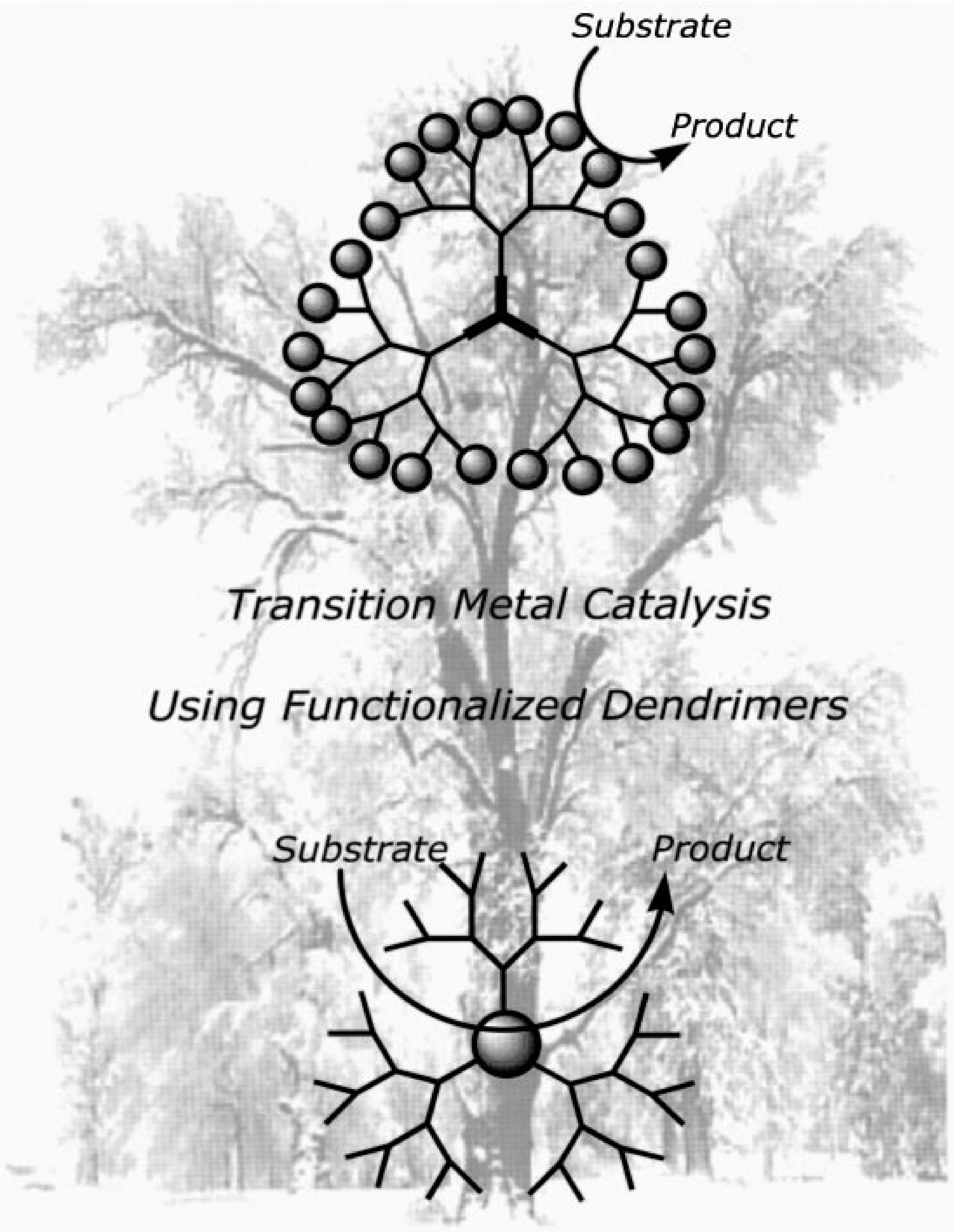

# Transition Metal Catalysis Using Functionalized Dendrimers

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# Transition Metal Catalysis Using Functionalized Dendrimers

G. Eric Oosterom, Joost N. H. Reek,* Paul C. J. Kamer, and Piet W. N. M. van Leeuwen*

Dendrimers are well-defined hyperbranched macromolecules with characteristic globular structures for the larger systems. These novel polymers have inspired many chemists to develop new materials and several applications have been explored, catalysis being one of them. The recent impressive strides in synthetic procedures increased the accessibility of functionalized dendrimers, resulting in a rapid development of dendrimer chemistry. The position of the catalytic site(s) as well as the spatial separation of the catalysts appears to be of crucial importance. Dendrimers that are functionalized with transition metals in the core potentially can mimic the properties of enzymes, their efficient natural counterparts, whereas the surface-functionalized systems have been proposed to fill the gap between homogeneous and heterogeneous catalysis. This might yield superior catalysts with novel properties, that is, special reactivity or stability. Both the core and periphery strategies lead to catalysts that are sufficiently larger than most substrates and products, thus separation by modern membrane separation techniques can be applied. These novel homogeneous catalysts can be used in continuous membrane reactors, which will have major advantages particularly for reactions that benefit from low substrate concentrations or suffer from side reactions of the product. Here we review the recent progress and breakthroughs made with these promising novel transition metal functionalized dendrimers that are used as catalysts, and we will discuss the architectural concepts that have been applied.

**Keywords:** catalysts · chirality · dendrimers · immobilization · transition metals

## 1. Introduction

Dendrimers are highly branched macromolecules, obtained by an iterative sequence of reaction steps, having precisely defined molecular structures. This new class of macromolecules, pioneered by the groups of Vögtle,[1] Tomalia,[2] Newkome,[3] and Fréchet,[4] has inspired many chemists in several fields. The initial focus was on the efficient synthesis and characterization of dendrimers.[5] The development of new and better analytical techniques such as high-field NMR spectroscopy, matrix-assisted laser-desorption/ionization time of flight (MALDI-TOF) and electrospray mass spectrometry, and size-exclusion chromatography has assisted this development significantly.

Generally two synthetic strategies can be applied:

- The divergent route starting from the core building layers around it.
- The convergent route making wedges that can be connected to a core in the last step of the synthesis.

Although the development of novel types of dendrimers still continues, the synthesis of different types of dendrimers is now well established and some are even commercially available. Obviously this is of major importance when considering applications of dendrimers. Furthermore, detailed knowledge about the macromolecular structure of dendrimers is required to understand and predict the properties of functionalized dendrimers.[6] In several examples it has been shown that dendrimers do not adopt the ideal spherical structures their drawings might suggest. Especially amphiphilic dendrimers have structures that are far from spherical.[7]

In several scientific fields the application of dendrimers has been explored. The different properties of large dendrimers compared to their conventional polymeric counterparts make these molecules interesting compounds for materials science. Furthermore, it has been shown that dendrimers can possess cavities within their macromolecular structure that can be used to accommodate guest molecules.[8] Several groups are exploring the use of this property for the development of sophisticated drug-delivery systems; host–guest complexes based on dendrimers have often been reported in the light of this application. Other potential applications are artificial antennae for the efficient conversion of light energy, magnetic resonance imaging (MRI) agents, immuno-

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diagnostics, gene-delivery vectors, and unimolecular micelles.[6, 9]

Transition metal catalysis based on functionalized dendrimers is another very promising application of dendrimers.[10] Here we review the progress that has been made in the exciting field of dendritic transition metal catalysis.

### 1.1. Dendritic Transition Metal Catalysts: The New Generation?

To give an answer to the question "what can dendrimers add to the field of catalysis?" we have to take a closer look at the ideal catalyst. From a catalytic point of view the ideal catalyst is highly active and selective under mild conditions, very stable and can be separated from the product using a relatively simple process. Right from the start, the regular monodisperse structure and multiarm topology of dendrimers inspired chemists to propose dendrimers with peripheral catalytic sites as soluble supported catalysts. In 1994, Tomalia and Dvornic discussed the promising outlook of surface-functionalized dendrimer catalysts.[11] Dendritic catalysts are often 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,[12] 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. Moreover, their globular shape makes these systems more suitable for recycling than soluble polymer-supported catalysts.

In principle, dendritic catalysts can provide systems that…

… show the kinetic behavior and thus the activity and selectivity of a conventional homogeneous catalyst. Catalysts supported on highly cross-linked polymer beads generally suffer from diminished activity compared to the homogeneous analogues, which is because of a reduced accessibility.[13] Organic polymers show solvent-dependent swelling properties that can strongly influence the catalytic performance.


