

The Use of Ultra- and Nanofiltration Techniques in Homogeneous Catalyst Recycling

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ABSTRACT

In recent years, the application of membrane technology in homogeneous catalyst recycling has received widespread attention. This technology offers a solution for the major drawback of homogeneous catalysis, that is, recycling of the catalyst. From both an environmental and an industrial point of view, this technology is very interesting, since it allows the future application of homogeneous catalysts in the synthesis of commercial products, leading to faster, cleaner and highly selective *green* industrial processes. In this Account, an overview is given of the promising results obtained in the field of homogeneous catalyst recycling using nanofiltration membrane technology.

1. Introduction

Homogeneous catalysts are frequently used in highly selective organic transformations. Especially in asymmetric syntheses, the contribution of homogeneous catalysts is significant.¹ Nevertheless, in industry, most catalytic processes are still catalyzed by heterogeneous catalysts because of the facile separation of these catalysts from the product stream. In the field of homogeneous catalysis, separation of the catalyst from the product mixture is

Harm Dijkstra obtained his M. Sc. in Chemistry from the University of Groningen in 1997. Currently, he is finishing his Ph.D. research at the Debye Institute of the Utrecht University under supervision of Professor Gerard van Koten. This research focuses on the development of shape-persistent macromolecular materials containing organometallic pincer sites and their application as recyclable homogeneous catalysts in a nanofiltration membrane reactor and as templates in the construction of supramolecular structures.

Gerard van Klink obtained his Ph.D. from the Vrije Universiteit, Amsterdam, under supervision of Professor Bickelhaupt on the mechanism of formation of organomagnesium compounds. He worked as a postdoctoral fellow on the design and synthesis of cocatalysts for Ziegler–Natta polymerization processes and on low-valent catalysts for olefin polymerization in the group of Prof. Eisch at the State University of New York at Binghamton, both in cooperation with DSM Research. In 1998, he joined the group of Prof. van Koten at the Utrecht University where he currently is working as a lecturer.

Gerard van Koten has been professor of organic synthesis at the Debye Institute of the Utrecht University since 1986. He is scientific director of The Netherlands Institute for Catalysis Research (NIOK). His research interests comprise the study of fundamental processes in organometallic chemistry, the application of organometallic complexes as homogeneous catalysts (in particular, for fine-chemical synthesis), and as materials with special physicochemical properties (molecular wires and switches). The preparation and use of the first examples of homogeneous metallo-dendrimer catalysts demonstrate his interest in supramolecular systems with (organometallic) catalytically active functionalities.

Table 1. Homogeneous vs Heterogeneous Catalysis

	homogeneous	heterogeneous
activity	+++	–
selectivity	+++	–
catalyst description	+++	–
reaction conditions	+++	+
catalyst recycling	–	+++
quantity of catalyst	++	+++
TTN ^a	+	+++

^a TTN = total turnover number.

rather complicated, preventing large-scale industrial processes. Nevertheless, a number of important large-scale industrial processes are catalyzed by homogeneous catalysts, such as the production of adiponitrile by Dupont, acetic acid by Monsanto, and butanal by Ruhr Chemie, pointing at the importance of homogeneous catalysis.² Mainly homogeneous catalysts that can be used in very low concentrations find commercial application, since the catalyst quantity in the product stream is at the parts-per-million level, and thus, separation of the catalyst is not necessary.³ In Table 1, the features of homogeneous versus heterogeneous catalysis are summarized. Homogeneous catalysts are superior in terms of activity and selectivity and possess a high atom efficiency. Furthermore, the reaction conditions are relatively mild, and the actual catalytic species are well-defined, allowing an easy fine-tuning of the catalytic properties, an aspect that is not easily achieved with heterogeneous catalysts. Heterogeneous catalysts on the other hand, are very easy to separate from the product stream and can be recycled efficiently. As a consequence, the quantity of catalyst needed is rather low, and high total turnover numbers are obtained, making the catalysts relatively cheap. Therefore, finding a way to integrate the advantages of homogeneous and heterogeneous catalysis into one chemical process would be extremely interesting, from both an environmental and a commercial point of view.

An attractive approach to achieve this goal is the development of recyclable homogeneous catalysts.⁴ This approach will create catalytic processes that possess a high selectivity and activity, leading to high product yields and minimal amounts of side-products and waste materials. In particular, the need for processing of the product stream can also be minimized. Furthermore, catalyst recycling allows an efficient use of the generally expensive homogeneous catalysts, making such a process commercially feasible. In addition, it also allows catalytic processes in which higher catalyst loadings are required. Ultimately, development of such systems and applying them industrially will lead to green catalytic processes.

An interesting and promising development in the area of homogeneous catalyst recycling is the attachment of homogeneous catalysts to soluble organic supports. In this way, macromolecular homogeneous catalysts are created

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that can be recovered from the product stream by ultra- or nanofiltration techniques and reused again. This Account will discuss the achievements of membrane technology in the field of homogeneous catalyst recycling as well as review a number of representative examples of recyclable, soluble enzymes using enzyme membrane reactors.

2. Membrane Technology

In the field of membrane filtration,⁵ a distinction is made between different kinds of membrane processes on the basis of the size and geometry of the particles to be retained, that is, microfiltration, ultrafiltration, nanofiltration,⁶ and reverse osmosis. Ultra- (UF) and nanofiltration (NF), the two types of filtration techniques discussed in this Account, are defined to retain macromolecules with dimensions between 8 and 800 nm and 0.5–8 nm, respectively.

The demand on industry for better environmental solutions and cleaner technologies has been pushing membrane technology into the forefront.⁷ In the future, end-of-pipe solutions for purification of effluent streams will to a larger extent be substituted by closed systems with integrated process solutions, resulting in simpler and cleaner industrial processes. Applying this membrane technology in the field of homogeneous catalyst recycling depends on a number of important features of the membranes used. Most UF and NF membranes are asymmetric membranes; the pore-sizes on the solute side of the membrane are smaller than those on the permeate side, thereby preventing clogging of the membranes. Furthermore, the stability of the membranes under various conditions is very important, because it determines the number of potential catalytic applications using this technology. In addition, the interactions of the various compounds and intermediates in the catalytic process with the membrane surface have to be considered. In general, the latter aspects are still a matter of trial and error, since for most membranes, data concerning these aspects are often not available.

Usually, the molecular weight cutoff (MWCO) is used as the quantitative criterion for the retention characteristics of a membrane. The MWCO is defined as the molecular weight at which 90% of the solutes are retained by the membrane. It should be kept in mind, however, that pore-size distribution (which exists in all UF and NF membranes), charge effects, and hydrophilicity, hydrophobicity, and polarity (of the solvent) can also greatly influence the permeability of the membrane. Furthermore, in the case of macromolecules, the molecular shape is an important factor. For example, globular proteins are more efficiently retained by membranes in comparison to flexible polymers with elongated chains.

For separation processes using membranes, an additional important feature is the retention (R) of the material to be separated from the product mixture. The retention of a material is defined by the ratio of the concentration of a component A in the permeate and the

retentate and is expressed in the following equation.

$$R = 1 + \left(\frac{1}{\theta}\right) \ln\left(\frac{[A_R]}{[A_P]}\right) \quad (1)$$

where R is retention, $[A_R]$ is the concentration of component A in the retentate, $[A_P]$ is the concentration of component A in the permeate, and θ is the number of exchanged reactor volumes. The suitability of membrane technology in a chemical process roughly depends on the features described above. However, to describe the physical processes that take place in membrane filtration processes, various other features, such as pressure, polarity, permeability of the membrane, etc., have to be taken into account as well.

