Continuous Application of Chemzymes in a Membrane Reactor: Asymmetric Transfer Hydrogenation of Acetophenone

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Abstract: The application of homogeneously soluble catalysts is limited by the recovery in cases where the price of the catalyst is high. Biological catalysts, enzymes, can be efficiently recycled by means of an ultrafiltration membrane due to their high molecular weight, for example, in the continuously operated membrane reactor. In order to transfer this principle to chemical catalysis, we have attached a transfer hydrogenation catalyst, first invented by Gao and Noyori, to a polymer. The resulting homogeneously soluble, polymer-bound catalyst (chemzyme) can now be retained by ultrafiltration membranes like enzymes. On applying this catalyst in continuously operated membrane reactors, a continuous isopropoxide dosage is necessary in order to compensate deactivation caused by water residues in the feed stream. Thus, high space-time yields up to 578 g L^{-1} d^{-1} and enantioselectivities up to 94% can be achieved. These results were compared to an enzyme catalyzed system consisting of a carbonyl reductase that also utilizes 2-propanol as a hydrogen source for the cofactor regeneration of NADH.

Keywords: asymmetric catalysis; catalyst immobilization; enzyme catalysis; hydrogen transfer; membranes

Introduction

Enzymes are ideal catalysts, optimized by nature over several generations. They are homogeneously soluble, highly selective biocatalysts and can be retained by ultrafiltration membranes due to their size.[1] Thus, the recycling of such catalysts is possible, for example, by use of a continuously operated enzyme membrane reactor (EMR).[2] However, generally one of the major restrictions in using biocatalysts is the requirement of water as a solvent.[3]

Today, homogeneously soluble chemical catalysts can reach enantioselectivities and chemoselectivities similar to those of enzymes.[4] These catalysts can also be employed in organic solvents. Nevertheless, a continuous operation with such catalysts is still difficult, although promising approaches such as two-phase systems[5] and heterogenization methods[6] have been optimized.[7] In order to combine the advantages of the chemical and enzymatic approach, chemical catalysts (oxazaborolidines[8] and amino alcohols for diethylzinc reduction[9]) were bound to homogeneously soluble polymers (polystyrenes, methacrylates). The resulting soluble polymer-bound catalysts (chemzymes) can now be retained by ultrafiltration membranes like enzymes and, therefore, can be applied in a chemzyme membrane reactor (CMR).[8c,10] Similar approaches have been developed for other classes of catalysts attached to polymers[11] or dendrimers.[12] Even the direct retention of a DuPHOS ligand by a nanofiltration membrane was described.[13]

Here, we present our recent efforts in optimizing the chemzyme approach for transfer hydrogenation in comparison to an enzyme catalyzed system (Scheme 1).

Transfer hydrogenation represents a promising method for the production of secondary alcohols.[14] Due to the low costs of 2-propanol or formate as reduction sources, no hazardous hydrogen – in contrast to the very successful hydrogenation methods[15] – is used. As shown in Scheme 1, 2-propanol can also be used as a hydrogen source for enzyme-catalyzed reductions in aqueous solution,[16] if it is applied in concentrations that do not destabilize the enzyme. One major difference is the need for a cofactor acting as a hydrogen mediator, which has to be regenerated during the course of reaction. Here, for example, a *Candi-*

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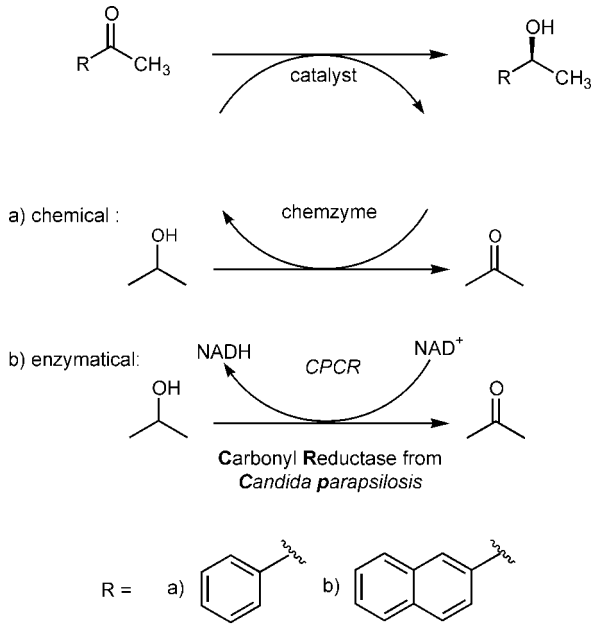


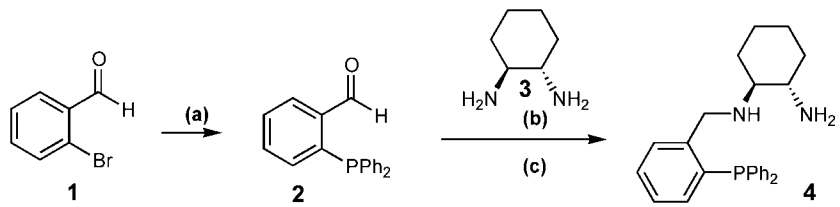
Scheme 1. Reduction of aromatic ketones with chemzymes and enzymes.

da parapsilosis carbonyl reductase, (*CP*CR) [E.C. 1.1.1.1] can be used both for reducing the substrate and regeneration of the cofactor by oxidizing the 2-propanol.[17] Effective methods have been developed for the economical recycling of the cofactor.[18]

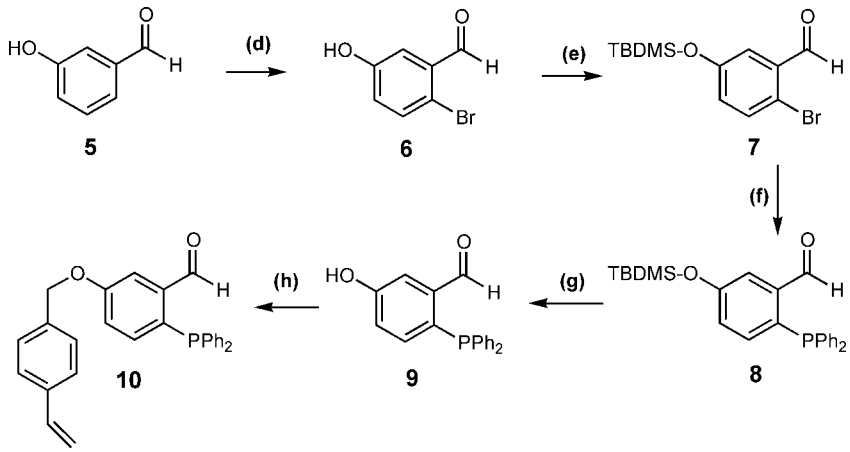
Results and Discussion

In the chemzyme approach, 2-propanol could be used both as reducing agent and solvent. We have developed a 12-step, convergent synthesis, whereby a ruthenium-based transfer hydrogenation catalyst, first employed by Gao and Noyori,[19] could be linked via hydrosilylation to a polysiloxane **13**. For that purpose, we developed two routes leading to the key compounds **4** and **10** (Scheme 2 and Scheme 3).