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… can easily be removed from the reaction mixture by membrane or nanofiltration techniques because of their large size compared to the products (an advantage of heterogeneous catalysts).

… allow mechanistic studies, because of the monodisperse, uniform character of their catalytic sites and the symmetry of the molecules (an advantage of homogeneous catalysts),

… allow fine-tuning of their catalytic centers by precise ligand design (an advantage of homogeneous catalysts),

… require relatively low metal loading (an advantage of homogeneous catalysts over heterogeneous catalysts).

In the first instance dendritic catalysts were proposed to be easily recyclable homogeneous catalysts. The question is, however, if they also can provide systems that are either more active or selective or more stable than their homogeneous monomeric analogues? This would yield systems with interesting novel catalytic properties providing an intrinsic solution for the homogenous catalyst separation problem. These novel properties induced by the dendritic framework depend on the location of the functional group within the structure. One should distinguish periphery-functionalized (dendrimer or a dendritic wedge), core-functionalized, and focal-point-functionalized (dendritic wedge) systems (see Figure 1). A combination of these conceptual approaches might lead to systems with different catalytic centers, which are ideally suited for cascade reactions. Such systems, however, have not been reported yet.

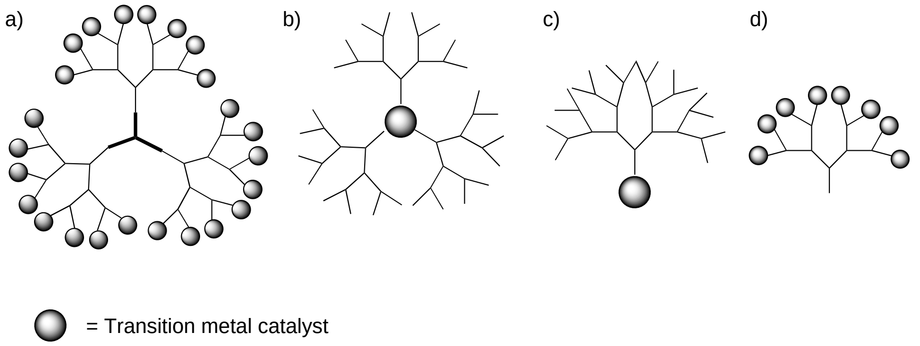


Figure 1. Catalytically active transition metal complexes can be attached to the periphery (a), the core (b), at the focal point of a wedge (c), and at the periphery of a wedge (d).

Periphery-functionalized dendrimers have their ligand systems, and thus the metal complexes, at the surface of the dendrimer. The transition metals will be directly available for the substrate, in contrast to core-functionalized systems, for example, in which the substrate has to penetrate the dendrimer prior to reaction. This accessibility allows reaction rates that are comparable with homogeneous systems. On the other hand, the periphery-functionalized systems contain multiple reaction sites and ligands, which results in extremely high local catalyst and ligand concentrations. For example, a second-generation carbosilane dendrimer functionalized with phosphine ligands (with 36 terminal phosphines; section 2.3) results in local concentrations of 8 M of ligand (dendrimer–$PPh_2$) and 4 M of catalysts ((dendrimer–$PPh_2$)$_2$Pd). In reactions where excess ligand is required to stabilize the catalyst this local-concentration effect can indeed result in stable systems. Furthermore, if a reaction proceeds by a bimetallic mechanism, the dendritic catalysts might show better performance than the monomeric species.[14] On the other hand, several deactivation mechanisms operate by a bimetallic mechanism, for example, ruthenium-catalyzed metathesis,[15a] palladium-catalyzed reductive coupling of benzene and chlorobenzene,[15b] and reactions that involve radicals.[16] These deactivation pathways will be invigorated in periphery-functionalized systems.

In core- (and focal-point-) functionalized dendrimers the catalyst could benefit especially from the site isolation created by the dendritic environment. Site-isolation effects in dendrimers can be beneficial for other functionalities and a general review on this topic has recently appeared.[17] For reactions that are deactivated by excess ligand or in cases in which a bimetallic deactivation mechanism is operative, core-functionalized systems can specifically prevent such deactivation pathway, whereas periphery-functionalized systems might suffer from relative low activity. Core-functionalized dendrimers may benefit from the local catalyst environment created by the dendrimer. Effects of desolvation of the substrate during the penetration of the dendrimer might be of importance, but very little is known about these effects. In nature, enzymes make use of these effects when substrates enter the active site of such systems.

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 application can also be limited by the solubility of the system (to dissolve 1 mmol of catalyst 20 $g L^{-1}$ is required ($M_W$ 20000 Da, 1 active site) compared to 1 $g L^{-1}$ ($M_W$ 20000 Da, 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.

## 1.2. Dendritic Catalysts in Continuous Processes

Membrane reactors have been investigated since the 1970s.[18] Although membranes can have several functions in a reactor, the most obvious application is the separation of reaction components. Initially the focus was mainly on polymeric membranes for enzymatic reactions. The membrane materials have improved significantly ever since, and nowadays nanofiltration membranes suitable to retain relatively small compounds are commercially available (e.g. mass cut-off 400 Da). Two forms of leaching have to be considered when using dendritic transition metal catalysts in membrane reactors: leaching of the dendritic catalyst through the membrane and metal leaching from the dendrimer (and further leaching through the membrane). For practical applications the overall retention of the (dendritic) catalyst must be extremely good to keep a high activity in a continuous reactor for longer reaction times. (The required retention obviously depends on the application; processes for the bulk industry generally require more efficient catalyst recycling—higher turnover number (TON)—than those of fine chemicals.) In Figure 2 the theoretical activities of dendritic catalysts are given using different retention factors. If a dendritic catalyst has a retention of 0.95 then less than 25 % of the catalyst remains in the reactor after the reactor has been flushed with 30 times its reactor 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.

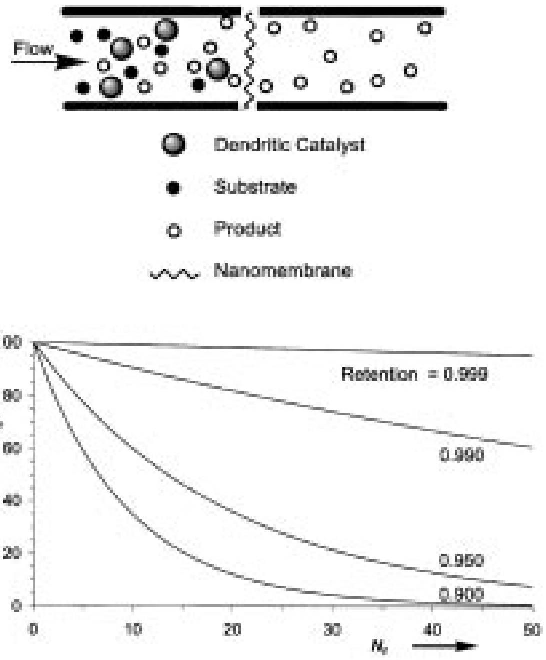


Figure 2. Top) Schematic representation of the usage of dendritic catalysts in a continuous membrane reactor. Bottom) theoretical relative concentrations of (dendritic) catalysts ($c_r$) with various retention factors versus number of residence times ($N_r$) in a continuous process.

Kragl et al. pioneered the use of dendrimers in catalytic continuous processes using membranes. Initially soluble polymeric catalysts were used in a continuous membrane reactor for the enantioselective addition of $Et_2Zn$ to benzaldehyde.[19] The polymer was retained almost completely ($>0.998$), and a higher turnover number was obtained using this setup than with a batch reactor. Dendrimers are particularly suited for application in this type of reactor because of their globular morphology.[2b] So far only a few examples have appeared in the literature describing the use of dendritic catalysts in continuous systems and they will be discussed (Sections 2.2, 2.3, 2.7, and 3.2).

This review is divided in the following topics: periphery-functionalized dendrimers, core-functionalized dendrimers, enantioselective dendritic catalysis using periphery and core-functionalized systems, and metal nanocomposites in the dendrimer interior as catalysts. Within each topic we have chosen to organize the systems by reaction type.

