: A model should be able to describe the system by involving a minimum of physically meaningful parameters. A random coordination with rate-limiting successive formation of bound products—Hougen–Watson kinetics—was chosen as a basis. Reaction rates for the two parallel equilibrium reactions were described independently by Equations (3) and (4)].

$$f_S = \frac{r_S}{[C]_0} = \frac{k_S[\text{C-A-I}] - k'_S[\text{C-}S\text{-Ac}]}{D'} \quad (3)$$

$$f_R = \frac{r_R}{[C]_0} = \frac{k_R[\text{C-A-I}] - k'_R[\text{C-}R\text{-Ac}]}{D'} \quad (4)$$

Both rate terms share the same denominator D' because the active sites are the same for both reactions. D' consists of all major catalyst species present in the system (Figure 2) [Eq. (5)].

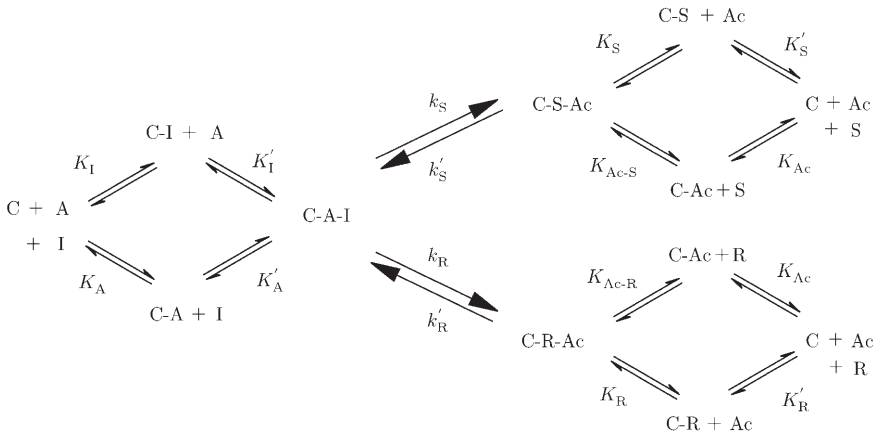

Figure 2. Reaction system for the random-Bi-Bi mechanism assumed for the kinetic description of asymmetric transfer hydrogenation.

$$D' = [C] + [\text{C-AP}] + [\text{C-I}] + [\text{C-}S] + [\text{C-}R] + [\text{C-Ac}] + [\text{C-A-I}] + [\text{C-}S\text{-Ac}] + [\text{C-}R\text{-Ac}] \quad (5)$$

In previous kinetic modelling approaches, reverse reactions were found to have no significance and were consequently omitted.[23,24]

Fast equilibrium was assumed, so that in Equations (3) and (4), all catalyst species can be substituted with mass-action terms of accessible concentrations. For example, [Eq. (6)]:

$$[\text{C-A-I}] = \frac{[C][A][I]}{K_A K'_A} = \frac{[C][A][I]}{K_I K'_I} \quad (6)$$

Substitution of all concentrations with corresponding equilibrium equations and division by catalyst concentration [C] yields turnover-frequency equations for the parallel reactions. Furthermore, it was assumed that the adsorption equilibria are independent. Thus, corresponding equilibrium constants are equal[34] (Figure 2, for example, $K_{AcS} = K'_S$). As only a small fraction of catalyst is activated, contributions of mixed adsorption terms in the denominator were assumed to be small and could be neglected. To further simplify the model, K_I was assigned the same value as the initial concentration of 2-propanol; $K_I = [I]_0 = 10.5\,\text{M}$ (80:20 2-propanol:DCM). The rate equations for parameter estimation were thereby reduced to those shown in Equations (7) and (8),

$$f_S = \frac{k_S \frac{[A][I]}{K_A K_I} - k'_S \frac{[Ac][S]}{K_{Ac} K_S}}{D} \quad (7)$$

$$f_R = \frac{k_R \frac{[A][I]}{K_A K_I} - k'_R \frac{[Ac][R]}{K_{Ac} K_R}}{D} \quad (8)$$

with the common denominator [Eq. (9)].

$$D = 1 + \frac{[I]}{K_I} + \frac{[A]}{K_A} + \frac{[Ac]}{K_{Ac}} + \frac{[S]}{K'_S} + \frac{[R]}{K'_R} \quad (9)$$

That species with two bound molecules can be omitted from the adsorption term may indicate an Eley–Rideal-type mechanism. However, this evidence is not strong, as we did not alter driving terms in the nominator accordingly.

