Continuous Homogeneous Catalysis

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This review article illustrates possible aspects for molecular-weight enlargement and immobilisation of transition-metal complexes that have been developed for bridging the gap between homogeneous and heterogeneous catalysis. The recycling of homogeneous catalysts can be performed using different types of supports, such as dendrimers, hyperbranched polymers, nanostructured materials or stabilized nanoparticles in combination with suitable filtration methods and equipments. Continuous homogeneous catalysis is ideally performed in a continuously operated membrane reactor. A general overview of molecular-weight enlargement along with selected examples and recent developments in continuous homogeneous catalysis is provided.

Introduction

The contribution of soluble transition-metal complexes as selective homogeneous catalysts for a number of chemical transformations under mild reaction conditions has increased significantly during the last decades. A number of important large-scale processes, such as the production of adiponitrile, α-olefins (SHOP process), acetic acid and acetic anhydride, and butanal are nowadays based on homogeneous catalysis.[1] A notorious drawback, however, is the tedious separation of the catalyst from the reaction products, a problem not encountered with typical heterogeneous catalysts and often accompanied by thermal strain on reactants and products. For large-scale industrial processes, individual solutions have been developed for catalyst separation and recovery in each case.

In most cases, the development of materials combining the advantages of classical homogeneous and heterogeneous catalysts has remained an elusive goal. However, molecular-weight enlargement and immobilisation of transition-metal complexes in combination with filtration methods offers the possibility to still operate the catalyst under homogeneous reaction conditions, hence maintaining the intrinsically high selectivity and activity, while avoiding mass-transfer limitations.[2] Furthermore, low energy consumption of the separation step and the potential for continuous homogeneous catalysis is provided. However, the synthesis of molecular-weight-enlarged catalyst systems is strongly related to the development of new membranes and reactors, which are compatible with homogeneous reaction conditions.

The Concept: Molecular-Weight Enlargement of Transition-Metal Complexes

A prerequisite for the application of filtration methods is a significant difference in molecular size of the catalyst, the reactants and products, as well as a suitable filtration unit. Different methods have been developed for the molecular-weight enlargement of transition-metal complexes in order to make them amenable to filtration methods. A general overview is given below, while specific examples will be given later on.

The first examples of the concept of binding catalytically active metal complexes to soluble supports were reported in the 1970s, when Rh-containing soluble polymers were successfully applied as hydrogenation catalysts.[3] Since then, functionalised soluble polystyrenes (**A**),[4] poly(ethylene glycol)s (**B**),[5] poly(methyl methacrylate)s (**C**),[6] poly(vinylpyrrolidine)s,[6] polyethylene oligomers,[6] poly(vinylchloride)s,[6] hyperbranched polymers[7] or polyelectrolytes (**D**)[8] have been applied as soluble polymeric supports for transition-metal complexes (Figure 1).[9]

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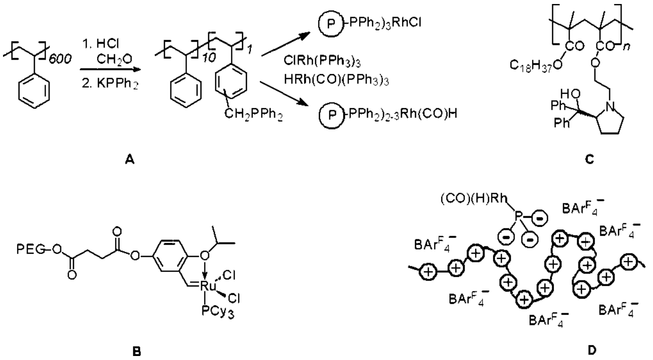

Figure 1. Functionalised polymeric supports.

Dendrimer-based systems are more defined soluble support structures. Most commonly, carbosilane (**1**), polyphenylene, poly(benzyl ether), DAB, PANAM (**2**) and PPI dendrimers have been applied for the immobilisation of transition-metal complexes.[10]

More recently, carbosilane dendrimers have been attached to polyhedral oligosilsesquioxane cages (POSS) (**3**).[11] In a different approach, this POSS cage has been used as the molecular-weight enlargement unit and directly linked to arylphosphane or aryl phosphite ligands (**4**).[12]

POSS-enlarged systems provide the unique properties of being rigid, three-dimensional and mostly kinetically and thermodynamically stable compounds whose size can easily be adjusted by the choice of the substituents attached to the silicon atoms.

In the above-mentioned examples, the transition-metal complexes, which are the catalytically active sites, are either covalently tethered to the support or through ionic interactions. A different approach is the stabilisation of catalytically active metal clusters on soluble supports, such as polyglycerols, polyamides or dendrimers (Figure 2). Metal atoms constituting nanoparticles can be generated in the presence of such a protecting agent, which forms a shell that prevents agglomeration of the particles into larger, and therefore less active, clusters. The protectors can be divided into two categories: those providing electrostatic and those providing steric stabilisation. Popular steric agents are polymers, poly(vinylpyrrolidone), cyclodextrins and dendrimers. Ionic surfactants protect nanoparticles by both electrostatic and steric mechanisms (Figure 2).

Membranes for Catalyst–Product Separations

Filtration processes can be classified into micro-, ultra-, nanofiltration and reversed osmosis, depending on the size of the particles that are retained by the membrane (Figure 3). In most cases ultra- or nanofiltration is used for catalyst separation and recycling.

An important parameter of a membrane is the molecular weight cut-off (MWCO), which is defined as the molecular weight at which 90% of the solutes are retained by the membrane. However, the pore size of many ultra- and nano-

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Marije Nijkamp was born in 1973 in Paramaribo, Surinam. She finished her masters thesis in Inorganic Chemistry and Heterogeneous Catalysis at Utrecht University in 1998. In the same year she started her Ph.D. on Hydrogen Storage using physisorption, modified carbon nanofibres and related materials at Utrecht University with Prof. Dr. Krijn de Jong. In 2003 and 2004 she worked on a postdoctoral research project at Eindhoven University of Technology with Prof. Dr. Dieter Vogt where she investigated the use of polyglycerol- and polyamide-stabilized palladium colloids in continuous homogeneous catalysis. Currently she is employed by Engelhard De Meern B.V.

