Dendrimers as Support for Recoverable Catalysts and Reagents

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Received March 12, 2002

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I. Introduction

The development of well-defined catalysts that enable rapid and selective chemical transformations and can be separated completely from the product is still a paramount challenge.[1] The recent success of homogeneous catalysis is reflected in the number of applications that is known today both in the laboratory and in the industrial practice, but so far there is not a single solution to the catalyst−product separation problem. In fact, all "unit operations" for separation, including distillation, liquid−liquid separation or extraction, stripping, catalyst destruction, and crystallization, are being applied in industry. While several methods are being applied commercially, the search for new approaches continues. These new methodologies include fluorous phase catalysis,[2] the use of ionic liquids,[3] the use of supercritical fluids,[4] and supported aqueous phase catalysis.[5] A widely studied approach to facilitate catalyst−product separation is the attachment of homogeneous catalysts to insoluble organic, inorganic, or hybrid supports.[6] Inorganic materials such as silica are particularly suited as heterogeneous catalyst support because of their high physical strength and chemical inertness. The main problems related to this approach are the nonuniform and partly unknown structures of the heterogenized catalysts, mass transport limitations due to slow diffusion, the generally lower activity compared to the homogeneous analogue, and metal leaching. Metal leaching can be suppressed by using properly chosen ligands

10.1021/cr0103874 CCC: $39.75
Published on Web 09/19/2002

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that coordinate strongly to the metal. The use of soluble supports leads to recyclable catalyst systems that do not suffer from mass transfer limitations, and therefore they should lead to systems with activities similar to their monomeric analogues. In particular, dendrimers as soluble support have recently attracted a lot of attention, since these well-defined macromolecular structures enable the construction of precisely controlled catalyst structures. The number of catalysts attached to the support as well as their location can be regulated, which can be of crucial importance for the catalytic performance of the system. Moreover, the globular shapes of the higher generations of dendrimers are particulary suited for membrane filtration. Dendrimer chemistry has been extremely popular in the past decades, and several potential applications of dendrimers, including catalysis,[7] have been explored and are well-documented in various reviews.[8] In this review, we will specifically focus on catalysts recovery using functionalized dendrimers and the use of dendrimers as supports for reagents, and for contributions on dendritic catalysis that do not include recycling studies we refer to other reviews.[7]

In 1994, Tomalia and Dvornic discussed the promising outlook of surface-functionalized dendrimer catalysts.[9] Dendritic catalysts have often been proposed to fill the gap between homogeneous and heterogeneous catalysts. However, keeping in mind that heterogeneous systems generally contain at least 10^{12} active sites per conglomerated particle,[10] it is fair to state that the class of dendritic catalysts containing at most 1000 active sites is closer to the monomeric homogeneous systems. A better formulation is that functionalized dendrimers potentially can combine the advantages of both homogeneous and heterogeneous catalytic systems. In principle, dendritic catalysts can show the kinetic behavior and thus the activity and selectivity of a conventional homogeneous catalyst, while they can be recovered from the reaction medium easily. Catalysts supported on highly cross-linked polymer beads generally suffer

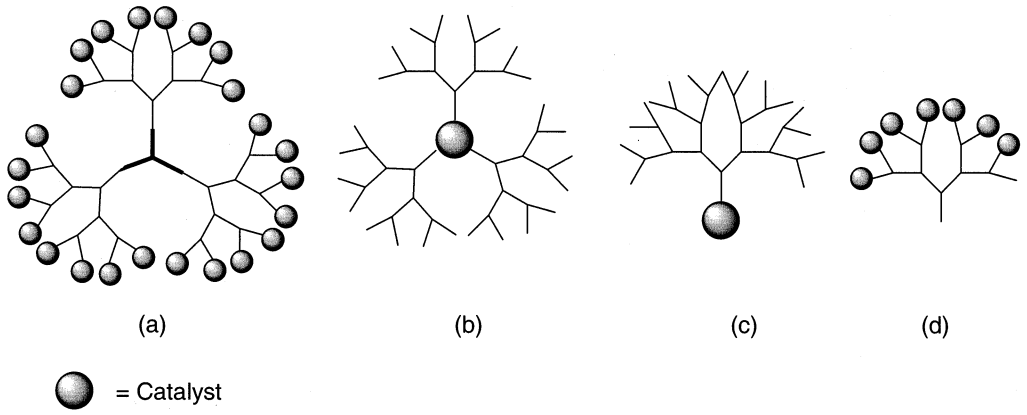


Figure 1. Different dendritic architectures: catalyst located at the periphery (a), core (b), focal point of a wedge (c), and periphery of a wedge (d).

from diminished activity compared to the homogeneous analogues, which is due to a reduced accessibility.[11] Organic polymers show solvent-dependent swelling properties that can strongly influence the catalytic performance. Other advantages of dendritic catalysis include the ability to fine-tune the catalytic centers by ligand design and the ability to perform mechanistic studies on these uniformly distributed catalytic sites attached to the support.

The catalytic performance, i.e., the activity, selectivity, stability, and recyclability of the system, depends on the dendritic architecture that is used and therefore one should distinguish periphery-functionalized (of a dendrimer or a dendritic wedge), core-functionalized and focal point-functionalized (on a dendritic wedge) systems (see Figure 1).

Periphery-functionalized dendrimers have their catalysts located at the surface of the dendrimer support, and these active sites are therefore directly available to the substrate, which is in contrast to core-functionalized systems in which the substrate enters the dendrimer prior to reaction. The high accessibility allows reaction rates that are comparable with homogeneous systems. On the other hand, the periphery-functionalized systems contain multiple reaction sites, which results in extremely high local catalyst concentrations. This can lead to cooperative effects in, for example, reactions that proceed via a bimetallic mechanism.[12] On the other hand, several deactivation mechanisms operate via a bimetallic mechanism, i.e., ruthenium-catalyzed metathesis,[13] palladium-catalyzed reductive coupling of benzene and chlorobenzene,[14] and reactions involving radicals.[15] These deactivation pathways will be invigorated in periphery-functionalized systems.

In core (and focal point)-functionalized dendrimers the catalyst could especially benefit from the site isolation created by the environment of the dendritic structure. Site isolation effects in dendrimers can be beneficial for other functionalities, and general reviews on this topic have recently appeared.[16] For reactions that are deactivated by excess ligand or in cases that a bimetallic deactivation mechanism is operative, core-functionalized systems can specifically prevent such deactivation pathways. Core-functionalized dendritic catalysts may benefit from the local environment (polarity) created by the dendrimer which differs from the bulk solution.

Another significant difference between core and periphery-functionalized dendrimers is the molecular weight per catalytic site. Much higher costs will be involved in the application of core-functionalized systems, and possible applications can also be limited by the solubility of the system (To dissolve 1 mmol of catalyst/L, 20 g L^{-1} is required (MW 20 000, 1 active site) compared to 1 g L^{-1} (MW 20 000, 20 active sites)). On the other hand, for core-functionalized systems the solubility of the dendritic catalyst can be tuned by changing the end groups.

Dendritic catalysts can be recycled using similar techniques as applied for their monomeric analogues such as precipitation, two-phase catalysis, and immobilization on insoluble supports. In addition, the large size and the globular structure of the dendrimer, compared to the substrates and the products, can be utilized to facilitate catalyst−product separation by means of nanofiltration. Nanofiltration can be performed batchwise and in a continuous-flow membrane reactor (CFMR). The latter has significant advantages; the conditions such as reactant concentrations and reactant residence time can be controlled accurately. These advantages are especially important in reactions in which the product can further react with the catalytically active center to form side products.

Membrane reactors have been investigated since the 1970s.[17] Although membranes can have several functions in a reactor, the most obvious application is the separation of reaction components. Initially, the focus has been mainly on polymeric membranes applied in enzymatic reactions and ultrafiltration of enzymes is commercially applied on large scale for the synthesis of fine chemicals (for example L-methionine).[18] Membrane materials have been improved significantly ever since, and nowadays nanofiltration membranes suitable to retain relatively small compounds are commercially available (e.g., mass cutoff 400 Da).[19] Two forms of leaching have to be considered using dendritic transition metal catalysts in membrane reactors: depletion of the dendritic catalyst through the membrane and metal leaching from the dendrimer (and further leaching through the membrane). For practical applications,

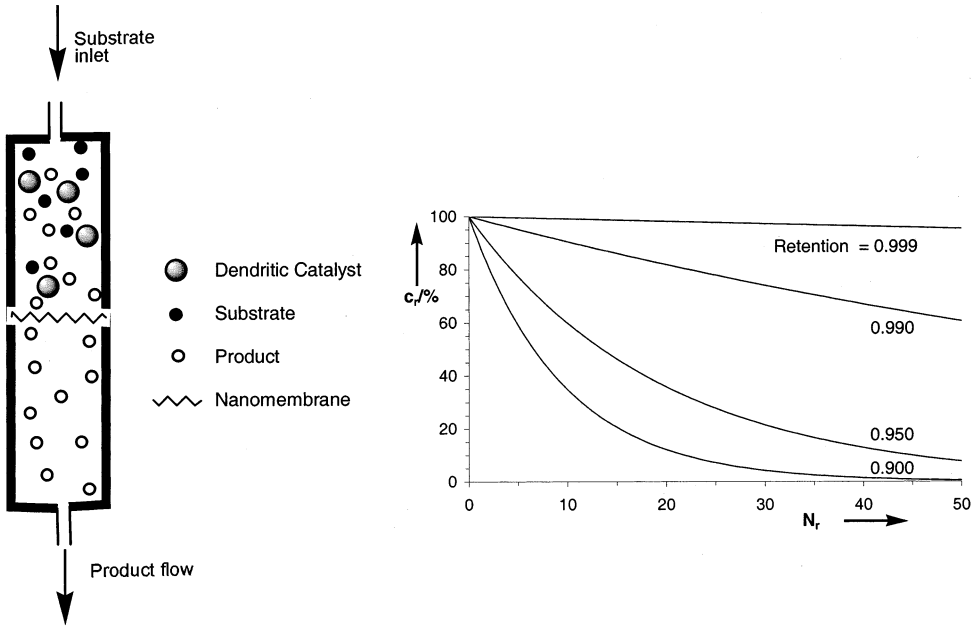
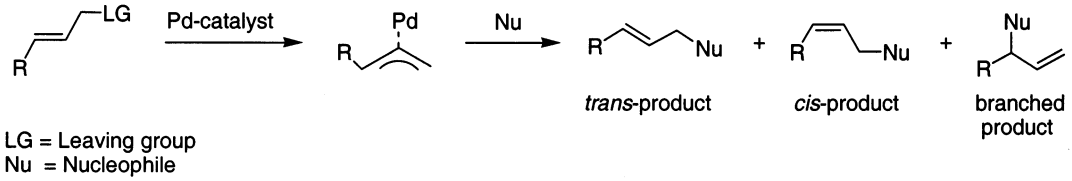


Figure 2. Schematic presentation of a membrane reactor (left) and theoretical relative concentrations (C_r) of the dendritic species versus the substrate flow (in residence times N_r) calculated for various retention factors.

Scheme 1



the overall retention of the (dendritic) catalyst must be extremely high to keep a high activity in a CFMR for long reaction times. (The required retention obviously depends on the application; processes for the bulk industry generally require more efficient catalyst recycling (higher TON) than those for high value added fine chemicals). In Figure 2 the theoretical activities of dendritic catalysts are given using different retention factors. If a dendritic catalyst would have a retention of 0.95, only 25% of the catalyst remains in the reactor after the reactor has been flushed with 30 times its volume. To obtain a catalyst system that remains in the reactor over a prolonged period of time a retention of at least 0.999 is required.

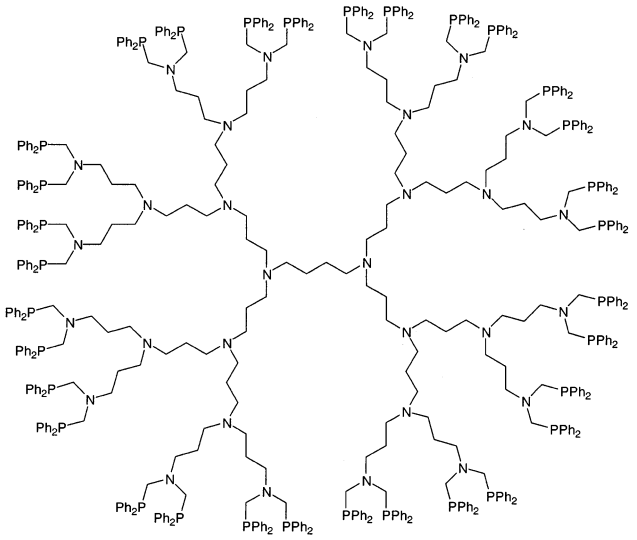
II. Catalyst Recycling Using Nanofiltration in a Continuous-Flow Membrane Reactor

Kragl pioneered the use of dendritic catalysts in continuous processes using membranes for the separation. Initially, he used soluble polymeric catalysts in a CFMR for the enantioselective addition of Et_2-Zn to benzaldehyde.[20] The ligand, α,α-diphenyl-L-prolinol, was coupled to a copolymer prepared from 2-hydroxyethyl methacrylate and octadecyl methacrylate (molecular mass 96 000 g mol^{-1}). The polymer was retained almost completely (>0.998) upon using a polyaramide ultrafiltration membrane (Hoechst Nadir UF PA20). The enantioselectivity obtained with the polymer-supported catalyst was lower than the monomeric ligand (80% ee versus 97%). The activity of the catalyst, however, was similar to the monomeric catalyst, which is in contrast to systems in which the ligand was coupled to insoluble support (reduction to 20% of activity). Importantly, the turnover number obtained with the polymer-supported catalyst applied in this reactor setup was optimized by changing the operating conditions.

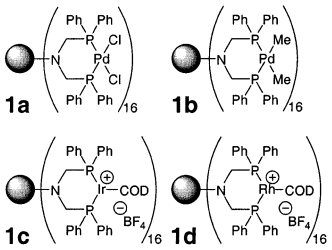
1. Allylic Substitution Using Dendritic Catalysts in a CFMR

The palladium catalyzed allylic substitution reaction has been extensively studied during the past decades and provides an important tool for the formation of carbon−carbon and carbon-heteroatomic bonds.[21] The key intermediate is an (η^3-allyl)Pd(II) species, formed by oxidative addition of the unsaturated substrate, which after attack of the nucleophile yields the substituted product (Scheme 1). To date several nucleophiles have been used, mostly resulting in formation of carbon−carbon bonds and carbon−nitrogen bonds. The majority of the studies have been focused on the enantioselectivity and regioselectivity of the reaction. More recently, the recycling of this type of palladium catalyst received some attention.[22]

Commercially available DAB-dendrimers were equipped with diphenylphosphine groups at the periphery (**1**) by Reetz et al. via a double phosphination of the amines with diphenylphosphine and formaldehyde.[23] Transition metal complexes **1a** to **1e** have been prepared in which the dendrimer-*N*-(CH_2-PPh_2)$_2$ groups act as bidentate ligands.

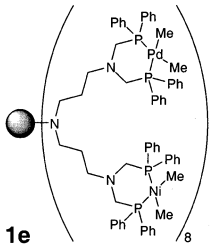


1



1a 1b

1c 1d



1e

Brinkmann et al. reported the use of these phosphine-based dendritic catalysts for allylic substitution reactions in a continuous membrane reactor.[24] Prior to catalysis retentions up to 0.999 were measured for G3 dendrimer **1b** (molecular mass of 10 212 g mol^{-1}). Although the dendrimer was retained in the reactor, some palladium leaching was observed. Metal−ligand dissociation results in low molecular weight Pd species that will be washed out of the reactor. During the reaction, leaching was compensated by addition of allyl palladium chloride to the feed solution. In this way, **1b** was applied in palladium-catalyzed allylic substitution and the CFMR could be operated for over 60 residence times with a conversion of up to 12%, but the product was obviously contaminated with palladium. Better results were obtained using in situ prepared Pd complexes of a G4 dendrimer (calculated molecular mass 20 564 g mol^{-1} for 100% palladium loading of the 32 diphosphines). After 100 residence times, the conversion had decreased from 100% to ~75% (Figure 3).

Only very little palladium leaching was observed during this experiment (0.14% per residence time), which could only partly explain the decrease in conversion. The formation of inactive $PdCl_2$ complexes was proposed to account for the additional drop in

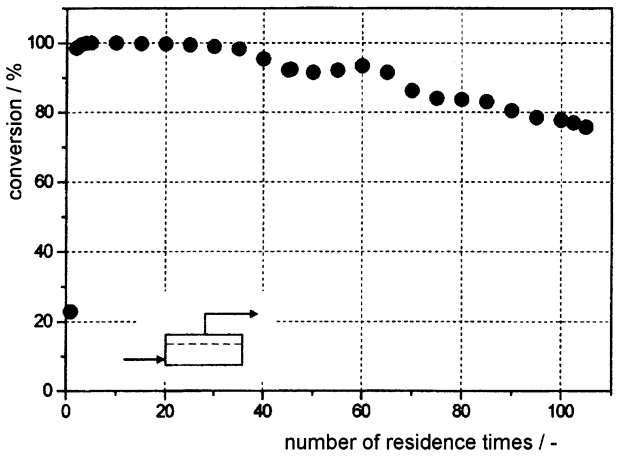
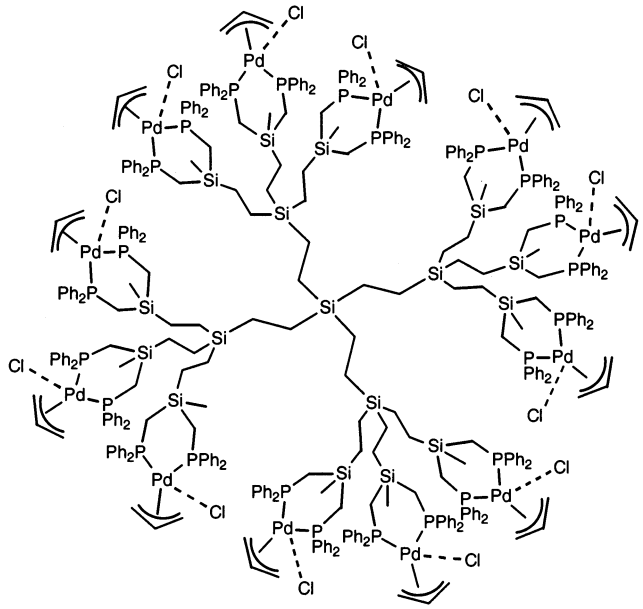


Figure 3. Allylic substitution in a CFMR with **1b** as the catalyst. (Reprinted with permission from ref 24. Copyright 1999 Academic Press).

activity. The conditions were significantly altered compared to the previous experiment (different reactor material and 10-fold increase in catalyst concentration). A solid conclusion about the effect of the dendritic catalyst used requires more experiments.

De Groot et al. used Pd(allyl) complexes of different generations phosphine functionalized carbosilane dendrimers (4, 8, 24, and 36 phosphine endgroups) as catalysts in the allylic alkylation reaction of allyl trifluoroacetate with sodium diethyl 2-methylmalonate.[25a]



2

Allyl trifluoroacetate was used as a substrate in a CFMR since this leads to the formation of soluble sodium trifluoroacetate as side product. In a batch process, this substrate was converted very rapidly by all the dendritic catalysts and only small differences in reaction rates were observed for the different generations. Using a substrate-to-Pd ratio of 2000 the yield after 5 min were 49, 45, 47, and 55% using dendrimers with 4, 8, 24, and 36 phosphine ligands,

respectively. This showed that all active sites located at the periphery of the dendrimer support act as independent catalysts. The palladium catalyst based on the dendrimer with 24 phosphine endgroups (**2**) was used in a CFMR. For the continuous process a solution of allyl trifluoroacetate and sodium diethyl 2-methylmalonate in THF (including *n*-decane as an internal standard) was pumped through the reactor.

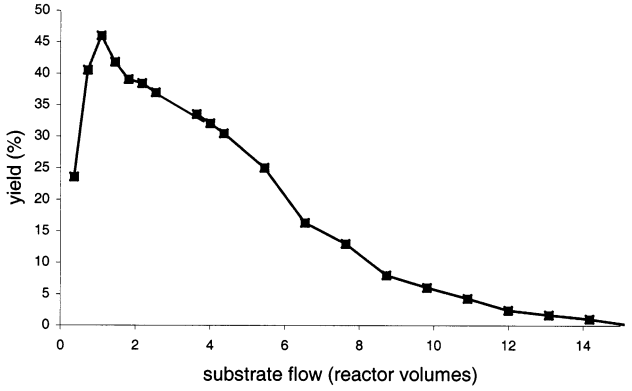
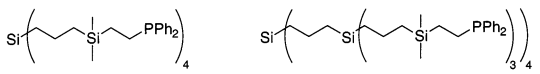


Figure 4. Application of dendritic ligand **2** in the continuous allylic alkylation of allyl trifluoroacetate and sodium diethyl 2-methylmalonate in a membrane reactor (Koch MPF-60 NF membrane, molecular mass cutoff = 400 Da).[25a]

Figure 4 shows the conversion level as a function of the amount of substrate solution (expressed in reactor volumes) pumped through the reactor. The reaction started immediately after addition of the catalyst and reached its maximum yield after two reactor volumes. A huge drop in yield, however, was observed after this point. On the basis of the retention time of the dendrimer (99.7% in dichloromethane), the decrease was not due to dendrimer depletion, and it was therefore ascribed to decomposition of the palladium catalyst. This is in agreement with the observation that samples taken from the product flow were not catalytically active, indicating that no active palladium catalyst had passed through the membrane. Induced coupled plasma atomic emission spectroscopy (ICP-AES) analysis showed that after the reaction all the palladium had passed through the membrane. Batch experiments performed in the presence of pieces of membrane material gave similar results as those without membrane suggesting that the membrane material did not play a role in the deactivation process. When **2** was applied in the allylic amination of crotyl acetate and piperidine in the CFMR a similar rapid deactivation of the catalyst was observed.[25b]

Several experiments were devoted to gain insight into the deactivation process. A model compound $\{(CH_3)_2Si(CH_2PPh_2)_2\}(\eta^3\text{-}C_3H_7)PdCl$ was prepared and its decomposition was monitored by ^1H- and $^{31}P\text{-}\{^1H\}$-NMR spectroscopy. The formation of $\{(CH_3)_2Si(CH_2PPh_2)_2\}PdCl_2$ by reaction with the solvent was observed, but it proved to be only slightly less active than $\{(CH_3)_2Si(CH_2PPh_2)_2\}(\eta^3\text{-}C_3H_7)PdCl$ in the allylic amination of crotyl acetate and piperidine. Therefore, the formation of $\{(CH_3)_2Si(CH_2PPh_2)_2\}PdCl_2$ cannot account for the fast deactivation of the catalyst, as was suggested by Brinkmann et al.[24] Dendritic catalyst **2** was found to be stable according to a retention measurement in dichloromethane as all the palladium was in the reactor after flushing the reactor with 10 times its volume. Also the addition of one or more equivalents of diethylamine, which converts (after nucleophilic attack) Pd(II) into Pd(0), did not result in leaching of palladium. It was therefore concluded that the presence of the allyl acetate facilitated the decomposition.



Dendrimers with an ethylene-spacer between the terminal silicon atom and the phosphorus atom (**3** and **4**) were prepared. The largest dendrimer (**4**) was applied as a ligand in the continuous allylic amination reaction. Figure 5a shows that the maximum

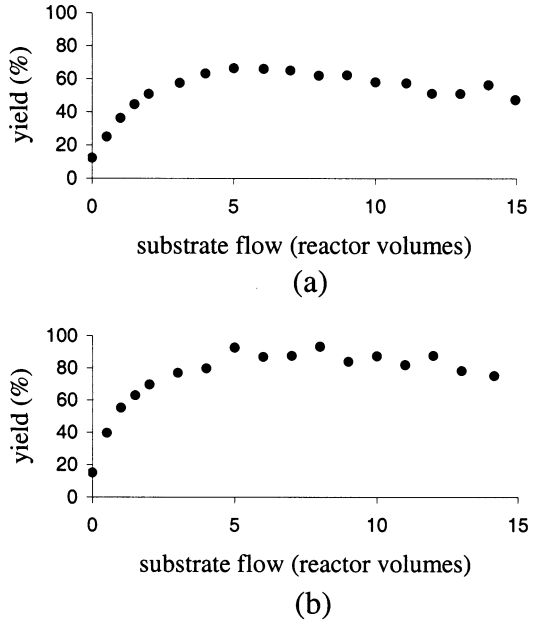
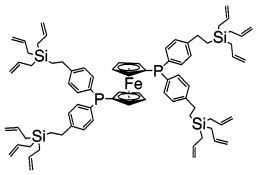


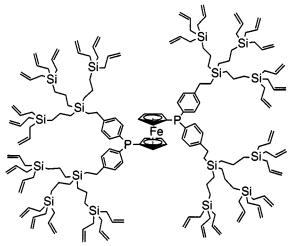
Figure 5. Application of dendritic ligand **4** in the allylic amination of crotyl acetate and piperidine using a CFMR (yield in % conversion of crotyl acetate in the product stream, (a) P/Pd = 2, (b) P/Pd = 4, Koch MPF-60 NF membrane, molecular mass cutoff = 400 Da).[25b]

yield is reached after approximately five reactor volumes of substrate solution have been pumped through the reactor. This dendritic catalyst clearly is much more stable than **2**, and during the next 10 reactor volumes the formation of product was fairly constant. After this period, the conversion was still more than 70% of the maximum reached, a decrease that corresponds to a retention of the dendritic catalyst of more than 98%. Under similar conditions with a P/Pd ratio of 4 instead of 2 (Figure 5b), the dendritic catalyst was more active and also the stability had increased. The slight decrease in yield during this experiment is completely attributed to depletion of very small amounts of dendritic catalyst. On the basis of the curve in Figure 5b the retention of the dendritic complex is estimated to be 98.5−99%, which is in the expected range. It is interesting to note that the stability of the palladium catalyst is sensitive to relatively small changes of the dendritic backbone.