Fitting of parameters

Forward-reaction parameters were estimated by fitting to classical rate measurements. By adding different amounts of product enantiomers separately, dissociation constants K'_S and K'_R were determined from the resulting decrease in rate.

A similar approach for the reverse reactions with high concentrations of acetone was not possible, because activation of catalyst is achieved by adding potassium 2-propoxide as base. Side reactions, most probably aldol condensation, led to yellowish solutions and new aliphatic signals in ^{1}H NMR spectra. These phenomena were not detectable under normal catalytic conditions. Remaining parameters for reverse reactions, k'_S and k'_R, were calculated by using the Haldane equation. At equilibrium, forward and reverse reactions occur at the same rate, so that net rate or TOF, respectively, is zero. At equilibrium, product distribution must be racemic, thus product concentrations $[S] = [R] = [\text{Ac}]/2$. Therefore, the rate constants can be calculated from parameter values already estimated and equilibrium thermodynamics by using Equation (10).

$$\frac{k'_S K_A K_A}{k_S K_S K_{Ac}} = \frac{k'_R K_A K_A}{k_R K_S K_{Ac}} = 2\frac{[A]_{eq}[I]_{eq}}{[Ac]_{eq}^2} = 2K^{-1} \quad (10)$$

Errors were estimated by using Gaussian error propagation. Estimated parameter values are given in Table 1.

Table 1. Parameter values.

Parameter	Value	Error	Unit
K_A	81	±10	mM
k_S	1.81	±0.01	min^{-1}
K_S	116	±21	mM
k_R	0.048	±0.0015	min^{-1}
K_R	262	±82	mM
K_{Ac}	245	±41	mM
k'_S	0.27	±0.07	min^{-1} [a]
k'_R	0.016	±0.008	min^{-1} [a]
$f_{S,max}$	2.20	±0.06	min^{-1}
K_S^{base}	0.97	±0.07	mM
$f_{R,max}$	0.15	±0.04	min^{-1}
K_R^{base}	4.3	±2.2	mM

[a] Calculated by using Equation (10).

Notably, maximum enantioselectivity is possible if the backward reaction is negligible ([Ac]=0). According to the model, maximum *ee* and enantiomeric ratio (e.r.) can be calculated as $ee_{max}=(k_S-k_R)/(k_S+k_R)=0.947$ ($e.r._{max}=k_S/k_R=36.7$). Deviation from the maximum experimental value of $ee_{max}=0.96$ (e.r.=49) is small and is due to experimental error in the determination of kinetic constants for the reaction to *R*. Reaction rates for the *R*-selective reaction are about one order of magnitude lower than the *S*-selective rates under similar conditions. This is also reflected in the larger relative standard deviations of *R*-related parameters (Table 1).

Activation: Influence of base: Activity as a function of base concentration can be described by a hyperbolic function [Eqs. (11) and (12)] (Figure 3).

$$f_S = f_{S,max}\frac{[base]}{K_S^{base}+[base]} \quad (11)$$

$$f_S = f_{R,max}\frac{[base]}{K_R^{base}+[base]} \quad (12)$$

Remarkably, activity of the monomeric catalyst is slightly higher than that of the polymer-bound catalyst C (Figure 3). In particular, affinity to the base, K^{base}, is decreased in the polymeric case (data not shown). Whether this is a direct influence of polymer enlargement, or due to side reactions between the base and the polymer, is unclear.[19] Nevertheless, $f_{S,max}$ is lowered by 4%, whereas $f_{R,max}$ is lowered by 32%. A satisfactory explanation is still pending for this effect, which rather enhances enantioselectivity for the polymer-bound catalyst, C. It cannot be deduced from experimental data whether this is due to conformational changes or interactions with the polymer backbone.

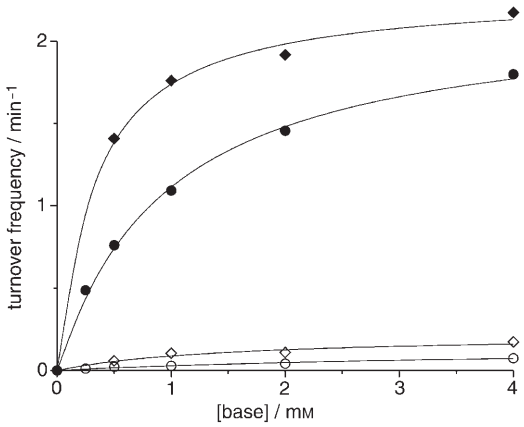

Figure 3. Turnover frequency (S: filled symbols, R: hollow symbols) for polymer-bound (C) (circles) and monomeric catalyst (diamonds) as a function of base concentration ([A]=0.25 M, [C]=0.50 mM).