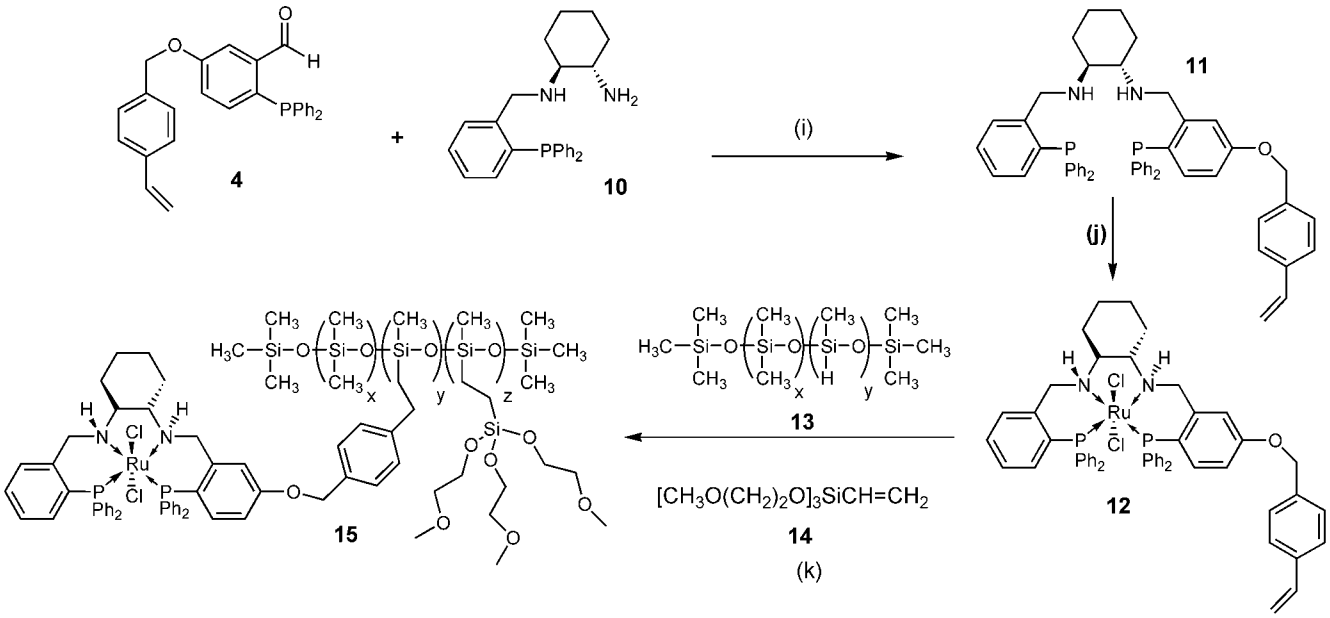
In the first route, a palladium-catalyzed phosphination of 2-bromobenzaldehyde allowed the effective introduction of the diphenylphosphine (85%). Thus, the reaction was possible without prior protection of the aldehyde as previously described in literature.[20] Next, the selective mono-functionalization of (1*R*,2*R*)-diaminocyclohexane (**3**) was achieved by slow addition of **2**. The course of the reaction was monitored by NMR, because the imine proton of the mono- and difunctionalized products can be clearly distinguished.[21] However, the attempt to isolate the monofunctionalized imine by aqueous work-up resulted in up to 10% of difunctionalized imine as by-product. This was most likely caused by hydrolytic regeneration of **2**, which reacted to the difunctionalized imine during the removal of solvent. Therefore, subsequent to generating the monofunctionalized imine, it was directly converted to the corresponding amine



Scheme 2. Synthesis of the monofunctionalized diamine half unit **4**. Reagents and conditions: (a) 1.3 equiv. $HPPh_2$, 0.6% $Pd(PPh_3)_4$, Et_3N, toluene, reflux; (b) 4-fold excess of **3**, slow addition of **2**, EtOH, 0 °C; (c) EtOH, $NaBH_4$, rt.



Scheme 3. Synthesis of linker half unit **10**. Reagents and conditions: (d) Br_2, $CHCl_3$; (e) TBDMSCl, imidazole, DMF; (f) 1.3 equiv. $HPPh_2$, 0.6% $Pd(PPh_3)_4$, Et_3N, toluene, reflux; (g) KF, aqueous HBr (48%), DMF; (h) NaH, vinylbenzyl chloride, DMF.



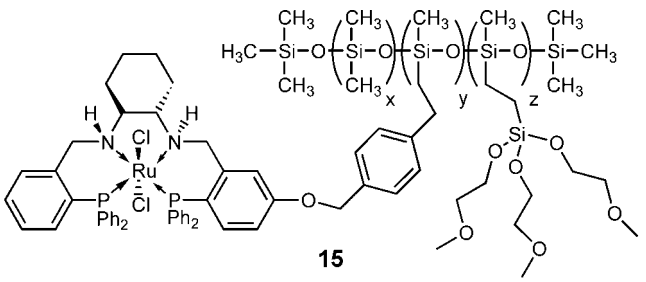
Scheme 4. Synthesis of chemzyme **15**. Reagents and conditions: (i) EtOH, reflux; $NaBH_4$, EtOH, rt; (j) $Ru(DMSO)_4Cl_2$, toluene, reflux (k) platinum-divinyltetramethyldisiloxane, toluene, 50 °C.

4 by reduction with sodium borohydride. The purification of the product was carried out by precipitation as the hydrochloride (51%).