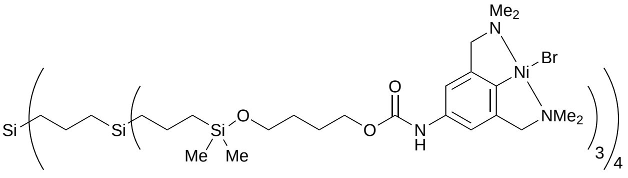
## 2. Periphery-Functionalized Dendritic Catalysts

### 2.1. Terpolymerization of Ethene, Propene, and CO

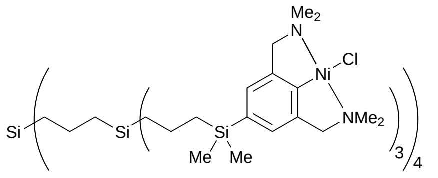
The first dendritic effect on catalysis was described by Van Leeuwen and co-workers at Shell.[20] A hexaphosphine catalyst containing a benzene core was used in the palladium-catalyzed polyketone formation (alternating polymerization of CO and alkene). Mononuclear palladium catalysts gave as much as 50 % fouling, that is, precipitation of the polymer on the reactor wall. Using the dendritic catalyst under comparable conditions this fouling was reduced to only 3 %. A possible explanation is that in the dendritic catalyst the palladium ions remain attached to the surface of the growing polymer and do not go into solution during the chain-transfer reaction (which may lead to fouling).

### 2.2. Nickel-Catalyzed Kharasch Addition

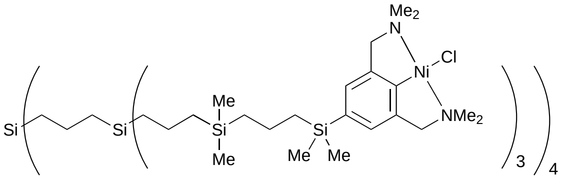
Another early example of a dendritic catalyst was reported by Van Leeuwen, Van der Made, and Van Koten, who functionalized generation zero and 1 (G0 and G1) carbosilane dendrimers with up to twelve pincerlike NCN–nickel(II) groups (**1a**).[10a] These dendrimers were applied as catalysts for the Kharasch addition of CX to alkenes (Scheme 1). The catalytic activity of the dendritic catalyst was slightly lower than that of the monomeric parent



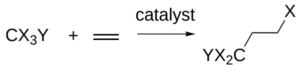
**1a**



**1b**



**1c**



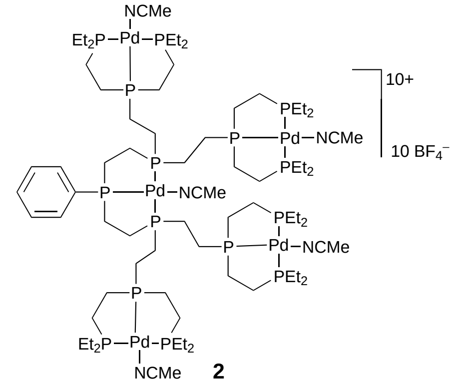
Scheme 1. The Kharasch addition reaction (X = halogen; Y = H, halogen, or $CF_3$).

compound; 80% of the activity was found for G0 (four Ni centers) and 70% for G1 (**1a**, twelve Ni centers). The selectivity was the same in all experiments resulting in a clean and regiospecific formation of the 1:1 addition product.

Molecular models showed that the accessibility of the catalytic sites was similar for dendrimers and monomer, and it was proposed that the lower rates were because of the high local concentration of nickel centers. In a subsequent paper this effect was studied in more detail using dendrimers with different spacer lengths.[21] 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 **1c** with 12 active sites yielded a much better catalyst for the Kharasch addition reaction than **1b** (the turnover frequency (TOF) increased from 39 for **1b** to 85 for **1c**). It was proposed that the catalyst deactivation was caused by an interaction between neighboring $\mathrm{Ni^{II}}$ and $\mathrm{Ni^{III}}$ sites, which is clearly more pronounced in systems were surface congestion is larger. Alternatively one might propose that local high radical concentrations lead to termination and $\mathrm{Ni^{III}}$ formation. For this reaction core-functionalized systems that are large enough to induce site isolation might lead to more stable and active systems. Amino acid based dendritic wedges that were functionalized at the periphery with up to four NCN pincerlike nickel(II) groups also showed activity in the Kharasch addition reaction. No significant influence of the sterically different and more polar amino acid backbone was observed.[22]

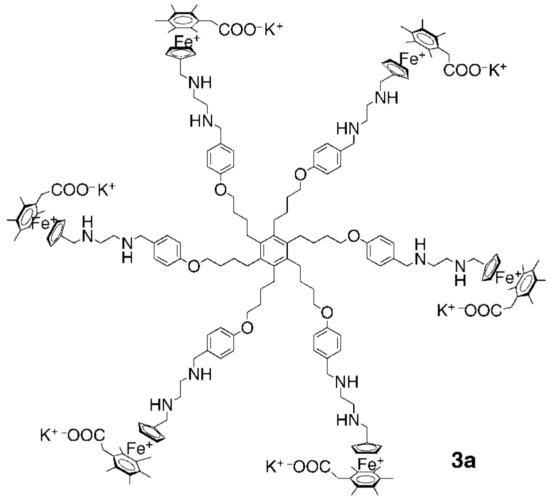
Some preliminary results on membrane filtration experiments have been reported. Compound **1a** exhibited decomposition while being applied in a continuous membrane reactor,[23] which was ascribed to hydrolysis of the Si–O bond of the linker between ligand and carbosilane backbone, thus the catalytically active complexes were disconnected from the support and subsequently washed out of the reactor. In **1b** the NCN ligands are directly attached to the carbosilane backbone and therefore much more stable.[24] Initial tests showed that **1b** was retained to 80% in the continuous membrane reactor after 100 reactor volumes (retention 0.9975) which is acceptable for many practical applications.[25]

Similar to the nickel–nickel interaction in the pincer-functionalized dendrimers, DuBois et al. observed metal–metal interactions in palladium-functionalized systems. Dendrimers were constructed containing up to 15 phosphines in both the periphery and backbone and the palladium complexes (**2**) were prepared by the addition of $[\mathrm{Pd(CH_3CN)_4}](\mathrm{BF_4})_2$.[26] These systems catalyze the electrochemical reduction of $\mathrm{CO_2}$ to CO, and the rates and selectivities observed for the dendritic systems were comparable to those of the monomeric complex. The electrochemical data, however, suggested the formation of Pd–Pd bonds during the electrochemical reactions. To avoid this type of dimerization a better spatial separation of the palladium sites in the dendrimer should be arranged.

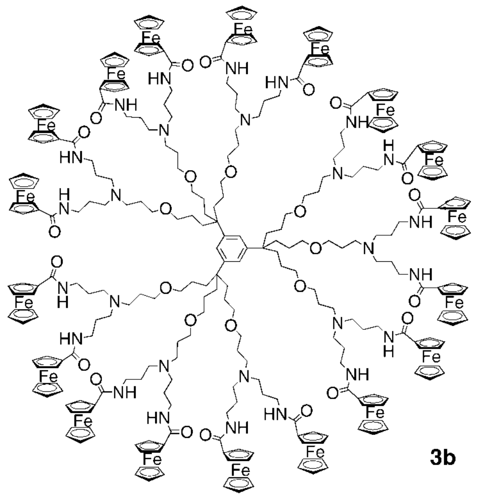


**2**

Astruc et al. recognized this problem and suggested constructing star polymeric structures instead of dendrimers.[27] In their opinion the steric congestion around the catalytic centers located at the periphery of these functionalized star polymers would be sufficiently reduced to overcome interactions between the catalytic sites. Star shaped hexanuclear polymeric catalysts **3a** containing six $\mathrm{CpFe^{I}}$(arene) complexes (Figure 3) were indeed as efficient as single-site complexes in the redox-catalyzed reduction of nitrite and nitrate to ammonia.[28]



**3a**

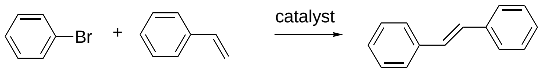


**3b**

Figure 3. The star-shaped catalyst (**3a**) having electrochemically active iron centers for the redox-catalyzed reduction of nitrite at the periphery, and for comparison, the corresponding dendritic system (**3b**).