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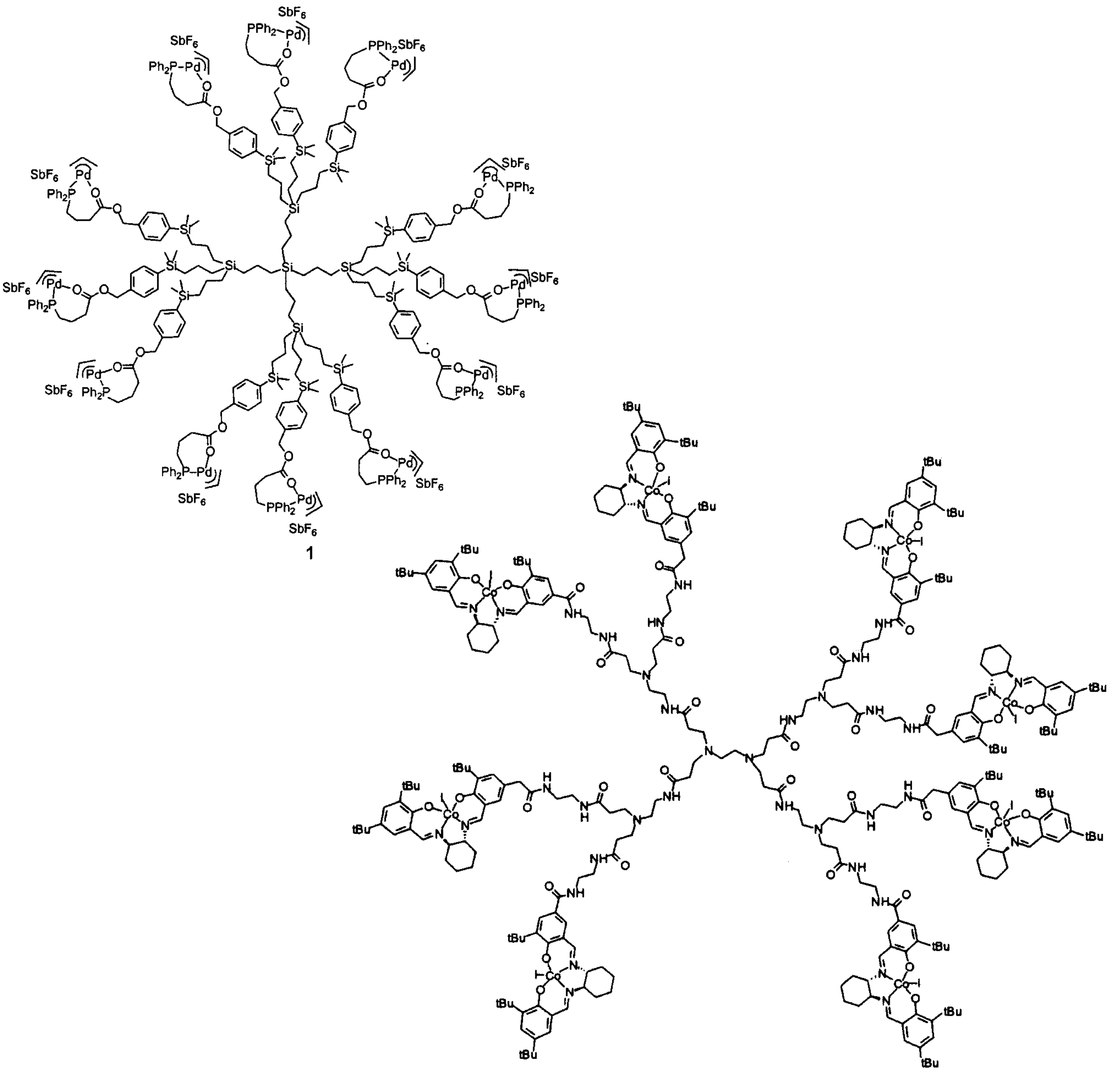

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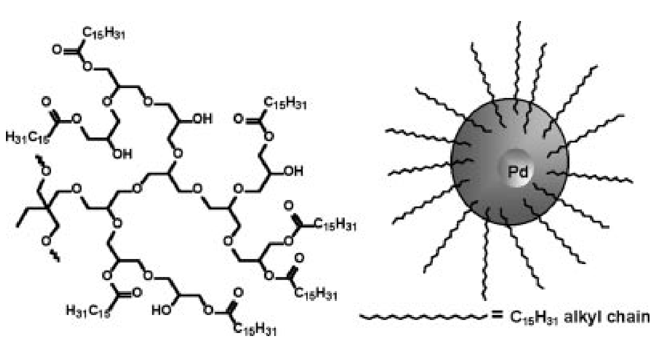
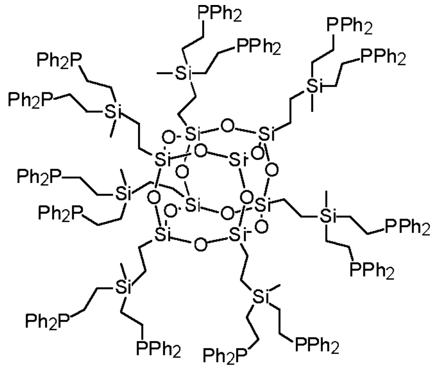


Figure 2. Stabilisation of metal clusters by soluble supports.

filtration membranes is greatly influenced by the reaction conditions, such as temperature and solvent, and should be taken into account.

As for the membrane material itself, basically two types of membranes are frequently used: organic (polymer) membranes and inorganic (ceramic) membranes. The most widely applied commercial organic membrane is the MPF series of Koch Int., which are basically silicon-derived membranes in the MWCO range of 400–700 Da (Figure 4, **a**).[13] Due to their polymeric nature, the MWCO is highly dependent on the solvent used.[14] Another common membrane is the STARMEM series from MET (polyimide-based), with MWCOs in the range of 200–400 Da.[15] Ceramic membranes are much less common, and published



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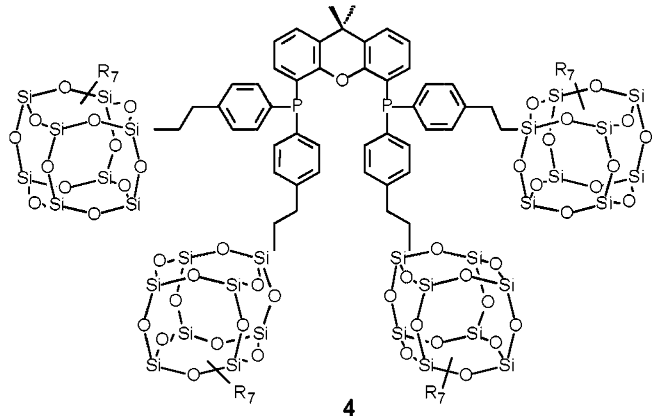