2.1. Continuous Membrane Reactors. Two types of continuous membrane reactors are mainly used in this research field (Figure 1). In a collaborative project with the group of Vogt,⁸ we make use of the *dead-end-filtration* to recycle our homogeneous catalysts (see Figure 2). With this technique, the catalyst is compartmentalized in the reactor and is retained by the nanofiltration membrane. Reactants are continuously pumped into the reactor, whereas products (and unreacted materials) cross the membrane and can be further processed. Concentration polarization of the catalyst, that is, accumulation of the catalyst near the membrane, can occur using this technique. In contrast, when a *loop reactor* is used, such behavior is prevented, since the solution is continuously circulated through the reactor, and only small particles (products and unreacted materials) can cross the membrane lateral.

3. Biotechnology: (Co)-Enzyme Recycling

Often enzymes are regarded as the ideal catalysts, since they possess extremely high activities and selectivities, which are often impossible to obtain with synthetic homogeneous catalysts. Recycling of the often expensive biocatalyst is an important goal in applied biocatalysis. An interesting approach to achieve this is by applying membrane ultrafiltration, for example, in an enzyme membrane reactor.⁹ This method has to be distinguished from systems in which the enzyme is immobilized on or in a membrane. Soluble enzyme systems have the major advantage that almost every enzyme is retained by the same membrane, whereas for the immobilized enzymes, every immobilization protocol can be different. In this section, representative examples of soluble enzyme systems that are recycled by applying membrane filtration technology are discussed.¹⁰

Amino acylase I is used for the resolution of racemic amino acids in an enzyme membrane reactor (Scheme 1).¹¹ By this method, Degussa AG produces proteinogenic and nonproteinogenic amino acids, such as norvaline, aminobutyric acid, and (*S*)-benzylcysteine in a continuously operated enzyme membrane reactor on an annual multiton scale.

In a second example, optically pure α -amino acids are synthesized via reductive amination of α -keto acids using

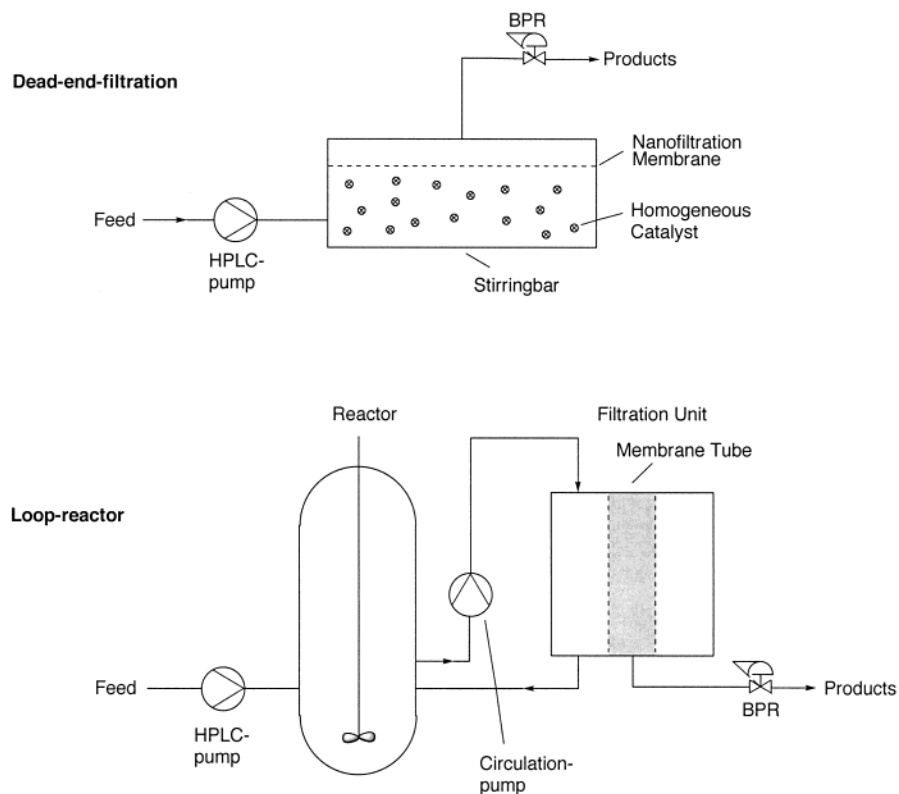


FIGURE 1. Continuous membrane reactors.

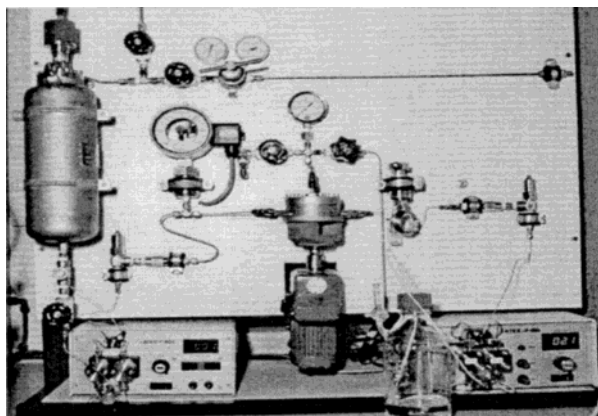
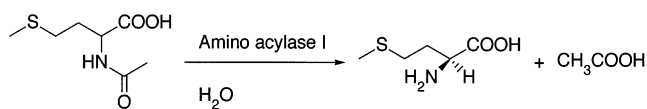


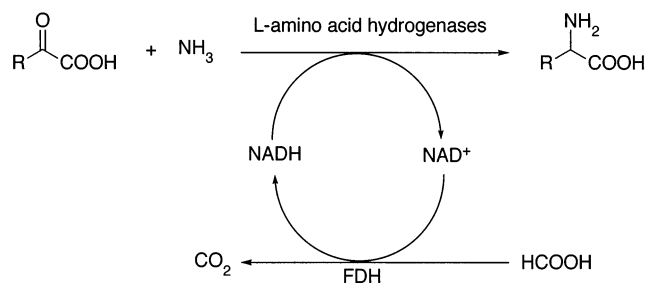
FIGURE 2. Setup of a nanofiltration membrane reactor (Prof. D. Vogt, Eindhoven University of Technology).

Scheme 1. Enzymatic Synthesis of L-Menthionine



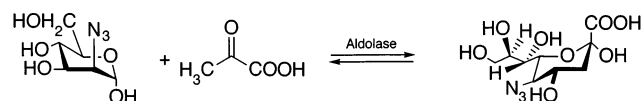
recyclable L-amino acid dehydrogenases (Scheme 2).^{9,11,12} Degussa uses this system on a multi-kg scale using an enzyme membrane reactor. To avoid the stoichiometric use of the expensive cofactor NADH,¹³ a regeneration step using FDH, a fairly cheap enzyme, was developed. Later, it was found that cofactors NADH and NADPH used in the same catalytic system could also be recycled by means of nanomembrane filtration in a continuous enzyme membrane reactor.¹⁴ Attachment of cofactors to homogeneously soluble polymers, which can be recycled by

Scheme 2. Synthesis of Chiral α -Amino Acids^a



^a FDH = Formate Dehydrogenases

Scheme 3. Synthesis of Neu5N₃ Using Enzymatic Synthesis

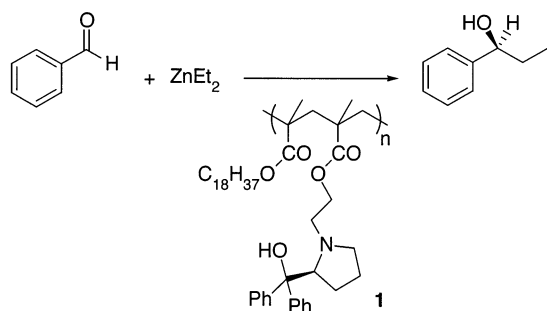


ultrafiltration membranes or the use of charged UF-membranes, is another method to improve the performance of cofactors.^{15,16}

In a final example, 5-azido-neuraminic acid (Neu5N₃) is prepared using an aldolase in a bench-scale experiment applying a repetitive batch technique in a UF cell (Scheme 3).¹² This system has a constant conversion for 25 h with a conversion rate of >80%.