The effective phosphination reaction described in Scheme 2 was also used for preparation of the second key compound **10**. Therefore, 2-hydroxybenzaldehyde (**5**) was brominated according to literature procedures[22] yielding **6** with a moderate yield of 65%. The hydroxy group was protected with *tert*-butyltrimethylsilyl chloride (TBDMSCl), yielding compound **7** (97%). The phosphination was performed under analogous conditions as given above, with 80% yield of **8**. The cleavage of the TBDMS ether of **8** yielded **9** (81%). The resulting alcohol **9** was subjected to an ether synthesis with 4-vinylbenzyl chloride, giving **10** with a moderate yield of 56%. The vinyl function of **10** served as linking moiety for the successive polymer linkage (Scheme 4).

Both convergent routes were combined by reacting **4** and **10** as shown in Scheme 4 followed by immediate reduction of the resulting imine leading to **11** (79%). The ruthenium was introduced by ligand exchange of dichlorotetrakis(dimethyl sulfoxide)-ruthenium[23] with **11**. The resulting linkable catalyst **12** was purified by column chromatography (56%). Finally, **12** was attached to the hydrosiloxane moieties of the methylhydrosiloxane-dimethylsiloxane copolymer[24] **13** via an effective hydrosilylation reaction[8b,25] (>99%). Due to the quantitative linking reaction, various exact grades of polymer functionalization were achieved (2, 3, 5, and 10% with catalyst). A polysiloxane-polymer was chosen as backbone because coupling of ligands via linkers to siloxane-based matrixes is an established method.[6,8b] For an industrial application a more hydrolyzable, stable polymer has to be chosen. The remaining Si-H groups of **13** were end-capped by attaching polar tris(2-methoxyethoxy)vinylsilane (**14**) to the polymer backbone via the same quantitative catalytic link reaction. By this means the solubility of the polymer-bound catalyst (chemzyme) **15** in polar solvents is increased. Thus, the described technique gives the possibility to adjust functionalization and solubility of the chemzyme **15** as shown in Table 1.

Table 1. Functionalization of polymer bound transfer hydrogenation catalyst (chemzyme).



Functionalization [%]	x	y	z	M_n [g/mol][a]	TOF [min^{-1}][b]
2	135	3.3	22.7	19710	0.94
3	135	4.9	21.1	20768	1.1
5	135	8.1	17.8	23039	1.01
10	135	16.3	9.7	28630	0.43

[a] Calculated from gel permeation chromatography results and functionalization of original polymer.
[b] See experimental section

We tested various functionalizations of the chemzyme ranging from 2 up to 10% in terms of solubility, activity, and enantioselectivity. Activity was measured as the initial turnover frequency (TOF_0) by determination of the initial rates at an acetophenone concentration of 250 mM. A compromise of solubility and activity was found at a functionalization of 3%, which is equivalent to 0.235 mmol/g (NMR and elemental analysis). In the examined range of functionalization no significant effect on the enantioselectivity of the catalyst was observed.

With the chemzyme **15**, the same level of enantioselectivity has been observed for the reduction of acetophenone in 2-propanol, as with the free catalyst (up to 97% ee). However, the TOF_0 of the catalyst was reduced ($2.3\ min^{-1}$ compared to $2.2\ min^{-1}$ with 250 mM acetophenone under saturation conditions with isopropoxide). As common for most transfer hydrogenation catalysts, it is necessary to activate the catalyst by adding a base,[26] facilitating the replacement of a halide.[27] In our case, the activation was performed by adding an equimolar amount of potassium isopropoxide that enabled the reduction of acetophenone to (*S*)-phenylethanol. The reactor used for a continuous reduction is shown in Figure 1. In order to apply high catalyst concentrations (up to 25 mM), it was possible to add a cosolvent (up to 20% v/v CH_2Cl_2) without changing the enantioselectivity of the catalyst. However, as observed for other catalyst systems,[28] the addition of a cosolvent resulted in a 24% decrease of TOF_0.

Due to irreversible deactivation of the catalyst, oxygen had to be strictly excluded in the reaction system. Furthermore, as recognized with several other transfer hydrogenation catalysts, the catalyst is sensitive to water.[29] This was shown in batch reactions, in which a strong dependency of the activity on the water content was observed (data not shown). Presumably, as demonstrated with similar complexes,[30] water molecules are able to coordinate with the activated catalyst. Therefore, the water content in the feed stream had to be minimized. By use of the Karl–Fischer method, titration showed that the water content can

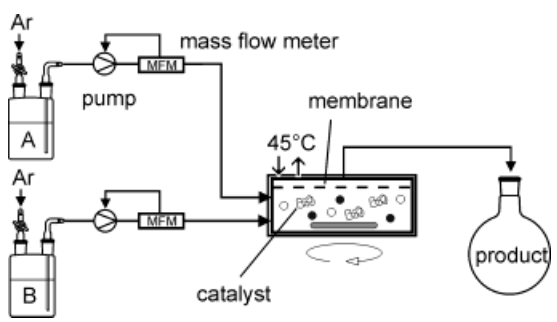


Figure 1. Reactor scheme of the continuously operated membrane reactor. (A: acetophenone in 80% v/v 2-propanol, 20% v/v CH_2Cl_2; B: isopropoxide in 80% v/v 2-propanol, 20% v/v CH_2Cl_2).

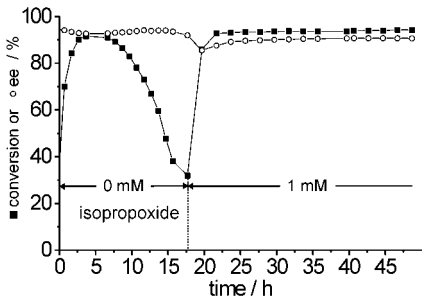


Figure 2. Time plot of continuous experiment in the chemzyme membrane reactor, showing conversion (squares) and enantiomeric excess (ee, circles) as a function of time. Conditions: 23 mM catalyst **15**, initial isopropoxide concentration 23 mM, 13 mM acetophenone, 80% v/v 2-propanol, 20% v/v CH_2Cl_2, 45 °C, residence time = 30 min.

be reduced to 0.005%. Nevertheless, in a continuous application, depending on different concentrations of water in the feed stream, a significant deactivation took place. The reason for this was a cumulative catalyst deactivation caused even by the small amounts of water which passed through the reactor over time. This deactivation was reversible and could be compensated by a continuous low isopropoxide dosage (between 0.5 and 1 mM) as shown in Figure 2.