It could be demonstrated that a constant dosage of base is necessary to maintain activity in continuous experiments.[19] However, the role and kinetics of base as an activating agent are still not fully understood. Water acts as an inhibitor of catalytic activity, and addition of base prevents deactivation. To compromise between the loss of enantioselectivity and an increase in activity, experiments were carried out typically at [base]=1.0 mM$\approx K_S^{base}$. In practice, similar values of activity and selectivity are obtained if base concentration is chosen in this way.

Simulation

Batch experiments: To simulate batch reactor data, a set of ordinary differential equations (ODE) was integrated numerically over time (see Supporting Information). The simulation was in good agreement with experimental data, apart from the starting conditions. Initially, a rate acceleration and a shift in selectivity are observed that are not influenced by starting conditions (Figure 4). This can, in principle, be described by extending the model, assuming a first-order activation of the *S*-selective catalyst species.[35] These effects

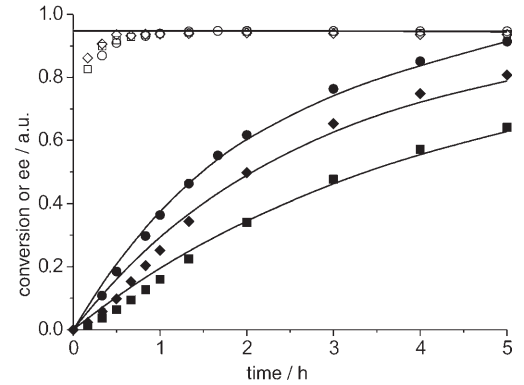

Figure 4. Conversion (filled symbols) and enantiomeric excess (*ee*, hollow symbols) as functions of time for batch reactor. Points denote experimental data and lines are simulated time plots. ([A]=0.50 M (circles), 0.25 M (diamonds), 0.50 mM (squares); [C]=0.5 mM).

were of minor interest in the simulation of continuous experiments in the enzyme or chemzyme membrane reactor employing macromolecular catalysts,[7,10,11,13,14,19,36,37] which is our main interest.

According to the model, racemisation is relatively slow. For example, for [A] = 0.50 M, equilibrium conversion is 0.91. At approximately $X_A = 0.85$, $f_S = f'_S$ occurs. However, racemisation is a slow process compared to initial conversion, explaining the high *ee* obtained experimentally.

As it is, in principle, possible to remove acetone from the reaction system,[38] simulation was performed for [Ac] = 0. Under these conditions, reverse reactions can be neglected, and under standard conditions, a constant maximum e.r. and *ee* is obtained with conversion greater than 0.99 after 30 h ([A] = 0.50 M, [C] = 0.1 mM, [base] = 1.0 mM). Thus, in situ removal of acetone is a favorable concept for asymmetric transfer hydrogenation.

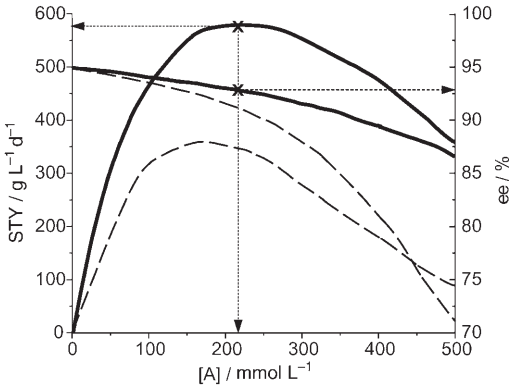

Figure 5. Simulated space–time yield (STY) and enantiomeric excess (*ee*) as functions of acetophenone concentration [A] in the CMR for X_A = 80% (solid line) and 85% (dashed line). Crosses denote optimum conditions for STY and corresponding *ee*.

Continuous experiment: As base dosage was proved necessary for catalytic activity,[19] the correction of active catalyst concentration by an empirical factor is required. This adaptation for process conditions is essential if conditions cannot be accounted for by independent kinetic measurements.[21] The increase in activity during continuous experiments was found to be linear for a 2-propoxide concentration of 1.47 mM^{-1}.