In conclusion, these illustrative examples nicely show the potential of membrane technology in enzymatic synthesis. One always has to keep in mind, however, that enzymes usually are very sensitive to reaction conditions. Examples are known in which enzyme deactivation occurs by interaction with the reactor material or even destabilization by interaction with the membranes.⁹

Scheme 4. Enantioselective Addition Using a Recyclable Polymer-Enlarged Catalyst



4. Recycling of Homogeneous Catalysts

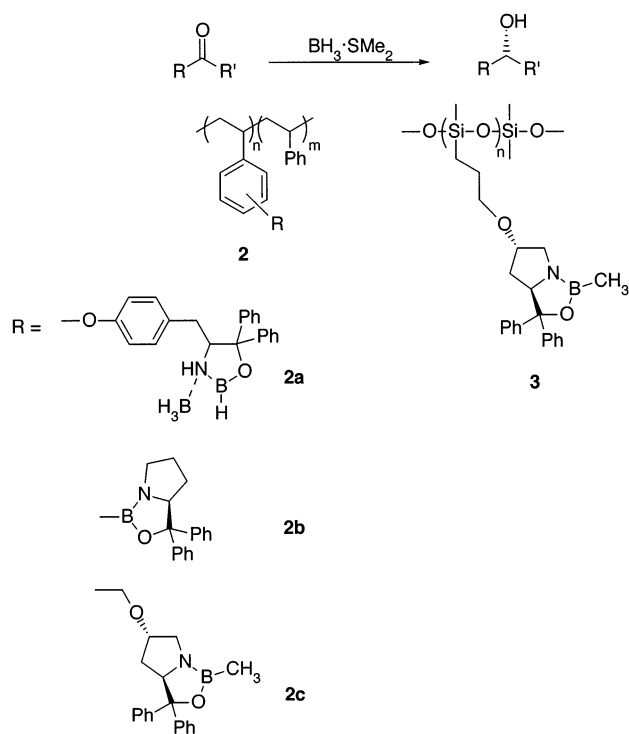
For increasing the number of applications of homogeneous catalysts on a large industrial scale, developing efficient recycling techniques is necessary. In this way, the total turnover number of the catalysts increases, and the costs are thus decreased, also allowing catalytic processes that need higher catalyst loadings.

Currently, considerable attention is given to the development of homogeneous catalysts anchored on soluble supports, such as polymers and dendrimers. Such an approach allows the recovery (and reuse) of homogeneous catalysts from product streams by means of NF membranes in continuously operating catalytic processes. In this section, an overview is given on the state-of-the-art of homogeneous catalyst recycling using membrane systems.¹⁷

4.1. Polymer-Enlarged Homogeneous Catalysts. Kragl and Wandrey and co-workers described the use of polymer-enlarged homogeneous catalysts in continuously operating membrane reactors. In 1996, Kragl reported the first example of a polymer-enlarged chiral homogeneous catalyst (**1**) which was used in the enantioselective addition of diethylzinc to benzaldehyde (Scheme 4).¹⁸ α,α -Diphenyl-*L*-prolinol coupled to a copolymer made from 2-hydroxyethyl methacrylate and octadecyl was used as the chiral ligand and could be retained from the reaction mixture by UF membranes. It was found that >99.8% of the polymer-enlarged system was retained by the membrane. Under optimized conditions, the total turnover number (ttn) of this system under continuous conditions was raised by a factor of 10 to 500. For a system without catalyst recycling, a ttn of 500 corresponds to an effective chiral catalyst concentration of 0.2 mol %, which is still exceptional in asymmetric syntheses.³ Furthermore, the system did not show any signs of deactivation for a period of 7 days, implying the possibility of longer operating times in the reactor. The enantiomeric excess (ee) of this reaction using the polymer-enlarged system was considerably lower than the ee achieved with the noncoupled ligand (80 vs 97%). It has been suggested that this lower selectivity can be improved by higher catalyst concentrations.¹⁸

Polymer-enlarged oxazaborolidines **2a** and **2b** were also applied as homogeneous catalysts in enantioselective reductions of several ketones in a membrane reactor (Scheme 5).¹⁹ A solvent-stable NF membrane was used for

Scheme 5. Enantioselective Reduction Using Recyclable Polymer-Enlarged Catalysts

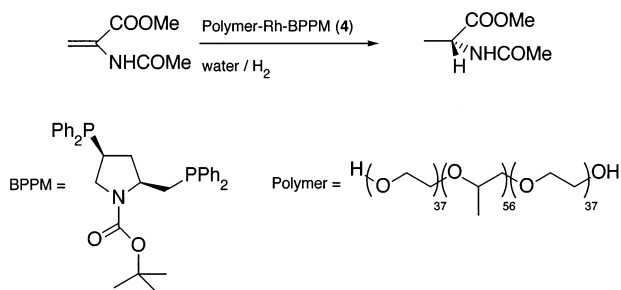


this setup. In comparison with the batch process in which the ketone was added in one portion, higher enantioselectivities were found. This is in agreement with additional reported data, according to which slow addition of the ketone to a solution of the other reagents resulted in higher ee's. Under the reaction conditions, the catalyst showed a slight deactivation (1.8%/h), and the reactor seemed to operate under stable conditions until the concentration of the active catalyst dropped below a critical value. Nevertheless, the total turnover numbers of these systems could be enhanced from 10 up to 560.

Immobilized oxazaborolidine catalysts **2c** and **3**, which are based on the Corey-diphenylprolinol, were also tested under similar catalytic reaction conditions (Scheme 5).²⁰ Polysiloxane-bound catalyst **3** ($R = 98.50\%$) could be used for 200 residence times at almost quantitative conversion and 96.8% ee, whereas polystyrene-bound catalyst **2c** ($R = 99.94\%$) even showed a constant conversion (>99%) and enantioselectivity (96.8%) for > 400 residence times. The average ee with both catalysts was somewhat lower as compared to the original Corey catalyst (>99% ee); however, the total turnover number was increased from 100 (batch) to 1374.