## 2.3. Palladium-Catalyzed Coupling Reactions

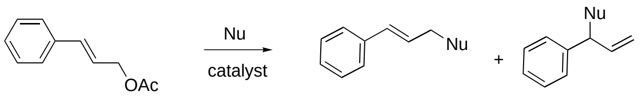
Several groups prepared systems that were functionalized with phosphine ligands at the periphery of the dendrimer (Sections 2.3–2.7). Commercially available DAB-dendrimers were equipped with diphenylphosphane groups at the periphery (**4**) by Reetz et al. by a double phosphination of the amines with diphenylphosphane and formaldehyde.[29] The transition metal complexes **4a** to **4d** were prepared in which the dendrimer-N-($CH_2PPh_2$)$_2$ groups act as bidentate ligands (cod = cycloocta-1,5-diene). Well-defined chelate complexes were obtained and complexes with metals bridging between different branches were not observed. The palladium complexes of these dendrimers (**4b**) were used as catalysts in the Heck reaction of bromobenzene and styrene to form stilbene (Scheme 2). Interestingly, the dendrimers showed larger turnover numbers than the monomeric parent compounds, which was ascribed to the higher thermal stability of the dendritic palladium complexes. Palladium black formation was only observed when the monomeric species was used. The catalytic activity using a 50 % palladium loading (M:L = 1:4) was similar to systems with 100 % loading. After the reaction the dendritic palladium catalyst completely precipitated upon addition of diethyl ether. In this way the catalyst was recycled and a second catalytic run gave similar results in the Heck reaction.



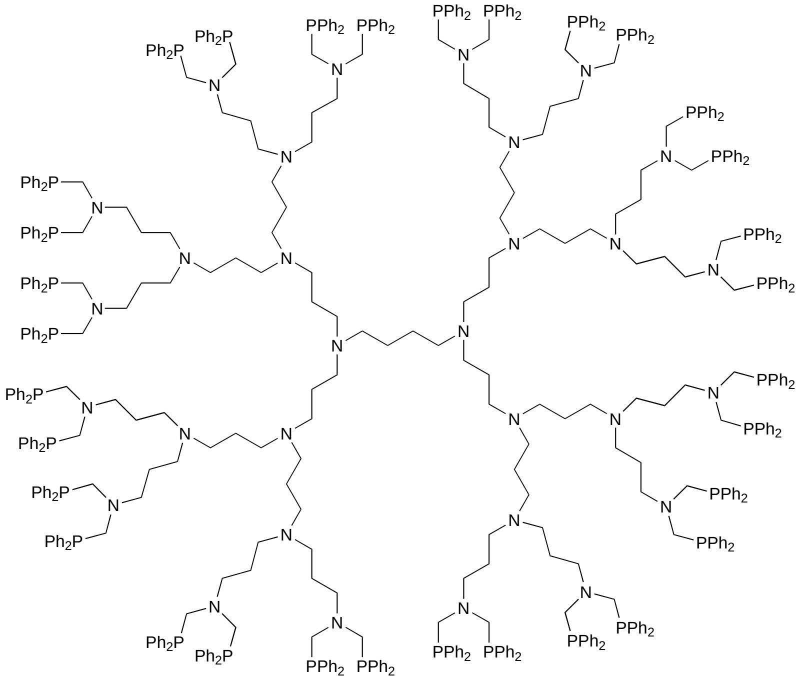
Scheme 2. The palladium-catalyzed Heck reaction of bromobenzene and styrene to form stilbene.

Heterobimetallic complexes **4e** have also been prepared. Half of the diphosphine ligands were used for complexation with palladium after which the remaining 50 % were treated with nickel. This strategy resulted in a statistical distribution of the metal atoms on the dendrimer surface. No catalysis using these systems has been reported to date, but interesting properties can be expected for a reaction in which a heterobimetallic mechanism is operative.[30]

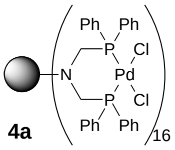
Reetz and Kragl et al. reported the use of phosphine-based dendritic catalysts for allylic substitution reactions in a continuous membrane reactor.[31] Prior to catalysis retentions up to 0.999 were measured photometrically for G3 dendrimer **4b** (molecular weight of 10212 g mol$^{-1}$). Although the dendrimer stayed in the reactor, some palladium leaching was observed. Metal–ligand dissociation gives a low molecular weight palladium species that will be washed out of the reactor. During the reaction the leaching was compensated by the addition of allyl palladium chloride to the feed solution. Applying G3 **4b** in palladium-catalyzed allylic substitution (Scheme 3) the continuous reactor could be operated for over 60 residence times with a conversion of up to 12 %, but obviously the product was contaminated with palladium. Better results were obtained using in situ prepared Pd complexes of a G4 dendrimer (calculated molecular weight 20564 g mol$^{-1}$ for 100 % palladium loading of the 32 diphosphines). After 100 residence times, the conversion had



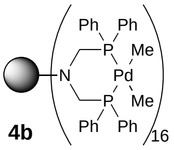
Scheme 3. The palladium-catalyzed allylic substitution reaction (Nu = nucleophile).



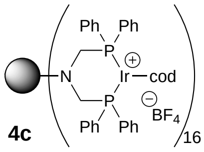
**4**



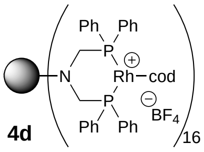
**4a**



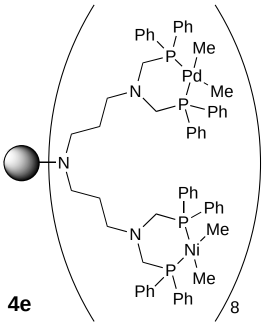
**4b**



**4c**



**4d**

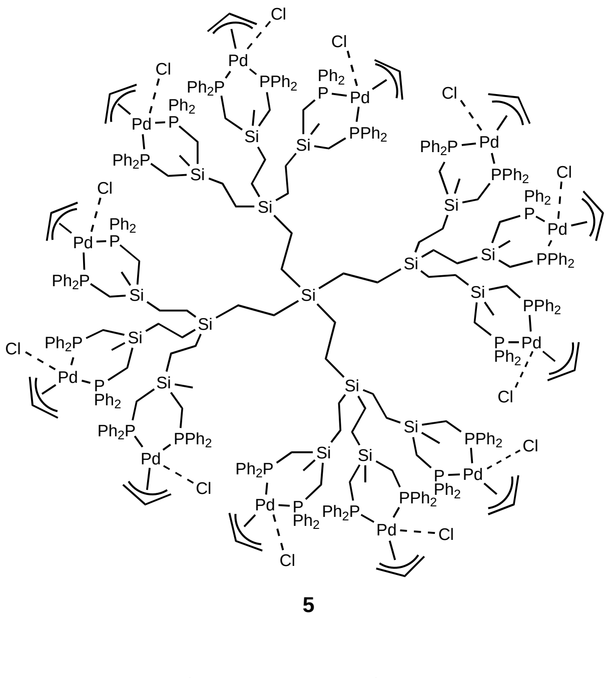


**4e**

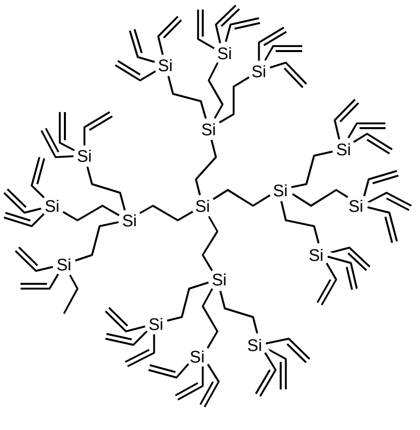
decreased from 100% to around 75%. Only very little palladium leaching was observed during this experiment (0.14% per residence time), which could only partly explain the decrease in conversion. The formation of inactive $PdCl_2$ complexes was proposed to account for the additional drop in activity. The conditions were significantly altered compared to the previous experiment (different reactor material and 10-fold increase in catalyst concentration) however, for definite conclusions about the effect of the dendritic catalyst used more experiments are required.

Several groups have reported the synthesis of carbosilane dendrimers functionalized with phosphine ligands.[32–35] These systems can be synthesized by a reaction with silicon chloride end groups (after hydrosilylation with $HSiCl_xMe_{3-x}$ of the terminal allyls) or by direct phosphination of the alkene. Van Leeuwen et al. reported carbosilane based dendritic catalysts with terminal mono- ($-SiMe_2CH_2PPh_2$) and diphosphine ($-SiMe(CH_2PPh_2)_2$) groups.[32] The largest dendrimer (G2) contained 36 terminal monodentate phosphines. Allyl palladium complexes of these ligands were formed upon the addition of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$. The bidentate ligands gave well-defined complexes like those observed for the DAB systems (**4**) whereas the dendrimers with the monodentate phosphines formed a mixture of complexes, differing in ring size (-P-Pd-P-dendrimer-). All the complexes were active in the palladium-catalyzed allylic alkylation using sodium diethyl methylmalonate as the nucleophile (batch reaction).[32] The rates were virtually independent of the dendrimer size, suggesting that all the active sites behaved independently.