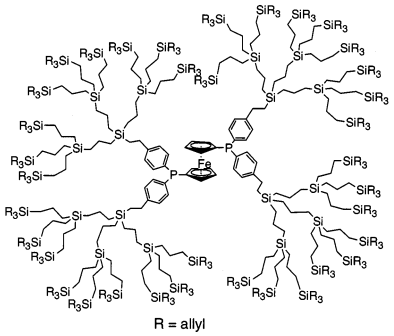
When the catalyst is located in the core of a dendrimer its stability can be increased by site-isolation effects. Such core-functionalized dendritic catalysts based on carbosilane dendrimers have been reported by Oosterom et al.[26] A novel route was developed to synthesize dendritic wedges with aryl bromide as focal point. These wedges were divergently coupled to a ferrocenyl diphosphine core to obtain dppf-like ligands **5**. Other core-functionalized phosphine ligand systems have also been prepared using the same strategy.[27]



5a



5b



5c

Bidentate palladium complexes of **5** were formed upon the addition of $PdCl_2$, which was evidenced by ^{31}P NMR, and even the largest systems formed cis complexes. Crotylpalladium chloride complexes were prepared in situ and used as catalysts in allylic alkylation reactions. The rate of alkylation of 3-phenylallyl acetate with sodium diethyl 2-methylmalonate slightly decreased upon increasing generation number. A change in product regioselectivity was observed when higher generations were used, resulting in an increase of branched product from 10% for dppf to 21% for the largest system (**5c**). The apolar microenvironment created within the carbosilane dendrimers caused this change in selectivity,[26] which is in line with recent results describing a relationship between solvent polarity and product regioselectivity in the palladium catalyzed allylic alkylation and Heck reactions.[28] The recyclability of a catalyst based on **5c** was tested by performing an allylic alkylation reaction in a CFMR. A mixture of third-generation **5c** and crotylpalladium chloride dimer in THF was incubated and injected into the reactor at room temperature. Subsequently, the reactor was fed with a solution of allyl trifluoroacetate, sodium diethyl 2-methylmalonate and decane as internal standard. Figure 6 shows that the conversion increased rapidly within the first 30 min until it stabilized at around 45%. The catalytic activity remained almost constant for 8 h and in that period the amount of 20 reactor volumes of substrate had been pumped through the reactor. These data show that the core-functionalized dendritic complex used was very stable and active during the course of the experiment, which was partly attributed to site-isolation effects.

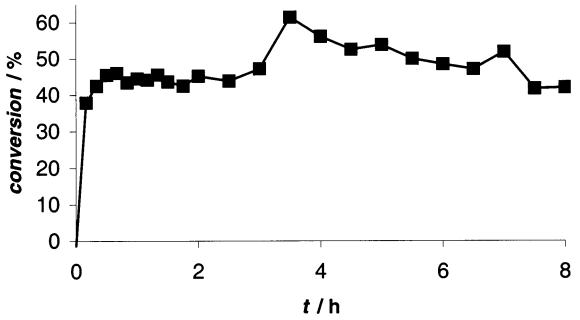


Figure 6. Allylic alkylation in a continuous flow membrane reactor using dendritic ligand **5c** (flow rate 50 mL h^{-1}; reactor volume 20 mL, Koch MPF-60 NF membrane, molecular mass cutoff = 400 Da; slight increases are due to pump failures).[26b]

1.1. Noncovalently Functionalized Dendrimers Applied in a CFMR

In most systems reported so far the catalyst is covalently linked to the dendritic support. An interesting alternative approach is the noncovalent anchoring of the catalyst to the soluble support using well-defined binding sites. The reversible nature of this type of anchoring allows controlled de- and refunctionalization of the support, the easy reuse of the support, and the variation of catalyst loading even during catalysis. Furthermore, using a noncovalent approach, multicomponent assemblies can be envisaged that are interesting for tandem reactions and combinatorial techniques. Such a novel approach was recently reported in which phosphine ligands were noncovalently anchored in the periphery of poly(propylene imine) dendrimers[29] using a specific binding motive that is complementary to that of the dendrimer support. The dendrimer provided directional binding sites for the strong but reversible binding of 32 guest molecules functionalized with the complementary binding motive. The binding is based on a combination of ionic interactions and the formation of multiple hydrogen bonds (Figure 7).

The binding constant of the anchor into the periphery of the dendrimer and that of the Pd to the ligand are very high; the guest−Pd−dendrimer complex remained intact during size exclusion chromatography (SEC). The dendrimer containing 32 phosphine-functionalized guest molecules was used as a multidentate ligand in the Pd-catalyzed allylic amination using crotyl acetate and piperidine as the reactants. The reaction was very fast; using a substrate−Pd ratio of 30, the yield was more than 80% after 10 min. Approximately the same rate was observed for the monomeric Pd-complex in absence of the dendrimer. The product selectivity induced by the dendrimer−guest−Pd-complex is the same as that by the monomeric Pd-complex (branched/trans/cis = 61:33:6).

The supramolecular guest−Pd−dendrimer complex, which has a retention of 99.4%, was studied in

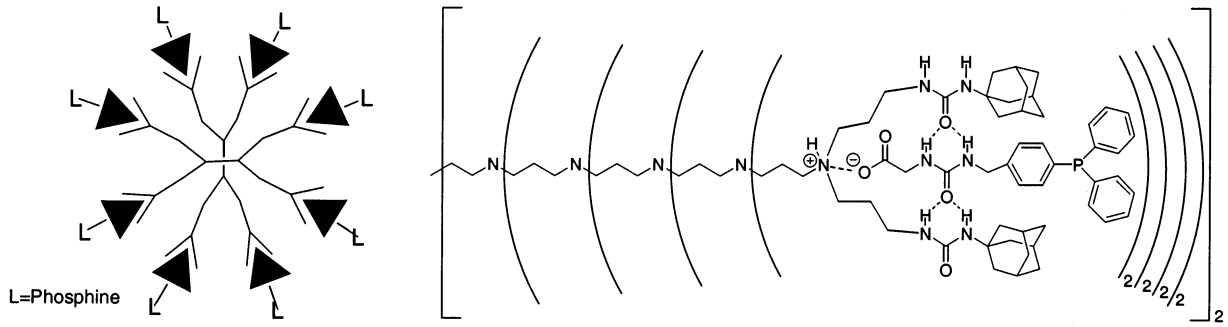


Figure 7. Schematic representation of the noncovalent immobilization of ligands to a dendrimer support and the actual supramolecular dendritic complex containing 32 phosphine ligands.[29]

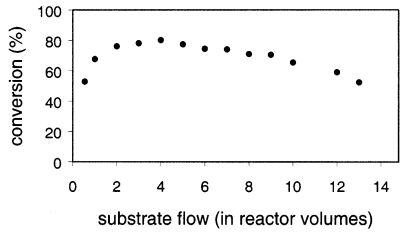
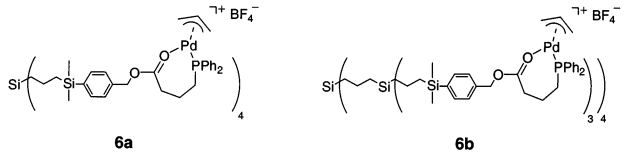


Figure 8. Application of a noncovalently functionalized dendrimer (see Figure 7) in a CFMR in the allylic amination of crotyl acetate and piperidine in dichloromethane (Koch MPF-60 NF membrane, molecular mass cutoff = 400 Da).[29]

the allylic amination reaction using a CFMR. A solution of crotyl acetate and piperidine in dichloromethane was pumped through the reactor. The conversion had increased to its maximum (ca. 80%) after approximately 1.5 h (which is equivalent to 2−3 reactor volumes of substrate solution pumped through the reactor). The conversion remained fairly constant during the course of the experiment (Figure 8). A slight decrease was observed, which is a result of slow deactivation of the catalyst, similar to that observed using the covalently functionalized dendrimers. This experiment clearly demonstrated that the noncovalently functionalized dendrimers are suitable as soluble and recyclable supports for catalysts. In a recent communication, Van de Coevering et al. reported on the synthesis of a polycationic dendrimer as a noncovalent support. Palladium(II)−pincer complexes bearing anionic sulfate groups were bound via ionic interactions.[30] The metallodendrimer assembly showed similar activity in the aldol condensation of benzaldehyde with methyl isocyanatoacetate compared to the monomeric analogue. Unfortunately, no recycling of the dendritic catalyst was reported.

2. Hydrovinylation Using Dendritic Catalysts in a CFMR

The hydrovinylation reaction—the codimerization of ethene and styrene, see Scheme 2—is of interest since it provides easy access to chiral building blocks from cheap carbon feedstock, which can be further used for the preparation of fine chemicals. Key problems in this reaction are the selectivity of the reaction and the stability of the catalyst. The main side reactions are oligomerization and isomerization of the product to internal achiral alkenes. The latter reaction can be suppressed by keeping the conversion low. Performing this reaction continuously is therefore interesting since it can combine a high space-time yield with a low conversion and thus a high selectivity.[31]



Eggeling et al. functionalized carbosilane dendrimers with hemilabile P,O-ligands at the surface (**6**) and palladium allyl complexes thereof were used as catalyst for the hydrovinylation reaction.[32] In a batch process, the dendritic catalysts were found to be less active than the monomeric analogues, which was attributed to a combination of enhanced catalyst deactivation and increased steric hindrance. Isomerization of the product occurred at high conversion but it was largely suppressed by stopping the reaction at low conversion. Retention of the multidentate ligand of **6a** (without palladium) was 85%, which was anticipated to be sufficient for initial experiments in a CFMR. The results of such experiments, displayed in Figure 9a, clearly show a rapid decrease in conversion (space time yield), which was due partly to depletion and partly to deactivation of the catalyst. This decomposition was corroborated by the observation of palladium precipitate on the membrane. Importantly, the selectivity to the desired chiral 3-phenylbut-1-ene was very high in the continuous hydrovinylation of styrene.

In a subsequent experiment the larger dendritic catalyst **6b** was used under optimized conditions, which was expected to result in a slower decrease in

Scheme 2

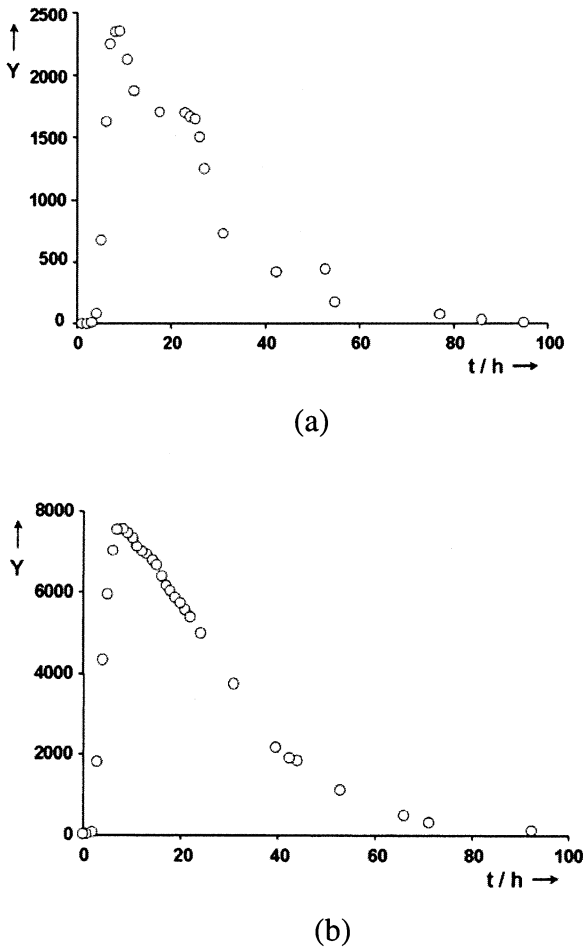


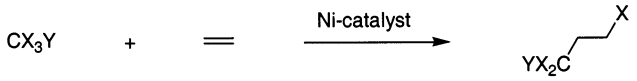
Figure 9. Hydrovinylation in a CFMR using **6a** (a) and **6b** (b): Conditions: T = 23 °C, p = 30 bar, flow rates: ethylene solution 2.5 mL h^{-1} (10 M), styrene solution 2.5 mL h^{-1} (1.8 M), τ = 4 h, MPF-60 NF membrane (Koch Int., Düsseldorf, Ger.). Y = space time yield (mg L^{-1} h^{-1}), for **6a**: 0.05 mmol Pd, L/Pd = 1; for **6b**, 0.13 mmol Pd, L/Pd = 1. (Reprinted with permission from ref 32. Copyright 2000 American Chemical Society.)

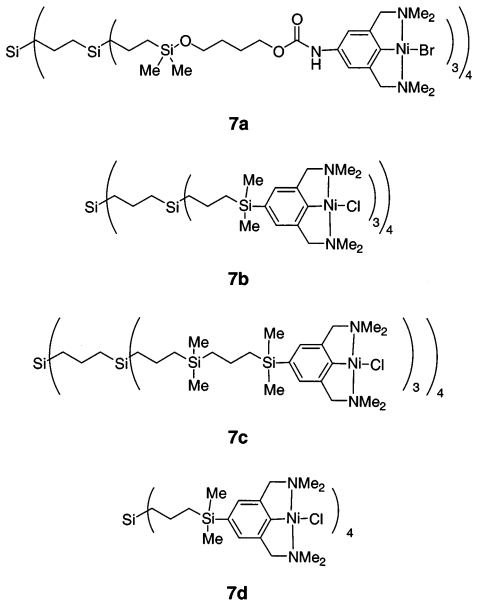
activity. The results (Figure 9b), however, did not show much improvement, indicating that catalyst deactivation was the major problem. To substantiate this, the authors compared the turnover number (TON) of a batch reaction with the continuous experiment. The TON of **6b** was 260 in the continuous process and 3273 in the batch reaction, whereas the monomeric model compound showed a TON of 6027.

3. Nickel-Catalyzed Kharasch Addition in a CFMR

An early example of a dendritic catalyst was reported by Knapen et al., who functionalized G0 (generation zero) and G1 carbosilane dendrimers with up to 12 NCN pincer−nickel(II) groups (**7a**).[33] These dendrimers were applied as catalysts in the Kharasch addition of organic halides to alkenes (Scheme 3).

Scheme 3





The catalytic activity of the dendritic catalyst was slightly lower than that of the monomeric parent compound; 80% of the activity was found for G0 (four Ni centers) and 70% for G1 (**7a**, 12 Ni centers). The selectivity was the same in all experiments resulting in a clean and regiospecific formation of the 1:1 addition product. It was proposed that the lower rates were due to the high local concentration of nickel centers. In a subsequent paper this effect was studied in more detail using dendrimers with different spacer lengths.[34a] An even larger decrease in activity was observed on using larger dendritic catalysts, which was attributed to surface congestion. This was strongly supported by the results of the more flexible dendrimers. The more flexible system **7c** with 12 active sites yielded a much better catalyst for the Kharasch addition reaction than **7b** (the TOF increased from 39 for **7b** to 85 for **7c**). It was proposed that the catalyst deactivation was caused by an interaction between neighboring Ni^{II}/Ni^{III} sites, which obviously is more pronounced in systems that have larger surface congestion. In a subsequent detailed report, this deactivation process was supported by EPR measurements and studies on model compounds. During the reaction a purple precipitate was formed that contained inactive Ni(III) species.[34b]

Preliminary results on using compound **7a** in a CFMR indicated that the dendrimer decomposed,[35] which was ascribed to hydrolysis of the Si−O bond of the linker between ligand and carbosilane backbone. The catalytically active complexes were disconnected from the support and subsequently washed out of the reactor. In **7b**−**7d** the NCN-ligands are directly attached to the carbosilane backbone and therefore much more stable.[34b] The retentions for **7d** and **7c** were measured to be 97.4 and 99.75% respectively, indicating that **7c** is sufficiently large for application in a CFMR without significant depletion of the catalyst after 100 cycles. During the experiments in the CFMR the precipitation of insoluble purple species was noted again. In an additional experiment **7c** was applied in the CFMR with a continuous feed of $[Bu_4N]Br$ to prevent catalyst precipitation (Figure 10). Despite the fact

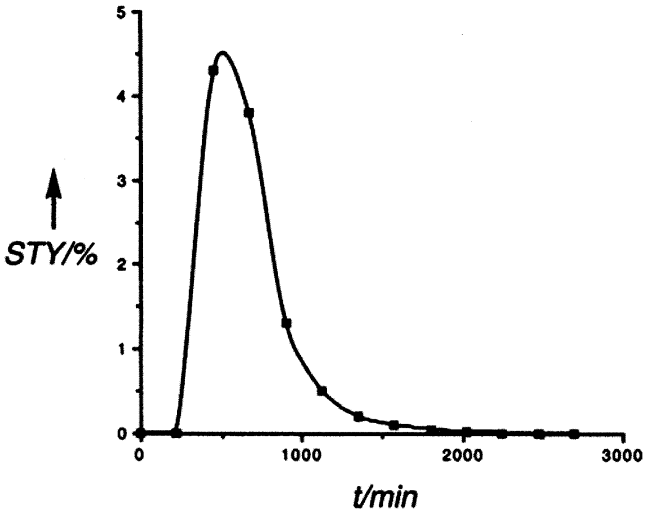
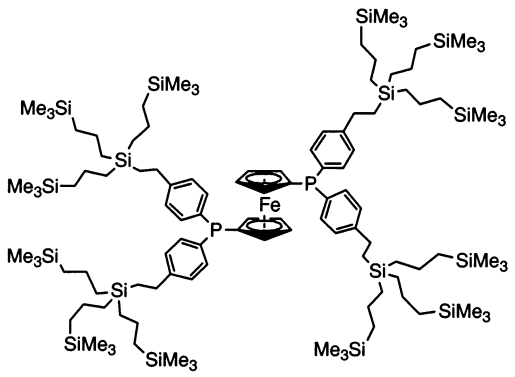


Figure 10. The application of **7c** as catalyst for the Kharasch addition of methyl methylacrylate and carbon tetrachloride in a CFMR using a SelRO-MPF-50 nanofiltation membrane. (Residence time (or cycle) is 43 min). (Reprinted with permission from ref 34b. Copyright 2000 American Chemical Society).

that **7c** was successfully retained in the reactor and that precipitation was avoided, a fast decrease of the conversion was observed. The maximum activity (space-time yield) was reached after 600 min (after 15 cycles), and after 1800 min (45 cycles) the activity dropped to nearly zero. ICP mass spectrometric analysis carried out after the reaction showed that the retention of **7c** under catalytic conditions was 98.6%, which supports the assumption that the main decrease in activity is due to the formation of inactive Ni(III) species.

4. Rhodium-Catalyzed Hydrogenation in a CFMR

The rhodium catalyzed hydrogenation reaction comprises one of the success stories of transition metal catalysis. The asymmetric hydrogenation with a rhodium catalyst was commercialized for the production of L-Dopa, and in 2001 the inventor, Knowles, was awarded the Nobel prize. After this invention, (enantioselective) hydrogenation has been subject to intensive investigations.[36] In general, hydrogenation reactions proceed under relatively mild conditions and, therefore, this reaction can be applied in a membrane reactor. For this purpose, a rhodium complex of dendritic ligand **8** was used and compared with dppf.[27]



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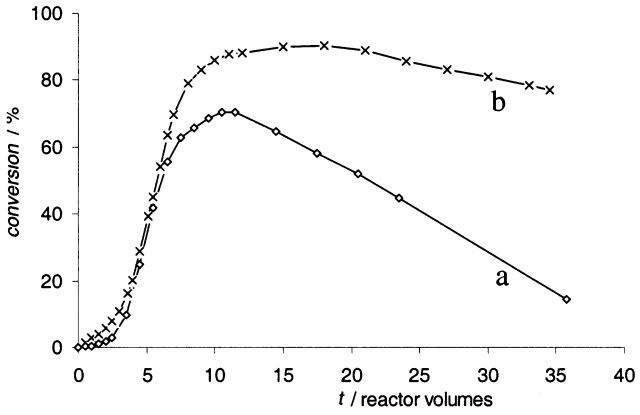
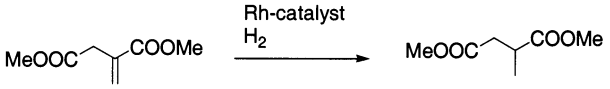


Figure 11. The continuous hydrogenation of dimethyl itaconate using dppf (a) and the dendrimeric ligand **8** (b), conversion (in %) versus time (expressed in reactor volumes pumped through the reactor).[27]

Before examining the catalytic performance in the continuous process, the dendritic dppf-type ligands were tested in the batchwise rhodium-catalyzed hydrogenation of dimethyl itaconate (see Scheme 4).

Scheme 4



The rhodium complexes were prepared in situ from the rhodium precursor $[Rh(nbd)_2](ClO_4)$ (nbd = 2,5-norbornadiene) and applied in the hydrogenation experiments under an initial hydrogen pressure of 5 bar at 35 °C. The dendrimer structure did not affect the activity of the catalyst.

Before starting the continuous reaction, the substrate solution was saturated with hydrogen gas by stirring under 5 bar of H_2 for 16 h. Subsequently, a premixed solution of the ligand and the rhodium precursor $[Rh(nbd)_2](ClO_4)$ was injected into the membrane autoclave, after which the substrate solution was pumped through the reactor.

Figure 11 shows the conversion of dimethyl itaconate versus time for two experiments using dppf and dendritic ligand **8** under identical conditions. The hydrogenation activity using dppf increased to a maximum conversion of around 70% in approximately 10 reactor volumes, after which it rapidly decreased to a conversion of only 15% after 35 reactor volumes. In contrast, after reaching its maximum at ~85% the conversion using dendritic ligand **8** remained high, showing a conversion of 77% after 35 reactor volumes. The lower maximum conversion using dppf was attributed to a combination of 10% lower activity of the catalyst and leaching of active complex in the first 10 reactor volumes. The amount of metal and ligand depletion during the catalytic experiment was determined using ICP-AES analysis. The amount of metal leaching is similar to that of the phosphine, indicating that the ligand−metal interaction was sufficiently strong to suppress metal leaching. The ICP-AES analyses show that the loss of both ligand and rhodium metal from the reactor in the hydrogenation experiment using dendritic ligand **8** is much lower than that for dppf. The

experimental curves in Figure 11 can be explained completely by the retentions of 97% for the dppf−rhodium(nbd) complex and 99.8% for the dendritic catalyst, based on the ICP-AES analyses. A further improvement of the recyclability of these catalyst systems may be expected if larger dendrimers were to be used.

III. Catalyst Recycling Using Nanofiltration in Batch Processes

In the previous section, we discussed the use of dendritic catalysts in CFMRs in which the product is continuously separated from the reaction mixture. An alternative use of the nanofiltration technique is in a batch process. In such a process, the dendritic catalyst is separated from the reaction mixture after the reaction has completed. The additional advantages of continuous-flow experiments obviously do not apply to these type of experiments. On the other hand, the requirements with respect to stability and retention of the dendritic system are less stringent. The problem of metal leaching applies to the state of the catalyst after reaction, as catalytst leaching can only take place during the recycling procedure. The majority of nanofiltration experiments with dendritic catalysts reported in the literature are primarily performed to assess whether these catalysts can be operated in a continuous membrane reactor. It should be borne in mind that the results obtained in a batchwise process cannot be extrapolated to those of a CFMR. A typical example of a system for which large differences between batch experiment and continuous experiment may be encountered is a carbonylation reaction; in a flow system metal carbonyl species may form that will facilitate leaching in the presence of CO, but when recycling is performed via a batch experiment in the absence of CO all metal may return to the immobilized ligand.