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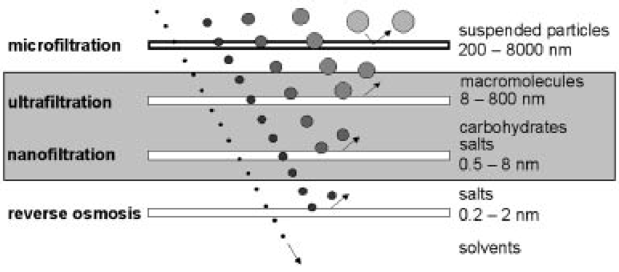


Figure 3. Classification of filtration types.

results are only available for the tubular microporous silica membranes provided by ECN (Petten, The Netherlands).[16] These membranes have pore sizes between 0.5 and 0.8 nm and consist of several support layers of α- and γ- alumina, while the selective top layer at the outer wall of the tube is made of amorphous silica (Figure 4, **b**).[17]

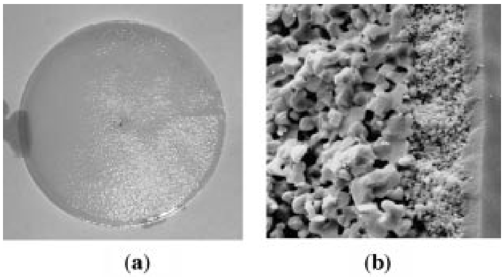


Figure 4. Organic (a) and ceramic (b) membranes.

Reactors for Continuous Homogeneous Catalysis

Decoupling of the residence times of the catalyst and the reactants by means of membrane technology provides the opportunity to control homogeneously catalysed processes by means of reaction engineering – an essential advantage largely restricted to heterogeneous catalysis to date. This is particularly desirable in the case of possible consecutive reactions, which can result in large amounts of undesired by-products. Such control of homogeneous catalysis would represent the break of a paradigm in fine chemicals production, where generally only batch processes are used nowadays.

For initial investigation of catalyst performance, a simple laboratory-scale dead-end ultrafiltration unit (Figure 5, a) with a commercially available flat membrane can be employed. Dead-end filtration means that the product flow is perpendicular to the surface of the membrane. This eventually is a disadvantage because concentration polarisation can occur. The dead-end filtration setup in Figure 5 was developed by us for applications at high pressures and used for the hydrovinylation of styrene (vide infra). In this reaction, ethylene was used as a solution in dichloromethane, prepared separately in a stainless-steel tank, while the second substrate (styrene), dissolved in dichloromethane, was pumped with a second HPLC pump into the reactor. The catalyst solution, on the other hand, was introduced via an HPLC injection valve. Products and unreacted compounds cross the membrane and leave the reactor on top.[18]

In a cross-flow filtration setup (Figure 5, **b**), the product flow is parallel to the membrane surface, which requires a separation unit next to the actual reactor and an additional pump to provide a rapid circulation across the membrane. A special type of cross-flow reactor has been developed in our laboratories to handle continuous gas/liquid reactions. The challenge in the reactor design was the combination of efficient gas/liquid mixing, liquid level control in the reactor, turbulent flow across the membrane and efficient gas/liquid separation to avoid gas contacting the membrane, which would lead to a shunt of gas. Ceramic membrane tubes (HITK) with higher temperature stability and much better solvent resistance are used.

Selected Examples of Continuous Homogeneous Catalysis

1) Polymer-Enlarged Homogeneous Catalysts

The use of homogeneous catalysts bound to soluble polymeric supports[19] in continuously operating membrane reactors was pioneered by Wandrey and co-workers as well as Kragl and Dreisbach. The catalyst consists of a soluble polymeric support – a copolymer of 2-hydroxyethyl methacrylate and octadecyl methacrylate – combined with α,α-

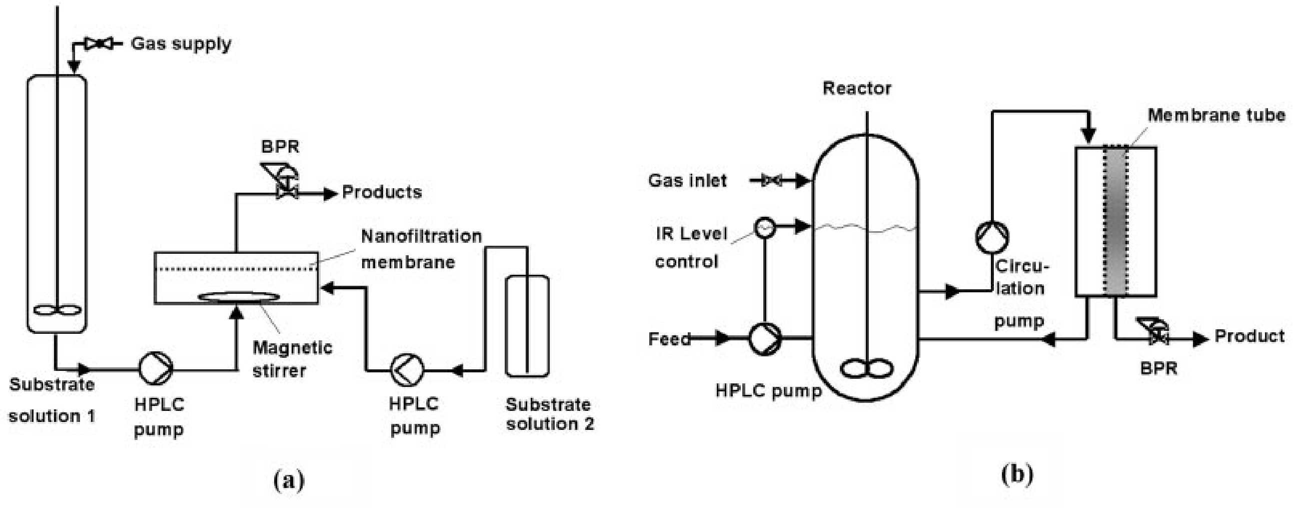
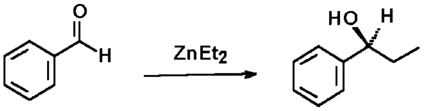