The role of this low isopropoxide concentration is assumed to replace coordinated water molecules with the catalyst, comparable to the initial catalyst formation. This assumption would be in accordance with Noyori's work on ruthenium-diamine catalysts,[31] which shows that the addition of a base in batch reactions is required only for the formation of the active catalyst, not for maintaining the catalytic reaction. However, as a consequence of the continuous base dosage, two side effects were observed. High concentrations of isopropoxide (> 5 mM) resulted in a decreased enantioselectivity of the catalyst, possibly due to an abstraction of the second chloride, which might cause a change in the catalyst geometry. Furthermore, a side reaction of the isopropoxide with the polysiloxane-polymer resulted in a fragmentation of the polymer. This effect was observed by the increased amount of small cyclosiloxane fragments as a product of fragmentation[32] (especially octamethylcyclotetrasiloxane $[\text{-Si}(CH_3)_2\text{O-}]_4$), monitored in the reactor outlet by GC. As seen in Figure 3, minimal fragmentation and high enantioselectivities were achieved by the careful adjustment of the isopropoxide concentration.

Nevertheless, it could be shown that, even without any fragmentation (without base dosage), the retention of the chemzyme is only 99.8%. This retention value was calculated by the amount of chemzyme that was isolated after 50 residence times. As a consequence of the fragmentation reaction at a continuous base dosage of 1 mM, this value is further decreased

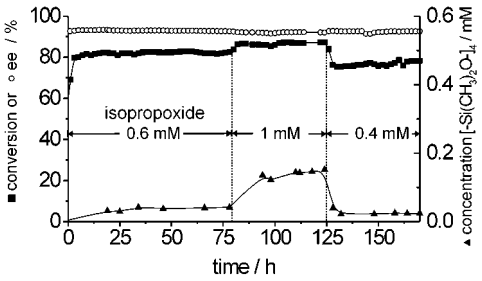


Figure 3. Continuous experiment in the chemzyme membrane reactor, showing conversion (squares) and enantiomeric excess (ee, circles) as a function of time. Conditions: 15 mM initial catalyst **15** concentration, 0.075 mM continuous catalyst addition, initial isopropoxide concentration 15 mM, 100 mM acetophenone, 80% v/v 2-propanol, 20% v/v CH_2Cl_2, 45 °C, residence time = 60 min.

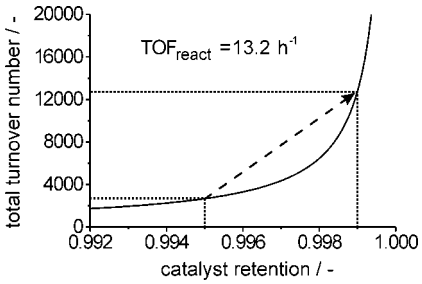


Figure 4. Influence of chemzyme retention on the maximum TTN for a given TOF. Retention value and TOF are achieved with the experimental details given in Figure 3.

to 99.5%. Therefore, a continuous loss of catalyst took place. These losses (referred to as wash-out of catalyst) were compensated by continuously supplementing 0.5% chemzyme per residence time to the reactor. In addition to the fragmentation reaction, hydrolysis of the tris(2-methoxyethoxy)silane side group might result in a change of the solubility of the catalyst. However, an increase in filtration back-pressure was not observed, which would accompany precipitation and blocking of the membrane due to insolubility of the catalyst. Furthermore, leaching of transition metal was investigated by determining the ruthenium concentration in the reactor outlet by inductive coupled plasma mass spectrometry (ICP-MS). The observed ruthenium concentration, which was equal to or even smaller than 0.5% of the initial ruthenium concentration per residence time, could be attributed to the continuous catalyst losses as a result of the wash-out. Therefore, we can conclude that leeching of uncomplexed transition metal is not critical for the continuous reaction. Applying the reaction conditions as given in Figure 3, a continuous transfer hydrogenation was carried out with steady conversions of about 87%, enantiomeric excesses of 94% and space-time yields up to 255 g L^{-1} d^{-1}. The achievable total turnover number (TTN) can be calculated as quotient of the catalyst activity under reaction conditions ($TOF_{reaction}$ = 5.80 h^{-1}) and the catalyst consumption, given as deactivation constant (k_{des} = 0.005 h^{-1}), which is equivalent to the continuous chemzyme replacement of 0.5% per residence time. Thus, the TTN was determined to 1160. Repeating the same experiment for 75 residence times with an acetophenone concentration of 250 mM a conversion up to 79%, enantiomeric excess of 91% and space-time yield of 578 g L^{-1} d^{-1} was achieved. Here the $TOF_{reaction}$ was 13.16 h^{-1} and the TTN 2630.

The results with the chemzymes will be compared here to the enzyme-catalyzed enantioselective reduction of the more hydrophobic substrate, 2-acetylnaphthalene.[17] Comparable to the chemical case, in which the catalyst concentration could be increased by adding a cosolvent, in the enzymatic approach the substrate solubility can be increased about 150-fold, to 20 mM by addition of 50 mM hepta(2,6-di-*O*-methyl)-β-cyclodextrin (DIMEB).[17] The advantage of this method is that no influence on the catalyst is observed. Besides using DIMEB to increase the starting material concentration, other approaches have been developed, such as adsorbing the substrate on to anion exchange resins[33] or continuous extraction of the product.[18] Nevertheless, the chosen example demonstrates that the low solubility of the organic hydrophobic substrates remains one of the key problems in the enzyme approach.

For the continuously operated enzymatic reduction, a comparable reactor setup as shown in Figure 1 can be used. Here, an aqueous buffer containing the substrate (20 mM) with the DIMEB and the reduction source 2-propanol (260 mM) is pumped through the reactor. High conversions up to 82% yielding (*S*)-1-(2-naphthyl)ethanol with ee values of 99% have been achieved. The details of these results have been evaluated elsewhere.[17] The best results of both approaches are summarized in Table 2.

Despite the very high activity of the enzyme, due to the low solubility of the substrate in water only low space-time yields of 118 g L^{-1} d^{-1} can be achieved. With the unlimited substrate solubility in the organic solvent, the limiting aspect in the chemical approach is the possible catalyst concentration. In this case, the economical use of high catalyst concentrations is obtained by decoupling the residence times of reactants and catalyst by retaining the catalyst. Therefore, even with high catalyst concentrations high TTN can be achieved. Furthermore, as result of the high catalyst concentration, even with low activities (up to 0.22 min^{-1} compared to $2.3 \cdot 10^4$ min^{-1}) high space-time yields up to 578 g L^{-1} d^{-1} are possible. The application of high catalyst concentration can be achieved because it is possible to bind a number of catalysts to one polymer molecule. Thus, the molecular mass per

Table 2. Comparison of chemical and enzymatic approach for the reduction of ketones to chiral alcohols via transfer hydrogenation.