1. Acylation Reactions

Marquardt and Lüning immobilized concave pyridines on two types of dendrimers (**9** and **10**) to obtain a recoverable acylation catalyst.[37] For comparison, they also immobilized the concave pyridines to a Merrifield resin and a soluble poly(vinylbenzyl chloride) polymer. Whereas complete functionalization of the dendrimers was achieved, only 9% of the Merrifield resin and 29% of the poly(vinyl benzyl chloride) polymer functional groups had reacted with the concave pyridine. The enhanced selectivity in an intermolecular competition acylation experiment of diphenylketene with ethanol, 2-propanol, and *tert*-butyl alcohol (Scheme 5) which was caused by the

Scheme 5

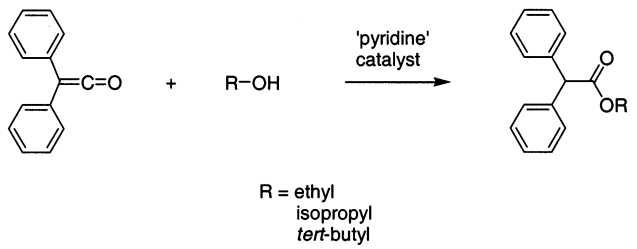
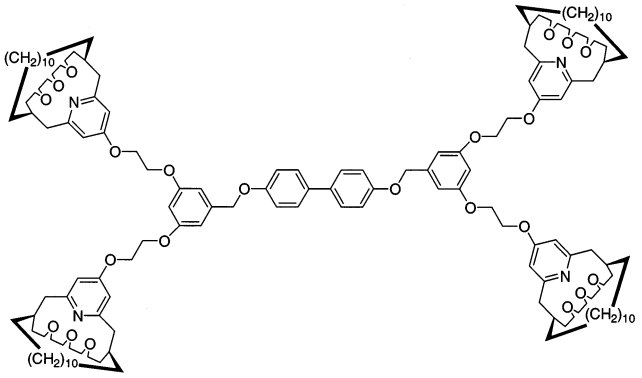


Table 1. Intermolecular Competition Acylation Experiment of Ethanol, Isopropanol, and *tert*-Butyl Alcohol with Diphenylketene[a]

immobilized pyridine	ethyl ester	isopropyl ester	*tert*-butyl ester
9	12.0	1	0
10	11.4	1	0
Merrifield resin	7.4	1	0
poly(vinyl benzyl chloride) polymer	9.5	1	0

[a] Conditions: [alcohol] = [catalyst] = 50 mM; [ketene] = 5 mM.

concave pyridines on the four different supports was studied (Table 1).



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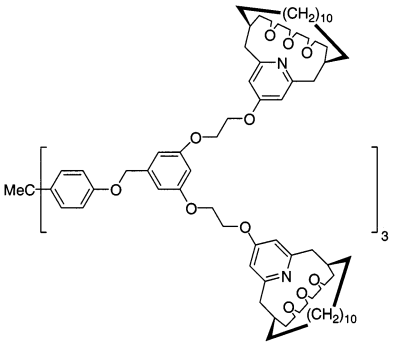

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The observed selectivity of the acylation with diphenylketene toward the ethyl, isopropyl, and *tert*-butyl ester product of the monomeric concave pyridine, **9** and **10** were almost the same. Lower selectivities were found when the modified Merrifield resin and poly(vinyl benzyl chloride) polymer were used. Dendrimer **10** (M_w = 3863 g mol^{-1}) could be recovered from the reaction mixture in 70−90% yield by nanofiltration over a membrane. The authors envisage that immobilization of the concave pyridines on a higher generation dendrimer would result in complete retention and thus these dendrimers would be suitable for application in a CFMR.

2. Asymmetric Hydrogenation

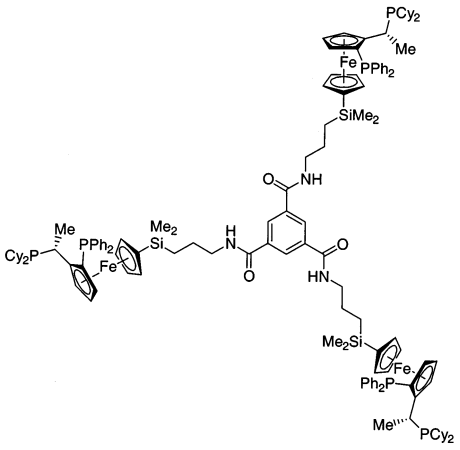
Köllner et al. prepared a Josiphos derivative containing an amine functionality that was reacted with benzene-1,3,5-tricarboxylic acid trichloride (**11**) and adamantane-1,3,5,7-tetracarboxylic acid tetrachloride

Table 2. Asymmetric Hydrogenation of Dimethyl Itaconate[a]

ligand	enantiomeric excess (%)
Josiphos	99.0
11	98.6
12	98.7
13	98.1
14	98.0

[a] Conditions: 1 mol % RH catalyst, 1 bar H_2 pressure, MeOH.

(**12**).[38] The second generation of these two types of dendrimers (**13** and **14**) were synthesized convergently through esterification of benzene-1,3,5-tricarboxylic acid trichloride and adamantane-1,3,5,7-tetracarboxylic acid with a phenol bearing the Josiphos derivative on the 1,3-positions. The rhodium complexes of the dendrimers were synthesized, isolated and subsequently used as chiral dendritic catalysts in the asymmetric hydrogenation of dimethyl itaconate in MeOH (1 mol % catalyst, 1 bar H_2 pressure). The obtained enantioselectivities were only slightly lower compared to the Josiphos parent compound (Table 2). Preliminary nanofiltration experiments of **13** and **14** (MD 4.8 and 6.5 kDa, respectively) showed complete retention of the rhodium-complexed dendrimers using a Millipore Centricon-3 membrane having a pore size of 3 kDa and methanol as the solvent.



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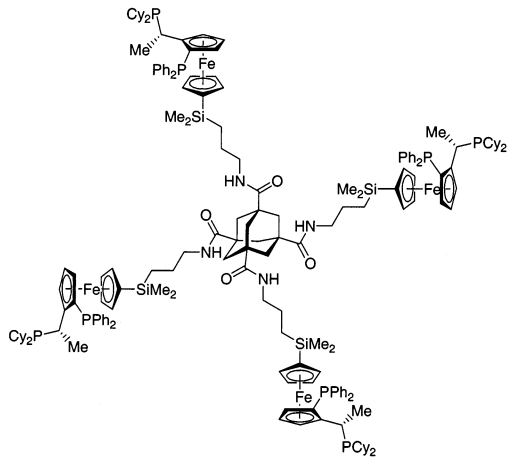

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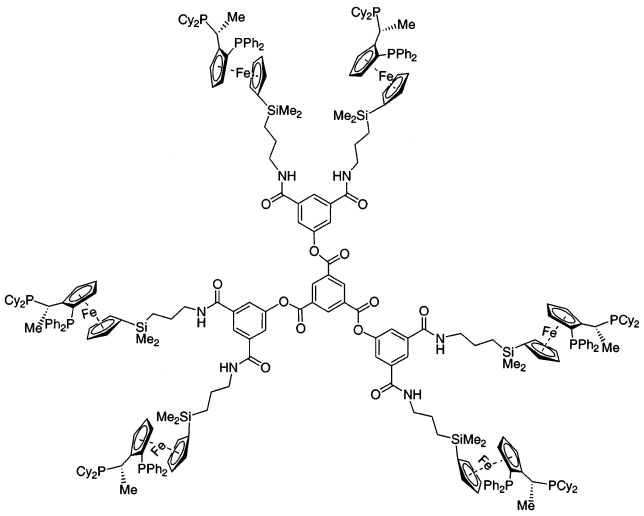

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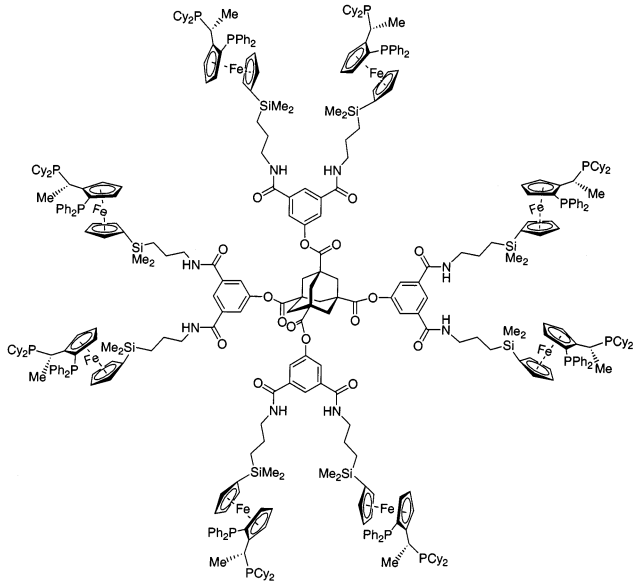

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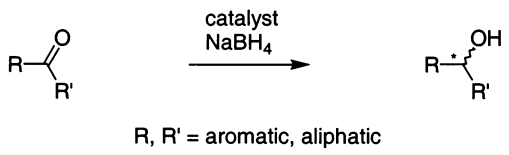
3. Asymmetric Borohydride Reductions

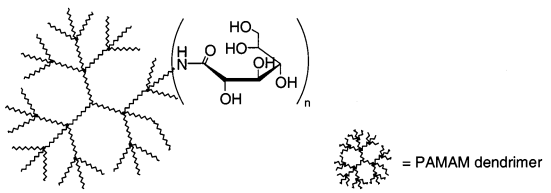
Schmitzer et al. synthesized four generations of peripherally D-gluconolactone functionalized polyamidoamine (PAMAM) dendrimers (**15**−**18**).[39] The dendrimers were used as chiral ligands for the sodium borohydride reduction of prochiral aromatic ketones either homogeneously in water or heterogeneously in tetrahydrofuran (Scheme 6). In the latter

Scheme 6



case, high enantioselectivities were achieved with the third generation (**16**) dendrimer even for aliphatic ketones that are notorious for giving low enantioselectivities. The asymmetric reduction of acetophenone

with a stoichiometric amount of sodium borohydride was studied in both water and THF.



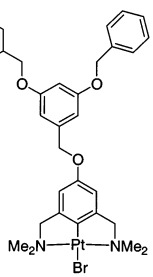
n = 8 **15** n = 32 **17**

n = 16 **16** n = 64 **18**

In water the third and fourth generation induced chirality toward the (*S*)-enantiomer (50% ee for **16** and 98% ee for **17**). In THF high enantiomeric excess was achieved only for the third generation (99% (*S*) ee for **16** and 3% (*S*) ee for **17**). Dendrimer **16** was recovered from the heterogeneous reaction mixture by nanofiltration on a Millipore microporous membrane system. After regeneration of the dendritic species in HCl/MeOH it was reused up to 10 times showing the same catalytic results.

4. Kharasch Addition

Albrecht et al. synthesized a series of polybenzyl ether dendrimers containing a pincer−metal (Ni, Pt) at the focal point of the wedge (**19**−**22**).[40] Coordination of SO_2 to the pincer−platinum complex resulted in a change in color of the dendrimer solutions from colorless to orange. The obtained SO_2 complexes were utilized as dyes to study the recoverability of these dendrimers by membrane filtration. The generation dependent leaching of the dendrimers from a membrane-capped immersion vial was followed over time by UV−Vis spectroscopy. The retention of the first generation dendrimer (**19**) was moderate ($t_{1/2}$ = 108 h). The second generation (**20**) displayed a half-life time of ca. 300 h, whereas the third generation (**21**) had a half-life time of over 60 days. The third generation nickel−pincer functionalized dendrimer (**22**) was applied in the Kharasch addition of CCl_4 to methyl methacrylate. The dendritic catalyst **22** (0.33 mol %) showed the same reaction rate and turn-over number as the parent nickel−pincer complex (TON = 310). When performed in the membrane-capped immersion vial the dendritic nickel catalyst could be recovered after completion of the reaction by washing the dendrimer containing immersion vial with pure solvents. It should be noted that this recycling process of the dendritic catalyst is based on diffusion which limits the product flux.



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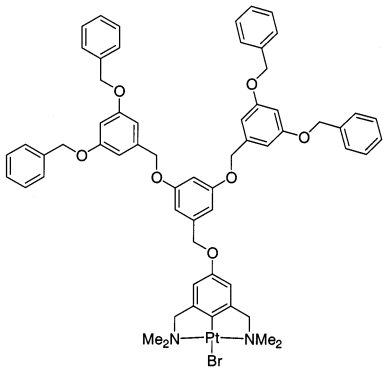

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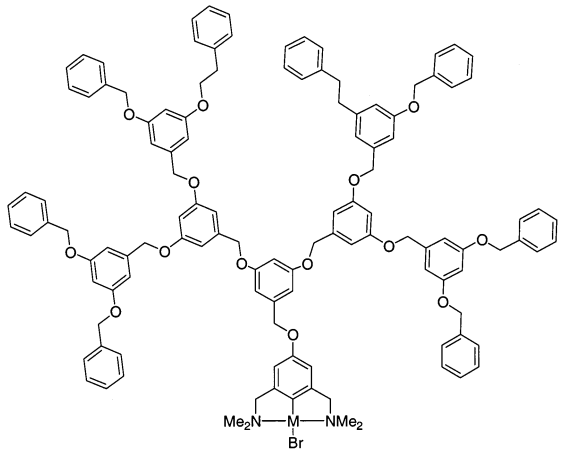


21 M = Pt

22 M = Ni

5. Hydroformylation

Tulchinsky and Miller patented dendritic macromolecules, their metal-complexes and the use in catalytic processes such as hydroformylation.[41] Dendrimers containing organophosphites, organophosphonites, and/or organophosphinites are claimed. Examples of the synthesis of five generations phosphite functionalized PAMAM dendrimers, their use in the hydroformylation, and separation via nanofiltration are described. A ligand precursor has been synthesized by a reaction of 4-hydroxybutyl acrylate with (3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl) phosphorochloride in the presence of pyridine. The precursor was subsequently reacted with five generations PAMAM dendrimers (G0−G4; Michael addition) yielding G0−G4 dendrophites (Scheme 7, zeroth generation shown). The dendrophites were used in the hydroformylation of propene. A decrease in reaction rate was observed upon using the higher generations dendrophites, while the linear-to-branched ratio was the same for all systems (Table 3).

After the hydroformylation reaction, mixtures were passed through nanofiltration (reverse osmosis) membranes MPF-50 (available from Membrane Products Kiryat Weizmann Ltd., Israel), cross-linked GKSS membranes with an active layer thickness of 1 and 10 μm (available from GKSS, Forschungszentrum Geesthach GmbH, Germany) using Texanol as the

Scheme 7

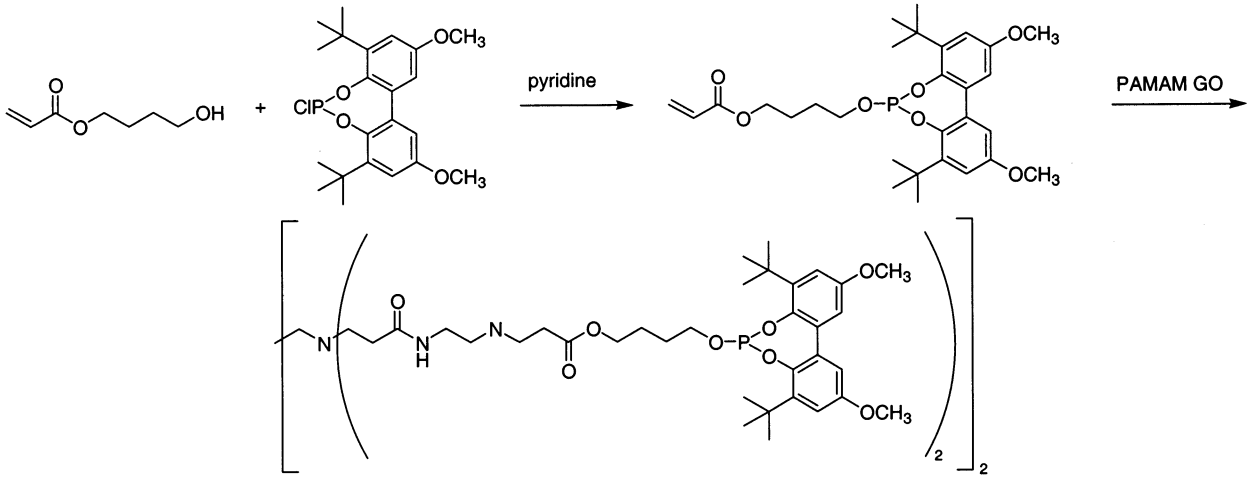
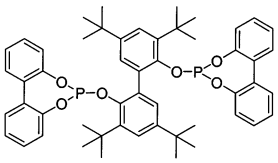


Table 3. Hydroformylation of Propene Using Dendrophites G0−G4[a]

ligand	rate (mol L^{-1} h^{-1})	l/b ratio
Dendrophite G0	3.2	1.32
Dendrophite G1	2.9	1.38
Dendrophite G2	2.0	1.41
Dendrophite G3	1.9	1.38
Dendrophite G4	1.8	1.40

[a] Conditions: 0.039 mmol Rh; P/Rh = 8:1; p = 100 psi, propene:CO:H = 1:1:1; T = 70 °C; 15 g of Texanol solution in a 100-mL reactor.

solvent. No detectable amount of dendritic material was found in the permeate solutions, indicating that under these conditions the dendrimer is stable. The retention of rhodium and the permeate flux rate were measured (Table 4). The experiment was also performed using a bidentate phosphite ligand (**23**), showing a lower retention compared to the higher generations dendrimers. The use of the GKSS (10 μm) membrane led to the highest retentions. Remarkably, using these dendrimers rhodium leaching was almost completely suppressed, which may be explained in several ways. The ligands on the dendritic surface are in close proximity of each other thereby creating a chelating effect that prevents leaching. Another explanation may be the binding of polar groups (e.g., amides and esters) present in the dendritic backbone during the recycling procedure which is performed under syngas deficient conditions. Interestingly, the best retentions were found for the third generation dendrimers and not for the fourth generation. Also a significant drop in the flux rate was observed using the fourth generation dendrimer.



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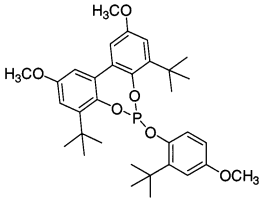

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The same nanofiltration experiments were performed using a 50 Å ultrafiltration membrane (available from US Filter/Membralox, Warrendale, PA), this time using a monodentate phosphite ligand (**24**) for comparison and toluene as the solvent (Table 5). Both higher retentions and flux rates for the dendrimers were obtained compared to the reverse osmosis membranes. Dendrophite G4 was used in three subsequent reactions using this procedure.

Recycling experiments were performed using the second and third generation dendrophites. Propene was hydroformylated in toluene, followed by separation of the dendritic catalyst from the reaction

Table 4. Rhodium Retention and Flux Rate Measured for the Nanofiltration of Hydroformylation Mixtures[a]

	MPF-50		GKSS (1 μm)		GKSS (10 μm)	
ligand	% Rh retention	flux rate (GFD[b])	% Rh retention	flux rate (GFD[b])	% Rh retention	flux rate (GFD[b])
G0	99.59	0.15	99.60	0.70	99.84	0.20
G1	99.74	0.34	99.86	0.52	99.86	0.30
G2	99.88	0.11	99.95	0.14	99.96	0.18
G3	99.92	0.10	99.94	0.24	99.96	0.24
G4	99.89	0.063	99.93	0.063	99.94	0.067
23	65	0.3−0.5	n.d.	n.d.	88	0.15−0.2

[a] Conditions: Flow rate: 100 mL min^{-1}; p = 300 psig for MPF-50 and GKSS (1 μm); p = 150 psig for GKSS (10 μm); solvent: Texanol. [b] GFD = gallon $foot^{-2}$ day^{-1}.

Scheme 8

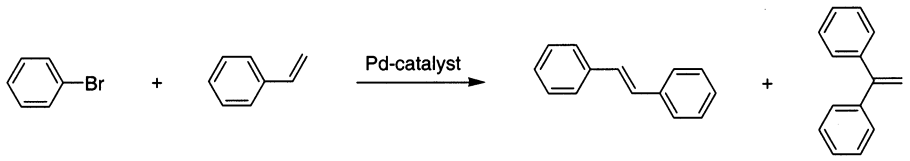


Table 5. Rhodium Retention and Flux Rate Measurements Using a 50 Å Ultrafiltration Membrane[a]

ligand	cycle	% Rh retention	flux rate (GFD[b])
24	1st	83−86	4.2
Dendrophite G2	1st	99.994	2.0
Dendrophite G3	1st	99.997	1.9
Dendrophite G4	1st	99.9975	1.3
Dendrophite G4	2nd	99.9974	2.2
Dendrophite G4	3rd	99.994	2.1

[a] Conditions: flow rate: 100 mL min^{-1}; solvent: toluene. [b] GFD = gallon $foot^{-2}$ day^{-1}.

mixture by passing it over the 50 Å ultrafiltration membrane. The catalysts solution was used in a second hydroformylation reaction. The differences in reaction rate between the two runs were only 2 and 3% for the second and third generation dendrimer, respectively.

IV. Dendritic Catalyst Recycling by Precipitation

Separation of catalysts from high-value products such as fine chemicals or pharmaceuticals is often accomplished by precipitating the catalyst from the product solution. Provided that these catalysts do not decompose, recycling of these catalysts is possible. In industry, the catalyst recovery by means of catalyst precipitation is applied only in relatively small batch processes. An example of such a process is the production of (−)-menthol by Takasago comprising an asymmetric isomerization process of *N*,*N*-diethylgeranylamine.[42] In this process, a Rh−BINAP isomerization catalyst converts the olefinic substrate into (*R*)-citronellal in high yield (99%) and enantioselectivity (98.5% ee). After distillation of the solvent (THF) and product the catalyst is recovered from the residue by precipitation with *n*-heptane.

The physical properties of dendrimers such as solubility, arising from their hyperbranched globular shape and the peripheral groups, can be modified by end-group modification. A distinction should be made between core- and periphery-functionalized dendrimers. In core-functionalized dendrimers, the immiscibility of the wedges with a solvent enables precipitation and subsequent separation by filtration. In periphery-functionalized dendritic catalysts, the functional groups (often organometallic compounds) at the surface determines the solubility and miscibility and thus the precipitation properties. Many dendrimers functionalized with organometallic complexes do not dissolve in apolar solvents and the presence of multiple metal-centers at the periphery facilitates precipitation upon addition of this type of solvents. It should be emphasized that the use of dendrimer-immobilized catalysts aiming at the recovery through precipitation is only worthwhile if the precipitation properties of the dendritic system exceeds that of its monomeric equivalent.

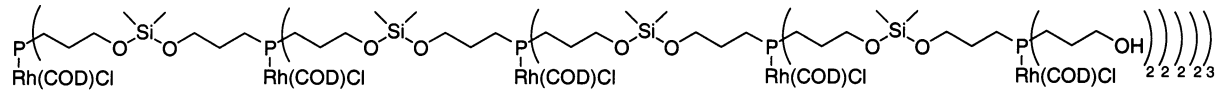
1. Heck Reaction

Reetz et al. were the first to recover and recycle a dendritic catalyst through a precipitation procedure.[23] Phosphonated DAB-dendr-$[N(CH_2PPh_2)_2]_{16}$ dendrimer dimethylpalladium complex (**1a**) is an active catalyst for the Heck reaction of bromobenzene and styrene giving *trans*-stilbene (89% *trans*-stilbene and 11% 1,1-diphenylethylene, conversion of 85−90%, Scheme 8).

In contrast to the monomeric catalyst, no metallic palladium was observed when **1a** was used. The 0.125 mol % dendritic metal complex used could be recovered from the reaction mixture by precipitation with diethyl ether (yield > 98%) and subsequent filtration. The precise structure of the recovered palladium complex was not determined. The palladium containing dendrimer showed a small decrease in activity only (91% *trans*-stilbene and 9% 1,1-diphenylethylene, conversion of 77%). In the same study, cyclooctadiene rhodium functionalized DAB-dendr-$[N(CH_2PPh_2)_2]_{16}$ (**1d**) was used in the hydroformylation reaction of 1-octene to nonanal and 2-methyloctanal (l/b = 60:40; TOF = 360 h^{-1}). The recycling of this catalyst system was not reported.

2. Hydrogenation

Kakkar et al. prepared organophosphine dendrimers up to the fourth generation (**25**) via a divergent route starting from $P\{(CH_2)_3OH\}_3$ and subsequent reaction with $(CH_3)_2Si(NMe_2)_2$ and $P\{(CH_2)_3OH\}_3$.[43] The corresponding Rh(I) organometallic dendrimers − having Rh(I) coordinated to every branching point − were obtained by a reaction with $[(COD)Rh(\mu\text{-}Cl)]_2$. Alternatively, the organometallic dendrimers could be synthesized using the rhodium complex $((COD)\{HO(CH_2)_3\}_3PRhCl)$. All Rh(I) organometallic dendrimers were efficient catalysts for alkene hydrogenation reactions. Generation 1 to 4 of the dendrimers (containing, respectively, 4, 10, 22, and 46 Rh(I) metal sites) were employed in the hydrogenation of 1-decene in THF under standard conditions (25 °C, 20 bar H2, 30 min, metal-to-substrate ratio = 1:200). The activity of all dendritic catalysts was similar to the monomeric analogue $(COD)\{HO(CH_2)_3\}_3PRhCl$ (TOF ≈ 400 h^{-1}) and there was only a slight decrease in activity observed for the larger systems. The recoverability and stability of the fourth generation dendrimer (having 46 Rh(I) centers) was tested. Pentane extraction of the hydrogenation product from the reaction mixture followed by recrystallization from a THF/hexanes mixture resulted in recovery of the fourth generation organometallic dendrimer. The recovered dendrimer was applied in a second hydrogenation run under the same conditions giving an activity of 95% of the first run. Unfortunately, the same recycling procedure was not tested for the lower generations.