Figure 5. A dead-end filtration reactor (**a**) and cross-flow filtration reactor (**b**) described by Vogt et al.[18]

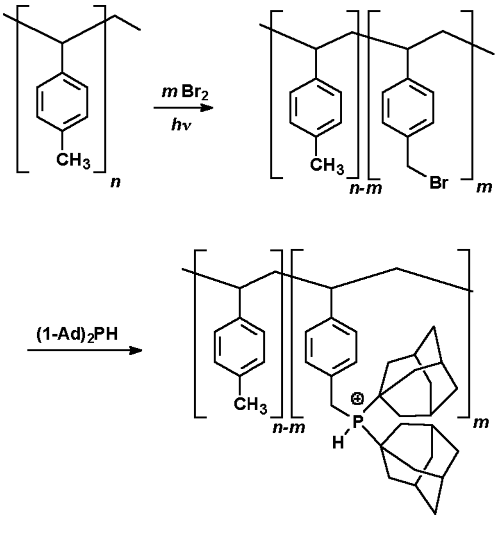
diphenyl-L-prolinol as the active organocatalytic site (see C), which was used for the enantioselective addition of diethylzinc to benzaldehyde [Equation (1)].



(1)

The reaction was carried out in a continuous way by using an ultrafiltration membrane (Hoechst-Nadir-UF-PA20). A retention of the polymeric support of more than 99.8% was observed. Even though the *ee* achieved with the molecular-weight-enlarged catalyst was lower (80%) than with the non-supported analogue (97%) the proof of principle to run the reaction in a continuous way was shown. Interestingly, the total turnover number (tTON) of the chiral organocatalyst under continuous conditions could be raised by a factor of 10, to 500. After seven days, no deactivation of the catalyst could be observed.[20]

Plenio et al. have used a polymer-enlarged catalyst formed from (1-Ad)$_2$P-substituted poly(methylstyrene) (Scheme 1), a suitable palladium source {[PdCl$_2$(PhCN)$_2$], Pd(OAc)$_2$, or Pd(dba)$_2$} and a base (HN*i*Pr$_2$ or K$_3$PO$_4$).[21] This system was used to efficiently mediate carbon–carbon coupling reactions of the Suzuki, Sonagashira and Heck type for aryl bromides and aryl chlorides. Such catalysts were also studied in nanofiltration separation experiments. The linear 5000 Da polymer backbone [poly(*p*-methylstyrene)] is sufficiently large to be retained quantitatively by a PMDS nanofiltration membrane. The leaching of the catalyst into the product-containing permeate is very small (<0.05%). The catalyst was reused up to nine times by using the catalyst-containing retentate after filtration from the product. Further evidence for the recyclability of the catalyst was derived from the constant and high yields in the Sonogashira and Suzuki reactions and from the unchanged TOF. In the Heck reaction, the highly polar and aprotic solvents are detrimental to the integrity of the polymeric membranes. It is therefore impossible to draw conclusions on the suitability of using this catalyst in repeated Heck coupling reactions. A disadvantage of the system is the multistep synthesis of the polymer. The polymer is prepared by anionic polymerisation of *p*-methylstyrene and then treated with Br$_2$ to convert up to 18% of the CH$_3$ groups into CH$_2$Br. Subsequently, a phosphane group is loaded onto the polymer (Scheme 1) and the Pd catalyst is formed in situ. This multi-step synthesis makes such a polymer relatively expensive and therefore less suitable for industrial applications. Also, it should be noted that the catalyst was employed in a batch reaction and after completion of the reaction was recycled by nanofiltration. These experiments were not performed in a continuous manner.



Scheme 1. Preparation of a polymer-supported phosphonium salt.

2) Dendrimers as a Soluble Support

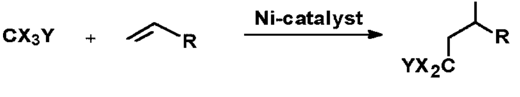
Dendrimers have attracted considerable attention since the pioneering work by Vögtle et al. on these systems.[22]

While (perfectly branched) dendrimers provide a well-defined structure, their syntheses are usually tedious and expensive and, correspondingly, commercial applications of dendrimers are scarce. Dendrimers differ in the position of the catalytic site(s). Surface-functionalised dendrimers lead to catalysts that are sufficiently large to be retained by membranes. However, detailed studies on the macromolecular structure of dendrimers have revealed that they do not always adopt the ideal spherical structures their drawings suggest – amphiphilic dendrimers, in particular, have structures that are far from spherical.[23]

In principle, dendritic catalysts can show the kinetic behaviour and thus the activity and selectivity of a conventional homogeneous catalyst. The transition metals on the outer sphere are directly available for the substrate, which allows for reaction rates that are comparable with homogeneous systems. On the other hand, these periphery-functionalised systems contain multiple reaction sites and ligands, which results in extremely high local catalyst and ligand concentrations. For example, a second-generation carbosilane dendrimer functionalised with 36 terminal phosphanes results, theoretically, in local concentrations of 8 M of ligand and 4 M of catalyst. In reactions where excess ligand is required to stabilize the catalyst this local-concentration effect can indeed result in stable systems. However, several deactivation processes can operate by a bimetallic mechanism. Examples of these are ruthenium-catalysed metathesis,[24] palladium-catalysed reductive coupling of benzene and chlorobenzene[25] and reactions that involve radicals.[26]

A difficult problem in the use of dendrimers is leaching. Two forms of leaching are known: leaching of the dendritic catalyst through the membrane and metal leaching from the dendrimer into the solution and further leaching of the active metal through the membrane, usually in the form of small homogenized complexes. For industrial applications, the overall retention of the dendritic catalyst must be extremely good to keep a high activity in a continuous reactor for longer reaction times. The required retention obviously depends on the application, since processes for the bulk industry generally require more efficient catalyst recycling (higher TONs) than those for fine chemicals. Generally, a retention of at least 99.99% is required to obtain a catalyst system that remains in the reactor for a prolonged period of time, even for fine chemical production processes.

The groups of van Koten and van Leeuwen have reported G_0 and G_1 carbosilane dendrimers functionalised with up to 12 pincer NCN-nickel(II) groups (**5**).[27] These dendrimers were then applied as catalysts for the Kharasch addition of CX_3Y to alkenes [Equation (2)]. While being used in a continuous membrane reactor the compound showed decomposition, which has been ascribed to hydrolysis of the Si–O bond of the linker between the ligand and the carbosilane backbone. In a further modification of the system, the NCN ligands were attached directly to the carbosilane backbone of **5**.