Parameter	Unit	Chemical reduction	Enzymatic reduction
[ketone]	mmol L^{-1}	250	20
[cofactor]	mmol L^{-1}	no cofactor	0.5
[catalyst]	mmol L^{-1}	15	$0.04 \cdot 10^{-3}$
solubilizer		20% v/v CH_2Cl_2	50 mmolar DIMEB
total turnover number	–	2630	$2.4 \cdot 10^{8}$
turnover frequency	min^{-1}	0.22	$2.3 \cdot 10^{4}$
molecular weight of catalyst	g mol^{-1}	21000	78000
active centers per catalyst	–	5	1
mass per active centers	g mol^{-1}	4200	78000
half-life of catalyst	days	5.8	31.1
space-time yield	g L^{-1} d^{-1}	578	118
ee value	%	91	>99

active site is much lower for the chemzyme than for the enzyme. This enables a high concentration of catalyst without a critical increase of viscosity. The parameters in Table 2 clearly show that both approaches have their advantages and disadvantages. Nevertheless, in terms of stability, TTN, and enantioselectivity the effectiveness of the enzyme approach is still not reached. One main reason for the high TTN is the effective retention of the biocatalyst. There is still a potential here in case of the chemzyme, since the increase of retention by applying larger and inert polymer molecules would have a strong impact on the achievable TTN as shown in Figure 4. Increasing the retention from 99.5% to 99.9% would increase the TTN from 2630 to approximately 12000.

Conclusion

Applying the chemzyme **15** in continuous reactions represents, to the best of our knowledge, the first example for a transfer hydrogenation process in a continuously operated membrane reactor. Comparing these results with an enzymatic process also using isopropanol as reducing agent, it becomes obvious that both approaches offer different advantages and therefore are complementary. The enzymatic approach delivers high ee values, high total turnover number, and low catalyst consumption due to the high stability. The chemzyme approach does not need any cofactor as a hydrogen mediator and is superior in space-time yield that even can be increased by optimizing substrate and chemzyme concentrations. The continuous application of oxidoreductases in membrane reactors has already been commercialized.[34] In cooperation with industry, the continuous application of chemzymes has reached the bench scale.

Experimental Section

General Information

All reactions and manipulations were performed under an atmosphere of dry argon using standard Schlenk-type techniques. Acetophenone was freshly distilled and stored over molecular sieves. 2-Propanol was distilled from CaH_2. 2-Propanol and dichloromethane were stored over molecular sieve and degassed by simultaneously passing helium and argon through the solution. All other solvents and reagents were used without further purification. The potassium isopropoxide solution was produced by adding the appropriate amount of potassium to absolute 2-propanol and determination of the concentration by acid-base titration. Conversion, enantiomeric excess, and concentration of octamethylcyclotetrasiloxane were determined by a HP6890 GC, equipped with a cyclodex-β/1P column from Chromatographie Service Langerwehe, Germany (50 m, 120 °C isotherm, 1.2 bar H_2, retention times: octamethylcyclotetrasiloxane 2.8 min, acetophenone 6.7 min, (*R*)-phenylethanol 10.1 min, (*S*)-phenylethanol 10.6 min) by external standard. NMR spectra were recorded on a Bruker AMX 300. GC-MS were measured on an HP-6890 equipped with an MSD 5973.

2-Diphenylphosphanylbenzaldehyde (2)

2-Bromobenzaldehyde (**1**; 5 mL, 43 mmol), diphenylphosphine (9.6 mL, 55.9 mmol), tetrakis(triphenylphosphine)-palladium (334 mg, 0.3 mmol), and triethylamine (5.9 mL, 43 mmol) were refluxed in absolute toluene (150 mL) for 2 h. The progress of the reaction was monitored by GC-MS. After completion, the reaction solution was filtered, washed with saturated ammonium hydrochloride solution (3 × 100 mL) and saturated sodium chloride solution (100 mL). The organic solvent was removed under reduced pressure. The resultant crude product was recrystallized from methanol, yield 10.61 g (85%); data in accordance with literature.[20]

(1*R*,2*R*)-*N*-(2-Diphenylphosphanylbenzyl)cyclohexane-1,2-diamine (4)

A solution of **2** (2.5 g, 8.6 mmol) in absolute ethanol (250 mL) at 45 °C was added over a period of 16 hours to a

solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (**3**; 3.3 g, 28 mmol) in absolute ethanol (500 mL) at 0 °C. Reaction control by ^{1}H NMR showed conversion of the carbonyl compound and the formation of an imine (disappearance of the carbonyl-proton signal at 10.44 ppm and generation of an imine-proton signal at 8.74 ppm in $CDCl_3$). Sodium borohydride (1.37 g, 36 mmol) was added and the reaction solution stirred for a further 12 hours at room temperature. ^{1}H NMR reaction control showed complete reduction of the imine. The reaction was quenched by adding acetone (100 mL) and the solvent was removed under reduced pressure. The residue was dissolved by stirring with saturated ammonium hydrochloride solution (100 mL) and dichloromethane (100 mL). After extraction of the aqueous phase with dichloromethane (2 × 50 mL), the combined organic phases were washed with water (100 mL) and 10% hydrochloric acid (100 mL) was added. The product, a colorless precipitate (hydrochloride), was filtered off and dried under vacuum; yield: 2.54 g (70%).

The free amine **4** was dissolved in saturated sodium hydrogen carbonate solution (100 mL) and extracted with dichloromethane (3 × 60 mL). The combined organic phases were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the resulting clear oil dried under vacuum; yield: 1.71 g (51% overall yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 – 1.0 (m, 1H, CH_2), 1.0 – 1.32 (m, 3H, CH_2), 1.55 – 1.8 (m, 5H, CH_2 + NH_2 + NH), 1.82 – 1.9 (m, 1H, CH_2), 1.92 – 2.0 (m, 2H, NCH, CH_2), 2.2 – 2.3 (m, 1H, NCH), 3.9 (d, 1H, CH_2-N*H*R, $^1J_{H,H}$ = 13 Hz), 4.1 (d, 1H, C*H*$_2$-NHR, $^2J_{H,H}$ = 13 Hz), 6.8 – 6.9 (m, 1H, *o*-CH), 7.1 – 7.2 (m, 1H, CH), 7.2 – 7.4 (m, 11H, CH), 8.5 – 8.6 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.15 (CH_2), 25.26 (CH_2), 31.28 (CH_2), 35.48 (CH_2), 49.36 (d, CH_2-NRH, $^3J_{C,P}$ = 16 Hz) 55.33 (CH), 63.63 (CH), 128.4 – 128.6 (m, 8CH), 129.26 (d, CH, $^3J_{C,P}$ = 7 Hz), 133.81 (d, 5CH, $^2J_{C,P}$ = 19 Hz), 135.64 (d, C_{tert}, $^1J_{C,P}$ = 13 Hz), 136.7 – 136.8 (m,2 C_{tert}), 145.40 (d, C_{tert}, $^2J_{C,P}$ = 24 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ = –16.09; FAB-MS: *m/z* = 389.2 [M^+ + H].