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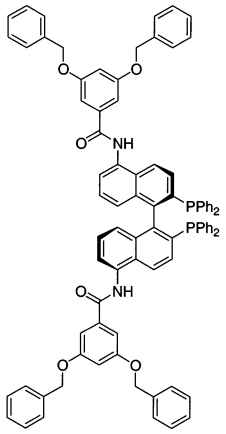

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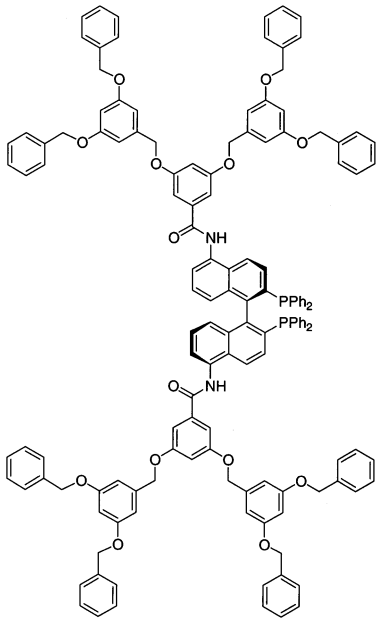

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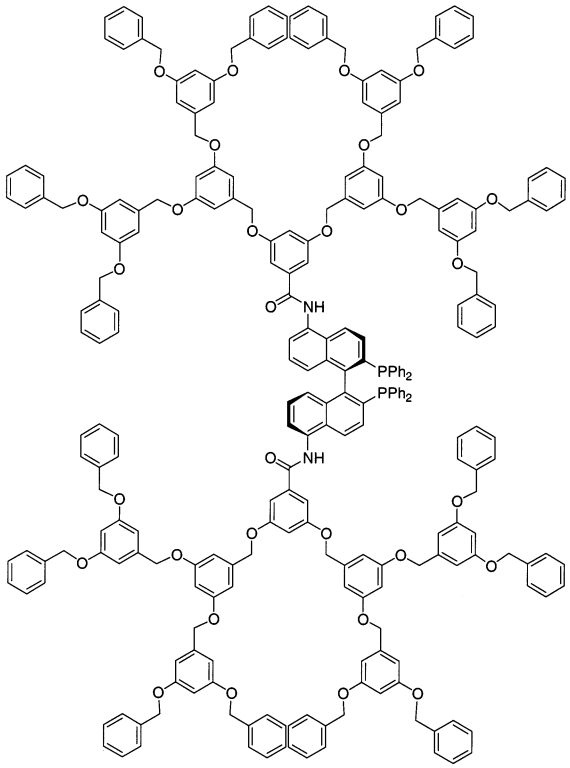

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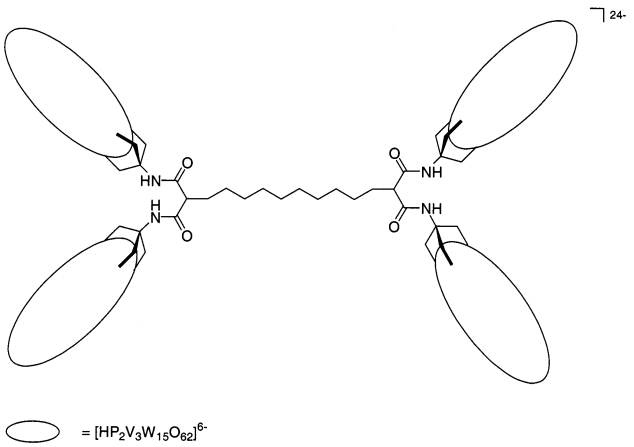
Three generations of (*R*)-BINAP core-functionalized dendrimers were synthesized by Fan et al. via condensation of Fréchet's polybenzyl ether dendritic wedges to (*R*)-5,5′-diamino-BINAP (**26**−**28**).[44] The different generations BINAP core-functionalized dendrimers were tested in the ruthenium catalyzed asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)-phenyl]acrylic acid under an 80 bar H_2 pressure and in a 1:1 (v/v) methanol/toluene mixture. The in situ prepared cymene ruthenium chloride functionalized dendritic catalysts displayed a higher activity upon going to a higher generation (TOF, respectively, 6.5, 8.3, and 21.4 h^{-1}). Compared to the (*S*)-BINAP system (TOF 6.3 h^{-1}, ee 89.8% (*S*)) higher activities and (opposite) enantioselectivities were found for the dendritic catalysts inducing similar enantiomeric excesses (ee: **26** 91.8% (*R*), **27** 92.6% (*R*), and **28** 91.6% (*R*)). The dendritic catalyst composed of **28** was quantitatively recovered by precipitation with methanol. The catalyst was reused three times and the catalyst showed constant activity and enantioselectivity.

3. Oxidation

Zeng et al. reported the synthesis and catalytic activity of tetra(polyoxometalate) dendrimers.[45] The catalytically active polyoxometalate (POM) $(^nBu_4N)_5[H_4P_2V_3W_{15}O_{62}]$ was esterified with two types of dendrimers containing four tris(hydroxymethyl) groups (**29** and **30**). Via an ion-exchange process the dendrimers counterions $^nBu_4N^+$ were fully replaced by H^+. The POM functionalized dendrimer **29** and its H^+-exchanged form (**29-H**) were tested in the oxidation of tetrahydrothiophene by tBuOOH in both acetonitrile and toluene. The oxidation activity of **29-H** and **29** in the presence of *p*-toluene sulfonic acid was higher than the reaction in the absence of dendrimer with *p*-toluene sulfonic acid. POM dendrimer **29** by itself showed hardly any activity. The POM dendrimers **29-H** and **29** were recovered from the reaction mixture by precipitation after the addition of diethyl ether and the recycled catalyst did not show loss in activity.



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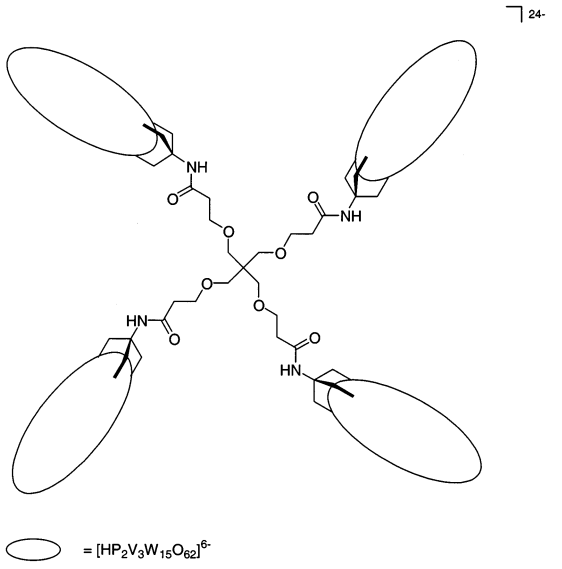

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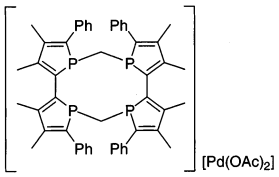
4. Stille Couplings, Knoevenagel Condensations, and Diastereoselective Michael Additions

Maraval et al. synthesized core- and periphery-functionalized ruthenium and palladium dendritic diphosphines (Figure 12) that were applied in three different reactions (Stille coupling, Knoevenagel condensation, and diastereoselective Michael addition) and were recovered using the precipitation strategy.[46]

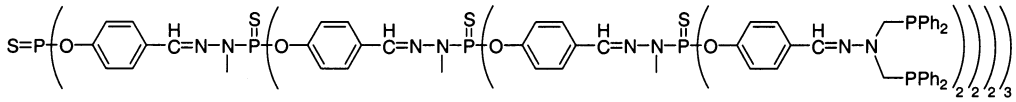
The third generation dendrimer palladium complex (**31**, containing 24 $PdCl_2$ groups) was applied in the Stille coupling of methyl-2-iodobenzoate with 2-(tributylstannyl)thiophene in DMF (Scheme 9). The recoverability was tested using 1 mol % of **31**. Contrary to the monomer $(PPh_3)_2PdCl_2$, no palladium metal formation was observed when **31** was applied in the Stille coupling. The dendrimer could be precipitated and recovered easily by the addition of diethyl ether to the reaction mixture. No significant loss of activity was observed in three consecutive runs (80% conversion after 12 h). NMR analysis on the isolated dendrimer complex clearly indicated that no degradation had occurred.



31b

Application of the same dendrimer **31** in the Stille coupling of iodobenzene with tributylvinyltin in DMF (Scheme 9, 5 mol % catalyst) showed equal activity as the tetraphosphole macrocycle complex $(Fu_3P)_4Pd(OAc)_2$ (**31b**, 100% conversion after 15 min). In contrast to the monomer, the dendritic catalyst could be recycled, but the recycled dendritic catalyst showed a slight decrease in activity (95% conversion after 15 min). A better performance was achieved with the in situ prepared catalyst **32** by mixing the parent third generation diphosphine dendrimer with $Pd(OAc)_2$ (P/Pd ratio = 4/1). The same activity as the monomeric complex $(Fu_3P)_4Pd(OAc)_2$ was observed (100% conversion after 15 min) even after three consecutive runs.

The phosphine containing dendrimers were also applied as diphosphine dendritic ligands in the ruthenium-catalyzed Knoevenagel reaction of malonitrile and cyclohexanone in THF as the solvent (Scheme 10). The application of 1 mol % of isolated diphenylphosphinoruthenium dihydride functional-



31 = ligand·24 $PdCl_2$

32 = ligand·12 $Pd(OAc)_2$

33 = ligand·24 $RuH_2(PPh_3)_2$

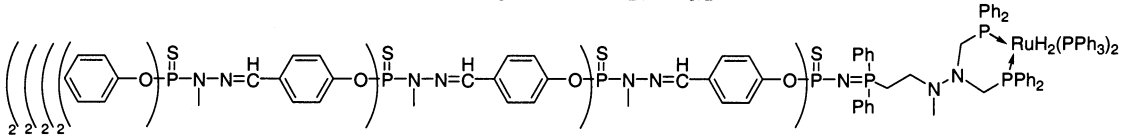


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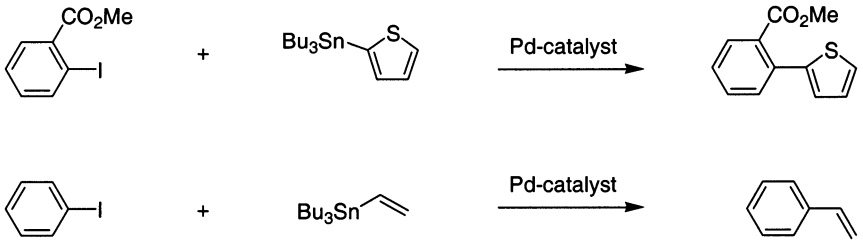
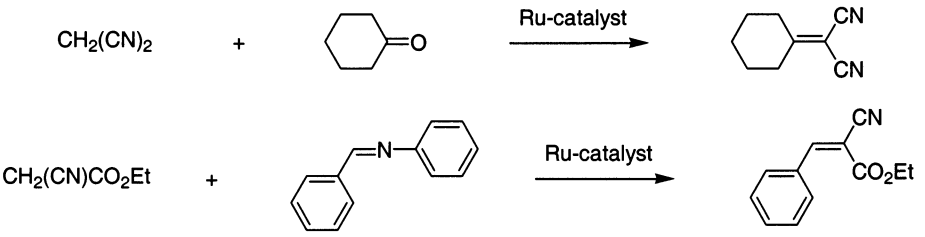
Figure 12. Periphery- and core-functionalized ruthenium and palladium dendritic diphosphines.

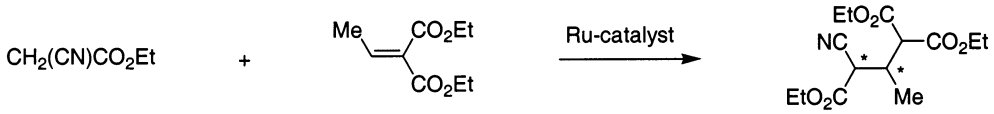
Scheme 9



Scheme 10



Scheme 11

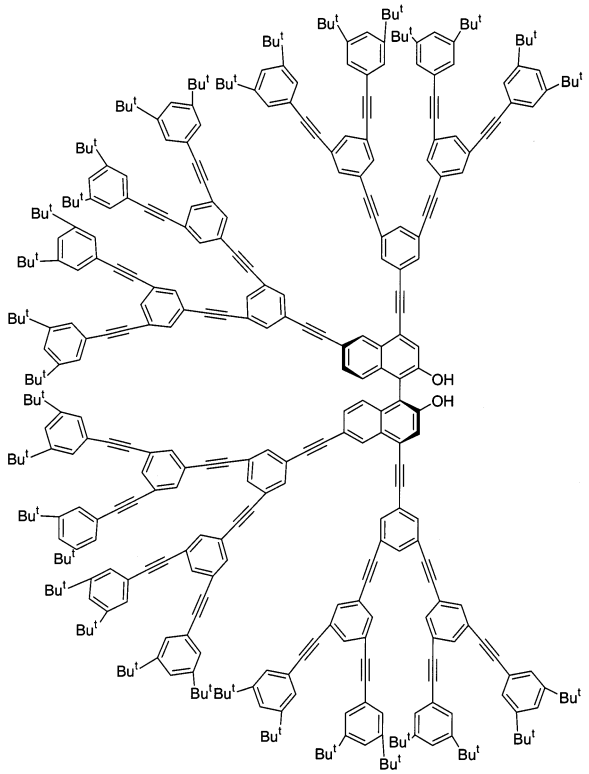


ized dendrimer **33** in the Knoevenagel reaction resulted in complete formation of the unsaturated nitrile product after 24 h. Remarkably, the activity of **33** is higher than that of the monomer complex $[Me_2N\text{-}N(CH_2PPh_2)_2RuH_2(PPh_3)_2]$ which gave 80% conversion after 24 h. Whereas the monomer complex could not be recovered by the precipitation method, **33** was recycled efficiently by precipitation with diethyl ether and used in three runs without a significant drop in activity. The same efficient recoverability of **33** (1 mol %) over three consecutive runs was found in the Knoevenagel condensation of ethyl cyanoacetate and *N*-benzylideneaniline to ethyl benzylidenecyanoacetate (Scheme 10).

The diphenylphosphinoruthenium dihydride dendrimer **33** was found to be an active catalyst for the diastereoselective Michael addition of ethyl cyanoacetate to diethyl ethylidenemalonate in THF (Scheme 11). The dendritic catalyst showed similar activity and selectivity as the reference compound $RuH_2(PPh_3)_4$, a complete conversion after 24 h and a diastereoselectivity of 7/3 using 3 mol % of catalyst.[47] The dendritic catalyst was recycled two times by precipitation with diethyl ether without loss in activity and selectivity. An attempt was made to affect the diastereoselectivity of the Michael addition by synthesizing a core-functionalized dendrimer **34**. It was anticipated that the steric hindrance of the dendritic shell around the metal center might change the diastereoselective outcome of the reaction. The use of 1 mol % **34** showed the same activity and recoverability over three runs, however, no change in selectivity was observed.

5. Asymmetric Addition of Diethylzinc to Aldehydes

Hu et al. reported chiral conjugated 1,1′-binaphthyl core-functionalized phenylacetylene-based dendrimers ((*S*)-**35**), which were used as catalysts in the asymmetric reaction of benzaldehyde with diethylzinc in toluene.[48] The reaction performed in the presence of (*S*)-**35** (5 mol %) displayed a much higher conversion after 24 h than the parent monomer (*S*)-BINOL, respectively, 98.6 and 37%. Interestingly, (*S*)-**35** gave rise to the formation of the opposite enantiomeric product. These results were explained by the site-isolation effect of (*S*)-**35**, which prevents aggregation of the Zn species through Zn−O−Zn linkages. These aggregates result in reduced Lewis acidity for the zinc/BINOL complex. Complexation of $Ti(O\text{-}^iPr)_4$ to (*S*)-**35** (20 mol %) and (*S*)-BINOL resulted in comparable activities and enantioselectivities for the addition of diethylzinc to both benzaldehyde (100% conversion, 89% ee) as well as to 1-naphthaldehyde (100% conversion, 90% ee). It is likely that for these complexes similar catalytically active (monomeric) species are formed. (*S*)-**35** could be recovered easily from the reaction mixture by precipitation with methanol. Unfortunately, no recycling experiments were reported.

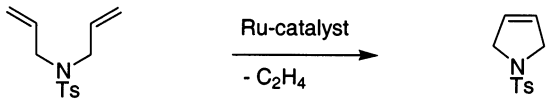


(*S*)-35

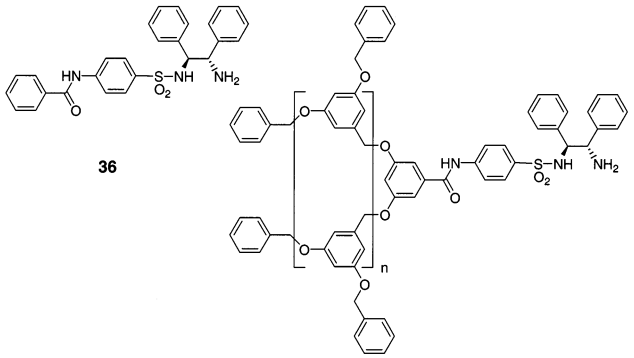
6. Asymmetric Transfer Hydrogenation

Chen et al. reported on the asymmetric transfer hydrogenation of acetophenone using four generations of core-functionalized dendritic catalysts.[49] Polybenzyl ether dendritic wedges were coupled via a condensation reaction to an amine analogue of the

Scheme 12



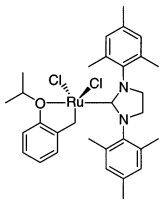
[(*S*,*S*)-TsDPEN] ligand (**37**−**40**). The cymene ruthenium chloride dendritic catalysts were prepared and the transfer hydrogenation was performed in CH_2Cl_2 with formic acid as the hydrogen donor. Compared to reference compound **36** the dendritic catalysts gave similar activity with a slightly shorter induction period. All catalysts induced a high enantioselectivity (ee >96%). The third and fourth generation dendritic catalysts were recycled four and five times, respectively, by evaporation of the CH_2Cl_2 followed by the addition of dry methanol, centrifugation, removal of the methanol, and subsequent washing with methanol. After three cycles, only a small loss in reactivity was observed, while the enantioselectivities remained high. In the fifth run, a dramatic loss in activity, but not in enantioselectivity, was found for the third generation **39** (52% conversion after 20 h, ee 95.0%), whereas the fourth generation **40** still displayed reasonable activity (73% conversion after 20 h, ee 96.3%). The fourth generation dendritic catalyst was even used in a sixth run, in which the reactivity decreased further accompanied with a drop in the enantioselectivity (52% conversion after 20 h, ee 87.0%). The higher stability of **40** was proposed to be due to a site-isolation effect imposed by the large dendrimer.



V. Catalyst Recovery by Column Chromatography

1. Metathesis

Garber et al. utilized the physical properties of dendrimers to enhance the separation on a silica column of dendritic metathesis catalysts and products.[50] A mononuclear ruthenium catalyst with an imidazolin-2-ylidene carbene ligand (**41**) was synthesized for the application in the ring closing metathesis (RCM) of dienes into hetero- and carbocyclic trisubstituted alkenes (Scheme 12). The catalytically active species is formed by reaction of **41** with the substrate under formation of 2-isopropoxystyrene. The imidazolin-2-ylidene carbene ligand gave a more catalytically active species than that with tricyclohexylphosphine as a ligand. By addition of 2-isopropoxystyrene to the reaction mixture after the reaction had completed, catalyst **41** was recovered using column chromatography (silica, >95% yield). Reuse in a consecutive run gave no significant loss in activity. When the tricyclohexylphosphine ligated complex was used, recycling did lead to loss in activity.



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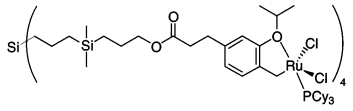

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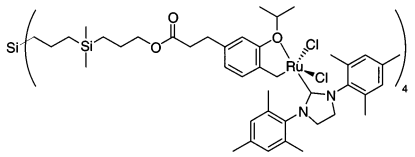

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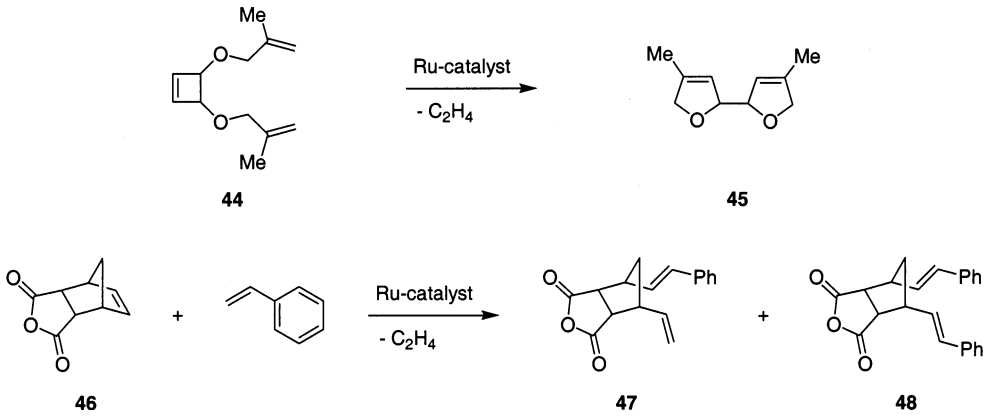
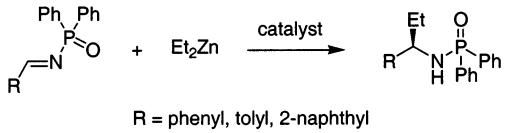
The monomeric catalyst fraction showed similar R_f values as the metathesis products, which was a drawback of the chromatographic recycling procedure. The author envisioned that immobilization of the ruthenium catalyst on a dendrimer would facilitate the chromatographic separation. The presence of multiple (polar) organometallic sites on the dendrimer periphery results in stronger adsorption interactions between the dendritic catalyst and the silica and thus a better separation from the product. Two types of dendritic catalysts were prepared in which either tricyclohexylphosphine (**42**) or an imidazolin-2-ylidene carbene (**43**) acted as a ligand. Dendritic catalyst **42** was applied in the RCM reaction of diallyl tosylamine (1.25 mol % **42**, CH_2Cl_2, 40 °C, 15 min). The catalyst was recycled five times by column chromatography over silica using CH_2Cl_2 to isolate the cyclic product and ether for the elution of the dendritic catalyst. The cyclic product was isolated in more than 87% yield in all the cycles. Although some ruthenium metal had depleted from the recovered dendritic catalyst (13% after the first run), this did not affect the ring-closing activity (48% Ru content in the sixth cycle gave 87% yield after 15 min). Furthermore, remetalation of the vacant styryl sites on the dendritic support was possible. Dendritic catalyst **43** exhibits a higher activity than **42**. In contrast to **42** and its mononuclear analogue, **43** catalyzed the ring-closing metathesis of diene carbinol giving the product in a 78% yield. The dendritic catalyst was recovered in 90% yield after column chromatography with an 8% loss in Ru loading. Catalyst **43** also catalyzed effectively the tandem ROM/RCM of **44** to **45** (94% yield, 90% catalyst recovery, 8% Ru loss, Scheme 13) and the ROM/CM of **46** with styrene to **47** (70% yield) and **48** (18% yield) (>98% trans-alkenes, 95% catalyst recovery, 5% Ru loss, Scheme 13). In contrast to the mononuclear complex **41** dendritic catalyst **43** was com-

Scheme 13



Scheme 14



pletely separated from the reaction products via column chromatography.

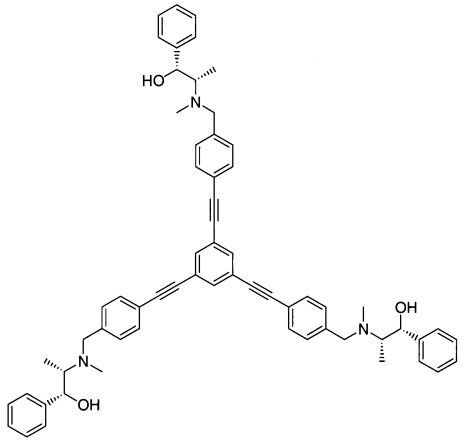
It should be emphasized that in these systems the ruthenium catalysts are released from the dendritic support during the reaction, and therefore, on one hand the activities are high, but, on the other hand, it hampers the application of this type of catalysts in continuous processes.

2. Asymmetric Dialkyl Zinc Addition

Sato et al. synthesized two generations poly(phenylacetylene) dendrimers (**49**−**50**) derivatized with (1*R*,2*S*)-ephedrine.[51] The dendrimers were used as ligands for the asymmetric diethylzinc addition to aryl *N*-diphenylphosphinyl imines (phenyl, 2-naphthyl, tolyl, Scheme 14). Slightly higher enantioselectivities were reached with **49** compared to **50** in the diethylzinc addition to phenyl, 2-naphthyl, and tolyl *N*-diphenylphosphinyl imine (respectively, 89, 94, 89% ee for **49** and 87, 90, 85% ee for **50**). After the reaction of diethylzinc with phenyl *N*-diphenylphosphinyl imine ligand **50** was recovered from the reaction mixture in 80% yield using thin-layer chromatography on silica gel. The dendritic ligand was used in a consecutive reaction with slight loss in enantioselectivity (87% ee in the first run, 81% ee in the second run).

The same dendritic ligands were used for the dialkyl zinc (isopropyl and ethyl) addition to aldehydes (phenyl, 2-naphthyl, tolyl).[52] Both ligands were equally selective toward the (*R*)-alcohol product (77% ≤ ee ≤ 86% depending on the substrate). Dendrimer **49** was recovered after the reaction between diethylzinc and benzaldehyde by thin-layer chromatography and reused in a consecutive run without loss in enantioselectivity.