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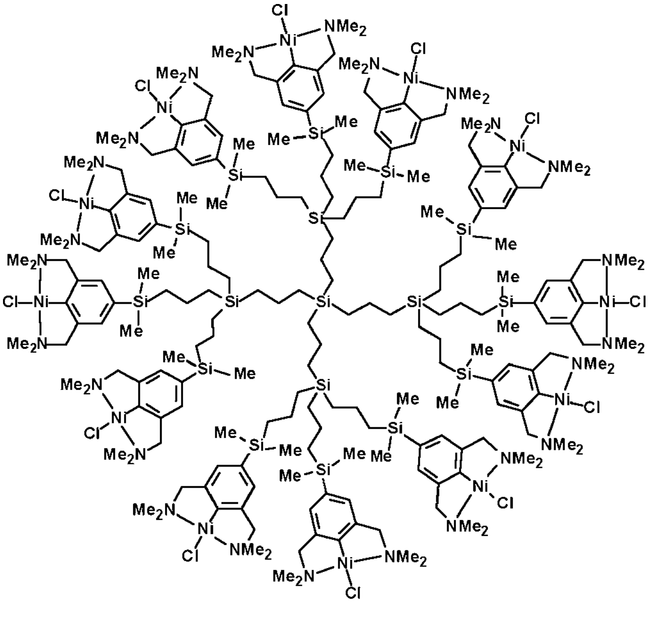

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While retentions of the molecular-weight-enlarged systems of up to 99.75% were observed, the formation of insoluble purple species occurred under continuous flow conditions. Addition of Bu_4NBr prevented catalyst precipitation but a fast decrease in conversion was detected: after 45 cycles, the activity of the catalyst dropped to almost zero, most likely due to the formation of inactive Ni^{III} species (Figure 6). Furthermore, the carbosilane support plays a pivotal role in the accessibility of the active sites: surface congestion can lead to the formation of mixed-valence Ni^{II}/Ni^{III} complexes on the dendrimer periphery that compete for reactions with substrate radicals.

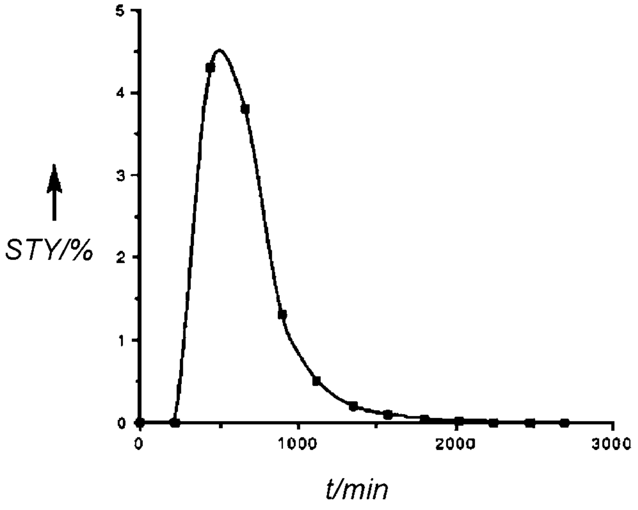
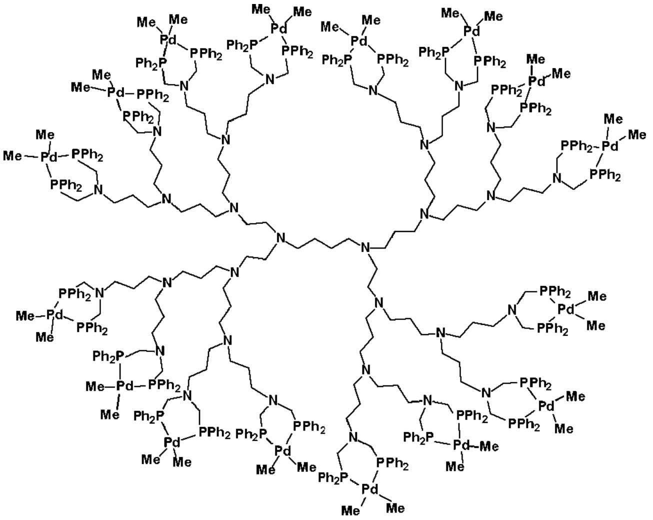


Figure 6. A continuous Kharasch addition (reprinted with permission from ref.[27d] Copyright 2000 American Chemical Society.

Commercially available fourth- and fifth-generation DAB dendrimers have been functionalised with diphenylphosphanyl groups at the periphery by Reetz and Kragl and their respective co-workers.



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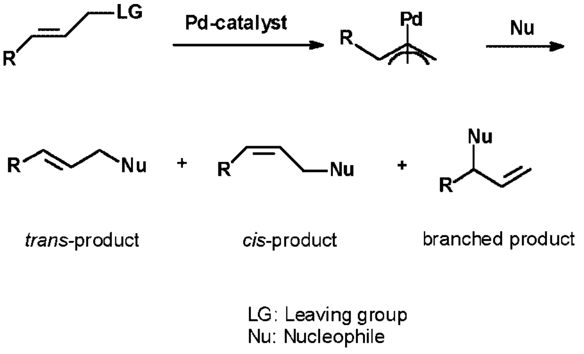
The corresponding Pd complexes (**6**) were used for the Pd-catalysed allylic amination to yield *N*-[3-phenyl-2-propenyl]morpholine in a continuously operating dead-end filtration [Equation (3)].