2-Bromo-5-(*tert*-butyldimethylsilanyloxy)benzaldehyde (7)

A solution of 2-bromo-5-hydroxybenzaldehyde (**6**; 10 g, 49 mmol), *tert*-butyldimethylsilyl chloride (8.9 g, 59.6 mmol) and imidazole (8.11 g, 120 mmol) in dimethylformamide (50 mL) was stirred for 1 hour at room temperature. After stirring the reaction solution with saturated ammonium hydrochloride solution (50 mL) for 15 minutes, the crude solution was extracted with dichloromethane (3 × 100 mL). The combined organic phases were then washed with water (3 × 100 mL) and saturated sodium chloride solution (100 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product dried under vacuum; yield: 14.98 g (97%) . GC-MS analysis indicated a purity of 97%, thus the product was used without further purification in the next step; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 [s, 6H, $(CH_3)_2$Si], 1.0 [s, 9H, $(CH_3)_3$CSi], 6.89 (dd, 1H, CH, $^3J_{H,H}$ = 18 Hz, $^4J_{H,H}$ =3 Hz), 7.36 (d, 1H, CH, $^4J_{H,H}$ = 3 Hz), 7.51 (d, 1H, 1-CH, $^3J_{H,H}$ = 18 Hz), 10.29 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.32 (C-Si), 25.75 (*C*-C-Si), 118.5, 120.6, 127.9, 134.8, 155.8 (C-O), 192.0 (CHO); GC-MS: *m/z* = 316 [M^+], 259 [M^+ – $C(CH_3)_3$], 150 [M^+ – $C(CH_3)_3$].

5-(*tert*-Butyldimethylsilanyloxy)-2-diphenylphosphanylbenzaldehyde (8)

A solution of **7** (15.15 g, 48 mmol), diphenylphosphine (10.8 mL, 62 mmol), tetrakis(triphenylphosphine)palladium (334 mg, 0.3 mmol), and triethylamine (8.7 mL, 62 mmol) in absolute toluene (150 mL) was heated under reflux for 2 hours. The progress of the reaction was monitored by GC-MS. After completion, the reaction solution was filtered, washed with saturated ammonium hydrochloride solution (3 × 100 mL) and saturated sodium chloride solution (100 mL). The solvent was removed under reduced pressure. According to GC-MS and ^{1}H NMR analysis, the product (16.14 g, 80%) was of 92% purity and directly used for the following reaction step; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 [s, 6H, $(CH_3)_2$Si], 0.98 [s, 9H, $(CH_3)_3$CSi], 6.80 – 7.98 (m, 1H, CH), 7.20 – 7.30 (m, 1H, CH), 7.30 – 7.40 (m, 10H, CH), 7.45 – 7.50 (m, 1H, CH), 10.55 (d, 1H, CHO, $^4J_{H,P}$ = 6 Hz); ^{15}C NMR (75 MHz, $CDCl_3$): δ = 18.32 (C-Si), 25.70 (*C*-C-Si), 128.65 – 129.10 (m, 6CH), 131.79 – 132.52 (m, 6CH), 133.84 – 134.18 (m, 4CH), 136.55 (d, 1C_{tert}, $^1J_{C,P}$ = 9 Hz), 140.18 (d, *C*-CHO, $^2J_{C,P}$ = 16 Hz), 156.86 (CHO); ^{31}P NMR (121 MHz, $CDCl_3$): δ = –17.11; GC-MS: *m/z* = 420 [M^+], 391 [M^+ – CHO], 150 [M^+ – $C(CH_3)_3$].

2-Diphenylphosphanyl-5-hydroxybenzaldehyde (9)

A solution of **5** (11.61 g, 28 mmol), potassium fluoride (3.2 g, 55 mmol) and 48% hydrobromic acid (1.29 mL, 7 mmol) in dimethylformamide (150 mL) was stirred for 1 hour at room temperature. The reaction solution was then combined with saturated ammonium hydrochloride solution (100 mL) and extracted with dichloromethane (3 × 60 mL). The combined organic phases were washed with water (3 × 100 mL) and with saturated sodium chloride solution (100 mL) and then dried with anhydrous magnesium sulfate. After removal of the solvent under reduced pressure and subsequent drying under vacuum, the residue was subjected to column chromatography on silica gel (*iso*-hexane:ethyl acetate = 3:1); yield: 6.94 g (81%); ^{1}H NMR (300 MHz, DMSO-d_6): δ =6.97 (dd, 1H, CH, $^3J_{H,P}$ = 5 Hz, $^3J_{H,H}$ = 9 Hz), 7.23 (dd, 1H, CH, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 3 Hz), 7.35 – 7.45 (m, 4H, CH), 7.53 – 7.60 (m, 6H, CH), 7.60 (dd, 1H, CH, $^4J_{H,H}$ = 3 Hz, $^4J_{H,P}$ = 3 Hz), 10.57 (d, 1H, CHO, $^4J_{H,P}$ = 5 Hz); ^{15}C NMR (75 MHz, DMSO-d_6): δ = 117.35 (CH), 121.43 (CH), 128.25 – 128.90 (m, 6CH), 131.52 (d, 1C_{tert}, $^1J_{C,P}$ = 12 Hz), 133.35 (d, 4CH, $^2J_{C,P}$ = 20 Hz), 135.54 (CH), 136.90 (d, 2C_{tert}, $^1J_{C,P}$ = 11 Hz) 139.87 (d, *C*-CHO, $^2J_{C,P}$ = 15 Hz), 158.57 (C-OH), 191.88 (d, CHO, $^3J_{C,P}$ = 18 Hz; ^{31}P NMR (121 MHz, $CDCl_3$): δ = –17.04; FAB-MS: *m/z* = 307.0 [M^+ + H].