Sato et al. synthesized two generations carbosilane dendrimers bearing, respectively, four and 12 (**51**) (1*R*,2*S*)-ephedrine ligands at their periphery.[53] The dendrimers were used as ligands in dialkylzinc (ethyl and isopropyl) additions to several arylaldehydes.



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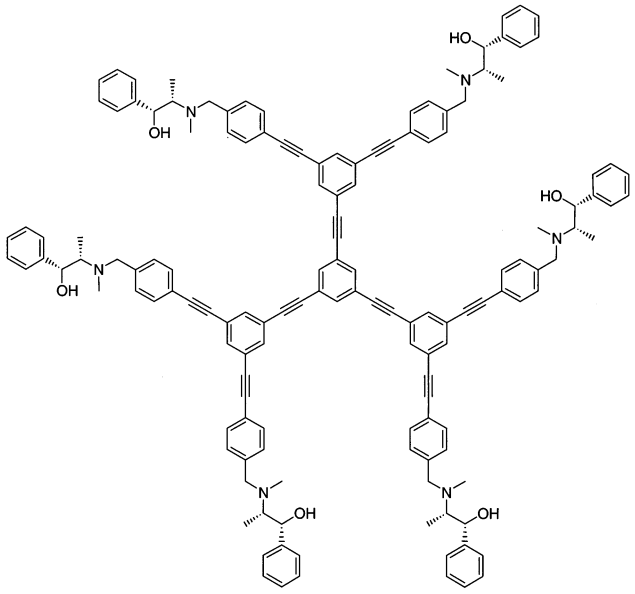
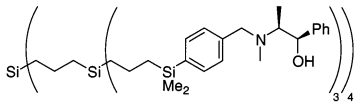


50

Comparable yields and stereoselectivities were obtained with both generation dendrimers, indicating

that the catalytic sites operate independently. Dendrimer **51** was recovered after the reaction by thin-layer chromatography and reused in a second run. A small drop in activity was observed (79% yield compared to 83% in the first run), while the stereoselectivity remained the same (83% ee versus 85% ee in the second run).

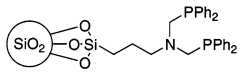


51

VI. Recovery of Heterogeneous Dendritic Catalysts

1. Supported Dendritic Catalysts for the Hydroformylation and Heck Reaction

Bourque et al. prepared phosphine-functionalized PAMAM poly(amido amine) branches that were anchored to the surface of silica particles. Primary amines were stepwise converted from G0 into G4.[54] Phosphination of the terminal amine groups occurred completely for G0 to G2 (**52**−**54**), but for G3 and G4 steric crowding prevented complete functionalization. Subsequent reaction with $[RhCl(CO)_2]_2$ gave the corresponding metal complexes, which were tested in alkene hydroformylation. Using styrene as a substrate, the dendritic catalysts afforded aldehydes in nearly quantitative yield even at room temperature. They showed high regioselectivity to the branched product (linear-to-branched ratios as high as 1:30). The third and fourth generation catalysts showed appreciable activity at elevated temperatures only.



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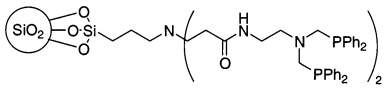

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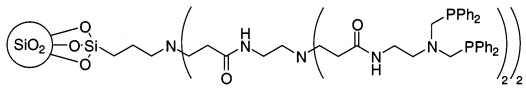

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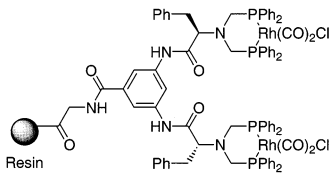
To study the impact of steric congestion on the hydroformylation reaction, a new series of ligands was prepared, differing in flexibility as a result of variation in spacer length.[55] From comparison of the catalytic activity of these ligands they concluded that steric congestion indeed lowered the activity.[56] The reusability of the immobilized catalysts has been tested by performing recycling experiments. Recovery of the catalyst was relatively easy since the particles were large enough to be separated by microporous filtration. No significant loss of activity or selectivity was observed during five consecutive runs.



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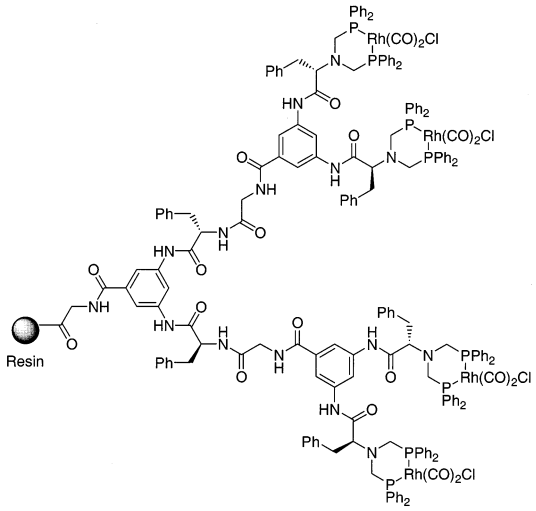

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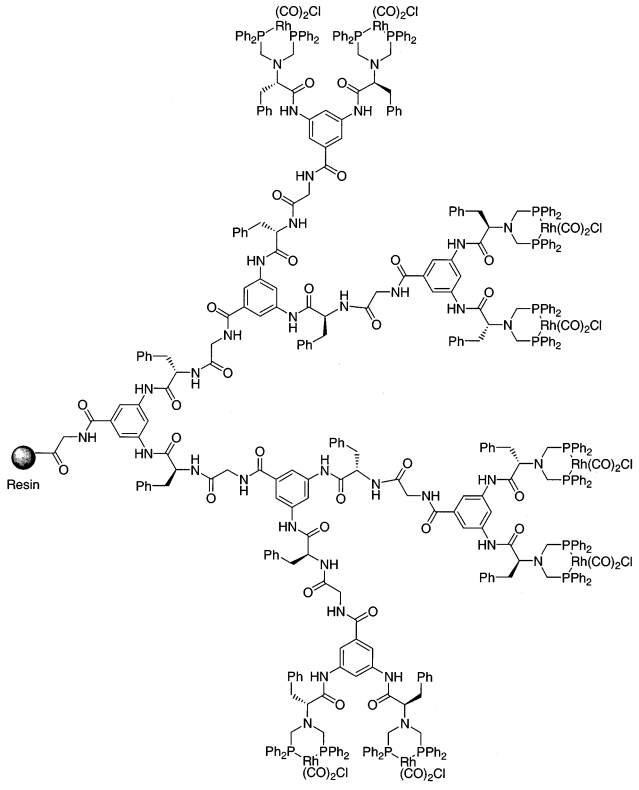

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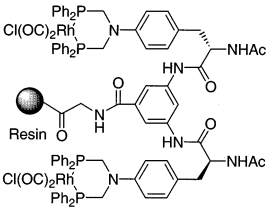
Arya et al. also immobilized rhodium complexes of dendrimers for the hydroformylation on polystyrene (PS) beads.[57] Three generations resin-bound rhodium-complexed dendrimers were constructed using solid-phase synthesis (**55**−**57**). The hydroformylation of styrene was studied and recycling experiments were performed with the three immobilized dendrimers over six consecutive runs. Applying a total pressure

of 1000 psi CO/H_2 (1:1) at 45 °C **56** and **57** gave complete conversion after 22 h for the first four cycles. The branched-to-linear ratio varied between 9:1 and 16:1. In the fifth and sixth run a drop in activity was observed for both **56** (respectively, 98 and 88% after 22 h) and **57** (respectively, 78 and 47% after 22 h). The activity of the second and third generations **56** and **57** surpassed that of the first generation **55** (85% conversion after 23 h in the third run). The second generation **56** was subsequently studied in three hydroformylation recycling experiments of vinyl acetate, vinyl benzoate, and *p*-methoxystyrene. The immobilized dendrimer was recycled three times in these experiments without loss in reactivity and regioselectivity. As expected, high selectivities toward the branched products were observed. Vinyl acetate as a substrate gave a branched-to-linear ratio of 15:1 in three subsequent runs. The branched-to-linear ratio obtained with vinyl benzoate as the substrate varied per cycle: first cycle b/l = 40:1, second cycle b/l = 60:1, and third cycle b/l = 22:1. Using *p*-methoxystyrene as the substrate a branched-to-linear ratio of approximately 10:1 was obtained.



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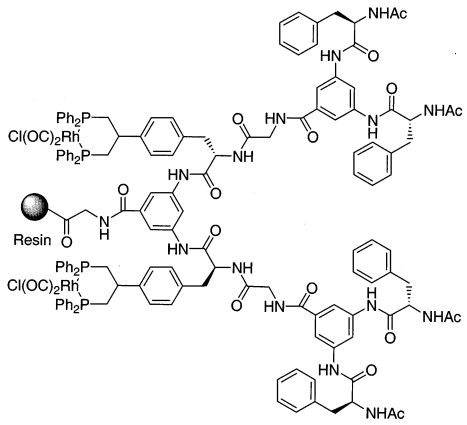


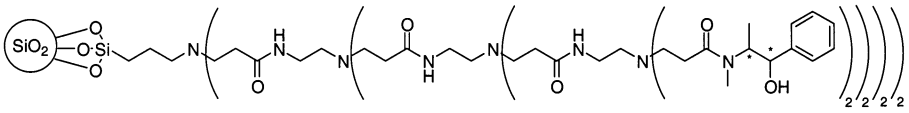
59

Arya et al. used solid-phase synthesis to prepare immobilized dendritic catalysts with the rhodium center in a shielded environment to mimic nature's approach of protecting active sites in a macromolecular environment (e.g., catalytic sites inside enzymes).[58] Two generations PS immobilized rhodium-complexed dendrimers, **58** and the more shielded **59**, were synthesized. The PS resin immobilized rhodium-complexed dendrimers were used in the hydroformylation of styrene, *p*-methoxystyrene, vinyl acetate, and vinyl benzoate using a total pressure of 1000 psi 1:1 CO/H_2 at 45 °C in CH_2Cl_2. Using styrene as substrate both **58** and **59** could be recycled four times without significant loss in activity or selectivity (>99% conversion after 20 h; branched-to-linear ratio ≈ 18:1). When *p*-methoxystyrene was used as a substrate the first three cycles did not suffer from deactivation (>99% conversion after 20 h, branched-to-linear ratio ≈ 17:1). The fourth cycle did not reach full conversion after 20 h, neither for **58** (56% conversion, branched-to-linear ratio = 30:1) nor for **59**, although this more shielded dendritic catalyst did reach a higher conversion (85% conversion, branched-to-linear ratio = 30:1). In the hydroformylation of vinyl acetate **58** and **59** gave similar results. Comparable selectivities (branched-to-linear ratio ≈ 17:1) and slightly declining activities per cycle were observed (99% conversion for the second cycle → 85% conversion for the fifth cycle). Using vinyl benzoate as substrate the immobilized dendrimers **58** and **59** could be recycled with constant activity and selectivity for three cycles (>99% conversion after 20 h, branched-to-linear ratio ≈ 25:1). In the fourth and fifth cycle deactivation of both catalysts was observed. A dramatic drop in activity was found for **58** (fourth cycle, conversion 43%; fifth cycle, conversion 20%). A smaller drop in activity was observed for **59** which was speculated to be due to the larger dendritic environment (fourth cycle, conversion 91%; fifth cycle, conversion 83%). Determination of the turnover numbers of both systems should give conclusive support for this dendritic effect.

Alper et al. also investigated the use of phosphine-functionalized PAMAM dendrimer immobilized on silica (**52**−**54**) as ligands in the palladium catalyzed Heck reaction.[59] Good yields were found in the Heck reaction of bromobenzene with styrene at 110−140 °C for the dendrimer generation 0, 1, and 2, generation 2 being the most active. Dendrimer generations 3 and 4 gave less active catalysts, which was also observed for the hydroformylation reaction and attributed to surface congestion. Again, this crowding problem was solved by utilizing longer spacers between the dendritic branch points (vide supra).[55] The effect of the base on the reaction rate was studied with the second generation dendrimer in the reaction between bromobenzene and styrene. The use of triethylamine resulted in a very low reaction rate whereas sodium acetate and potassium carbonate gave the best yields. A drop in activity was found when the catalyst was used in a second cycle (K_2CO_3: 53% *trans*-stilbene in the first cycle, 43% in the second cycle; NaOAc: 39−69% in the first cycle, 20−45% in the second cycle). Substrates ranging from electron donating to electron withdrawing para-substituted haloarenes (Cl, Br, I) were tested in the Heck reaction with styrene and butyl acrylate. The presence of electron withdrawing groups (nitro, ester) on the haloarene substrate results in lower yields in comparison to the electron donating substrates.

2. Supported Dendritic Catalysts for the Asymmetric Addition of Diethylzinc to Benzaldehyde

Chung et al. synthesized silica supported PAMAM dendrimers up to the fourth generation containing an (−)-ephedrine auxiliary (**60**) for the diethylzinc addition to benzaldehyde.[60] Silica particles with a low



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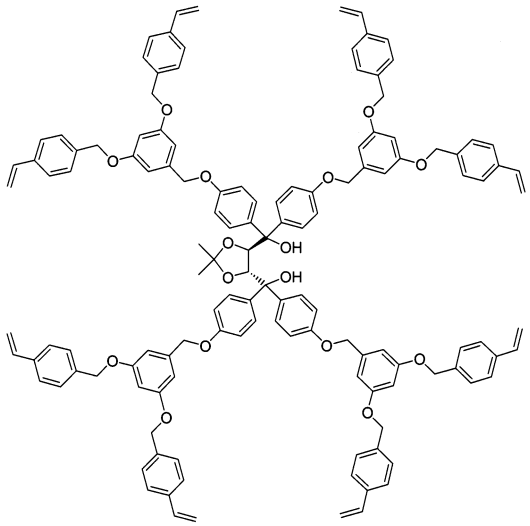

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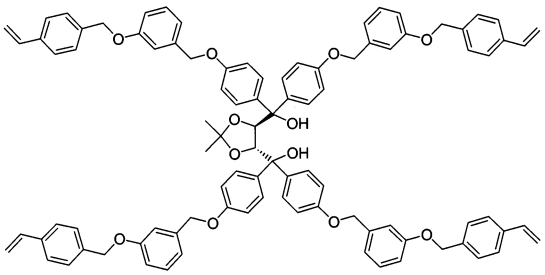

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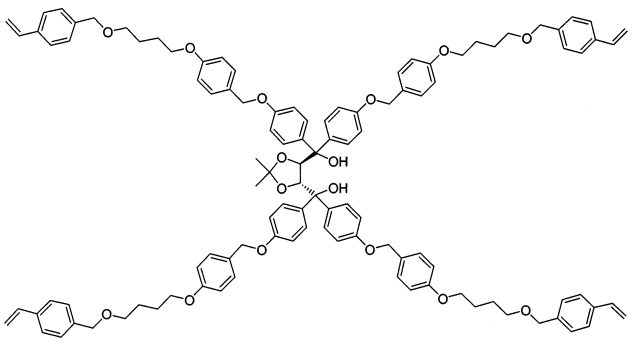

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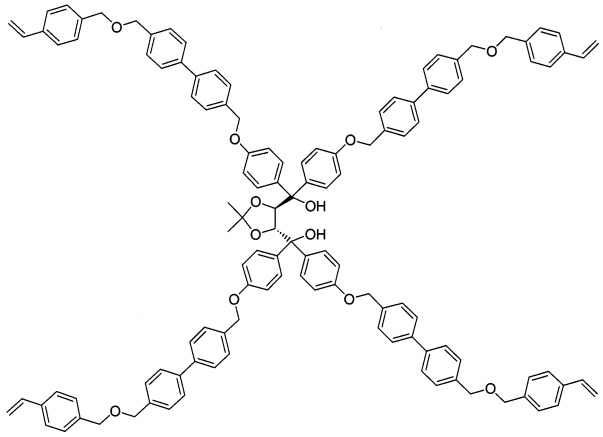

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and high PAMAM loading were prepared starting from 0.24 mmol g^{-1} and 0.9 mmol g^{-1} amine initiator sites, respectively. Amine end group analysis showed that propagation of dendrimer growth became increasingly difficult with the generation probably due to steric crowding. Larger deviations from the theoretical amine end group values were found for the high-loaded materials. The activity and (stereo)-selectivity in the diethylzinc addition to benzaldehyde of the two types of modified silica were investigated (5 mol % catalyst, 2.2 equiv of diethylzinc, 0 °C, toluene, 48 h). In the case of the high loading a gradual decrease in activity, selectivity, and enantioselectivity upon going to higher generation dendrimer-modified surfaces was observed. The diminished activity and selectivity is explained by a diffusional resistance induced by the irregular hyperbranched structure. The irregular branching, caused by incomplete functionalization during the dendrimer growth, is believed to generate different chiral environments leading to loss in enantioselectivity; in part the occurrence of the background reaction (no ligand: 45% conversion, 57% selectivity to the racemic mixture) can account for these results. Interestingly, a different trend is found for the low-loaded silica supports. The activity, selectivity, and enantioselectivity were found to increase upon going to the third generation. Under optimized reaction conditions, the third generation silica supported dendrimer gave identical results in the addition reaction as the homogeneous monomer (−)-ephedrine. The fourth generation showed a slightly lower activity and stereoselectivity probably due to hindered access of the reagents to the catalytic sites. This effect was also found for similar dendritic catalysts in solution.[61] The third generation silica supported dendrimer was recycled three times without loss in activity, selectivity, and enantioselectivity.

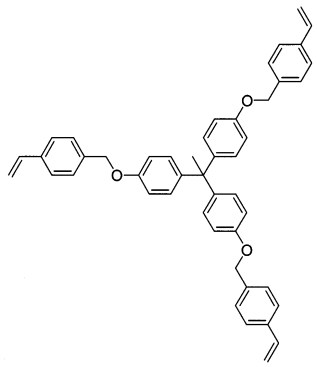
Rheiner et al. developed strategies to incorporate dendritic ligands (TADDOL and BINOL based) in a polystyrene matrix.[62] A first and second generation TADDOL core-functionalized polybenzyl ether dendrimer with peripheral styryl groups (respectively, 8 and 16) have been synthesized and build into a polystyrene matrix through a suspension copolymerization. The Ti-TADDOLate derivatives were synthesized by reacting the beads with $Ti(OiPr)_4$. The polymer-incorporated dendritic Ti-TADDOLates proved much more active in the reaction of diethylzinc with benzaldehyde than a conventional PS bound Ti-TADDOLate, giving virtually the same enantioselectivities. The high activity was attributed to the dendritic structure preventing the burial of the

catalytic sites in the polystyrene matrix. Enantioselectivities comparable with those of the homogeneous Ti-TADDOLate could be reached when 0.2 equiv of the Ti-TADDOLates were used (99% ee (*S*), heterogeneous 98% ee (*S*)). Higher enantioselectivities were obtained when the Ti-TADDOLate content in the polymer was lower as a result of the lower degree of cross-linking. No difference between the first and second generation dendrimers was observed.

Sellner et al. studied this type of systems in more detail using cross-linkable TADDOL derivatives containing a variety of flexible linkers with peripheral styryl groups, including a dendritic analogue (**61**−**64**).[63] The derivatized TADDOL systems were copolymerized with styrene and treated with $Ti(OiPr)_4$ to yield the polymer-bound Ti-TADDOLates p-**61**−p-**64** (diameter in nonsolvent-swollen state $\sim 400\ \mu$m). The enantioselectivities in the reaction of diethylzinc with benzaldehyde (0.2 eq., toluene, −20 °C, 2 h) applying the different polymer-bound Ti-TADDOLates with a loading of 0.1 mmol g^{-1} over 20 cycles was investigated. The best results were obtained with the PS beads cross-linked with dendritic TADDOL derivative p-**61**, yielding a constant enantioselectivity (98% ee (*S*)) over the consecutive cycles. A kinetic study of the homogeneous TADDOL-Ti-complex and polymer-bound Ti-complex p-**61** revealed that the activity of p-**61** was slightly higher. Longer chain lengths of the linkers resulted in a dramatic drop in both selectivity and activity. Furthermore, the swelling properties of p-**62**, p-**63**, and p-**64** decreased after multiple uses, while p-**61** kept its high swelling properties. As was observed before, higher Ti-TADDOLate loadings of the polystyrene matrix gave lower selectivities.

In an attempt to circumvent the tedious synthesis of dendritic TADDOL cross-linkers such as p-**61**, Sellner et al. prepared cross-linked TADDOL polymers by copolymerizing achiral dendrimers **65**−**67** and TADDOL monomer **68**.[64] The polymers were synthesized with a comparable degree of cross-linking and loading as p-**61** (0.10 mmol g^{-1} and 0.24 mmol g^{-1}). The cross-linked polymers p-**65**−p-**67** with a loading of 0.24 mmol of TADDOL g^{-1} were converted into the Ti-TADDOLates p-**65**·$Ti(OiPr)_2$ − p-**67**·$Ti(OiPr)_2$ and tested for multiple usages in the diethylzinc addition to benzaldehyde. The stereoselectivities after the first run were with the different Ti-TADDOLates were comparable (97−98% ee). After 20 cycles a decrease in ee of 2−3% was observed in all cases, as well as a decrease in reactivity and swelling properties of the polymers. Decreasing the loading from 0.24 to 0.10 mmol g^{-1} did not improve the catalytic performance as was the case with p-**61**·$Ti(OiPr)_2$. From the better performance of p-**61** over p-**65**−p-**67** it was concluded that the location of the TADDOL in the core of a dendritic cross-linker is necessary to obtain polymeric materials with outstanding catalytic activity.

Sellner et al. applied the same immobilization technique using a BINOL ligand. The cross-linkable peripheral styryl functionalized BINOLs **69**−**71** and dendritic first generation **72** and second generation **73** were synthesized, copolymerized with styrene, and



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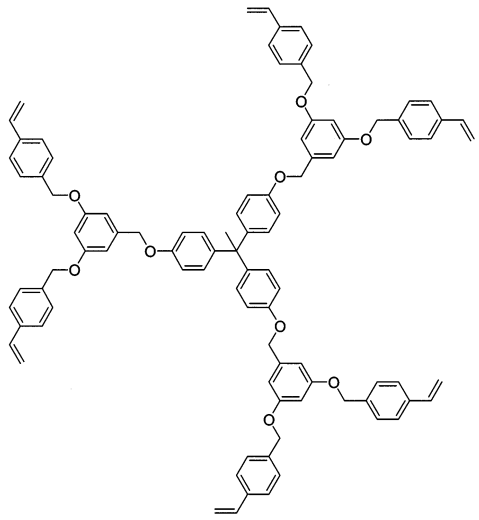

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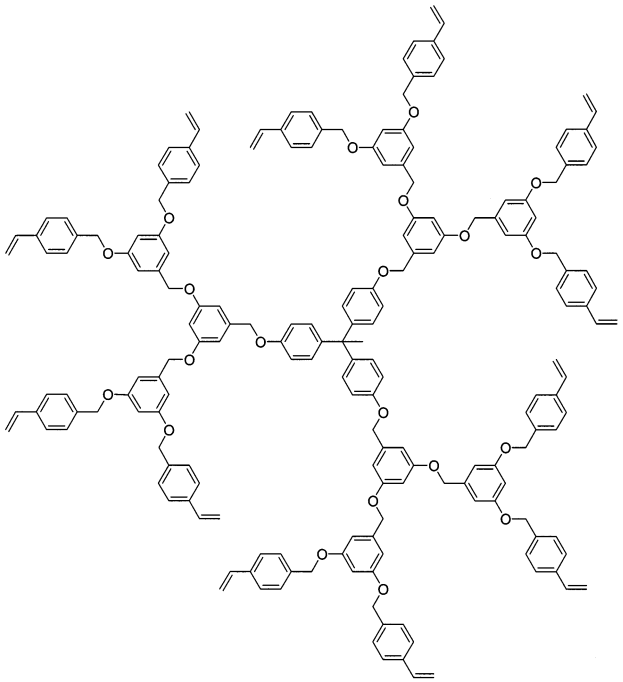

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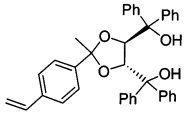

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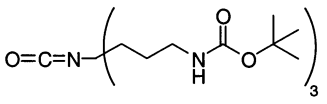
treated with $Ti(OiPr)_4$.[65] The recyclability over 20 cycles of the obtained Ti−BINOLates (loading 0.13 mmol g^{-1}) was studied in the addition reaction of diethylzinc to benzaldehyde. Again, the best results were obtained with the immobilized dendritic BINOLate p-**72** giving constant enantioselectivities (S/R 93:7) over 20 cycles. After 20 cycles polymer-bound BINOLates **70** and **71** displayed a slight loss of enantioselectivity (respectively, 5 and 7% loss). Materials based on **69** and **73** gave catalysts that were less stable.