Dendrimer **5** containing 12 diphosphine–palladium complexes was studied in a continuous membrane reactor. The catalytic activity (space–time yield) dropped dramatically to 10% of its initial activity within 10 residence times. The retention of unfunctionalized G2 dendrimer **6** was determined to be 0.981, that of dendritic catalyst **5** should be much higher since its molecular volume is three times larger. Therefore, leaching of dendritic catalyst cannot account for the observed drop in activity. This suggests that the catalyst decomposed or leached through the membrane probably as small soluble metal clusters that were dissociated from the dendrimer. The similarity of these observations with those of Reetz et al.[31] show that the practical application of dendritic palladium catalysts for the allylic substitution reaction in continuous processes is not straightforward and more investigations are required to understand the deactivation and leaching mechanisms.



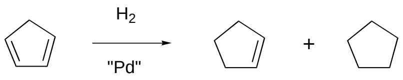
**5**



**6**

## 2.4. Palladium-Catalyzed Hydrogenation

$Pd^{II}Cl_2$ complexes of **4** (G3) were used as catalysts in the hydrogenation of a series of conjugated dienes and compared with the corresponding monomeric complex, the catalyst immobilized on non-cross-linked polystyrene, and heterogeneous palladium catalysts.[36] Higher activity in the hydrogenation of cyclopentadiene was found for **4** than for the corresponding monomeric complex and the polystyrene-bound catalyst (Scheme 4). The dendrimer backbone was proposed to act as a base to capture HCl, thereby accelerating the formation of the catalytically active (diphosphine)PdHCl species. In line with this, the monomeric complex was also much more active in the presence of a base. The heterogeneous systems (Pd/C and $Pd/Al_2O_3$), however, were still more active than the dendritic catalyst.



Scheme 4. Hydrogenation of cyclopentadiene.

Remarkably, excellent selectivity to cyclopentene was obtained on using the dendritic catalyst based on **4** in the hydrogenation of cyclopentadiene. This is a result of the relatively slow successive hydrogenation of cyclopentene as can be clearly seen in Figure 4 (slower hydrogen uptake); no explanation for this selectivity has been given. Although Pd/C

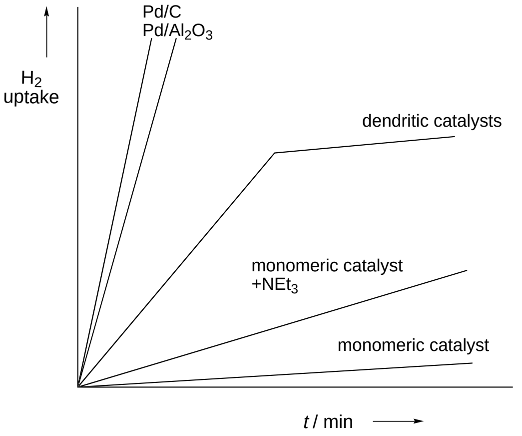


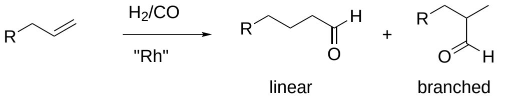
Figure 4. Schematic time courses of $H_2$ uptake in the hydrogenation of cyclopentadiene for various Pd catalysts.

and $Pd/Al_2O_3$ where more active catalysts the reaction was not selective; the rates of hydrogen uptake remained unchanged after conversion of cyclopentadiene into cyclopentene, yielding cyclopentane.

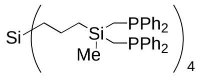
In the hydrogenation of 1,3-cyclooctadiene, dendritic **4**-$PdCl_2$ showed much higher rates than monomeric $[PhN(CH_2PPh_2)_2PdCl_2]$. The reaction was most efficient in ethanol while it was very slow in DMF. This is interesting since the dendritic complexes are not soluble in ethanol suggesting that in this solvent the catalyst system is heterogeneous, whereas in DMF the reaction proceeded homogeneously. Apparently, under heterogeneous conditions the active sites on the surface are still accessible. The hydrogenation rate was independent of the size of the substrates used, which supports this accessibility. In contrast, the polystyrene-immobilized system has the catalytic sites buried partially *within* its structure resulting in poor performance with DMF as the solvent. The heterogeneous dendritic catalyst could be recycled by centrifugation and showed only a slight decrease in activity in consecutive reactions.

## 2.5. Rhodium-Catalyzed Hydroformylation

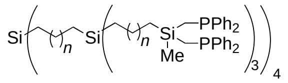
Rhodium complexes of the phosphine-functionalized carbosilane dendrimers are active in the hydroformylation of alkenes (see Scheme 5). The influence of the flexibility of the dendritic backbone on the catalytic performance was studied by comparing dendritic ligands **7a**–**c** (conditions: toluene, 80°C, 20 bar $CO/H_2$).[37] Remarkably, an increase in steric congestion on going from **7a** to **7b** and finally to **7c** did not affect the catalytic performance in this reaction, which is in contrast with the results of the Kharasch addition reaction (Section 2.2).



Scheme 5. Rhodium-catalyzed hydroformylation of alkenes.



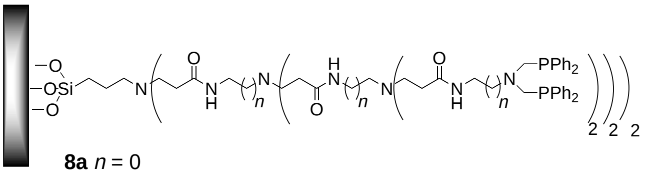
**7a**



**7b**: *n* = 0
**7c**: *n* = 1

Reetz et al. reported preliminary results on the rhodium-catalyzed hydroformylation using the multiphosphine DAB dendrimer **4** as the ligand and they observed activities and selectivities similar to that of the parent ligand.[29] The monodentate analogues of the phosphine-functionalized carbosilane dendrimers with the $SiMe_2CH_2PPh_2$ end groups showed a decrease in activity for the more congested systems.[37] By changing these steric properties the structure of the peripheral rhodium complexes also changes, metal complexes are formed between phosphines of different branches. This was proposed to be the origin of the lower activity.

A similar study has been performed by Alper et al; they prepared phosphine-functionalized poly(amido amine) (PAMAM) branches **8a** that were anchored to the surface of silica particles. Primary amines were stepwise converted into G0 to G4.[38a] Phosphination of the terminal amine groups occurred completely for G0 to G2, but for G3 and G4 steric crowding prevented complete functionalization. Subsequent reaction with $[\{RhCl(CO)_2\}_2]$ gave the corresponding dendrimer complexes, which were tested in catalytic alkene hydroformylation. Using styrene as a substrate, the G0–G2 dendritic catalysts afforded aldehydes in nearly quantitative yield even at room temperature. They showed good regioselectivity to the branched product (linear to branched ratios as high as 1:30). G3 and G4 catalysts showed only considerable activity at elevated temperatures. To study the impact of steric congestion on the hydroformylation reaction a new series of ligands was prepared (**8a**–**c**), differing in flexibility because of variation in spacer length.[38b] From comparison of the catalytic activity of these ligands it was concluded that steric congestion indeed lowered the activity. This is in contrast with the results obtained with the homogeneous dendritic systems. A detailed study using both systems under similar conditions should be performed before any conclusions can be drawn. 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 (for the branched product) was observed during five consecutive runs.