In a final example, micellar rhodium catalyst **4** was used in the asymmetric hydrogenation of α -acetamidoacrylic acid methyl ester in aqueous media in a repetitive batch experiment (Scheme 6).²¹ The triblock copolymer P105 was used as a surfactant in which the rhodium catalyst was embedded. Using a UF membrane, this micellar enlarged catalyst was found to have a retention of 0.991, causing slow leaching of the catalyst. Conversions and ee's were found to be constant for at least 6 runs. Traces of oxygen had to be avoided in this process, since

Scheme 6. Asymmetric Hydrogenation Using a Recyclable Micellar Catalyst



this rapidly decreased the activity of the system. Furthermore, since the rhodium is not covalently attached to the ligand system, a slightly higher rhodium leaching, which is determined by the complex stability between the metal and the phosphine ligand, than that found for the embed-

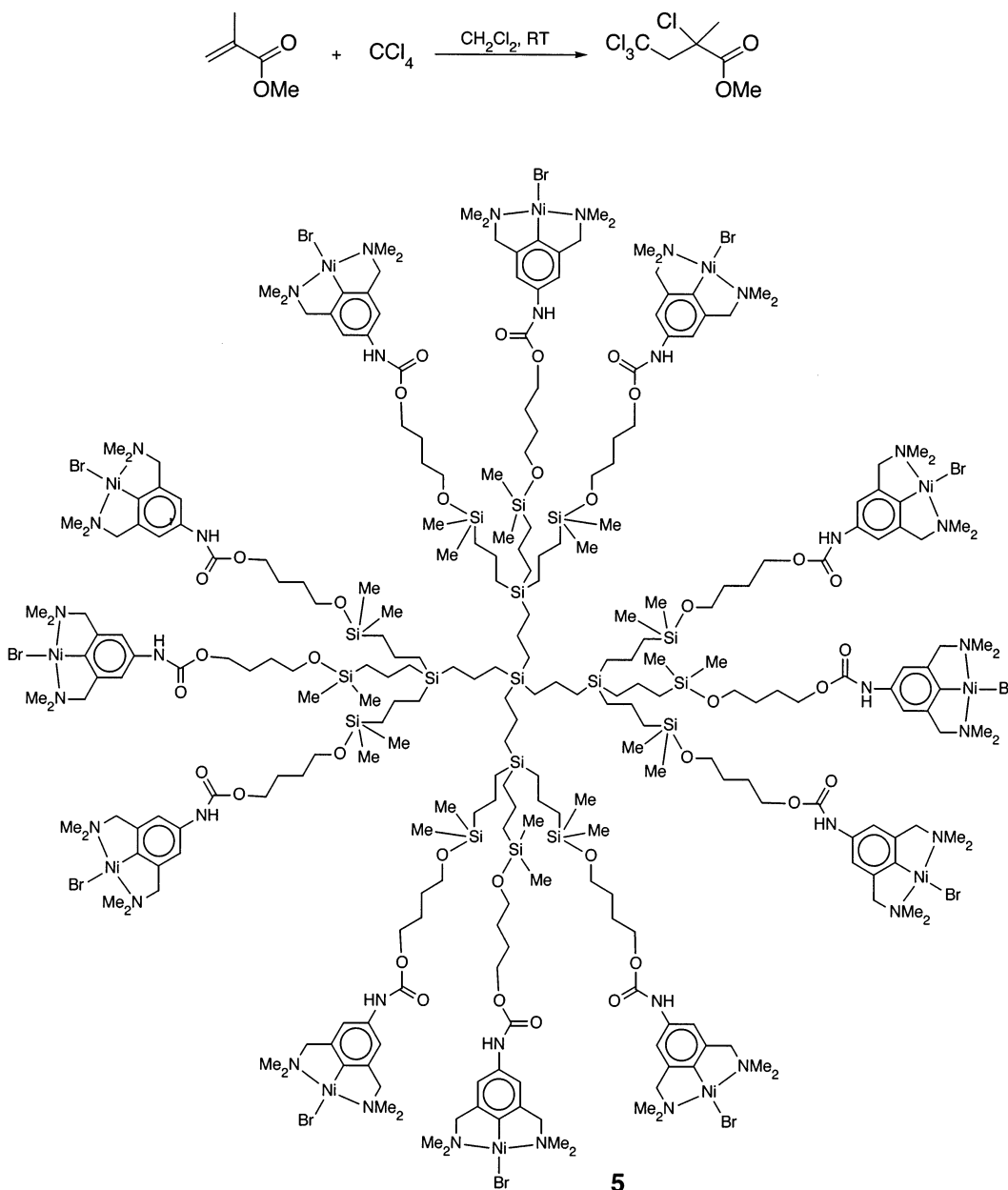
ded system ($R = 0.991$) was observed. Nevertheless, by applying this system, the ttn was doubled up to 194.

As shown in this section, anchoring homogeneous catalysts to soluble polymer supports and applying membrane-filtration technology greatly enhances their performance in catalytic processes (increased ttn). In addition, the selectivities of the catalytic reactions were in most cases found to be in the same range as the nonsupported catalysts.

4.2. Dendrimer-Enlarged Homogeneous Catalysts.

The use of dendrimers as soluble supports for homogeneous catalysts in membrane separation experiments has received considerable attention in recent years. Several groups focused on the incorporation or complexation of (transition) metal fragments onto dendrimers and nowadays a broad spectrum of so-called *metallo-dendrimers* are known that are active as homogeneous catalysts.²² In

Scheme 7. Kharasch Addition Catalyzed by a Metallo-dendrimer



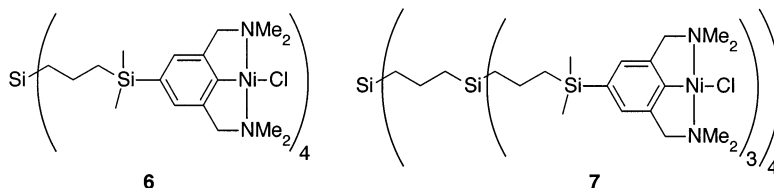


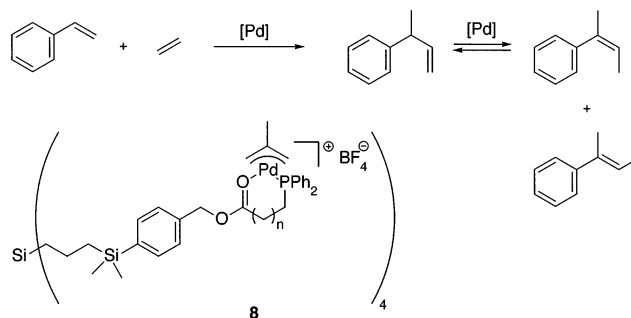
FIGURE 3. Nickelated carbosilane dendrimers active in Kharasch addition.

contrast to polymers, dendrimers are tree-like molecules with very well defined macrostructures. The dimensions can be altered quite easily by varying the generation of the dendrimer. In membrane separation technology, this is an important feature allowing fine-tuning of the retention rate of these dendritic catalysts. Because dendrimers are well-defined pseudospherical structures, the catalyst loading can be exactly determined, rendering a direct comparison with nonsupported mononuclear catalysts. Such a comparison is less straightforward, with the less well defined polymeric systems described in section 4.1, since in these systems, it is very difficult to accurately control the number and location of the catalytic sites. In this section, the use of dendrimers as support materials for homogeneous catalysts that can be retained and reused by applying NF membrane technology is discussed.