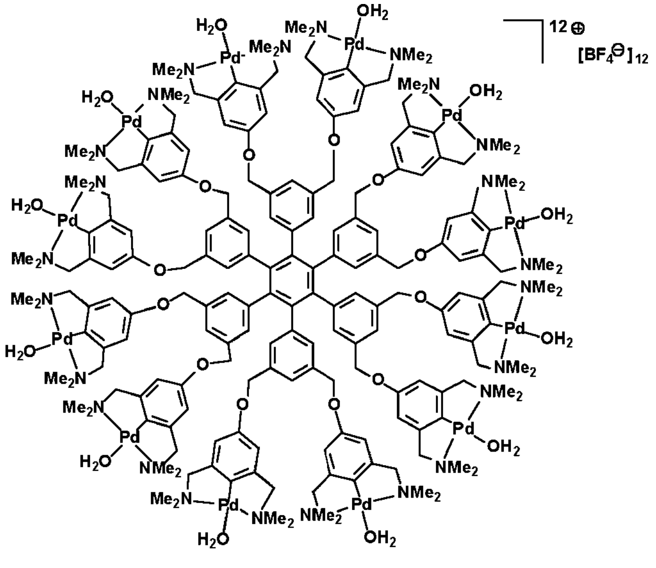


(3)

A conversion of 100% was obtained in the beginning but a 20% decrease was observed after 100 h, as well as palladium leaching of between 0.07 and 0.14% per residence time. The soluble support, on the other hand, was completely retained in the membrane reactor.[28] Several studies on the use of these types of palladium-functionalised dendrimers for allylic substitution reactions have all shown significant loss of activity during the reaction. In all cases, the leaching of the dendrimer through the membrane was much smaller than the observed loss in activity. These results suggest that the catalyst decomposes during the course of the reaction and leaches through the membrane as small soluble metal clusters.[28,29] The leaching gives rise to two problems, loss of expensive catalyst or active metal and contamination of the product with this metal. In some cases it can be economically acceptable to compensate for the loss in activity by addition of the active metal to the feed solution. However, the contamination of the product should be limited to an acceptable amount.

Van Koten et al. and ourselves have reported on shape-persistent multi-NCN-palladium and/or platinum complexes exhibiting one-, two- and three-dimensional geometries. These were subjected to nanofiltration experiments to investigate the influence of rigidity and geometry on the retention of these molecules by MPF membranes. A clear relationship between the dimensions calculated by molecular modelling and the retention rates of the synthesised complexes was observed. Furthermore, similar sized complexes with zero- and first-generation flexible dendrimers were compared and it was found that a high degree of rigidity in the backbone of the macromolecular complexes indeed leads to more efficient retention by the membrane.

In a later study, a very shape-persistent dendrimer, the dodecakis[NCN-Pd^{II}-aqua]$(BF_4)_{12}$ complex **7** was synthesised and employed as a Lewis acid catalyst in the double Michael addition reaction between methyl vinyl ketone and ethyl α-cyanoacetate. The efficiency of the reaction was significantly enhanced, as the TON was increased by a factor of more than 40. After prolonged reaction times (>25 h) a small decrease in activity was observed, which can be completely ascribed to slow leaching of the catalyst. The retention of the reaction was 99.5%.[30]



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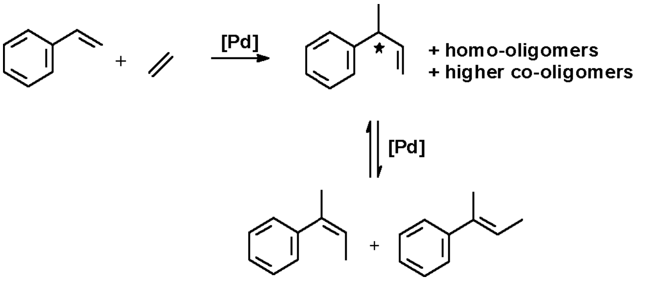
This shows that very shape-persistent dendrimers can be used in continuous homogeneous catalytic reactions. However, even under these optimised circumstances, the retention is still lower than desired (99.99%). Recycling of the catalyst by microporous filtration showed no significant loss of activity or selectivity during five consecutive runs. This is promising for use in a continuous process, but more experiments have still to be performed.

The above-mentioned examples describe catalytic reactions in which only liquid components participate in the chemical transformation. The situation becomes more complicated when one of the reactants is a gas. Typical reactors and membranes are not designed for use with certain organic solvents, high temperature and/or high pressure, and only a few examples of continuous catalytic gas/liquid reactions have been reported in the literature up to now. Therefore, C–H and C–C linkage reactions involving the consumption of one or more gases are usually performed in a batch-wise process with subsequent filtration through a membrane in order to separate the molecular-weight-enlarged catalyst from the product. In case of hydrogenation reactions, the saturation of the solvent with hydrogen is in most cases sufficient to run the reaction in a continuous way. However, the design of suitable reactors for applications under more drastic reaction conditions (e.g. elevated temperatures and pressures) is less obvious.

A pressure membrane reactor has been developed by us for the co-dimerisation of ethylene and styrene [the hydrovinylation reaction, Equation (4)] under continuous reaction conditions.



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Molecular-weight-enlarged carbosilane dendrimers (such as **1**), functionalised with four or 12 P–O ligands on the periphery have been used as catalysts in this reaction. Interestingly, the reaction runs almost without any isomerisation of the products to a mixture of the (*E*)- and (*Z*)-isomers of 2-phenyl-2-butenes or formation of any side products, which are usually observed at high conversions. The maximum productivity was reached after an induction period of about nine hours, followed by a steady decrease of activity (Figure 7). However, catalyst deactivation was also observed (precipitation of palladium on the membrane).[18]

The core-functionalised dendritic dppf analogue **8** (dppf = diphenylphosphanylferrocene) was synthesised by van Leeuwen et al. While the corresponding rhodium complex could only be applied in a batch-wise hydroformylation reaction [the hydroformylation reaction is typically performed at elevated temperature (40–80 °C) as well as under a syngas pressure of 10–20 bar], the hydrogenation of dimethyl itaconate could be performed under continuous reaction conditions. Interestingly, no deactivation of the catalyst occurred during the catalytic experiment, which has often been observed in continuous palladium-catalysed reactions. The drop in conversion (77% after 35 exchanged reactor volumes) could fully be explained by the retention of the dendritic system (99.8%).[31]