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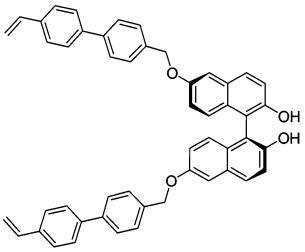

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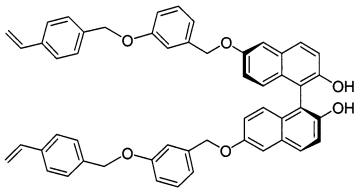

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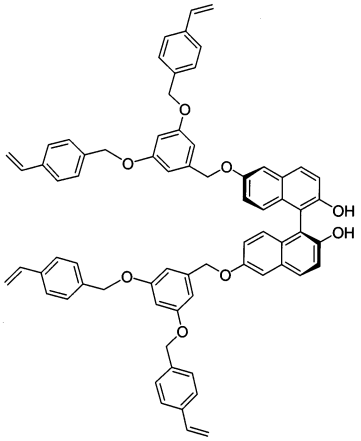
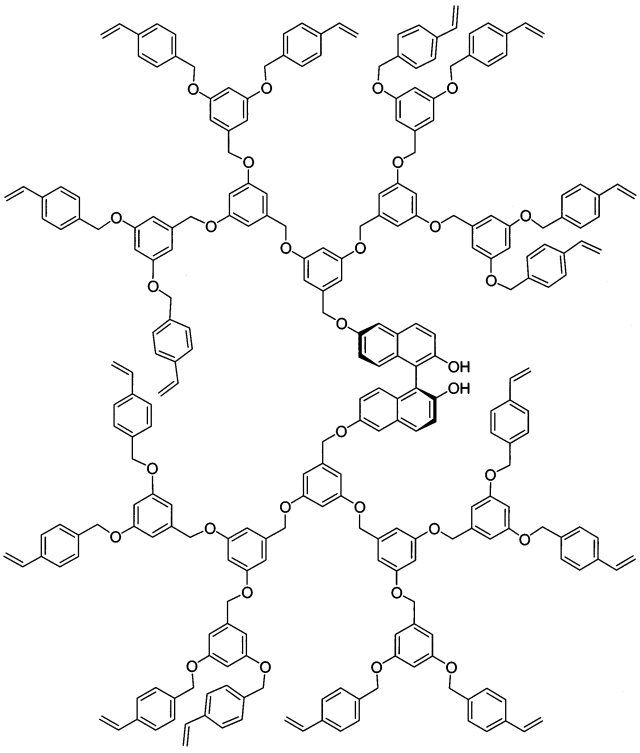


72

The cross-linked dendritic BINOLate p-**72** (20 mol %) was subsequently used in the asymmetric cyanosilylation of pivalaldehyde in CH_2Cl_2. The reaction was performed 20 times yielding the cyanohydrine product in >90% yield after each cycle. Initially, an increase in enantioselectivity was observed from 72% ee in the first run (*S*-enantiomer, comparable



73

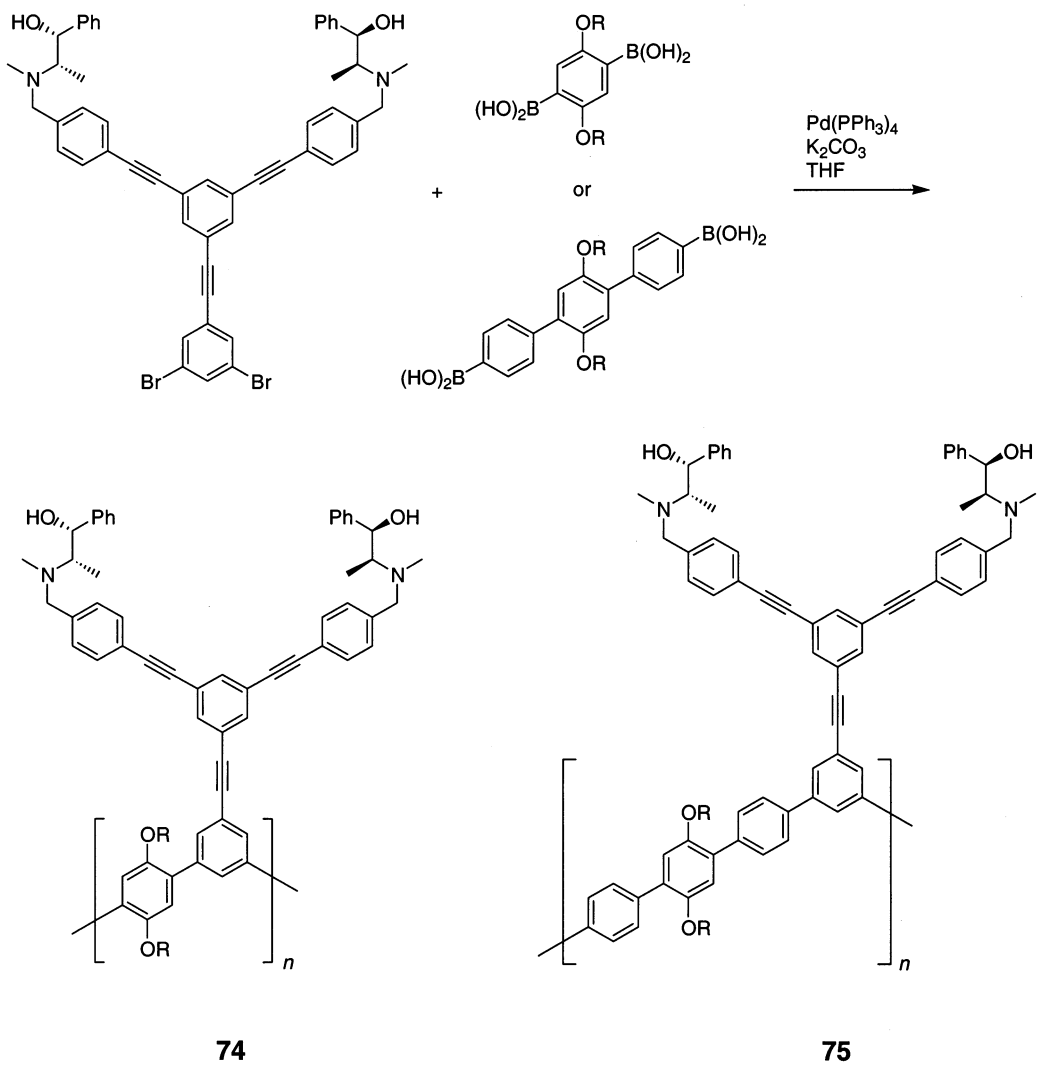
with the homogeneous BINOL-Ti catalyst) to 83% ee after the fifth run. After the eighth run, a gradual decrease in enantioselectivity was observed that was caused by leaching of the titanate. Reloading the vacant sites with $Ti(OiPr)_4$ caused a gradual increase of the enantioselectivity per cycle.

Hu et al. synthesized (1*R*,2*S*)-ephedrine functionalized dendronized polymers and applied these as ligands in the diethylzinc addition to benzaldehyde.[66] Linear dendronized polymers **74** and **75** were prepared by Suzuki polymerizations from a dendronized monomer and a specific diboronic acid (Scheme 15). Both dendronized (soluble) polymers were active in the diethylzinc addition to benzaldehyde giving stereoselectivities of 75% ee and 73% ee for **74** and **75**, respectively. These values are somewhat lower than that obtained with dendrimer **49** (78% ee).[51] In contrast to dendrimer **49**, **74** and **75** could easily be recovered by filtration (after precipitation) and reused without loss in both activity and stereoselectivity.

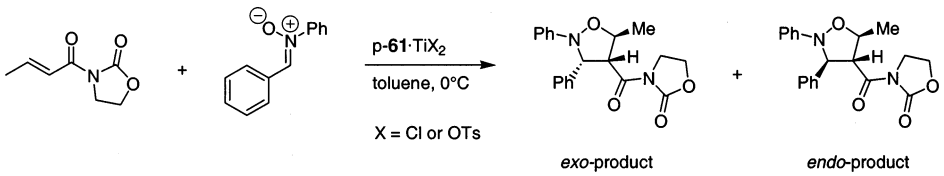
3. Supported Dendritic Catalyst for the 1,3-Dipolar Cycloadditions of Diphenyl Nitrone to [(*E*)-But-2-enoyl] Oxazolidinone

Sellner et al. loaded p-**61** with $TiCl_2(OiPr)_2$ and applied the obtained material in the enantioselective 1,3-dipolar cycloadditions of diphenyl nitrone to [(*E*)-but-2-enoyl] oxazolidinone (Scheme 16).[63] High conversion could only be obtained when 50 mol % of p-**61**· TiCl2 was used, affording an exo/endo ratio of 82:18 combined with a 75% ee of the exo-product at 93% conversion. The obtained selectivities were only slightly lower than those obtained with tetraphenyl $TiCl_2$-TADDOLate in a homogeneous reaction (exo/endo ratio = 90:10, 79% ee exo-product at 94% conversion).

Scheme 15



Scheme 16



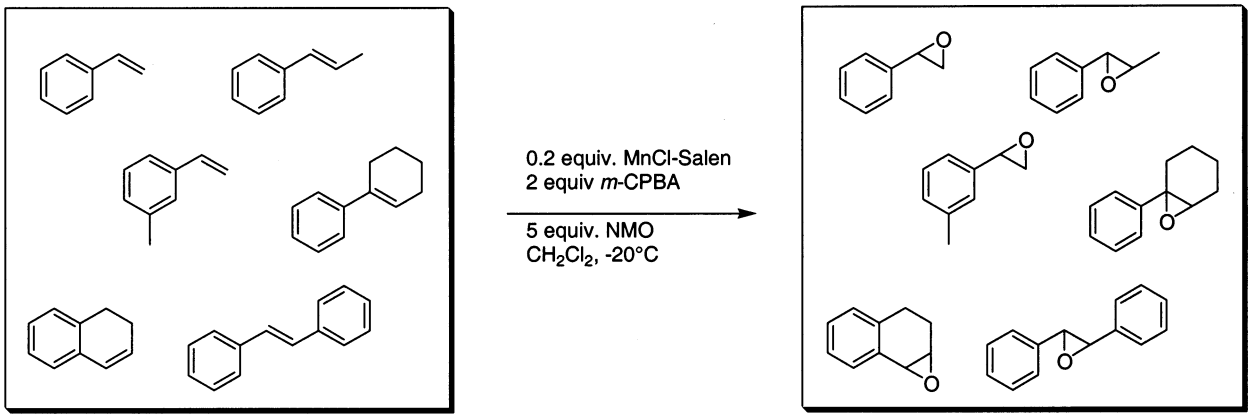
Recycling the Ti-TADDOLate by a simple filtration and washing procedure was not possible. Regeneration of the catalyst by an acidic hydrolysis and reloading of the polymer gave p-**61**·$TiCl_2$. The Ti-TADDOLate p-**61**·$TiCl_2$ could be reused six times applying this procedure without loss in the diastereo- and enantioselectivities (conversion between 80 and 96%).

The exo/endo ratio could be changed by using titanium tosylate as the precursor. Ti-TADDOLate p-**61**·$Ti(OTs)_2$ catalyzed the cycloaddition with an exo/endo selectivity of 12:88, yielding the endo-product in 93% ee at 72% conversion. These results were only slightly lower than those obtained for the homogeneous reaction using tetraphenyl $Ti(OTs)_2$-TADDOLate. Recycling of the p-**61**·$Ti(OTs)_2$ was only possible after regeneration of the active species after each cycle. No change in diastereo- and enantioselectivity was observed for 4 consecutive cycles.

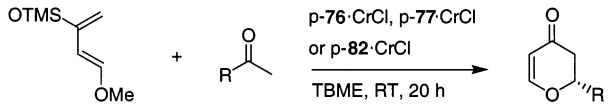
4. Supported Dendritic Catalyst for Enantioselective Epoxidations and Hetero-Diels Alder Reactions

In analogy with the immobilization of styryl-derivatives of TADDOL and BINOL ligands by suspension copolymerization with styrene, Sellner et al. used dendritically modified Salen cross-linkers to prepare recyclable catalyst for the enantioselective epoxidations and hetero-Diels Alder reactions.[67] (*R*,*R*)-1,2-Cyclohexane diamine and (*R*,*R*)-1,2-diphenyl ethylenediamine were used as backbones in the synthesis of the cross-linkable model compounds **76** and **77**, the first and second generation dendritically modified Salen cross-linkers **78**−**81**, and the first generation dendritically modified Salen cross-linkers **82** and **83**. These modified Salen ligands were copolymerized with styrene yielding polystyrene beads with an

Scheme 17

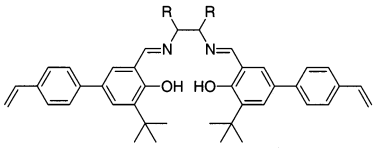


Scheme 18



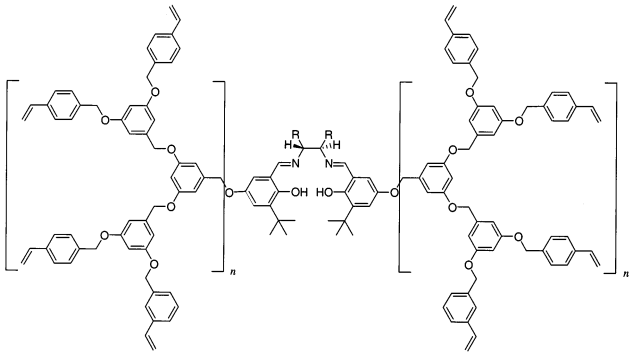
R = Ph, pentyl or cyclohexyl

average diameter of 500 μm. The beads were almost quantitatively loaded with either manganese chloride or chromium chloride (complexation >95% as determined by elemental analysis). Dendrimers analogous to **78**−**81**, but lacking the styryl peripheral groups, were also synthesized. The enantioselective epoxidations of a variety of alkenes using dendritic Salen manganese chloride and the cross-linked Salen complexes p-**78**·MnCl−p-**83**·MnCl (Scheme 17) were studied. It was found that the epoxidations performed with the cross-linked Salen complexes were in all cases comparable with the homogeneous analogues.



76 R = –$(CH_2)_4$–

77 R = Ph

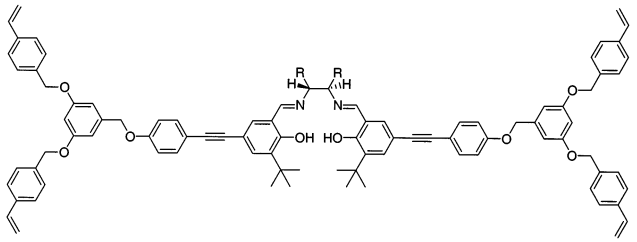


78 R = –$(CH_2)_4$–, n = 0

79 R = Ph, n = 0

80 R = –$(CH_2)_4$–, n = 1

81 R = Ph, n = 1



82 R = –$(CH_2)_4$–

83 R = Ph

The reusability of the cross-linked catalysts in the epoxidation of styrene and 3-methylstyrene was studied using complexes p-**76**·MnCl−p-**76**·MnCl and p-**82**·MnCl−p-**83**·MnCl; the catalysts were recycled 10 times. The model PS-bound Salen complexes p-**76** and p-**77** catalyzed the epoxidation without any loss in activity and selectivity. The dendritically cross-linked Salen complexes p-**78** and p-**79**, however, displayed a loss in activity and stereoselectivity, even after reloading the PS-support with fresh manganese chloride. The loss in activity was attributed to oxidation of the Salen moieties—probably due to the hydroquinone structure of the Salen core—during catalysis. The polymer-bound complexes p-**82**·MnCl and p-**83**·MnCl, having an acetylene spacer, could be recycled 10 times without loss in both activity and stereoselectivity.

The cross-linked CrCl−Salen complexes p-**76**·CrCl, p-**78**·CrCl, and p-**82**·CrCl were studied in the asymmetric hetero-Diels−Alder reaction between Danishefsky's diene and various aldehydes (Scheme 18). The selectivities obtained in all cases were only slightly lower than those obtained under homogeneous conditions using unsubstituted CrCl−Salen. The reusability of the polymer-bound CrCl−Salen complexes was studied by performing the hetero-Diels−Alder reaction in five consecutive runs. Both p-**76**·CrCl and p-**78**·CrCl displayed a decrease in conversion over the consecutive runs, which surprisingly was accompanied by an increase in the selectivity. The best result was obtained using p-**78**·CrCl, which could be recycled up to 10 times without any loss in activity or selectivity.

5. Scandium Cross-Linked Dendrimers as Lewis Acids Catalysts

Reetz and Giebel heterogenized sulfonylated poly(propylene imine) dendrimers by a cross-linking reaction with $Sc(OTf)_3$, resulting in a nonporous material (**84**, Figure 13).[68] The cross-linked scandium

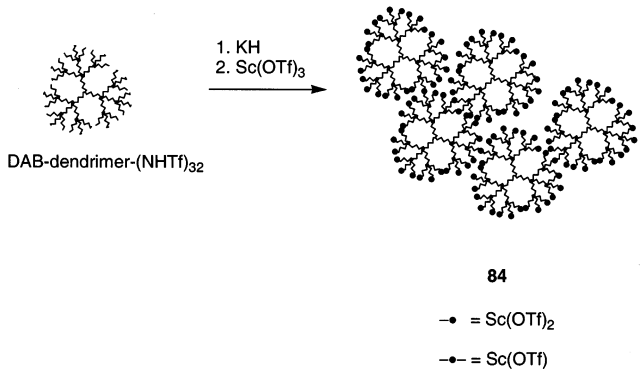


Figure 13. Schematic representation of a scandium triflate cross-linked fourth generation poly(propylene imine) dendrimer (DAB-dendrimer).

modified dendrimer was tested in a number of Lewis acid-catalyzed reactions, including Mukaiyama aldol additions to aldehydes and aldimines, Diels−Alder reactions and Friedel−Crafts acylations. The dendritic material was recovered by a simple filtration step. The Mukaiyama aldol addition was performed in a two-phase system, stirring benzaldehyde, aniline, and trimethyl-(1-phenyl-propenyloxy)-silane at room temperature in the presence of the dendritic material **84** (7 mol % of scandium). The aldimine product, β-amino ketone, was the only product formed in a yield of 89%. Recycling of the catalysts gave the same results (over three runs 88−89% yield was obtained). ICP analysis of the filtrate and the absence of catalytic activity of the filtrate proved that no scandium had leached from the dendritic material. The chemoselectivity of the dendritic material toward the aldimine adduct is much better compared to the "monomeric" $Sc(OTf)_3$ homogeneous catalyst that gave rise to a 86:14 product mixture of the β-amino ketone over β-alcohol ketone. This increase in selectivity was attributed to the ligand effect.

In the Mukaiyama aldol additions of trimethyl-(1-phenyl-propenyloxy)-silane to benzaldehyde and cinnamaldehyde catalyzed by 7 mol % heterogenized scandium catalyst 1:1 mixture of diastereomers were obtained. Again, the catalyst could be recycled easily without any loss in performance. The scandium cross-linked dendritic material appeared to be an efficient catalyst for the Diels−Alder reaction between methyl vinyl ketone and cyclopentadiene. The Diels−Alder adduct was formed in dichloromethane at 0 °C in 79% yield with an endo/exo ratio of 85:15. Finally the material was used as a Friedel−Crafts acylation catalyst (7 mol % scandium) for the formation of *p*-methoxyacetophenone in a 73% yield from anisole, acetic acid anhydride and lithium perchlorate at 50 °C in nitromethane.

6. Dendrimer-Bound Pd(II) Complex for Selective Hydrogenations

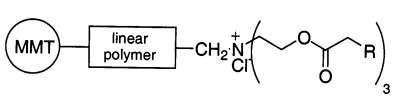
Mizugaki et al. synthesized dendritic complex **1a** and studied its catalytic activity in the selective hydrogenation of conjugated dienes to mono-enes.[69] The reactions were performed in ethanol in which the dendritic catalyst was not soluble. The hydrogenation activity was monitored by the hydrogen uptake in time. In the hydrogenation of cyclopentadiene complex **1a** displayed considerable activity toward the mono-ene (1.39 mL of H_2 min^{-1}). The subsequent hydrogenation to cyclopentane was significantly slower (0.1 mL of H_2 min^{-1}). The heterogeneous catalysts Pd/Al_2O_3 and Pd/C showed higher activity, but no selectivity toward the mono-ene product. The monomeric complex $PhN(CH_2PPh_2)_2PdCl_2$ was hardly active, whereas the addition of triethylamine resulted in moderate activity compared to **1a**. Cyclooctadiene was monohydrogenated with an initial rate of 1.80 mL of H_2 min^{-1} to cyclooctene. Complex **1a** was recovered from the reaction mixture by centrifugation, washed, dried, and reused in a consecutive run without considerable loss in activity (1.76 mL of H_2 min^{-1}).

7. Dendrimers Supported on Montmorillonite

Kenawy immobilized ammonium and phosphonium peripheral functionalized dendritic branches on a montmorillonite supported chloromethylstyrene/methyl methacrylate copolymer (**85**−**86**).[70] These polymer/montmorillonite supported dendrimers were employed as phase transfers catalysts (PTC) for nucleophilic substitution reaction between *n*-butyl bromide and thiocyanate, cyanide, and nitrite anions in a toluene or benzene/water system. Filtration of the functionalized montmorillonite from the reaction mixture allowed recycling of these PT catalysts. Generally higher activities were found at elevated (reflux) temperatures. The phosphonium-functionalized systems were found to be more active than the ammonium chloride analogues. A recycling experiment was performed in the reaction of *n*-butyl bromide with thiocyanate in benzene/water at reflux temperature (10% PCT **85b**). In three consecutive runs, only a small drop in activity was found (yield after 15 h respectively 100, 96, and 96%). A similar experiment was performed with PCT **86b** in toluene/water (5% PCT). At reflux temperature, a yield of 99% was obtained after 9 h, whereas in a consecutive run a slightly lower yield (95%) was obtained.

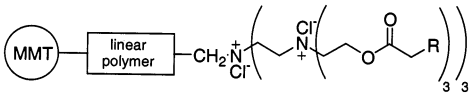
VII. Dendritic Catalysts Applied in Two-Phase Catalysis

The use of biphasic systems, in which the catalyst and product are dissolved in different phases facilitating separation and recycling, has been a subject of wide interest. The successful application of the two-phase rhodium-TPPTS Ruhrchemie/Rhone Poulenc hydroformylation of propene for the production of butanal, has stimulated the research in this area.[71] More recently, Horváth and Rábai introduced fluorous phases as an alternative for water, which



85a: R = $(NEt_3)^+Cl^-$

b: R = $(PPh_3)^+Cl^-$



86a: R = $(NEt_3)^+Cl^-$

b: R = $(PPh_3)^+Cl^-$

triggered the development of catalysts that are soluble in the fluorous phase.[2] Solubilization of the ligand in the desired phase by attaching either water-soluble groups or fluorous tails is generally sufficient to allow efficient recovery and recycling of the catalyst. Therefore, there is no urgent need to introduce a dendritic structure for these types of processes. As a result, the number of reports on the application of dendrimers in two-phase catalysis is limited.

1. Water-Soluble Dendritic Catalysts for Hydroformylation

Gong et al. synthesized four different water-soluble third generation monodentate phosphine containing PAMAM dendrimers (Figure 14, **87**−**90**).[72] In the dendrimers **87** and **89** the peripheral amine groups contribute to water solubility of the dendrimers, whereas in the analogues **88** and **90** the introduction of sulfonic acid groups assured the solubility in water. The hydroformylation of styrene and 1-octene with the rhodium complexes of the dendrimers with varying Rh/P ratios was studied (40 °C, water/toluene, $CO/H_2 = 1:1$ (20 bar)). For both substrates a higher branched-to-linear ratio compared to the reference ligand TPPTS was observed. Hydroformylation of styrene using **87** (Rh/P = 1:3) afforded a branched-to-linear ratio of 93:7 compared to 6:9 for TPPTS. A branched-to-linear ratio of 3:6 was found for the hydroformylation of 1-octene when **87** was applied as the ligand (TPPTS gave a ratio of 3:7[73]). Increasing the phosphorus-to-rhodium ratio resulted in a lower activity but a higher branched-to-linear ratio. Moreover, a higher phosphorus-to-rhodium ratio suppressed rhodium leaching into the organic phase (P/Rh = 2, 3.60 w%; P/Rh = 3, 1.86 w%; P/Rh = 4, 1.02 w%). Raising the reaction temperature facilitated the leaching of rhodium into the organic phase. Although the dendritic catalyst was separated from the product phase, no recycling experiments using these water-soluble dendritic catalysts have been reported.

2. Dendrimer-Encapsulated Palladium Nanoparticles for Hydrogenations

Zhao et al. developed a method for the synthesis of dendrimer-encapsulated metal nanoparticles based on sorbing metal ions into (modified) PAMAM dendrimers followed by a reduction. Dendrimers encapsulating copper,[74] palladium, and platinum nanoparticles have been prepared. Hydroxyl-terminated PAMAM dendrimers were used to prepare encapsulated Pd (PAMAM generations 4, 6, and 8) and Pt (PAMAM generation 4 and 6) nanoparticles. The dendrimer-encapsulated Pd and Pt nanocomposites catalyzed the hydrogenation reaction of allyl alcohol and *N*-isopropyl acrylamide in water.[75]

Extending their work Chechik et al. prepared self-assembled inverted micelles that encapsulated palladium nanoparticles.[76] The self-assembled inverted micelles were synthesized through an acid−base reaction between an amine-terminated fourth generation PAMAM Pd encapsulated-dendrimer and dodecanoic acid (Figure 15). The hydrogenation activity, using allyl alcohol as substrate, of the Pd nanoparticles encapsulated inverted micelles was compared with the activity of the hydroxy-terminated dendrimer-encapsulated Pd nanoparticles in water. The amine-terminated dendrimer-encapsulated Pd nanoparticles were solubilized in toluene containing 2% w/w of dodecanoic acid. The 0.05 mol % inverted micelle Pd catalyst gave a TOF of ∼760 mol of H_2 (mol of Pd)$^{-1}$ h^{-1} at 20 °C, whereas the water-soluble catalyst gave a TOF of 218 mol of H_2 (mol of Pd)$^{-1}$ h^{-1}. The inverted micelle could be extracted into the aqueous phase at pH 2, after which it could be reintroduced in the toluene/dodecanoic acid mixture after dialysis.