The groups of Van Koten, Van Leeuwen, and Vogt have developed different types of *carbosilane dendrimers* that were used as supports for homogeneous catalysts and could be retained by means of NF membrane technology. In 1994, the first examples of metallodendrimers that were used as homogeneous catalysts and were, in principle, suitable for retainment by NF-membranes were reported.²³ In this report, nickelated carbosilane dendrimers were used in a regioselective Kharasch addition of polyhalogenoalkanes to carbon-carbon double bonds (Scheme 7, example of dodecanickel carbosilane dendrimer **5**). The catalytic data suggested that each catalytic site acted as an independent unit, and even more important, the regioselective 1:1 addition without telomerization/polymerization of the alkene was similar to the mononuclear catalyst. No retention data of the enlarged homogeneous catalysts were provided. This report started a completely new research area in the field of dendrimer chemistry, that is, the development of catalytically active metallodendrimers.²²

Recently, other examples of soluble nickelated carbosilane dendrimers (**6** and **7**, Figure 3) as homogeneous catalysts in the Kharasch addition were reported by van Koten et al.²⁴ Tests with catalysts **6** and **7** in a NF membrane reactor showed retentions of 0.974 and 0.998 for **6** and **7**, respectively. Unfortunately, applying the dendrimer with the highest retention (**7**) in the Kharasch addition in a membrane reactor resulted in a fast deactivation of the catalyst. This deactivation is caused by the "proximity effect" (or dendritic effect) between peripheral Ni(II) sites, which translates into lower catalytic efficiencies and irreversible formation of insoluble, inactive Ni(III) sites.²⁵ This proximity effect was solved by introducing longer spacers between the catalytic site and the dendrimer branching points, thus creating a situation in

Scheme 8. Hydrovinylation of Styrene Using Palladated Dendrimers



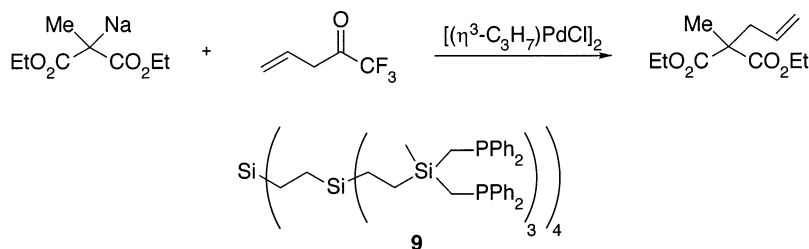
which the Ni centers are further away from each other. No experiments in a NF membrane reactor have yet been performed with this material.

Palladated carbosilane dendrimers with hemilabile P,O ligands were shown to be applicable as homogeneous catalysts in the selective hydrovinylation of styrene in a membrane reactor (Scheme 8).²⁶ In a continuous setup using G0-dendrimer **8**, a considerable decrease in activity was observed, which was partly explained by washout of the catalyst ($R = 0.85$ for a model compound) and partly by decomposition of the catalytic unit. A first-generation dendrimer with a higher retention showed almost the same deactivation behavior.^{26b} Thus, catalyst decomposition is most probably the main reason for the observed deactivation. Nevertheless, the G0-catalyst **8** afforded product for a period of 80 h.

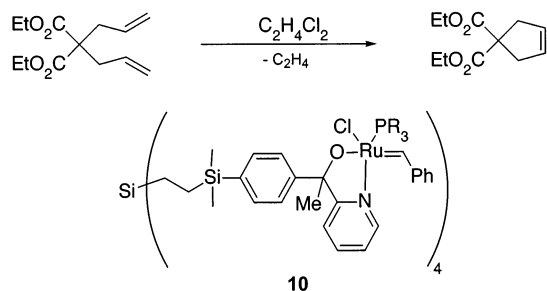
Van Leeuwen and co-workers reported palladated phosphine-functionalized carbosilane dendrimers as catalysts in the reaction between sodium diethyl methylmalonate and allyltrifluoroacetate in a continuous flow membrane reactor (Scheme 9).²⁷ In batch processes, the activity per palladium center of different generations Pd(allyl) dendrimer complexes was constant, indicating that all active sites act as independent catalysts. Under continuous reaction conditions, however, using the largest dendrimer (**9**) (Scheme 9, $R > 0.981$), an unexpected rapid decrease in activity was found that could not solely be ascribed to washout of the homogeneous catalyst. It was proposed that the catalyst decomposed during the process. The same dendritic ligands but in combination with rhodium were used in hydroformylation reactions.²⁸ Preliminary experiments with this catalytic system in a NF membrane reactor, however, showed that the NF membrane setup used is not compatible with the standard hydroformylation conditions because of its temperature and solvent restrictions.

Different generations of carbosilane dendrimers functionalized with ruthenium metathesis catalysts were also

Scheme 9. Allylic Alkylation Reaction Using Phosphine-Functionalized Dendrimers



Scheme 10. Ru-Functionalized Dendritic Catalyst in Metathesis



reported (Scheme 10).²⁹ The activity per metal center of the dendritic catalysts was found to be comparable to that of the corresponding mononuclear catalyst. Unfortunately, the metathesis reaction conditions were not compatible with the NF membrane setup, as was found with G0-catalyst **10** (Scheme 10); after 20% conversion, the reaction stopped. This phenomenon was proposed to be due to interaction of the catalyst with the membrane surface.

The first examples of metalated phosphine-functionalized dendrimers that were suitable as homogeneous catalysts were reported by Kragl, Reetz, and co-workers.^{30,31} When a DAB-based (DAB = 1,4-diaminobutane) phosphino dendrimer was loaded with Pd^{II} centers, the resulting system (**11**) was active in the allylic substitution of 3-phenyl-2-propenylcarbonic acid methyl ester (Scheme 11). The application of catalyst **11** in a NF-membrane reactor for a period of 100 residence times resulted in a conversion decrease to ~80%, which would be equivalent to a palladium leaching of ~0.07–0.14%/residence time. However, the retention of the catalyst was determined independently and was found to be 0.999. Therefore, the drop in conversion must be due partly to catalyst deactivation or decomposition.

Togni and co-workers reported the use of asymmetric dendritic catalysts derived from ferrocenyl bisphosphine ligands loaded with rhodium (**12**) for the asymmetric hydrogenation reaction of dimethyl itaconate (Scheme 12).³² In this paper, the authors claimed that dendritic catalyst **12** is completely retained by NF membranes; however, no data of the filtration experiments were provided.

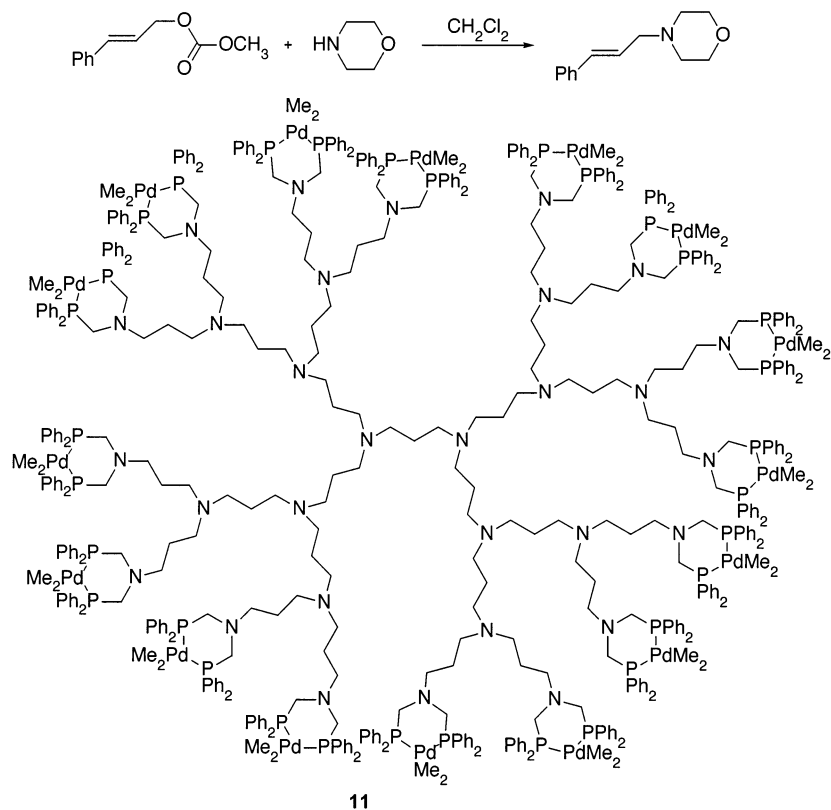
A nickel(II) catalyst anchored to a G3-Fréchet-type dendritic wedge (**13**, M = Ni) was also prepared and applied in a Kharasch addition reaction (Scheme 13).³³ In the setup that was used, third-generation dendritic catalyst **13** was compartmentalized in a NF-membrane-capped vial that was placed into the reaction mixture where