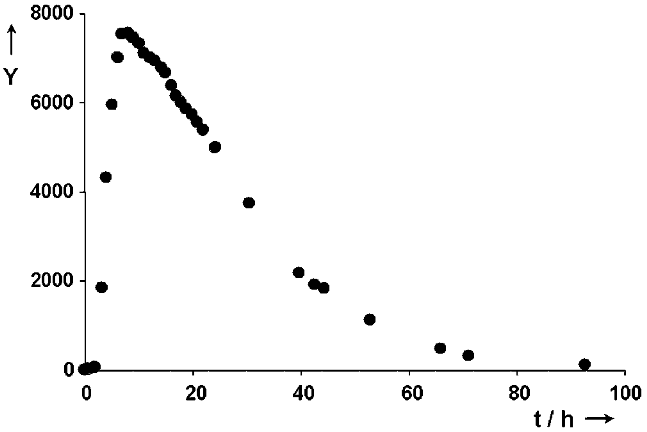
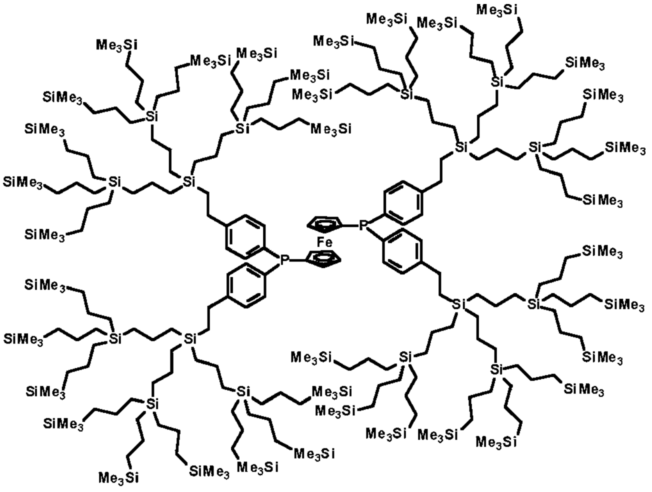


Figure 7. A continuous hydrovinylation experiment (reprinted with permission from ref.[18b] Copyright 2000 American Chemical Society.



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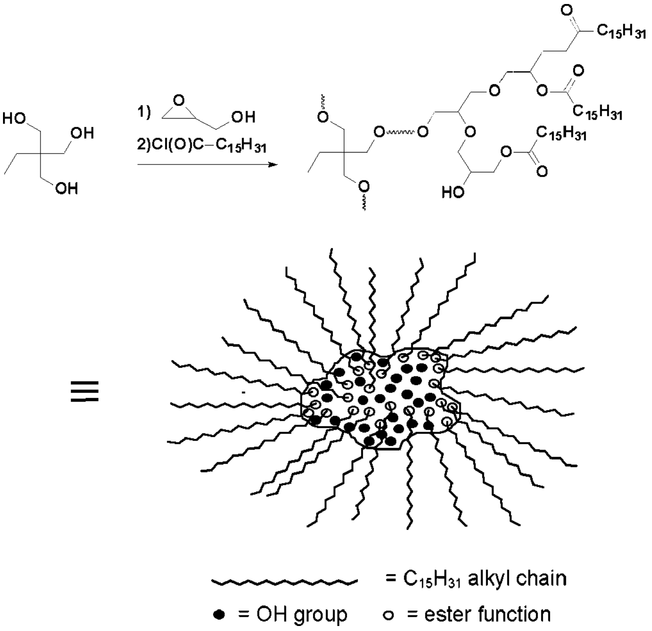
3) Nanocolloids: Metal Nanoclusters Stabilized in Dendrimers

Dendrimers can also be used as templates for the preparation of precise metal nanoclusters within their interior. Hydroxy-terminated poly(amido amine) dendrimers have been found to be particularly good for this purpose.[32] While high catalytic activity of metal clusters is well known, they tend to aggregate into larger and, therefore less-active, systems under catalytic conditions. Precise construction of nanocomposites in the cavities of dendrimers might lead to both cluster stability and full control over size and size distribution, while the dendrimer branches still allow substrate access to the catalytically active clusters. Additionally, dendrimers could enhance the solubility of the metal clusters, as they have good solubilities in a wide range of solvents. A water-soluble and stable G4-OH(Pd_{40}) dendrimer, for example, exhibits high activity for the hydrogenation of alkenes in water. It was reported to be sufficiently stable for recycling and reuse, although the actual data of such experiments were not provided.[32a] The use of a dendrimer gives a more reproducible and more robust backbone than the use of polymers, but the preparation of a dendrimer is infinitely more time consuming and expensive, while the sizes of the palladium particles are similar those which are stabilized by branched polyglycerols and polyamides.

4) Metal Nanoparticles Stabilized with Hyperbranched Polyglycerols and Polyamides

Catalytically active metal nanoparticles can also be confined by utilizing the structure of easily accessible, compartmented amphiphilic (statistically branched) hyperbranched polymers. Recently, a one-step synthesis allowing a convenient access to hyperbranched polyglycerols of controlled, narrow molecular weight distributions was found.[33] Partial esterification of the OH groups with long-chain fatty acids yields amphiphilic molecules (Scheme 2; $M_w/M_n < 1.7$), which can function as nanocapsules for the incorporation of individual hydrophilic dye molecules as guests.[34]



Scheme 2. Schematic representation of the preparation and structure of a hyperbranched amphiphilic polyglycerol.

Solubilisation of metal salts by such well-defined polymers and subsequent reduction (H_2, CO or thermally) can yield stable solutions of metal colloid/polymer hybrids, while the metal-particle sizes (ranging from 1 to ≥20 nm) increase with increasing polymer molecular weight.[35] A large portion of the individual metal particles appears to be confined in a single branched macromolecule. Such metal nanoparticle/hyperbranched polymer hybrid materials display a remarkable catalytic activity and stability in cyclohexene hydrogenation as a model reaction.[36] A total of 7×10^4 turnover over 30 h and well-behaved kinetics were observed at 1 atm hydrogen pressure. Further investigations have shown these materials to be stable in small-scale ultrafiltration experiments.

In order to achieve a better membrane performance, a loop filtration module was employed rather than the commonly used dead-end filtration cell (Figure 5, b). In this way, much more reliable and reproducible data, also with a view to possible applications, were obtained. The use of tubular membranes enables a facile scale-up and membrane surface enlargement.

With polyglycerols of different molecular weights (M_n = 2000–20000 g mol^{-1}) as a scaffold, functionalised polymers with varying degrees of substitution can be prepared. Apart from palmitoyl moieties, other lipophilic groups (e.g. bulky adamantoyl moieties or aromatic residues) and other linking units (e.g. ether instead of ester functions) were investigated. Thus, hyperbranched polymers of low polydispersity and controlled, variable hydrophilic-hydrophobic balance were produced.

The polymeric molecule environment of the metal particles can control the approach of substrates to the metal particles and the reactivity of the metal surface atoms. Hydrogenation reactions employing substrates differing in polarity and steric bulk serve as initial simple model reactions. For instance, cyclohexene has been hydrogenated to cyclohexane and the reaction was performed in a continuous membrane reactor with good retentions observed (R = 99.8%).[37] Eventually, C–C coupling reactions, such as Heck, Suzuki and Stille reactions, will be particularly intriguing. Such reactions are important for the preparation of fine chemicals, and are employed, for example, for the production of pharmaceuticals and other biologically active substances.