Using a similar approach Chechik and Crooks modified the PAMAM dendrimer-encapsulated Pd nanoparticles with perfluoropolyether tails utilizing noncovalent ion-pair interactions.[77] The catalytic hydrogenation of six substrates under biphasic conditions (toluene/perfluoro-2-butyltetrahydrofuran FC-

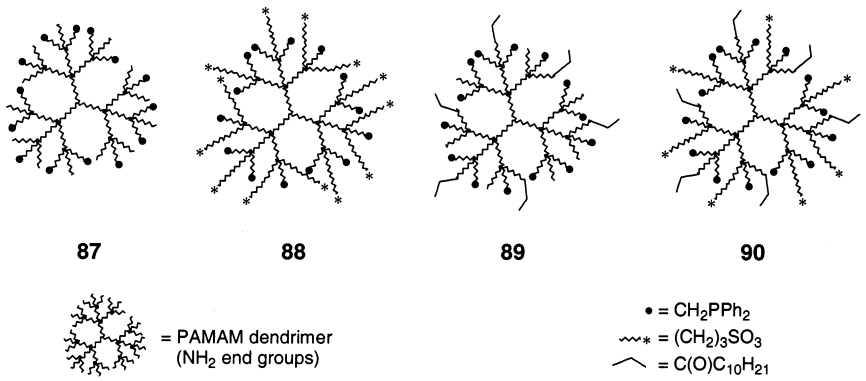


Figure 14. Schematic representation of four types of water-soluble PAMAM dendrimers containing phosphine ligands.

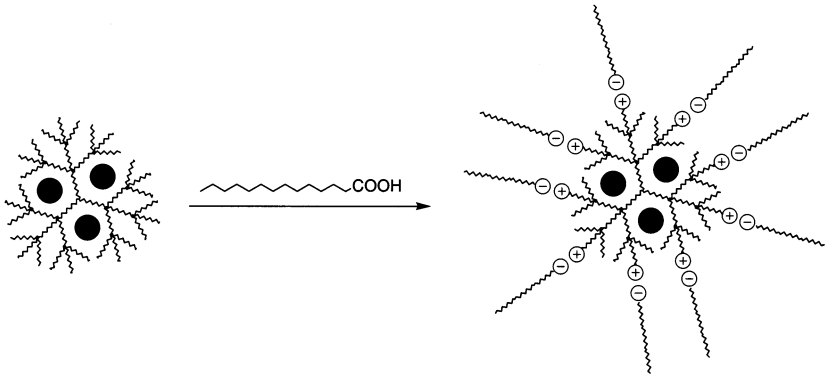


Figure 15. Schematic representation of the formation of an inverse micelle from a PAMAM dendrimer-encapsulated palladium nanoparticle.

75) was studied. Allyl alcohol, methyl acrylate, vinyl isopropenyl ether, and cyclohexene were hydrogenated with different turn-over frequencies (TOF, respectively, 400, 50, 10 and 3 mol of H_2 (mol of Pd)$^{-1}$ h^{-1}). The difference in activity is explained in part by the polar nano-environment within the dendrimer. The hydrogenation of 1-hexene resulted in the formation of hexane and the isomerized products 2- and 3-hexene. 1,3-Cyclooctadiene could be hydrogenated selectively to cyclooctene (99%). The Pd/dendrimer nanocomposite could be recycled up to 12 times without a significant loss in activity. No leaching of the catalyst into the organic phase was observed within experimental error.

3. Dendrimer-Encapsulated Palladium Nanoparticles for Heck Reactions

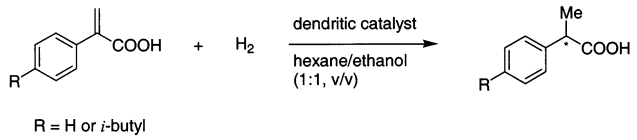
Yeung et al. synthesized dendrimer-encapsulated Pd nanoparticles from fluoropolyether modified poly(propylene)imine dendrimers G4 and G5 (containing 32 and 64 end groups, respectively) by introducing Pd^{2+} into the dendrimer interior followed by a reduction.[78] The Pd nanoparticles catalyzed the Heck reaction between bromo- or iodobenzene and *n*-butyl acrylate in a fluorocarbon/hydrocarbon solvent system at 90 °C. Higher yields were obtained with the nanoparticles prepared from the fifth generation dendrimer containing the same Pd loading (3−5%) as the fourth generation dendrimer. In the Heck coupling of bromobenzene to *n*-butyl acrylate the generation 4 dendrimer-encapsulated Pd nanoparticles gave 38% yield compared to 70% for the fifth generation dendrimer-encapsulated Pd nanoparticles. This effect was attributed to the difference in confinement of the Pd nanoparticles in the two dendrimers. The generation 5 dendrimer was proposed to give easier access to the substrates to reach the catalytic particles. The Pd nanoparticles could be reused although a loss of activity of 10−15% was observed in all cases. Pd analysis of the organic residue showed that no leaching of the metal into the organic phase had occurred (Pd content < 0.01 ppm). The loss in activity was explained by the change in morphology of the particle surface as a result of the redox cycling of the Pd atoms during the catalysis. The reaction could be performed in the absence of base (Et_3N) due to the presence of the tertiary amine groups in the dendrimer interior. In this case, however, the material becomes completely inactive after one run.

Rahim et al. studied the activity of hydroxyl modified PAMAM dendrimer-encapsulated Pd nanoparticles—previously prepared in the group of Crooks[75]—in the Heck reaction of arylhalides and acrylic acid.[79] They were able to catalyze the reaction with Pd loadings as low as 0.025 mol % in polar solvents (DMF or DMA) using sodium acetate as a base at 140 °C yielding the *trans*-cinnamic acid. No difference in catalytic activity was observed when using PAMAM-OH(G4)Pd_{60} or PAMAM-OH(G4)Pd_{40}. A recycling experiment in which the catalyst was contained in a dialysis bag was performed in DMF using triethylamine as the base. The yield in the Heck coupling of iodobenzene to acrylic acid was determined in three consecutive runs. A drop in activity was observed: 70% yield after the first run to 20 and 10% yield in the second and third run, respectively. The loss of activity was attributed to thermal decomposition of the PAMAM dendrimer.

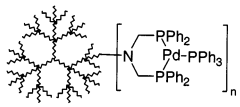
4. Two-Phase Allylic Aminations Using Thermomorphic Dendritic Catalysts

Mizugaki et al. recently utilized the thermomorphic properties of palladium(0)-complexed phosphinated dendrimers for dendritic catalyst recycling.[80] Using the method developed by Reetz et al.[23] they prepared dendritic ligands containing, respectively, 2, 8, 16, and 32 chelating diphosphines. Palladium dichloride was complexed to the dendrimers followed by a reduction in the presence of triphenylphosphine gave the palladium(0)-complexed dendrimers (**91**−**94**). The dendritic complexes were active as catalyst in the allylic amination reaction of *trans*-cinnamyl acetate with morpholine in DMSO at 40 °C yielding the linear and branched allylic amines (quantitative yield after 30 min for dendrimer **92**, linear-to-branched ratio = 90:10). No change in regioselectivity was observed for the different generation dendrimers applied. A change in the regioselectivity was observed when *cis*-3-acetoxy-5-carbomethoxycyclohex-1-ene was used as the allylic substrate and morpholine as the nucleophile. As a result of the steric congestion of the surface of the higher generation dendrimers, an increase in the selectivity toward the cis-product (up to 94% for **94**) was observed (tetra(triphenylphosphine) palladium gave 8% of the cis-product). The dendritic catalysts **91**−**94** could only be dissolved in polar solvents such as DMSO and DMF (in contrast to tetrakis(triphenylphosphine) palladium). This fea-

Scheme 19



ture allowed the reactions to be performed in a biphasic system. Recycling experiments were performed with dendrimers **91**−**94** catalyzing the allylic amination of *trans*-cinnamyl acetate with dibutylamine. The reaction was performed in a biphasic mixture of DMF and heptane, which became homogeneous at 75 °C. After the reaction the dendritic catalyst was recovered by cooling the reaction mixture to room temperature and decantation of the heptane phase containing the products. The catalytic activity remained high for three runs giving yields of 66% in the first, 99% in the second, the third, and the fourth run. Product distribution over the two phases decreased the yield of the first catalytic cycle.




= poly(propylene imine) dendritic backbone

91 n = 4 **93** n = 32
92 n = 16 **94** n = 64

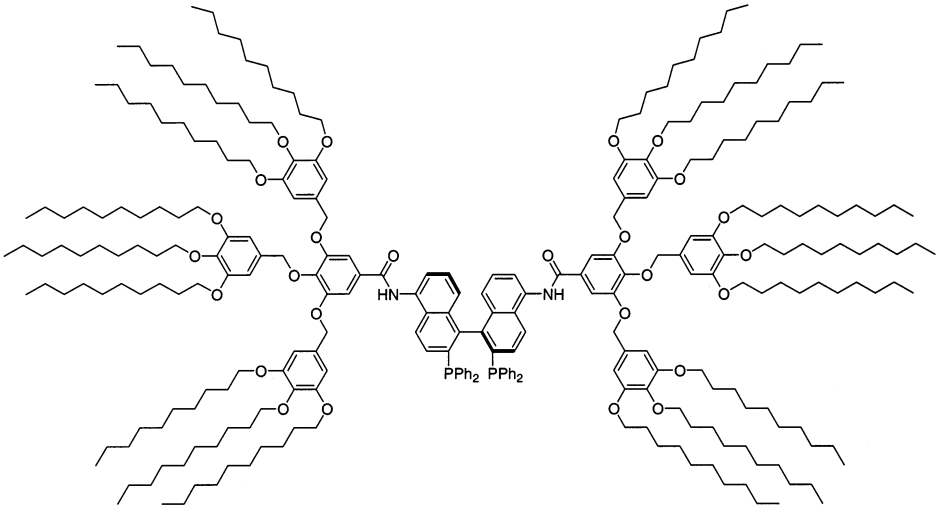
5. Recovery of Dendritic Hydrogenation Catalyst by Phase Separation

Deng et al. made use of the change from the miscible hexane/ethanol solvent mixture to a two-phase system upon the addition of a small amount of water.[81] Highly apolar first and second generation 5,5′-diamino-(*R*)-BINAP based dendritic ruthenium catalysts were synthesized from Fréchet-type wedges (both two and three branched) containing C_{10}-alkyl tails on their periphery. These dendritic catalysts were employed in the homogeneous hydrogenation of relatively polar substrates (2-phenylacrylic acid and 2-[*p*-(2-methylpropyl)phenyl]acrylic acid) in a 1:1 hexane/ethanol mixture (Scheme 19). At 80 bar of H_2 pressure complete conversion was reached after 4 h. The enantiomeric excesses obtained for all dendritic catalysts were almost identical to those obtained with (*R*)-BINAP as the ligand (87% ee for 2-phenylacrylic acid; 89% ee for 2-[*p*-(2-methylpropyl)phenyl]acrylic acid). A recycling experiment using 2-[*p*-(2-methylpropyl)phenyl]acrylic acid as substrate was performed with in situ prepared dendritic catalyst from the largest dendritic ligand **95** and $[RuCl_2(benzene)]_2$. The dendritic catalyst was recycled three times with only a slight loss in activity (50 bar H_2, 2 h; 72% conversion first run → 68% conversion fourth run) and stereoselectivity (84% ee first run → 82% ee fourth run). The application of a higher pressure resulted in higher activity and stereoselectivity (80 bar, 2 h: 84% conversion, 90% ee).

VIII. Dendrimers as Recoverable Organic Supports

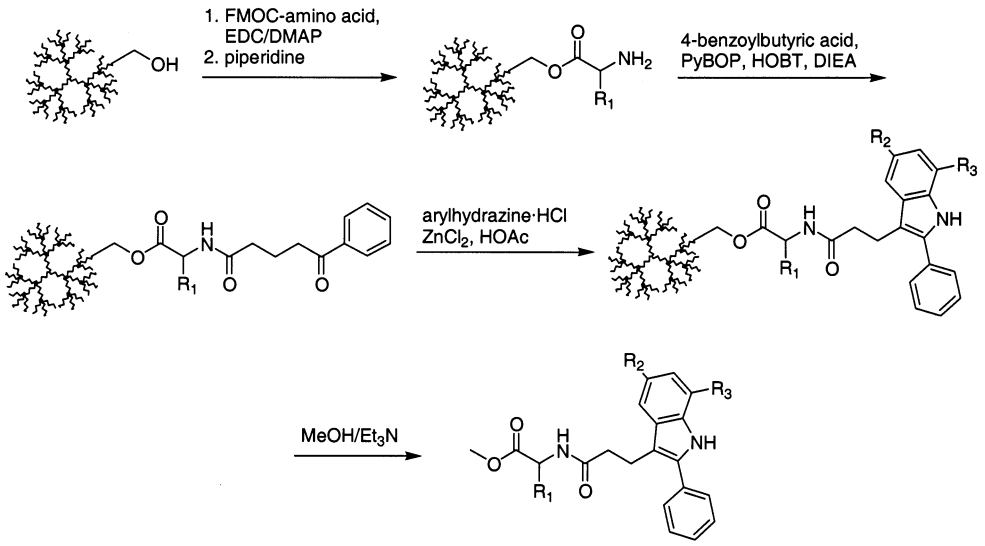
Solid phase chemistry has become a powerful tool in organic synthesis and has evolved enormously since the first reports by Merrifield. The ease of modifying functional groups on a polymeric support by using a large excess of reagents and simple workup by filtration and washing enables rapid (automated) synthesis which is especially important for combinatorial chemistry. Obviously, some drawbacks are associated with the heterogeneous nature of solid-phase chemistry. Accurate monitoring of the progress of the reaction and purity of the compounds on the beads is difficult, and the techniques available are limited. Furthermore, the translation of solution chemistry to solid-phase chemistry can be troublesome due to poor accessibility of the sites hidden in the polymeric matrix and the incompatibility of the support with reagents or reaction conditions.

The application of soluble polymers as supports for combinatorial chemistry circumvents most of the problems encountered in solid phase approach. Dendrimers as soluble supports have the additional



95

Scheme 20



advantage that multiple sites are present allowing higher loadings. The well-defined symmetric structure of dendrimers facilitates the analysis of the functionalized support by routine techniques as NMR and mass spectrometry (electron spray-MS or MALDI-TOF-MS). Removal of excess of reagents can be achieved easily by SEC, dialysis, or nanofiltration. The same techniques can be applied for purification of the product after cleavage from the dendritic support.[82]

1. Dendrimers as Soluble Supports

Kim et al. were the first to translate heterogeneous solid-phase synthesis to homogeneous dendrimer-supported combinatorial chemistry.[83] They modified a PAMAM dendrimer by introducing eight peripheral benzyl alcohol groups (HMPA linker, 4-(hydroxymethyl)-phenoxy acetic acid). This dendrimer was used as support for the synthesis of six different indoles which could be cleaved from the support by methanolysis (Scheme 20). The dendrimer-supported indole synthesis comprises an esterification of an amino acid, followed by a condensation with ketoacids and a subsequent reaction with an arylhydrazine hydrochloride.

The reactions were monitored quantitatively by ^1H NMR. All dendritic intermediates were purified by directly loading the crude reaction mixtures on a SEC column (Sephadex LH20). The six dendrimer supported indoles were isolated in yields > 90%. Electron spray mass spectrometry measurements indicated that the dendrimer-supported indole synthesis was very efficient.

A small 3 × 3 × 3 combinatorial library was synthesized based on the indole synthesis. Three different amino acids (Ala, Leu, Phe), ketoacids, and arylhydrazine hydrochlorides were used in a split-and-mix procedure to prepare the library. The dendritic, intermediate libraries were purified by SEC in which different dendritic species coeluted in a single fraction. The composition of the three sub-libraries was determined by HPLC analysis after cleavage of the indole products from the support. The sub-libraries contained the statistically expected product composition, and no impurities were observed.

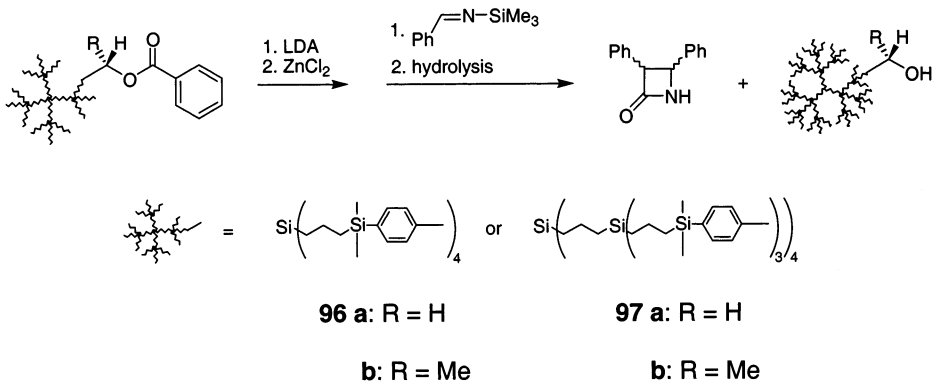
The dendrimer-support has a high loading capacity as is illustrated by the fact that the loading capacitiy of 1 mg of dendrimer equals 100 mg of a typical resin (capacity 0.23 mmol/g). The rate-limiting factor in the dendrimer supported combinatorial library synthesis presented is the purification of the dendritic intermediates by SEC. The synthesis of combinatorial libraries in a CFMR might circumvent this problem, but these systems have not been reported yet.

Hovestad et al. used modified carbosilane dendrimers as soluble supports for the zinc-mediated β-lactam synthesis.[84,85] Two generations benzyl alcohol and (*S*)-α-methyl benzyl alcohol terminated carbosilane dendrimers (**96** and **97**) were synthesized and subsequently converted into their benzyl ester analogues. The esterified dendrimer-supports were converted in situ to dendritic zinc-ester enolates by a reaction with LDA and a transmetalation with zinc chloride. Reaction of the dendritic supports with $PhCH{=}NSiMe_3$ afforded the β-lactam product (Scheme 21).

Isolation of the product was achieved either by extraction with a hexane/diethyl ether mixture (4:1) for **96** or SEC (Sephadex LH20) for **97**. The β-lactam was formed with high selectivity toward the trans-product (d.e. > 95%) in yields from 80 to 90%. Moderate enantioselectivities were obtained when **96b** and **97b** were used as the support in the β-lactam synthesis, 30% ee and 31% ee, respectively.

The preparation of a library of β-lactams via a combinatorial approach using **97a** was investigated. A 1:1 mixture of phenylacetyl chloride and pivaloyl chloride was reacted with the support yielding dendrimers bearing a statistical distribution of the pivaloyl and phenylacetyl esters as was determined by MALDI-TOF-MS analysis. Reaction of the modified support with a 1:1 mixture of 2-PyCH=NCH(Me)Ph and 2-PyCN=$NCMe_3$ afforded a library containing all four possible β-lactams in equal amounts in an 85% yield. The choice of ester used in the combinatorial procedure was important. The zinc-

Scheme 21



enolate derived from the pivaloyl ester was not active toward *N*-(Me_3Si)N=CHPh, whereas the zinc-enolate derived from the phenylacetyl ester was active. Preliminary nanofiltration showed that **97a** could be retained to a large extent by a MPF-60 NF membrane.

Zhang et al. made use of a colored dendrimer as a soluble support enabling direct monitoring of the SEC purification steps in dendritic soluble supported organic reactions.[86] For this purpose, a dye Red-1 core-functionalized dendrimer containing a tBoc-protected periphery was prepared.[87] The HMPA-linker was introduced on the dendrimer periphery (**98**) by deprotecting the peripheral amines, condensation of an activated ester of acetylated hydroxymethylphenoxyacetic acid and de-esterification. The dendrimer-support was used for the Suzuki coupling between *o*- and *p*-iodobenzoic acid and six boronic acids (Scheme 22).

The dendritic support was reacted with *o*- and *p*-iodobenzoyl chloride and purified using a Sephadex LH20 SEC cartridge. The Suzuki reaction between the support and the boronic acids was performed in DMF in the presence of $(PPh_3)_4Pd$ and Na_2CO_3. After the sample was washed with water to remove the salt side product, the dendrimers were purified on a Sephadex LH20 cartridge. The purifications were simplified by the red color of the dendrimers and took less than 30 min. The dendrimer-supported products were characterized by the conventional analytical methods. The Suzuki cross-coupled products were cleft from the dendritic support by TFA/CH_2Cl_2 and were extracted into a basic water layer, acidified, and subsequently analyzed using the standard analytical techniques. The precipitated dendritic support was recovered from the CH_2Cl_2 layer by filtration.

2. Dendrimers Supported on a Solid Phase

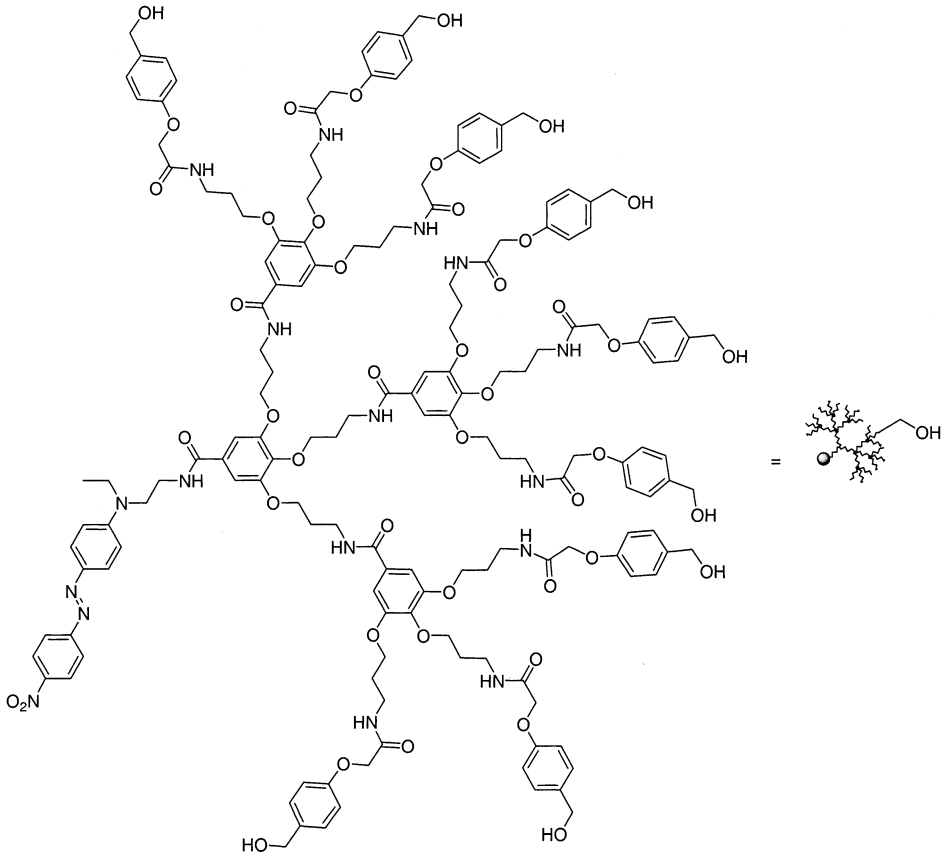
Although the synthesis of libraries on soluble supports has many advantages over the solid phase approach, the one-bead-one-compound concept makes the solid phase chemistry especially attractive for the split-and-mix methodology. Each bead can be separately screened for active compounds, which is a powerful feature that soluble supports lack. However, the small quantity of compound that is obtained from a single bead hampers routine screening. Furthermore, identification of active compounds on beads requires tagging or deconvolution techniques. These limitations to single-bead screening can be overcome by increasing the loading capacity one order of magnitude by attaching dendrimers to the solid support.[88]

Swali et al. used solid-phase chemistry to attach dendrimers to a resin thereby aiming at an increase of the loading capacity of the resin.[89] Four generations resin-bound PAMAM dendrimers were synthesized by reacting a polystyrene-poly(ethylene glycol) (PS−PEG) resin with an acid-labile linker and subsequently (repetitive) with large excesses (250 eq.) of methyl acrylate and either diaminoethane or diaminopropane (Scheme 23).