catalysis took place. After the reaction was completed, the vial, still containing the catalyst, could easily be removed and reused. In this case, no pressure was applied during filtration experiments, which resulted in a catalytic process that is rate-limited by spontaneous diffusion of the substrates through the membrane and by mass-transfer limitation due to the relatively small membrane surface area. This idea was supported by a control experiment in which the catalyst was not compartmentalized, resulting in complete conversion within 4 h, whereas the compartmentalized catalyst gave complete conversion after 36 h only. Most interestingly, the vial containing the catalyst could be removed and stored for prolonged times without loss in catalytic activity. This result is now used for the development of one-pot cascade reactions catalyzed by various compartmentalized homogeneous catalysts.³⁴

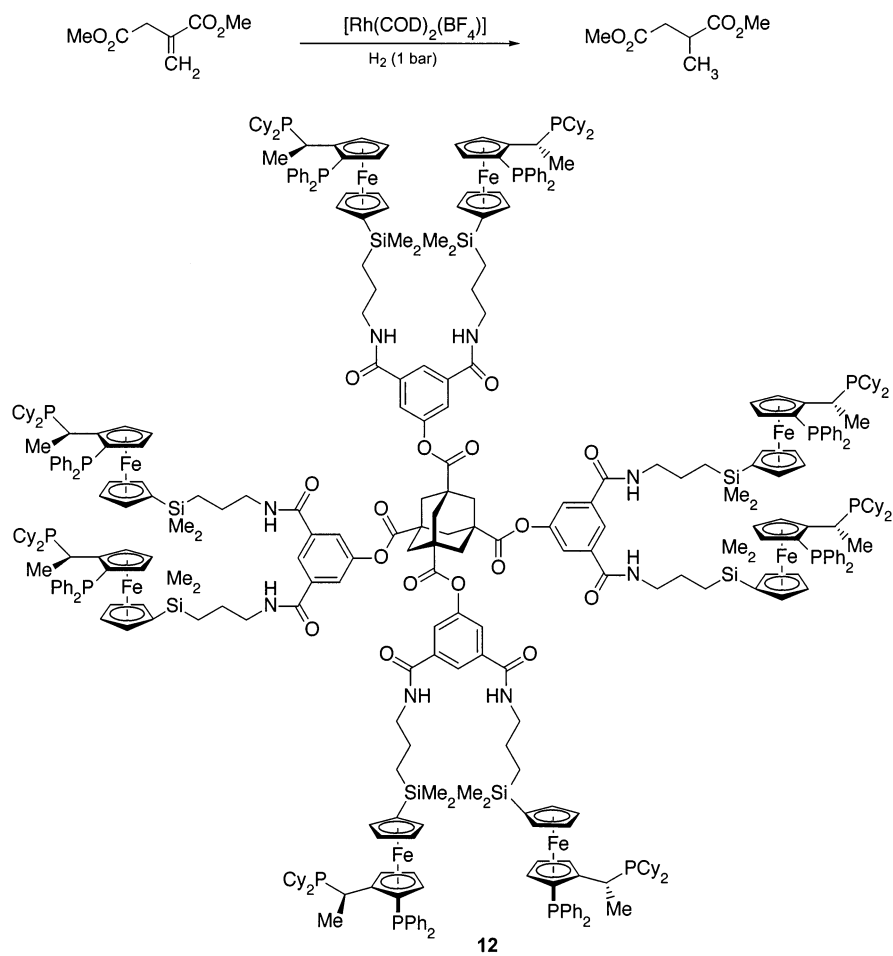
Another very interesting aspect of this work is the elegant way in which the retention rate of the G3 dendrimer was determined. The G3 dendrimer **13** in which Ni was replaced by Pt (thus keeping the overall properties for membrane retention measurements the same) was used for this purpose, since this material strongly colorizes upon exposure to sulfur dioxide.³⁵ This allows the detection of very low concentrations of **13** by means of UV/vis spectroscopy. Obviously, using such a sensitive analysis technique for determining retention rates is preferred over the generally used but less accurate weighing methods, since the analysis is performed in situ and does not require additional workup. Applying this procedure revealed that <20% of the G3 dendrimer **13** (M = Pt) was washed out of the membrane-capped vial in 280 h.³³

The latest example of a dendritic enlarged homogeneous catalyst that was recycled by means of nanofiltration technology was reported by Van Leeuwen and co-workers.³⁶ In an alternative approach, the catalytically active part was anchored to the soluble dendritic support via noncovalent linkages. The resulting system (**14**) was used as a homogeneous catalyst in the allylic amination of crotyl acetate in a continuous flow membrane reactor (Scheme 14). The catalyst precursor was prepared by mixing the dendritic ligand with a suitable palladium precursor, and the catalytic activity and selectivity of this supramolecular catalyst in a batch process was found to be similar to a mononuclear model compound. Retentions of 0.994–0.999 were found to be dependent on the P/Pd atomic ratio. Furthermore, a slow decrease in conversion was observed when the dendritic catalyst was applied in a continuous flow membrane reactor. This decrease could

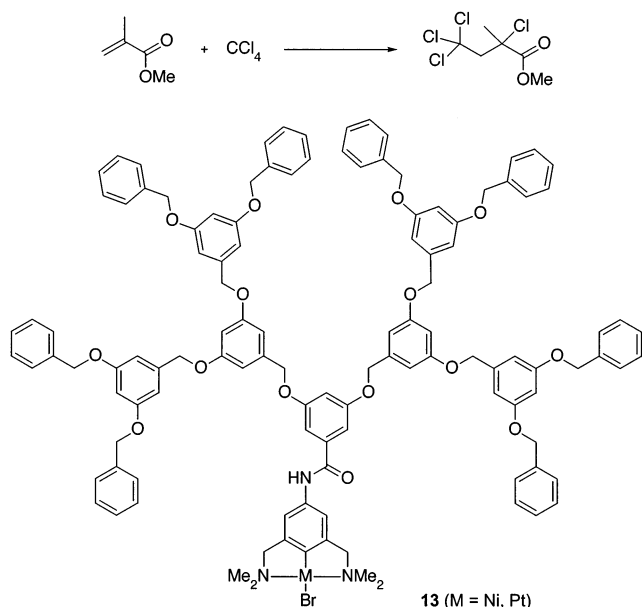
Scheme 11. Phosphine-Functionalized Dendrimer in Allylic Substitution