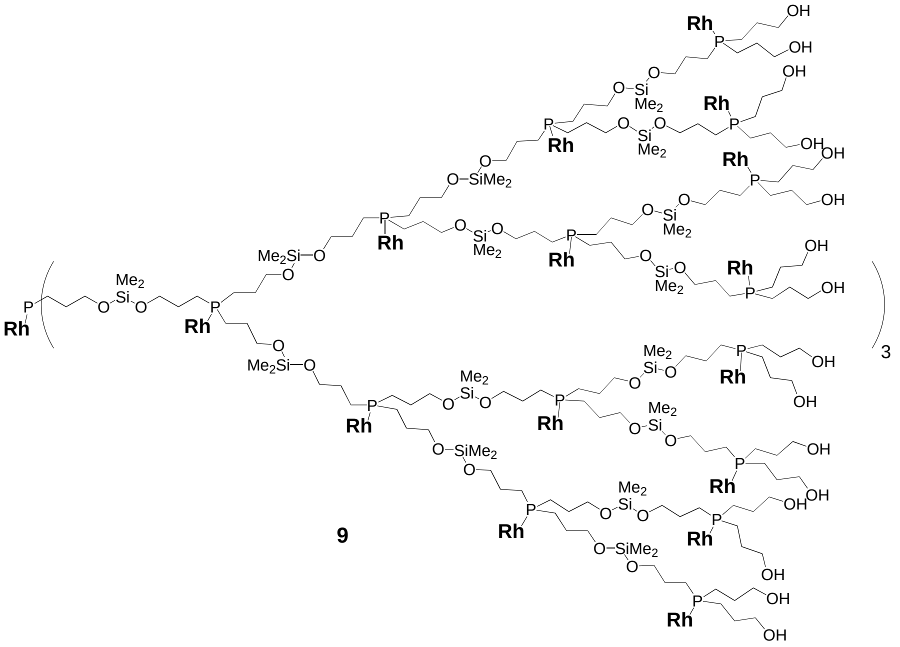


**8a** *n* = 0
**8b** *n* = 2
**8c** *n* = 4

Carbosilane dendrimers based on polyhedral oligosilsequioxane cores containing up to 72 vinyl groups (vinyl-POSS) have been phosphinated with $HPR_2$ (R = Me, Et, Hexyl, Cy, or Ph).[35] The rhodium complexes of the alkyl–phosphine-functionalized systems were catalytically active in hydroformylation reactions yielding alcohols instead of aldehydes. Interestingly, the dendritic catalyst with 24 $PEt_2$ end groups was slightly more selective for the linear product (linear: branched = 3.1) than the monomeric ligand $PEt_3$ (linear: branched = 2.4), whereas for the other dendritic catalyst the selectivity was lower. It was suggested that this higher selectivity was because of a subtle steric control over the reaction.

## 2.6. Rhodium-Catalyzed Hydrogenation

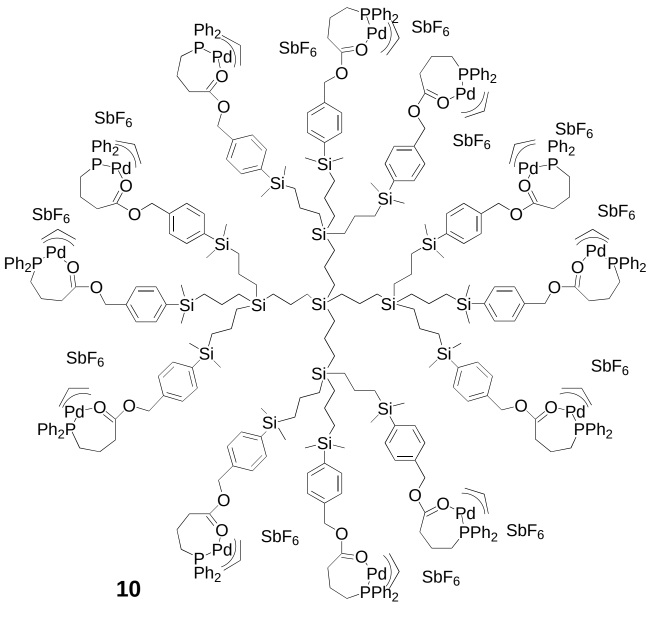
In the group of Kakkar, dendrimers such as **9** (**Rh** = [Rh(cod)Cl]), having phosphines as branching points, were synthesized by acid–base hydrolysis of aminosilanes with alcohols.[39] The synthesis of these dendritic systems is relatively straightforward, but the dendrimers contain labile silicon–oxygen bonds making them less suitable for application in continuous processes. The phosphorus donor atoms can be used to complex a variety of transition metals. Interestingly, the complexes can be formed before or after the acid–base reaction that forms the dendrimer. The $Rh^I$ metallodendrimers were catalytically active in the hydrogenation of decene, and the larger system **9** showed only a small decrease in activity compared to the monomeric rhodium complex. Rates around 400 mol(mol rhodium)$^{-1}$ h$^{-1}$ were obtained in THF at 25 °C and 20 bar of hydrogen. After extraction and recrystallization the catalysts were reused showing 95 % of the original activity in the second run. Unfortunately, the catalytic performance of the complexes at the periphery was not compared with those located in the interior.



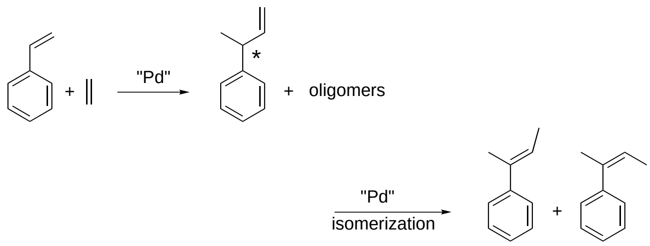
**9**

## 2.7. Palladium-Catalyzed Hydrovinylation

Van Koten and Vogt et al. prepared carbosilane dendrimers **10** that were functionalized with hemilabile P,O-ligands at the surface.[40] The palladium complexes of this system are active catalysts in the hydrovinylation reaction of styrene (Scheme 6), an important reaction since it potentially provides easy access to chiral building blocks for the preparation of fine chemicals. Key problems in this reaction are the selectivity of the reaction, oligomerization and isomerization side reactions, and the stability of the catalyst. The dendritic catalysts were found to be rather stable in the batch process. Isomerization of the product, which normally occurs at high conversion, could be suppressed by stopping the reaction at low conversion. 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.[40] Retention of the dendrimers with four or twelve palladium sites in a membrane reactor was at least 85 %, which should be sufficient to prove the concept. Indeed the selectivity to the desired chiral 3-phenylbut-1-ene was very high in the continuous hydrovinylation of styrene, but the rate of the reaction decreased rapidly because of decomposition of the catalyst **10**. This decomposition was confirmed by the observation of palladium precipitate on the membrane.



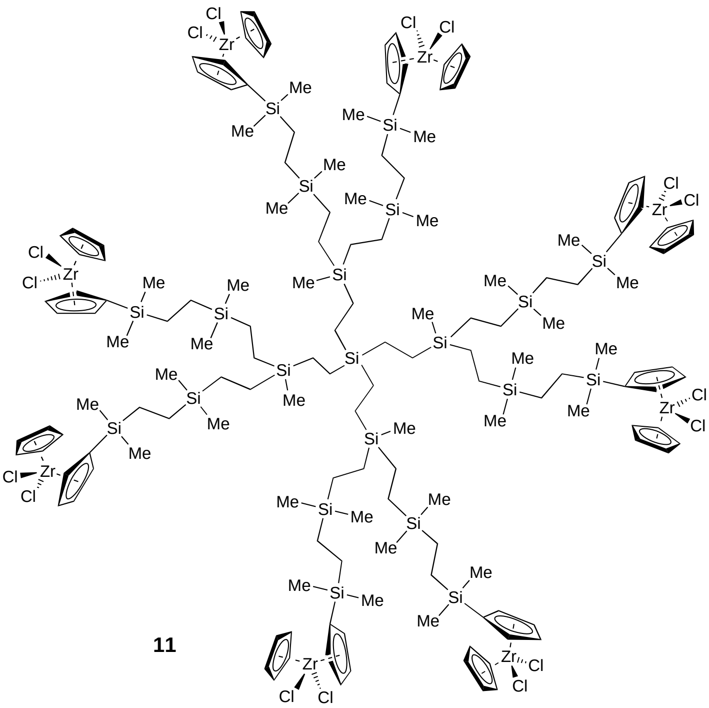
**10**



Scheme 6. Hydrovinylation of styrene.

### 2.8. Metallocene-Catalyzed Polymerization

Seyferth synthesized carbosilane dendrimers with 4, 8, and 12 peripheral zirconocene, hafnocene, and titanocene groups.[41] Dendrimer **11** containing eight zirconocene dichlorides was applied in the methylaluminoxane (MAO) activated olefin (co)polymerization (Table 1) and in silane polymerization.



**11**

Considerable activity of **11** in the ethylene polymerization and copolymerization (of two different alkenes) was found (5760 kg polyethylene (mol metal)$^{-1}$ h$^{-1}$). However, these systems are ten times less active than monomeric zirconocenes (Kaminsky et al.[42] reported activities as high as 60 900 kg (mol metal)$^{-1}$ h$^{-1}$). Hyperbranched polymers based on dimethylvinylsilane were prepared,[41b] which are attractive because in one step large dendrimerlike structures can be obtained. After functionalization of their irregular surface with zirconocenes, they were tested in ethylene polymerization. Unexpectedly, a higher activity (12 400 kg mol$^{-1}$ h$^{-1}$) was observed for these hyperbranched polymers than for **11**.