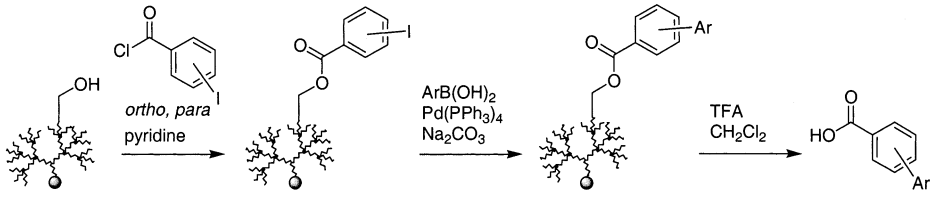
ES-MS analysis of dendrimers that were cleaved from the resin (50% TFA in CH_2Cl_2) revealed that a small portion of the third generation dendrimer contained a defect resulting in 14 instead of 16 peripheral amine groups. The loading capacities of the third and fourth generation dendrimer modified resins were determined to be, respectively, 5.6 nmol/bead (2.3 mmol g^{-1}) and 9.6 nmol/bead (2.8 mmol g^{-1}). After attachment of the acid-sensitive HMPB linker (HMPB = 4-(4-hydroxymethyl)-3-methoxy-phenoxy)-butyric acid) to the dendritic amine groups, a dipeptide was synthesized using Fmoc chemistry. The dipeptide was cleaved from the resin with 1% TFA in CH_2Cl_2 leaving the dendrimer attached to the support. Direct coupling of Fmoc-Lys(^{t}Boc)-Gly to the dendritic amine groups and a subsequent cleavage using 50% TFA in CH_2Cl_2 allowed the isolation of the dendrimer-bound dipeptide.

Wells et al. modified a PS resin with a PEG spacer and a second generation PAMAM dendrimer yielding a resin with an even higher loading capacity of 30 nmol per bead.[90] The dendrimer was connected to the PEG spacer via an acid labile Wang-linker. The HMPB linker was coupled to the dendrimerized resin and the peptide Fmoc-Val-Phe-Ala-OH was synthesized on the support. The cleavage of this peptide from the support was monitored in situ by ^{1}H NMR using 1% CF_3COOD in $CDCl_3$. Parts of the NMR sample were used for HPLC analysis and for ES-MS analysis, both showing the same result as for an authentic sample. A small library was synthesized based on the hexapeptide Leu-enkephalin-Lys. Twenty peptides of the structure X_{aa1-20}-Gly-Gly-Phe-Leu-Lys were synthesized and analyzed by HPLC and ES-MS. The expected peptides were formed in all cases. The synthesis of the dendrimerized PS−PEG resin (including a generation 3 dendrimerized resin) was

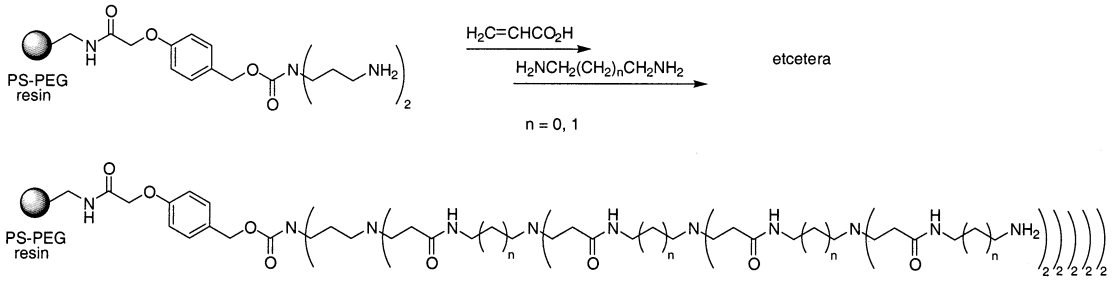
Scheme 22



98



Scheme 23

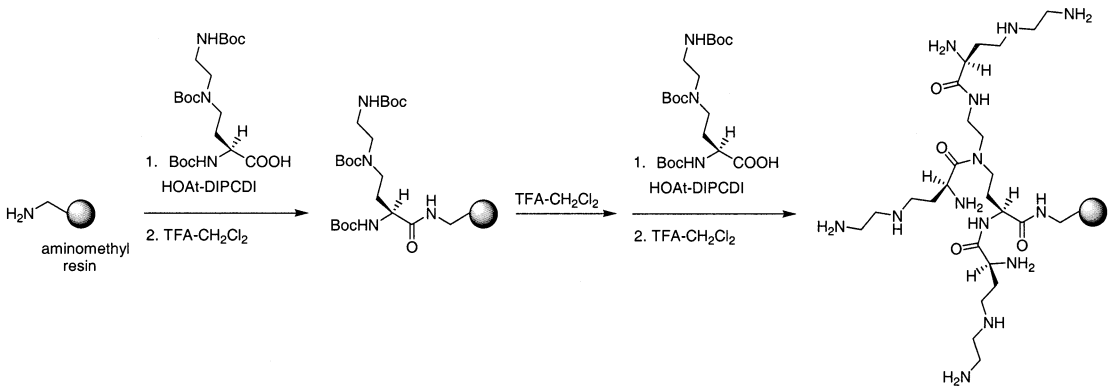


disclosed in detail in a separate report.[91] Besides the supported synthesis of the hexapeptide Leu-enkephalin-Lys, on the bead synthesis of Chlorambucil was reported.

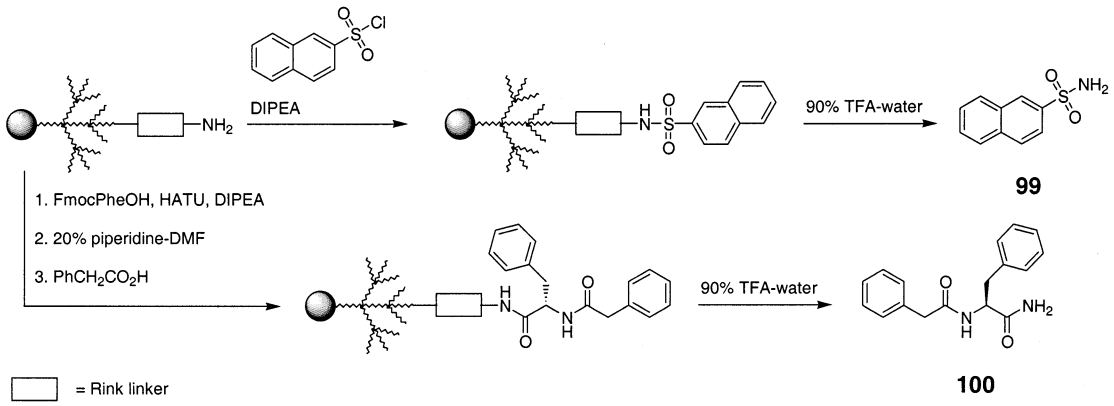
Mahajan et al. increased the loading capacity of an aminomethylated PS resin (0.8 mmol g^{-1}) by condensation of a tris-Boc amino acid.[92] Removal of the Boc protecting group yielded the first generation supported dendrimer with amine end-groups. The second generation amine resin was prepared by repeating these reaction steps (Scheme 24).

The Fmoc-protected Rink amide linker was coupled to the resin as an acid-labile linker for solid phase synthesis. The degree of substitution of the generations 1 and 2 resins was determined spectrophotometrically by monitoring the liberation of the Fmoc chromophore and was found to be 0.9 mmol g^{-1} and 1.17 mmol g^{-1}, respectively. Both dendrimerized resins were used for the solid-phase synthesis of 2-naphthalenesulfonamide (**99**) and *N*-phenylacetyl-L-phenylalaninamide (**100**, Scheme 25). Using the resin modified with the first generation dendrimer

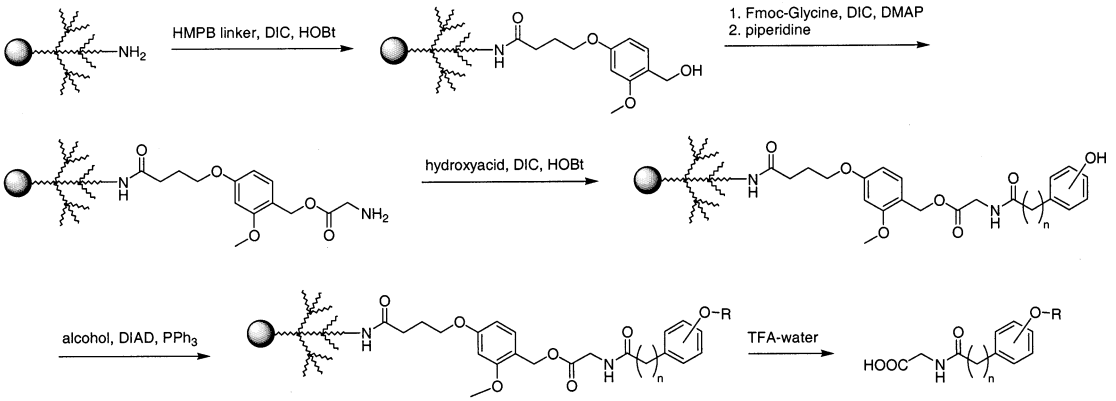
Scheme 24



Scheme 25



Scheme 26

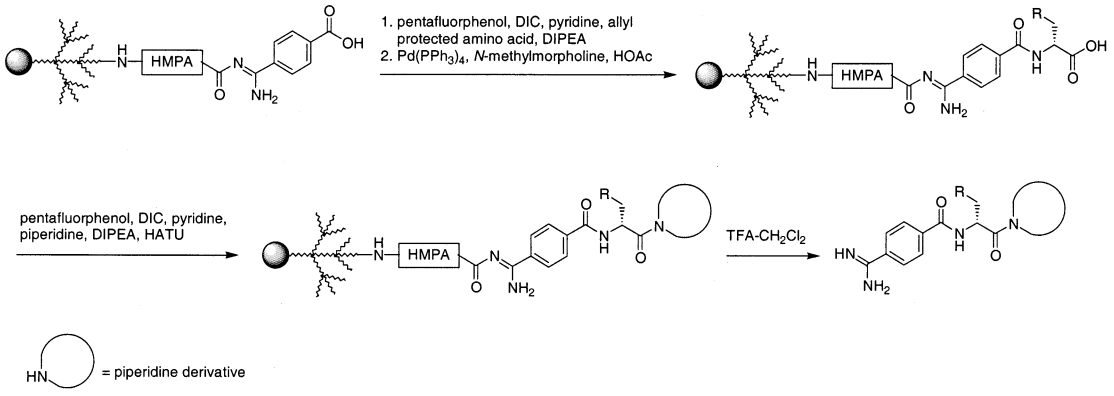


99 and **100** were isolated in 84 and 87% yield, respectively. Usage of the resins modified with the second generation dendrimer gave near quantitative yields of **99** and **100**.

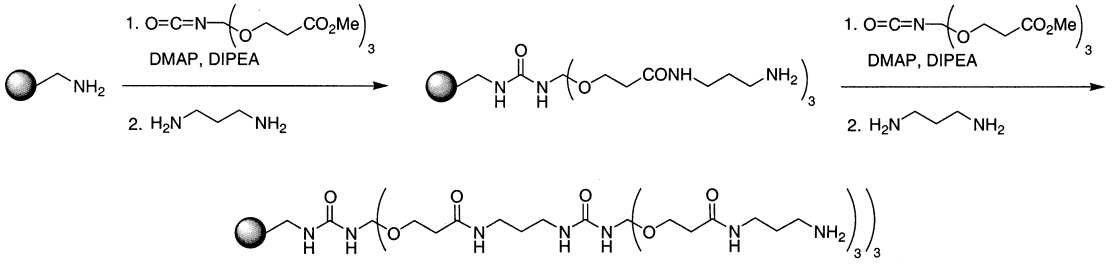
Basso et al. used their PAMAM dendrimerized resin (generation 3) for the synthesis of a small library of aryl ethers (Scheme 26).[93] The dendrimer modified resin was functionalized with the HMPB linker, a glycine spacer, and a hydroxyphenyl carboxylic acid. The Mitsunobu etherification conditions on the resin were tested. Much higher conversions were reached using the resin compared to the normal TentaGel resin (e.g., the etherification of 3,5-dichlorobenzyl alcohol: 93% conversion on the modified resin versus 45% conversion on the TentaGel resin). The reason for this effect remains unclear. A small library of 20 ethers was synthesized semiautomatically using five different phenolic acids and four different alcohols. All reactions gave pure products in good yields (>70%). The library was subjected to LC-MS, ^{1}H NMR, ^{13}C NMR, and single bead MS analysis.

Basso et al. used their highly loaded PS−PEG resin (generation 2)[89,90] for the synthesis of a library of amidines.[94] To this end, the HMPA linker was coupled to the resin, which was subsequently reacted with *p*-nitrophenyl chloroformate. The modified resin was reacted with allyl benzamidine-4-carboxylate displacing *p*-nitrophenol. After removal of the allyl protecting group the amidine library, synthesis could be started. Five different allyl protected amino acids, and, after allyl deprotection, three piperidines were reacted with the resin (Scheme 27). The different products were cleaved from the resin to give the

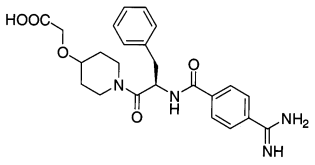
Scheme 27



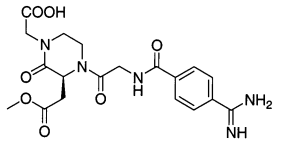
Scheme 28



amidine products in approximately 30% yield after semipreparative HPLC in >40% purity. Using the same synthetic procedure, the GP Iib-IIIa receptor antagonists Ro44−9883 (**101**) and TAK-029 (**102**) were synthesized on the resin. The products could be isolated after cleavage from the support in overall yields comparable with that obtained using solution chemistry.



101



102

Fromont et al. synthesized dendrimer modified resins with loading capacities up to 200 nmol per bead.[95] A tri-branching "dendritic monomer" was prepared and used in the synthesis of dendrimers up to the third generation on an aminomethylpolystyrene resin (0.7 mmol g^{-1}, 250−300 μm, Scheme 28).

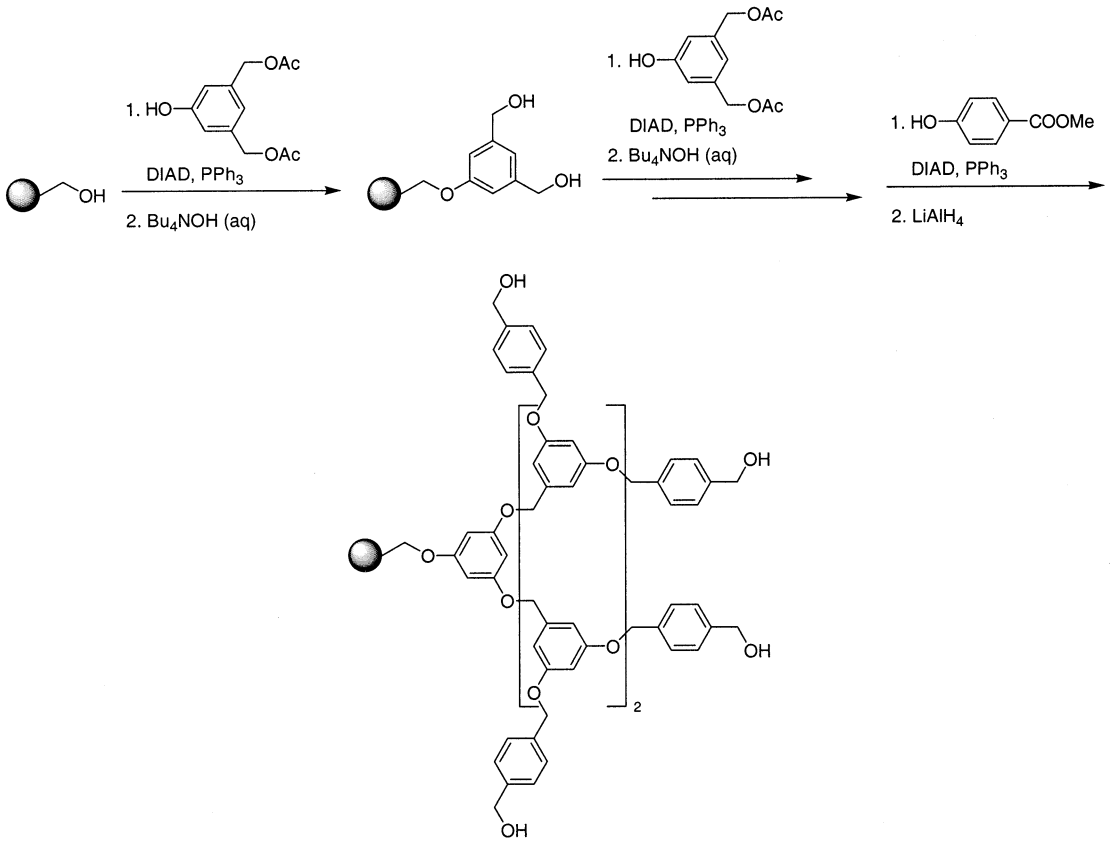
The loading capacity of the dendrimerized PS resin was determined to be 36 nmol per bead (generation 2) and 100 nmol per bead (generation 3). The use of larger starting PS beads (400−500 μm) modified with a linker containing two amine groups for the dendrimer synthesis resulted in higher loading capacities, 116 nmol per bead for generation 1 and 230 nmol per bead for generation 2. The supported synthesis of Fmoc-Val-Phe-Ala-OH and a supported Suzuki coupling of *p*-iodobenzoic acid with *p*-methylbenzene boronic acid were performed. Only a single bead was required for the analysis of the product by both HPLC and NMR analysis.

A synthetic route toward the synthesis of Fréchet type wedges on a Merrifield PS resin was developed by Basso et al.[96] This dendrimerized resin was considered to be less chemically reactive than their PAMAM analogues. A divergent synthesis route for the dendrimer was developed based on Mitsunobu etherification and ester hydrolysis (Scheme 29).

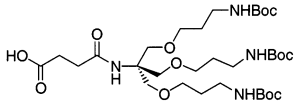
The synthesis was performed on a hydroxymethylpolystyrene (Merrifield) resin (1% cross-linked, 0.93 mmol g^{-1}, 90−106 μm). The dendrimer functionalized resin (generation 3) had a loading capacity 2.85 mmol g^{-1} (3 nmol per bead, 7× the loading of the initial resin). A Wang linker was introduced by condensation of *p*-hydroxybenzoate onto the resin, followed by a reduction with $LiAlH_4$. As a result of the modification the loading capacity was decreased to 2.3 nmol per bead. The resin was used for the supported synthesis of the hexapeptide Leu-enkephalin-Lys, which could be isolated in 66% yield after cleavage from the support (95% TFA-water).

Cho et al. synthesized a three-branched dendritic building block based on tris(hydroxymethyl)aminomethane (Tris, **103**) for the dendrimerization of a PS-*co*-PEG-NH2 (CutiCore) and a TentaGel resin.[97] The resins were dendrimerized by a repetitive coupling of **103** using BOP, HOBt, and DiPEA, followed by BOC deprotection using 50% TFA in CH_2Cl_2. The CutiCore resin (0.1 mmol g^{-1}) was dendrimerized up to the seventh generation, yielding a resin with a loading capacity of 4.0 mmol g^{-1}. The TentaGel resin (0.2 mmol g^{-1}) could only be grown to the fifth

Scheme 29



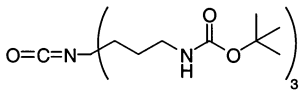
generation due to steric congestion. The loading capacity after dendrimerization was increased to 2.0 mmol g^{-1}.



103

A Rink amide linker was attached to the amino groups of the dendrimerized CutiCore resin. The solid-phase peptide synthesis of Leu-enkephalinamide (H-Tyr-Gly-Gly-Phe-Leu-NH_2) was performed on the resin in an automatic synthesizer operating in a continuous-flow mode. The peptide was synthesized in >96% purity according to HPLC. The purity of the peptide was comparable to that obtained from the parent CutiCore resin. This indicates that the 17× higher loading capacity of the dendrimerized resin does not reduce the efficiency of the coupling procedures.

Lebreton et al. prepared a three-branched dendritic building block containing an isocyanate focal point and Boc-protected amino endgroups (**104**) for solid-phase dendrimer synthesis.[98] Compound **104** was used for the dendrimerization of PS-aminomethyl resins (75−150 μm, 0.68 nmol $bead^{-1}$ and 250−300 μm, 17.9 nmol $bead^{-1}$) and a TentaGel resin (160 μm, 0.68 nmol amino endgroups $bead^{-1}$). The dendrimerization was achieved by repetitively reacting the isocyanate **104** with the resin followed by a TFA treatment. The PS (75−150 μm) resin and the TentaGel were grown to the third generation leading to loading capacities of 6.61 and 6.91 nmol $bead^{-1}$, respectively. The PS (250−300 μm) resin suffered from destruction of the resin upon preparation of the third generation as a result of the Boc-deprotection step.



104

Kinetic studies on the release of FMOC from the FMOC-Gly functionalized PS (250−300 μm) resins were undertaken to determine the synthetic applicability of the different generations dendrimerized resins for solid-phase chemistry. Complete deprotection of FMOC using 20% piperidine in DMF was achieved after 22 and 57 min for, respectively, generation 1 and 2 compared to 5 min for the parent resin.

The PS resin containing the first generation dendrimer (containing 2.3 times the initial loading) were functionalized with the HMPB linker and used for the synthesis of a tripeptide (FMOC-Ala-Val-Phe-OH) and a biaryl. Using the standard HOBt/DIC coupling procedure, the tripeptide was obtained after cleavage in quantitative yield with 100% purity according to HPLC. A biaryl was synthesized on the resin by attaching 4-iodobenzoic acid to the HMPB linker followed by a Suzuki coupling with 4-methylbenzene boronic acid. After cleavage from the resin the biaryl was obtained in 59% yield with 100% purity according to HPLC.

IX. Conclusions and Outlook

Numerous examples of dendritic transition metal catalysts based on different dendritic backbones functionalized at different locations have been reported. Many dendritic effects in catalysis have been observed, including increased/decreased activity, selectivity, and stability. It is clear from the contributions of many groups that dendrimers are suitable supports to prepare recyclable transition metal catalysts. Several separation techniques are applicable to these functionalized dendrimers including precipitation, two-phase catalysis, and immobilization of the dendrimer to insoluble support (polystyrene, silica). In addition, the large size and the globular structure of the dendrimers enable efficient separation by nanofiltration techniques. Nanofiltration can be performed batchwise and in a continuous-flow membrane reactor (CFMR). The common problems involved in catalyst recycling also pertain to dendritic catalysts. These include dendrimer or catalyst decomposition, dendrimer leaching, metal leaching, and catalyst deactivation. The demands are even more stringent for applications in continuous processes. It is interesting to note that small changes in the dendritic architecture can have a huge impact on the stability of catalytic systems. Also part of the problems as metal leaching and catalyst stability (high TON) can be solved by proper choice of ligands and dendrimer backbone. This stresses the importance of ligand and catalyst design and catalyst identification, which is feasible after immobilization on the dendrimer support.

Whether dendritic catalysis can compete successfully in commercial applications with other systems such as two-phase catalysis and other supports remains to be seen, although the increasing number of patents on dendritic catalysts shows an industrial interest.[99] Dendrimer supports are still relatively expensive, but for applications that do not require the well-defined structure of the dendrimer support, hyperbranched polymers can offer a cheaper alternative.[100] The price per active site of this type of materials competes with other supports as polystyrene and silica.[101] However, it is important to realize that high turnover numbers are required before these sophisticated systems become attractive for commercial applications.

Although dendritic catalysts have been applied in several reactions, more experiments are required to gain deeper insight in dendritic effects in catalysis and catalyst recycling. Since there is no single solution to the catalyst separation problem it is not expected that dendrimers will provide the general solution. The optimal process clearly depends on catalyst properties as stability, solubility, etc., as well as product properties. In the development of new recyclable catalysts systems based on dendrimers, the function of the dendritic part should be questioned. Optimal advantage of dendrimers as soluble supports for catalysts can be obtained when they are applied in a continuous-flow membrane reactor. The progress in membrane technology will be of importance for the future development of sophisticated reactors for applying dendritic systems. Moreover, dendritic systems functionalized with different catalytic sites at several well-defined locations can potentially be used for tandem reactions, reducing diffusion problems of intermediates. Hitherto the area of cascade reactions using dendrimers is largely unexplored.

Several examples of dendrimers as alternative for soluble polymeric supports have been reported. The well-defined macromolecular structure of these dendritic supports simplifies the characterization of intermediates in the synthesis of a library of functional compounds. The isolation and purification of the dendritic support has become the rate-limiting step in library synthesis, requiring time-consuming SEC techniques. Whereas the application of membrane filtration for the isolation of dendritic supports in principle would allow facile separation from excess reagents analogously to the solid-phase filtration/washing technique, no reports applying this concept have appeared. Optimization of the isolation step is required to speed up the combinatorial library synthesis. Also here hyperbranched polymers might provide a cheaper alternative to bridge the gap between academic research and commercial application.

Functionalization of solid phase resins with dendrimers has proven an effective means of increasing the loading capacities of resins. Resins can be synthesized that allow easy monitoring of compounds from a single bead by NMR spectroscopy, for example, which tremendously contributes to the potential of the split-and-mix methodology for screening purposes. For the increase in loading capacity the well-defined structure of the dendrimer is not required, and in several examples the increase in capacity suggest that the dendrimer part contains many defects. The development of one-step procedures to prepare materials with similar properties will reduce the price of these type of supports significantly.

Considering the recent progress in the development of dendritic supported catalysts and reagents, a bright future for these appealing molecules and their hyperbranched analogues can be foreseen.

X. Acknowledgments

We would like to thank Prof. B. Zwanenburg for fruitful discussions.

XI. References

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CR0103874