Scheme 12. Asymmetric Hydrogenation Using a Dendritic-Rhodium Catalyst



Scheme 13. Nickel-Functionalized Dendrimer in Kharasch Addition Reaction



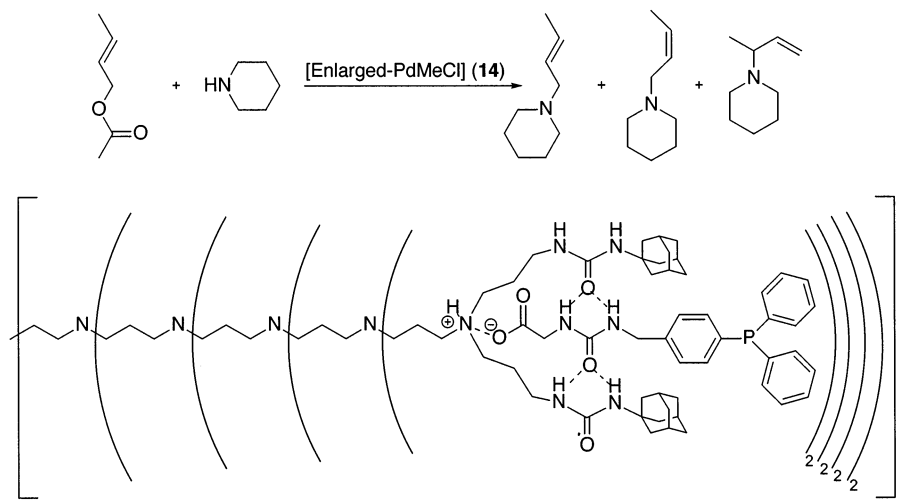
not completely be explained by washout of the catalysts; thus, most probably deactivation of the catalyst occurred, as well.

4.3. Other Enlarged Systems. Recently, we started to investigate which parameters are important for the retention of macromolecules by NF membranes.³⁷ From the dendritic systems discussed in section 4.2, we have seen that even high-generation dendrimers are still not fully retained by NF membranes. This behavior is most probably caused by the flexible backbone of these dendritic catalysts; going up one generation does not necessarily result in a significant increase in the size of the dendrimers, but rather results in backfolding of the dendritic branches, affording denser molecules.³⁸ Furthermore, the dendrimer size in solution is not well-defined and can vary upon altering the polarity of the solvent system or when pressure is applied. Therefore, shape-persistent catalysts **15–18**, containing rigid aromatic backbones, were

selected in order to investigate the importance of rigidity on the retention of macromolecules by NF-membranes (Figure 4). Unfortunately, hexametalated complexes **15** possessed very poor solubilities in common organic solvents and, therefore, could not be used for this study. Trimetalated complex **16** (M = Pt, L = Br), on the other hand, showed a retention of 0.939 in a NF membrane reactor, which is already remarkably high for such a small molecule (Br–Br distance = 17.5 Å).^{37b,c} Introducing an extra phenylene spacer between the central benzene core and the organometallic catalytic moiety resulted in a substantial increase as a retention of 0.987 was found for complex **17** (M = Pt, L = Br; Br–Br distance = 24.6 Å).^{37c} Finally, applying dodecametalated complex **18** (M = Pt, L = D), a more 3-dimensional structured compound as compared to **16** and **17**, in a NF membrane reactor resulted in a retention of >0.999 (diameter = 32.1 Å, thickness = 24.3 Å).^{37c} This preliminary investigation nicely shows that increasing the size of a multimetallic material possessing a shape-persistent backbone results in a linear increase of the retention of these molecules by NF membranes.

Complexes **16–18** (M = Pd, L = OH₂(BF₄)) are active as Lewis acid catalysts in the double Michael reaction between methyl vinyl ketone and ethyl- α -cyanoacetate (Scheme 15). This reaction was chosen as the model reaction, since it can be performed under mild reaction conditions (compatible with the NF membranes) and also in the same solvent (methylene chloride) used for the retention measurements. The results for **16** and **17** suggest that every site reacts as an independent catalyst, since the catalytic activity per palladium center was found to be similar to that of the mononuclear analogue. Catalyst **18**, on the other hand, shows an increased activity per palladium center, which is proposed to be due to cooperative effects between different catalytic sites, since the palladium centers are much closer together than in **16** and **17**.^{37c} No catalysis under continuously operating conditions has yet been performed with these systems.

Scheme 14. Noncovalently Bound Catalyst in Allylic Amination



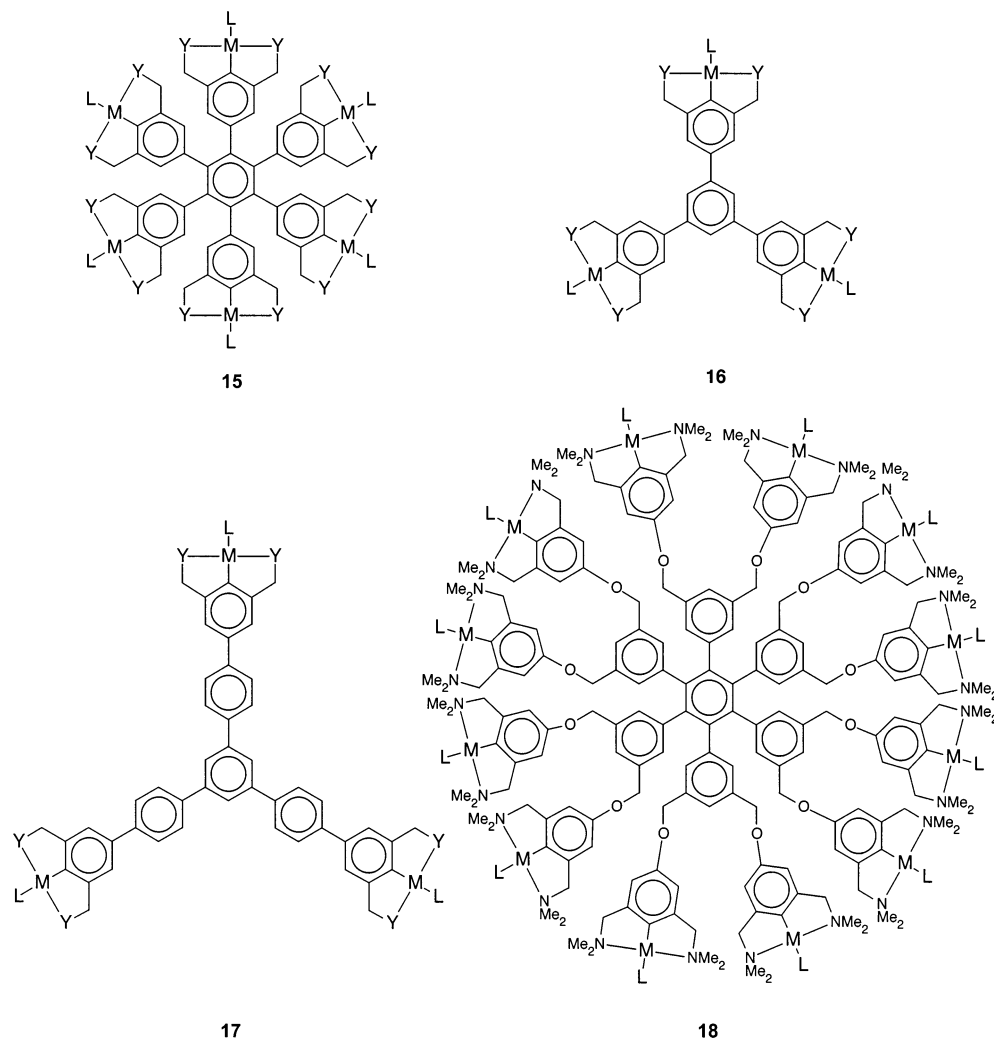
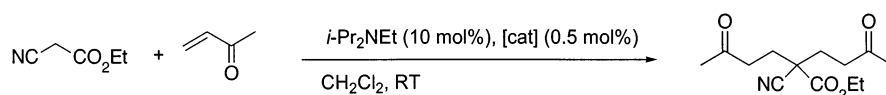


FIGURE 4. Shape-persistent nanosize catalysts.