Three process parameters were identified as objectives for optimisation; a high STY is desirable for optimal usage of the reactor volume, conversion X_A should be high for ease of downstream processing, and the *ee* or *er* values should also be high. These were simulated with a constant catalyst concentration [C] = 15.0 mM and [base] = 1.0 mM. It became clear that it is not possible to determine a global optimum, because firstly, trends are contradictory for optimisation objectives, and secondly, maxima are located at the boundaries that were chosen after practical considerations. For downstream processing, minimum acceptable conversion was estimated as $X_A = 0.80$. Mixtures of lower phenyl ethanol content are difficult to crystallise. Following the isoconversion path on the hyperplane, the maximum STY of 0.58 kg L^{-1} d^{-1} with e.r. = 26.8 (*ee* = 92.8%) is achieved with a residence time of $\tau = 0.9$ h at an inlet concentration of acetophenone of 0.22 M (Figure 5). By following the isoconversion paths at $X_A = 0.85$, the maximum STY = 0.36 kg L^{-1} d^{-1} decreases significantly with e.r. = 25.0 (*ee* = 92.3%).

Conditions close to the predicted optimum were employed in a chemical membrane reactor run, and results close to predicted values were obtained.[19] With $\tau = 1.0$ h and increased inlet concentration [A] = 0.25 M (instead of 220 mM), STY was 0.58 kg L^{-1} d^{-1}, even though conversion was slightly decreased. The obtained product *ee* (e.r.) was 92.8% (25.3), close to predicted values (Figure 6). Retention of catalyst under these reaction conditions suffered from instability of the polymeric backbone.[19] Therefore, to maintain a constant concentration of catalyst in the reactor, it was necessary to add 0.5% catalyst (0.075 mol) per residence time. The limiting total turnover number (TTN)

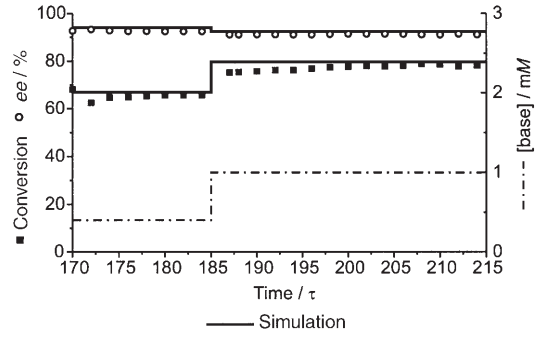

Figure 6. Excerpted time course of conversion and enantiomeric excess (*ee*) for a continuous CMR experiment compared to simulation ($\tau = 1$ h, [A] = 0.25 M, [C] = 15.0 mM, 0.075 mM constant addition of catalyst).

based on continuous dosage of catalyst is 2.6×10^3 at a turnover frequency TOF = 13 h^{-1}.

Analogous to the batch experiments, simulations with in situ removal of acetone proved that the reverse reaction limits maximum performance. At [Ac] = 0, *ee* is unaffected by inlet concentration. A discrete maximum of STY as a function of acetophenone concentration [A] was found with the reverse reaction, however, in the absence of reverse reaction, [A] does not limit STY. For an inlet concentration [A] = 0.50 mM, a STY of more than 1.2 kg L^{-1} d^{-1} results. Extrapolation to [A] = 1.00 M gives STY = 1.6 kg L^{-1} d^{-1} at TOF = 40 h^{-1}. By assuming the same loss of catalyst of 0.5% per residence time, the limiting TTN would be increased by about three times to 8×10^3.

It is now interesting to consider the conditions under which a comparable STY for batch-wise operation could be achieved. This was carried out by assuming that delay times for reactor loading and catalyst deactivation are negligible. To achieve similar STY at $X_A = 80\%$, starting concentrations $[A]_0 = 0.30$ M and [C] = 5 mM would be necessary. Thus, a more than 50-fold decrease in TTN would be achieved by batch operation.

Conclusion

The chemical membrane reactor (CMR) is an attractive alternative to batch operation. The use of polymer-enlarged soluble catalysts retains advantages of homogeneous catalysis. The increase in TTN of more than one order of magnitude justifies synthetic efforts for polymer enlargement and is not only of academic interest. This is the case even though TOF appears low and catalyst loading appears high in comparison to batch operation. By using soluble polymers as scaffold for homogeneous catalysts, catalytic activity remains high. In the given example, more than two thirds of catalytic activity is retained. Due to their greater loss of catalytic activity and additional mass-transfer limitations, heterogenisation methods may be at a disadvantage. On other hand, gaining operational stability and an increase of retention may outperform these shortcomings. Decisions should, therefore, be made on a case-by-case basis, by consideration of reaction engineering methods.

Kinetic modelling, partly adopted for continuous conditions that cannot be accounted for by batch investigations, provides a tool for optimising reaction conditions and simulation of extensions to the reactor setup.[21] In situ removal of the byproduct acetone (Ac) from the reaction mixture is likely to enhance reactor performance. In theory, a threefold increase of STY and increased enantioselectivity are expected from this approach.

Acknowledgements

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