Hyperbranched poly(ethylene imine) amides have been prepared by amidation of different carboxylic acid amide derivatives.[34,36,38,39] These poly(ethylene imine) amides proved more suited for structural investigations. The hyperbranched polyamine core binds metal precursors and consequently solubilises them in apolar organic solvents much more effectively than the polyether-polyol scaffold of polyglycerol, as expected. Silver nitrate (insoluble in toluene in the absence of the polymers) was found to be well suited as a model compound for structural investigations. For poly(ethylene imine) amides, the concept of solubilisation of a metal salt in a polymeric inverted unimolecular micelle, and formation of a metal particle in the micelle upon reduction, indeed proved to be applicable. Also, by contrast to unmodified poly(ethylene imine), the amphiphilic derivatives are not washed out by water.

Heck reactions have been studied with amphiphilic polyglycerol-stabilized colloids. Reaction conditions were studied extensively with respect to appropriate combinations of colloid stabilisation, solvent, substrates, base and temperature. Pivaloyl-modified polyglycerols were found to stabilize palladium colloids in dimethylacetamide effectively. With 4-bromoacetophenone and butylacrylate as substrates, potassium carbonate was found to be particularly suited as a base. The reaction solutions were filtered and the filtrates were found to contain small amounts of palladium, as determined by ICP-AAS, and to be very active upon reuse for a further Heck reaction. This points towards smaller species than the original metal nanoparticles as the active species.

5) Continuous Homogeneous Catalysis in Supercritical Fluids

As an example of a continuous-flow approach to the separation of homogeneous catalysts, the use of supercritical fluids should be mentioned.[40] As a clear advantage, the catalyst always stays in its active state inside the reactor. Additionally, high throughputs can be obtained from relatively small-sized reactors. Webb and Cole-Hamilton have reported on the rhodium-catalysed hydroformylation of long-chain alkenes.[41] This process can be carried out as a continuous process using a supercritical fluid–ionic liquid biphasic system. The authors observed reaction rates that were comparable to those obtained in the commercially performed rhodium-catalysed hydroformylation of propene. Furthermore, very low rhodium leaching (0.012 ppm in the recovered product) was observed. The catalyst was formed in situ from [3-methyl-1-propylimidazolium][$Ph_2PC_6H_4SO_3$] and [$Rh(acac)(CO)_2$] in [3-methyl-1-octylimidazolium][bistrifluoromethylsulfonyl amide], and supercritical CO_2 was used as the transport vector. The linear-to-branched ratio of the products could be improved from 3:1 to 40:1 by using a ligand based on the Xantphos backbone.[42] The major drawback of the system is that the overall pressure must be very high (200 bar) in order to extract the aldehyde from the ionic liquid in which it is soluble. However, the pressure can be reduced to 125 bar by omitting the ionic liquid and operating in such a way that the reaction product(s) is the solvent.[41b]

6) Continuous Homogeneous Catalysis Applying Zeolite Membranes

Molecular-weight enlargement of a homogeneous catalyst is not the only way to achieve a significant difference in molecular size of the catalyst, the reactants and products. Zeolite membranes, for example, have been developed by Turlan et al., with pore sizes in the 0.3 to 0.8 nm range.[43] For this work, silicalite was chosen with pores of 0.55 nm, well below the size of the homogeneous catalyst, but still able to permeate certain solvents and products.

The membranes were grown on the inner side of porous stainless-steel tubular supports.[44] Only separation experiments were carried out with model mixtures containing a Pd complex plus solvent and a possible reaction product. The reaction studied was the Heck reaction of 4-bromobenzonitrile with methyl acrylate. The chosen catalyst was $[Pd(\mu\text{-}Cl)(PPh_3)_2]_2(BF_4)_2$. This is a well-known Heck catalyst with a molecular diameter of 1.22 nm, which is considerably larger than the zeolite pores. The permeation rates were extremely low when DMA was used as a solvent, which suggests strong adsorption of the DMA in the zeolite pores, thus preventing permeation of catalyst and product. With the use of dichloromethane as solvent, complete catalyst retention was observed. Also, the permeation fluxes across the membrane were high. This shows the possibility to retain homogeneous catalysts of the right size behind very good membranes, without the need to molecularly enlarge their size. However, in order to truly evaluate these membranes, they have to be used in real continuous catalytic reactions and not to separate approximated reaction mixtures.

Conclusions

There is definitely not only one option for continuous homogeneous catalysis. Although many approaches exist to immobilize homogeneous catalysts, appropriate polymeric supports are not as readily available commercially. Furthermore, multi-step synthetic procedures are typically necessary to prepare the required ligand and the corresponding catalyst. Catalyst degradation and ligand oxidation have to be taken into account, especially when continuous processes are applied. Dendrimers have the advantage of high reproducibility and can be combined with a large variety of ligands and metals, which makes their catalytic scope very versatile. Also, they can be prepared with a very rigid backbone. In combination with a suitable filtration unit their retentions can be sufficiently high to be used in a broad range of utilisations. Similar to soluble polymeric supports, however, catalyst stability and their multistep synthesis is a major drawback and makes them relatively expensive and therefore less suitable for industrial applications. This also holds for the use of dendrimers as stabilizing agents for colloids.

Metal nanoparticles stabilized by polymers of different sizes and shapes can be more easily synthesised than dendrimers. They have proven their usefulness in hydrogenations and several types of C–C coupling reactions. The retentions are close to the desired amount for industrial purposes, so their future looks promising.

In general, both polymeric and ceramic membranes are used in these continuous processes and high retentions can be achieved with both options. The drawback of polymeric membranes is their solvent-sensitivity and their limited temperature resistance. Ceramic membranes can tolerate a wide range of solvents and higher temperatures, and the zeolite membranes are of special interest. Their very small pore diameters makes it possible to directly use some types of homogeneous catalyst without molecular-weight enlargement. Of course, such a small diameter also limits the possibilities for solvents and products, since they have to be able to penetrate the membrane.

The design of new membranes and reactors that are compatible with homogeneous reaction conditions is required to develop the fascinating area of continuous homogeneous catalysis to its full potential.

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