Scheme 15. Lewis Acid Catalyzed Double Michael Reaction



5. Nonenlarged Systems

The group of Jacobs reported the use of nonenlarged mononuclear ruthenium and rhodium bisphosphine systems in asymmetric hydrogenation reactions (Scheme 16).³⁹ In a first example, Rh-EtDUPHOS **19** was applied in the chemo- and enantioselective hydrogenation of methyl-2-acetamidoacrylate (MMA) (reaction I, Scheme 16) in a NF membrane reactor under continuous conditions. During 10 cycles, a decrease in conversion was observed that could not solely be ascribed to incomplete rejection of the catalysts by the membrane ($R = 0.97$). Therefore, it was proposed that a slow deactivation of the catalyst, probably as a result of oxidation of the phosphines, took place. In a second reaction, the Ru-BINAP system **20** was used in the continuous hydrogenation of dimethyl itaconate (reaction II, Scheme 16). In this reaction, a small decrease in conversion was also observed; however, this could be completely attributed to minor

washout of the catalyst ($R = 0.98$). No deactivation or decomposition of the catalyst was observed. These two examples nicely show that when the appropriate conditions (solvent, pressure, membrane, temperature, etc) are chosen, anchoring of the homogeneous catalyst to a soluble support is not always necessary in order to get high retention of the catalytic system by NF membranes.

6. Green Context and Future Predictions

Membrane technology can nowadays be applied in the recycling of homogeneous catalytic systems. This whole process started in biotechnology, in which UF and NF membrane systems were used for the recycling of expensive enzymes and co-enzymes, making these systems feasible for application in commercial production processes. With the development of more resistant membranes, it has also become possible to perform such

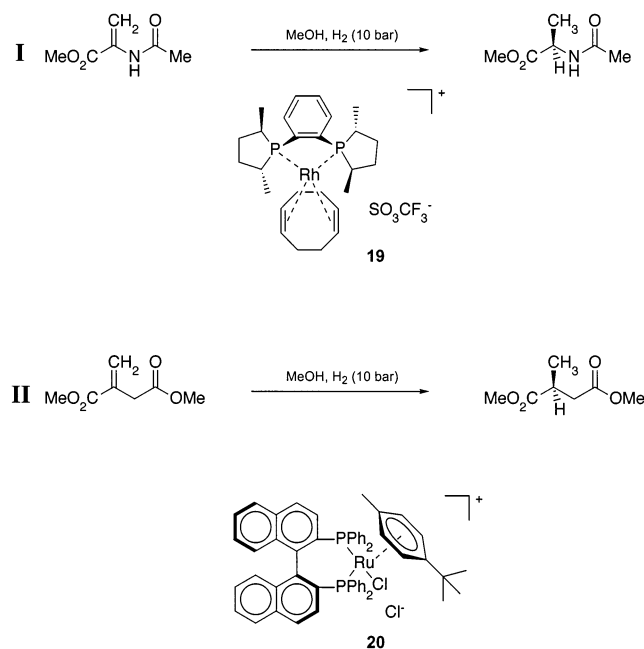
Table 2. Summary of Achievements in the Field of Homogeneous Catalyst Recycling Applying Membrane Filtration Technology

catalyst	catalyzed reaction type	M_w (g/mol)	solvent ^a	membrane ^b	retention	ref
1	ZnEt ₂ addition	9600	<i>n</i> -hexane	PAH-20	0.998	18
2a, b	reduction of ketones	13 800	THF	MPF-50	>0.98	19
2c, 3	reduction of ketones		THF	MPF-50	>0.985	20
4	asymmetrical hydrogenation	>7460	H ₂ O	YC05	0.991	21
6	Kharasch addition	1570	CH ₂ Cl ₂	MPF-50	0.974	24
7	Kharasch addition	4940	CH ₂ Cl ₂	MPF-50	0.998	24
8	hydrovinylation	2800	CH ₂ Cl ₂	MPF-60	>0.85	26
9	allylic alkylation	8252	THF	MPF-60	0.981	27
10	olefin metathesis	3230	C ₂ H ₄ Cl ₂	MPF-60	n.d.	29
11	allylic substitution	10 200	CH ₂ Cl ₂	PAH-5	0.992	30, 31
	allylic substitution	10 200	CH ₂ Cl ₂	MPF-50	0.999	30, 31
12	asymmetrical hydrogenation	7550	MeOH	Centricon-3	n.d.	32
13	Kharasch addition	2060	CH ₂ Cl ₂	MPF-60	n.d. ^c	33
14	allylic amination	>40 000	CH ₂ Cl ₂	MPF-60	0.994/0.999 ^d	36
16	Michael reaction		CH ₂ Cl ₂	MPF-60	0.939	37b,c
17	Michael reaction		CH ₂ Cl ₂	MPF-60	0.987	37c
18	Michael reaction		CH ₂ Cl ₂	MPF-60	>0.999	37c
19	asymmetrical hydrogenation	929	MeOH	MPF-60	>0.98	39
20	asymmetrical hydrogenation	723	MeOH	MPF-60	>0.97	39

^a Solvent in which the retention is determined. This solvent is not necessarily also the solvent in which catalysis was performed.

^b PAH-20 and PAH-5, MWCO = unknown, Hoechst Nadir. MPF-50, MWCO = 700 and MPF-60, MWCO = 400, Koch Int (www.koch-membrane.com). YC05, MWCO = 500, Amicon (www.Millipore.com). Centricon-3, MWCO = 3000, Amicon (www.Millipore.com). ^c Only system in which no pressure was applied; <20% of catalyst leached through the membrane in 380 h. ^d Retention depends on the P/Pd ratio: P/Pd = 1, *R* = 0.994; P/Pd = 2, *R* = 0.999.

Scheme 16. Nonenlarged Catalysts in NF-Membrane Recycling Setup



processes in organic solvents using polymer and dendrimer-enlarged homogeneous catalysts. To date, a number of very promising results have been obtained in this area (Table 2), showing the high potential of homogeneous catalysts in this research field.

Making a real comparison between the various systems described in this Account is not feasible, since the applicability of membrane technology in homogeneous catalyst recycling depends on many important variables. For example, catalyst stability, interaction of the catalysts with the membranes or reactor material and the polarity-dependence of the pore sizes of the membranes greatly influence the outcome of the whole process.

In conclusion, contrary to enzyme-catalyzed reactions that are normally performed under very mild conditions, homogeneous catalysts often need more severe reaction conditions, making application of homogeneous catalysts in membrane technology more difficult. Therefore, to increase the applicability, developing more-resistant membranes and improving the reactor technology is desirable. Nevertheless, membrane technology is a very promising technique for the development of selective and fast commercial catalytic processes using homogeneous catalysts. Further development of this technology is important, since it will lead to energy saving and cleaner industrial catalytic processes, that is, *green* processes.

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