Table 1. (Co)polymerization of alkenes using zirconocene-functionalized dendrimer **11**.

| Substrate 1 | Substrate 2 | Activity [kg mol (Zr)$^{-1}$ h$^{-1}$] |
|---|---|---|
| ethylene | | 5760 |
| 1-hexene | | 11 |
| cyclopentene | | 29 |
| ethylene | propylene | 1460 |
| 1-hexene | cyclopentene | 15 |

## 3. Core-Functionalized Dendritic Transition Metal Catalysts

In this section we will discuss the important contributions of core- and focal-point-functionalized dendrimers in catalysis. These two approaches result in similar systems intended to have similar properties. The choice of either the core- or focal-point-functionalization has mainly been based on synthetic accessibility. There is a difference, however, in that core-functionalized systems are more efficient in shielding the catalysts than the focal-point-functionalized ones. The latter require higher generations to give similar effects. To demonstrate this difference we performed molecular dynamics calculations of a first-generation (phosphine) core-functionalized and a second-generation focal-point-functionalized system (Figure 5).[43] In the core-functionalized dendrimers the phosphine ligand is located at the center of the molecule, thereby being shielded from the exterior environment by the dendritic architecture. In the focal-point-functionalized system the phosphine is located closer to the surface of the dendrimer, and the dendrimer shielding is less effectively.

The specific micro-environment created by dendritic structures shows great similarity to biological systems such as enzymes. This has greatly stimulated chemists to prepare systems based on core-functionalized dendrimers that mimic certain properties of biological systems, but these systems are generally not used for transition metal catalysis.[44] By using these mimics natural features, such as, hemoprotein–dioxygen binding, selective recognition of guest molecules, and stabilization of, for instance, iron–sulfur clusters have been studied. Dendritic iron porphyrins were examined as cytochrome mimics, reproducing the buried electroactive heme core (with the Fe$^{III}$/Fe$^{II}$ couple) within a dendrimer superstructure, which is a model for the natural protein shell.[44i] Several groups have studied recognition of guest molecules by dendritic receptors.[44f–h, 45] With respect to catalysis, core-functionalized systems can potentially mimic enzyme properties.

### 3.1. Polymerization

The first example of a catalytic reaction at the core of a dendrimer was provided by Fréchet et al. using dendritic alcoholates such as **12** as macro-initiators for anionic ring-opening polymerization of ε-caprolactone (Scheme 7).[46] Usually, in the polymerization of ε-caprolactone, alkali metal alcoholates yield low molecular weight ($M_W$) polymers with

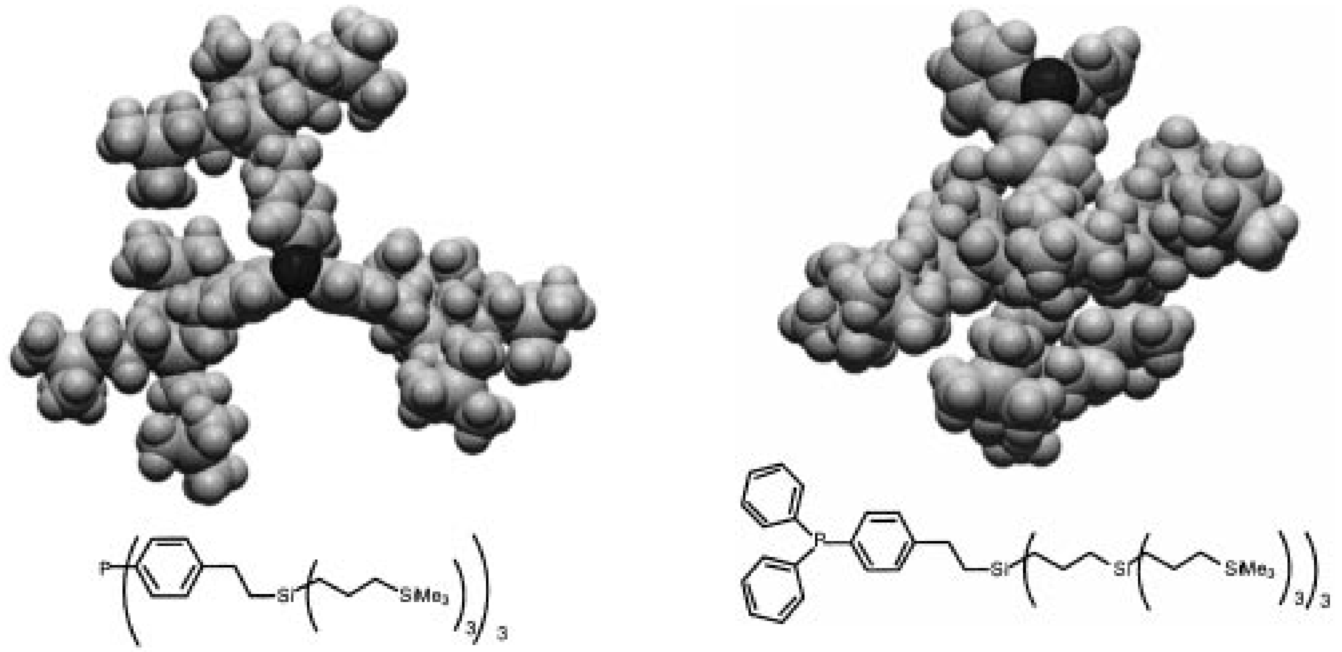
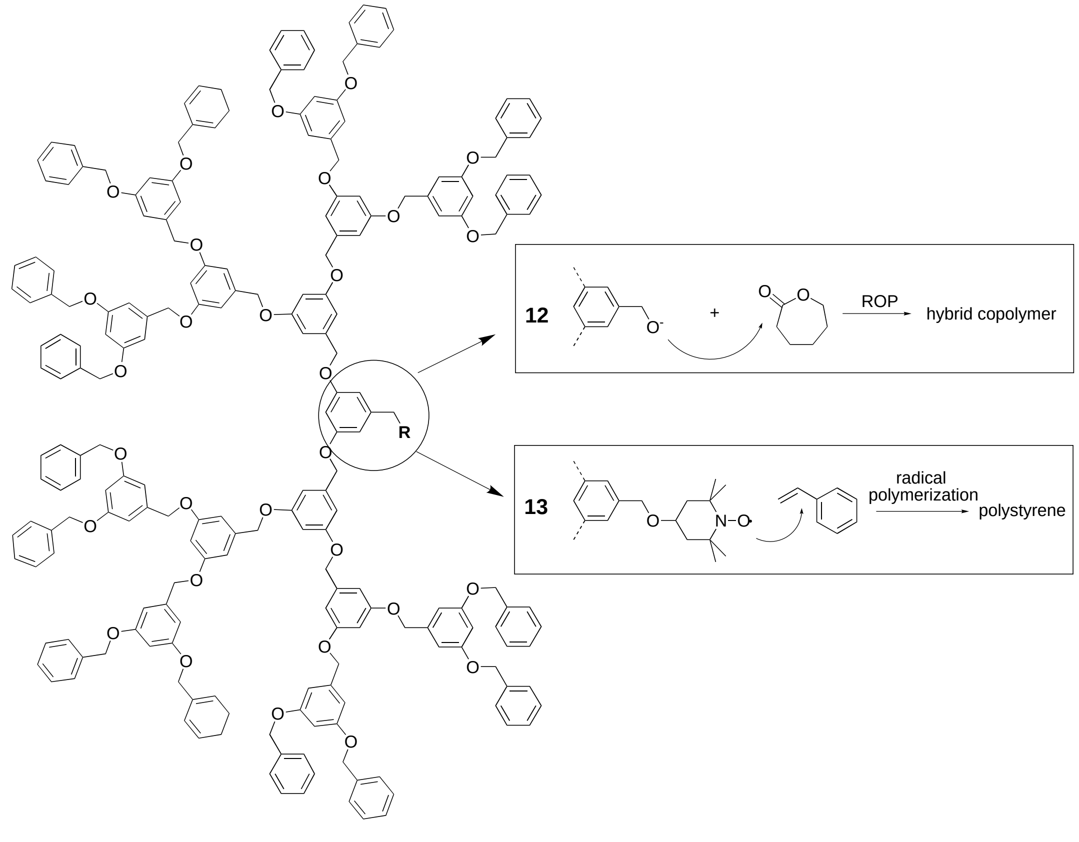


Figure 5. Molecular modelling (dynamics) clearly shows the efficient embedding of the phosphine ligand in the core-functionalized system (left) compared to the focal-point-functionalized wedge (right).