2-Diphenylphosphanyl-5-(4-vinylbenzyloxy)benzaldehyde (10)

Sodium hydride (2.41 g, 96 mmol) was added to a solution of **9** (7.3 g, 24 mmol) and 4-vinylbenzyl chloride (3.53 mL, 24 mmol) in dimethylformamide (100 mL) at room temperature. Saturated ammonium chloride solution (100 mL) was added after 12 hours of stirring and the mixture extracted with dichloromethane (3 × 60 mL). The combined organic phases were washed with water (3 × 100 mL) and with satu-

rated sodium chloride solution (100 mL). After drying with anhydrous magnesium sulfate the solvent was removed under reduced pressure and the residue subjected to column chromatography on silica gel (7:1 = *iso*-hexane:ethyl acetate); yield: 5.67 g (56%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.03 (s, 2H, benzyl-CH_2), 5.21 (d, 1H, *H*HC=CHR, $^3J_{H,H}$ = 11 Hz), 5.68 (d, 1H, H*H*C=CHR, $^3J_{H,H}$ =18 Hz), 6.64 (dd, 1H, *H*RC=CH_2, $^3J_{H,H}$ =11 Hz, $^3J_{H,H}$ =18 Hz), 6.85 (dd, 1H, CH, $^3J_{H,P}$ = 5 Hz, $^3J_{H,H}$ = 9 Hz), 7.03 (dd, 1H, CH, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 3 Hz), 7.19 – 7.41 (m, 10H, CH), 7.57 (dd, 1H, CH, $^4J_{H,P}$ = 3 Hz, $^4J_{H,H}$ = 3 Hz), 10.56 (d, 1H, CHO, $^4J_{P,H}$ = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 70.20 (benzyl-C), 114.32 (CH), 114.39 (CH_2=R), 121.66 (CH), 126.72 (CH), 128.03 (4CH), 128.03 (C-vinyl), 128.86–129.20 (m, 6CH), 132.32 (d, C_{tert}, $^1J_{C,P}$ =13 Hz), 132.62 (*C*=CH_2), 134.03 (d, 4CH, $^2J_{C,P}$ = 19 Hz), 135.89 (d, CH, $^2J_{C,P}$ =13 Hz), 136.56 (d, C_{tert}, $^1J_{C,P}$ = 9 Hz), 137.83 (C_{tert}), 140.40 (*C*-CHO), 159.72 (C-O), 191.75 (d, CHO, $^3J_{C,P}$ = 27 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ = –17.21; FAB-MS: *m/z* = 422.1 [M^+].

(1*R*,2*R*)-*N*-(2-Diphenylphosphanylbenzyl)-*N*'-[2-diphenylphosphanyl-5-(4-vinylbenzyloxy)benzyl]cyclohexane-1,2-diamine (11)

A solution of **4** (1.71 g, 4.4 mmol) and **10** (1.85 g, 4.4 mmol) in absolute ethanol (250 mL) was heated under reflux for 1 hour. Reaction control by ^{1}H NMR showed conversion of the carbonyl compound and the formation of an imine (disappearance of carbonyl-proton signal at 10.56 ppm and generation of imine-proton signal at 8.98 ppm in $CDCl_3$). The reaction mixture was then allowed to cool to room temperature. Sodium borohydride (1.66 g, 44 mmol) was added. After 3 hours, a reaction control by ^{1}H NMR showed complete reduction of the imine. The reaction was quenched by adding acetone (50 mL) and the solvents were removed under reduced pressure. The residue was dissolved by vigorous stirring in a mixture of saturated ammonium hydrochloride solution (100 mL) and dichloromethane (100 mL). The aqueous phase was extracted with dichloromethane (3 × 60 mL) and the combined organic phases were washed with water (100 mL). After drying over anhydrous magnesium sulfate the solvent was removed under reduced pressure and the resulting product dried under vacuum. According to ^{1}H NMR analysis, the product (yield: 2.83 g, 79%) was of 94 % purity and was directly used for the following reaction; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 – 1.0 (m, 1H, CH_2), 1.0 – 1.32 (m, 3H, CH_2), 1.55 – 1.8 (m, 2H, CH_2), 1.82 – 1.9 (m, 1H, CH_2), 1.92 – 2.1 (m, 2H, NCH, CH_2), 2.1 – 2.2 (m, 1H, NCH), 3.8 – 4.0 (m, 2H, CH_2-NHR), 4.0 – 4.15 (m, 2H, C*H*$_2$-NHR), 5.03 (s, 2H, benzyl-CH_2), 5.24 (d, 1H, *H*HC=CHR, $^3J_{H,H}$ = 11 Hz), 5.75 (d, 1H, H*H*C=CHR, $^3J_{H,H}$ =18 Hz), 6.75 (dd, 1H, *H*RC=CH2, $^3J_{H,H}$ =11 Hz, $^3J_{H,H}$ =18 Hz), 6.8 – 6.9 (m, 1H, o-CH), 7.1 – 7.2 (m, 1H, CH), 7.2 – 7.4 (m, 28H, CH), 7.5 – 7.6 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.99 (CH_2), 25.38 (CH_2), 31.28 (CH_2), 35.48 (CH_2), 49.3 – 49.5 (m, 2CH_2-NRH), 60.97 (CH), 61.11 (CH), 69.60 (benzyl-C), 112.21 (CH), 114.18 (CH), 126.4 – 129.2 (m, CH), 133.52 – 134.17 (m, C_{tert}), 135.89 – 137.36 (m, CH, RH*C*=CH_2), 159.80 (C-O); ^{31}P NMR (121 MHz, $CDCl_3$): δ = –15.69, –16.08, –17.83, –18.80; FAB-MS: *m/z* = 795.2 [M^+ + H].

Ruthenium Dichloride (1*R*,2*R*)-*N*-(2-Diphenylphosphanylbenzyl)-*N*'-[2-diphenylphosphanyl-5-(4-vinylbenzyloxy)benzyl]cyclohexane-1,2-diamine (12)

A solution of **11** (2.83 g, 3.5 mmol) and dichlorotetrakis(dimethyl sulfoxide)ruthenium(II) (3.36 g, 7 mmol) in absolute toluene (200 mL) was heated under reflux for 1 hour. The solvent was removed under reduced pressure in a rotary evaporator operating under an argon atmosphere. The residue was subjected to column chromatography on silica gel (*iso*-hexane:ethyl acetate = 2:1). The product was precipitated as a yellow/orange powder by adding *iso*-hexane; yield: 1.86 g (55%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 – 1.30 (m, 4H, CH_2), 1.80 – 1.94 (m, 2H, CH_2), 2.70 – 2.86 (m, 2H, CH_2), 2.91 – 3.10 (m, 2H, NH), 3.89 – 4.15 (m 4H, CH, C*H*$_2$-NRH), 4.65 – 4.80 (m, 2H, C*H*$_2$-NRH), 5.02 (s, CH_2, benzyl), 5.28 (d, 1H, *H*HC=CHR, $^3J_{H,H}$ = 11 Hz), 5.78 (d, 1H, H*H*C=CHR, $^3J_{H,H}$ = 18 Hz), 6.79 (dd, 1H, *H*RC=CH2, $^3J_{H,H}$ =11 Hz, $^3J_{H,H}$ = 18 Hz), 6.8 – 6.9 (m, 1H, CH), 7.1 – 7.8 (m, 30H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.98 (2CH_2), 30.94 (CH_2), 52.21 (CH_2-NRH), 55.52 (CH_2-NRH), 64.87 (CH), 64.92 (CH), 69.89 (benzyl-C), 113.18 (CH), 114.36 (*C*H_2=CHR), 126.58 – 129.3 (m, CH), 133.32 (CH), 134.59 – 136.49 (m, CH, RH*C*=CH_2), 142.51 (C_{tert}), 143.78 (C_{tert}), 143.85 (C_{tert}), 160.51 (C-O); ^{31}P NMR (121 MHz, $CDCl_3$): δ = 42.68, 42.42, 40.58, 40.32; FAB-MS: *m/z* = 966.0 [M^+].

Chemzyme (15) Functionalized with 3% of Gao-Noyori Catalyst

The reaction mixture containing a solution of **12** (381 mg, 0.40 mmol) and the methylhydrosiloxane-dimethylsiloxane copolymer[24] (1 g, 2.22 mmol Si-H) in absolute toluene (25 mL) was degassed (freeze/pump/thaw method). After addition of the platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane catalyst (10 μL, solution in xylene, 2.1 – 2.4% Pt, 0.05 μmol, purchased from Aldrich) the reaction solution was stirred for 1 hour at 50 °C. The course of the reaction was monitored by ^{1}H NMR spectroscopy (disappearance of vinyl proton signals at 5.2 and 5.7 ppm in $CDCl_3$). The remaining hydridosiloxane units (^{1}H NMR Si-H proton signal at 4.69 ppm in $CDCl_3$) were end-capped by addition of tris(2-methoxyethoxy)vinylsilane (**14**; 1 g, 3.5 mmol) and further stirring for 12 hours at 50 °C. Purification of **15** was performed by means of nanofiltration (MPF-50 membrane, Celfa, solvent dichloromethane, 10 mL reactor, 20 residence times). After removal of the solvent in a rotary evaporator under an argon atmosphere and drying under vacuum, **15** was obtained as brown mass (1.45 g, 82%, calculated mass = 20768 g/mol). ^{1}H NMR (300 MHz, $CDCl_3$) results indicate 2.9% functionalization: δ = –0.12 – 0.27, (m, 933H, CH_3Si), 0.51 – 0.7 (m, 65H, CH_2Si), 0.9 – 0.95 (m), 1.1 – 1.4 (m), 1.6 – 1.99 (m), 2.65 – 2.85 (m), 2.89 – 3.09 (m, 9.8H, NH), 3.20 – 3.48 (s, 190H, CH_3O), 3.50 – 3.60 (t, 126H, C*H*$_2$-O-CH_3, $^3J_{H,H}$ = 5 Hz), 3.80 – 4.0 (t, 126H, CH_2-O-Si, $^3J_{H,H}$ = 5 Hz), 4.0 – 4.2 (m), 4.65 – 4.80 (m), 4.80 – 5.05 (m), 6.6 – 7.39 (m, 151H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.49 (O_3Si-*C*-C-Si), 0.47 – 1.72 (m, Si-CH_3), 8.07 (CH), 24.88 (2CH_2), 30.77 (CH_2), 52.22 (m), 53.39 (CH_2), 58.82 (OCH_3), 61.98 (Si-O-CH_2), 63.08 (m), 69.92 (benzyl-C), 113.38 (CH), 126.93–129.55 (m, CH), 132.32 (CH), 133.85–137.0 (m, CH), 142.66 (C_{tert}), 143.3–

143.85 (m), 159.21 (C-O); gel permeation chromatography (GPC in THF versus polystyrol standard, 25 °C): M_n = 22133 g/mol, polydispersity 2.1; ^{31}P NMR (121 MHz, $CDCl_3$): δ = 39.99, 40.21, 42.17, 42.39 (2 diastereomers); anal. calcd. (%): C 44.10, H 7.66, N 0.66, O 20.7, Cl 1.67, P 1.46, Si 21.4, Ru 2.38; found (%): C 43.18, H 7.48, N 0.74, O 20.1, Cl 1.64, P 1.64, Si 22.1, Ru 2.61.

Determination of Activity

The reaction was performed in dry Schlenk tubes, thermostated to 45 °C. The catalyst (0.01 mmol) was dissolved in an 80/20 mixture (v/v) of absolute 2-propanol and dichloromethane (19.21 mL) followed by addition of the isopropoxide solution (200 μL of 0.1 M solution) and acetophenone (584 μL at 25 °C, 5 mmol). Samples were taken every 20 minutes and directly analyzed by GC. Activity was determined as initial rates (TOF_0).

Continuous Experiment with the Chemzyme Membrane Reactor

Before starting the reaction, the membrane reactor[2,8a,8c] (10 mL reactor volume) equipped with an MPF-50 membrane from Koch-Membrane-Systems, Germany, was rinsed with absolute 2-propanol (100 mL, 10 residence times). The chemzyme **15** (637 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (10 mL) and pumped into the reactor, thermostated to 45 °C. An alternating piston pump (Pharmacia P-500, Freiburg, Germany, equipped with mass-flow meters from Bronkhorst, Germany) was used for delivering the acetophenone solution (9 mL/h of a 277 mM solution in a 80/20 mixture of 2-propanol and CH_2Cl_2, additionally containing 0.083 mM of catalyst) and the isopropoxide solution (1 mL/h of a 5 mM solution in a 80/20 mixture of 2-propanol and CH_2Cl_2) to the reactor. After activating the catalyst by injecting a concentrated isopropoxide pulse in the inlet stream (3 mL of 0.1 M solution), samples were withdrawn every hour and analyzed directly by GC.

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