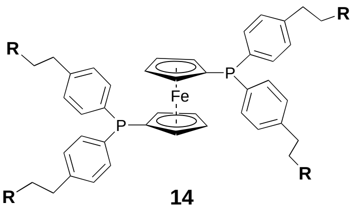
Scheme 7. Polymerization reactions at the focal point of a dendron: anionic ring-opening polymerization (ROP) of $\varepsilon$-caprolactone (**12**), and styrene radical polymerization (**13**).

broad $M_W$ distribution. Earlier studies had shown that steric bulk around the reaction center leads to suppression of side reactions as well as to a decrease of "backbiting", which is responsible for low $M_W$ products. Furthermore, solubility problems usually result in low $M_W$ polymers. The dendritic initiators appeared suitable initiators because of their excellent solubility in THF and their steric bulk prevented "backbiting". The G4 alcoholate acts as a highly effective initiator (Scheme 7) producing high $M_W$ polymers with a narrow $M_W$ distribution of 1.07. The initiator efficiency was estimated to be close to 100%, confirming the good accessibility of the reactive core. The G1 analogue produced only oligomers in very low conversions, which resembles the behavior of potassium *tert*-butoxide. Thus, the large dendrimers prevent termination of the polymerization by shielding the growing tip from reaction with a chain of another growing tip.

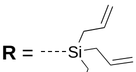
Similarly, dendritic wedges were designed for use in the synthesis of living polymers and living block copolymers by controlled radical polymerization.[47] A nitroxyl radical (TEMPO) was attached at the focal point of G1 to G3 wedges (**13**, Scheme 7). In polymerization reactions low polydispersities were obtained using the high generation dendrimers because of the irreversible release of the growing chains and slow recombination. This result shows the necessity of having polymer chains that are compatible with the dendrimers. Unfortunately, insolubility of the polymer–dendrimer complexes limited the growth of the chains.

### 3.2. Palladium-Catalyzed Allylic Alkylation

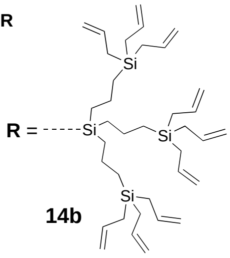
In our group core-functionalized dendritic catalysts based on carbosilane dendrimers have been prepared.[48] A novel route was developed to synthesize dendritic wedges with arylbromide as the focal point. These wedges were divergently coupled to a ferrocenyl diphosphine core to obtain dppf-like ligands **14** (dppf = bis(diphenylphosphanyl)ferrocene). Other phosphine ligand core-functionalized systems have also been prepared using the same strategy.[49]



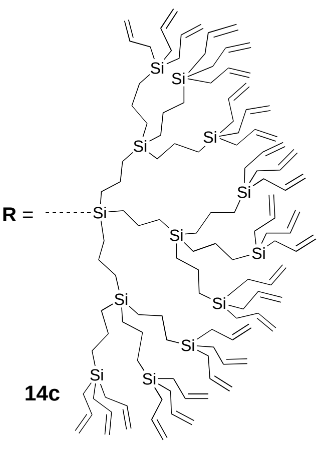
**14**



**14a**



**14b**



**14c**

Table 2. Activities and selectivities in the allylic alkylation reaction of 3-phenylallyl acetate with sodium diethyl methylmalonate using carbosilane dendrimers with a dppf core.

| L | TOF [mol mol$^{-1}$ h$^{-1}$][a] | Branched product [%][b] |
|---|---|---|
| dppf | 72 | 10 (±0.7) |
| **14a** | 76 | 12 (±1.2) |
| **14b** | 58 | 13 (±0.8) |
| **14c** | 17 | 21 (±0.4) |

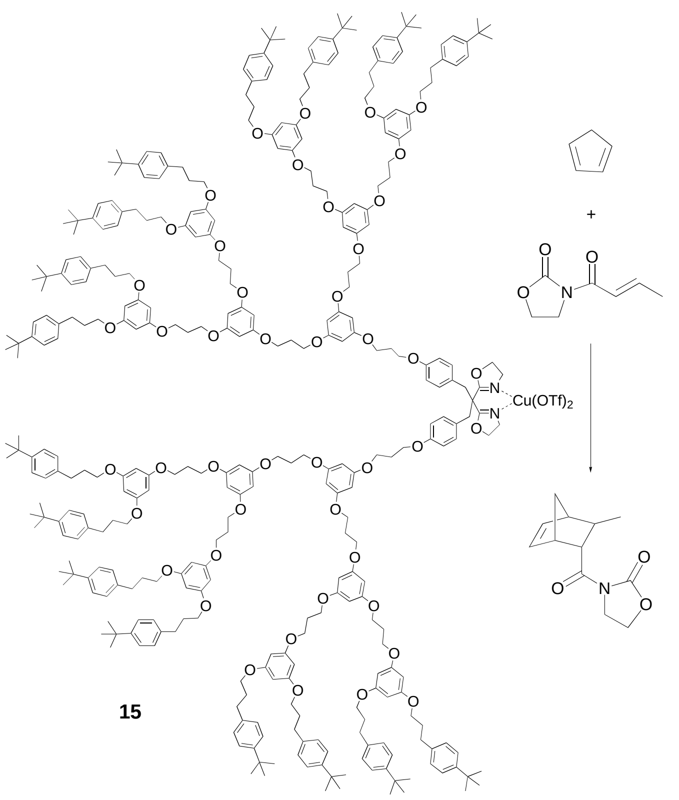
[a] All catalytic reactions reached full conversion in 24 h. [b] The selectivity of the reaction was independent of the conversion.

Bidentate palladium complexes of **14** were formed upon the addition of $PdCl_2$, as evidenced by $^{31}P$ NMR spectroscopy. Even the largest systems formed *cis* complexes. Crotylpalladium chloride complexes were prepared in situ and used as catalysts in allylic alkylation reactions (Table 2, Scheme 3). The rate of alkylation of 3-phenylallyl acetate with sodium diethyl methylmalonate slightly decreased upon increasing generation number. More importantly, a change in product regioselectivity was observed on going to higher generations, resulting in an increase of branched product from 10% for dppf to 21% for the largest system. It was proposed that the apolar microenvironment created within the carbosilane dendrimers caused this change in selectivity.[50] Recent studies of allylic alkylation and Heck reactions confirmed this relationship between solvent polarity and product regioselectivity.[51] In contrast, steric hindrance of the branches and an increase in the P-Pd-P bite angle because of increasing steric interactions between the dendritic substituents on the phosphorus atoms would preferentially lead to the linear product (for this substrate).[49, 52] Allylic alkylation using **14c** was also performed in a continuous membrane reactor. Catalytic activity was retained for at least 20 residence times without significant loss, suggesting that the stability of core-functionalized systems is larger than that of their periphery-functionalized analogues.[49]

The rhodium complexes of analogues of **14** (trimethylsilyl instead of allyl end groups) are active in the hydroformylation of 1-octene.[53] In contrast to the palladium-catalyzed allylic alkylation the activity for all generations of dendritic catalyst was similar. This clearly demonstrates that the relative activity for the higher generation core-functionalized dendrimers varies, depending on the type of reaction. This obviously depends on the steric demands of the rate limiting step of the reaction.

### 3.3. Copper-Catalyzed Diels–Alder Reactions

Chow et al. reported the synthesis of a series of poly(alkyl aryl ether) dendrons (G0–G3; G3 (**15**) is shown in Scheme 8) functionalized at the focal point with dendritic bis(oxazoline) ligands.[54] $Cu^{II}$ complexes of these dendrimers catalyze the Diels–Alder reaction between cyclopentadiene and *N*-2-butenoyl-2-oxazolidinone. A detailed study revealed that the reaction follows enzymelike Michaelis–Menten kinetics. A reversible formation of the copper–dienophile complex is followed by the rate-limiting conversion into the Diels–Alder adducts. The association constants of the catalyst–dienophile complex ($k_1/k_{-1}$) decreased slightly with the higher generation dendrimer. Upon complexation of the dienophile at the focal point the geometry at the metal center changes. This results in an increase in steric repulsion between the dendritic wedges which is more pronounced for the larger systems. Since the dienophile was used in large excess during the catalytic experiments the copper was present as a dienophile complex



**15**

Scheme 8. Diels–Alder reactions using Cu$^{II}$–bis(oxazoline) complexes located at the core of polyether dendrimers.

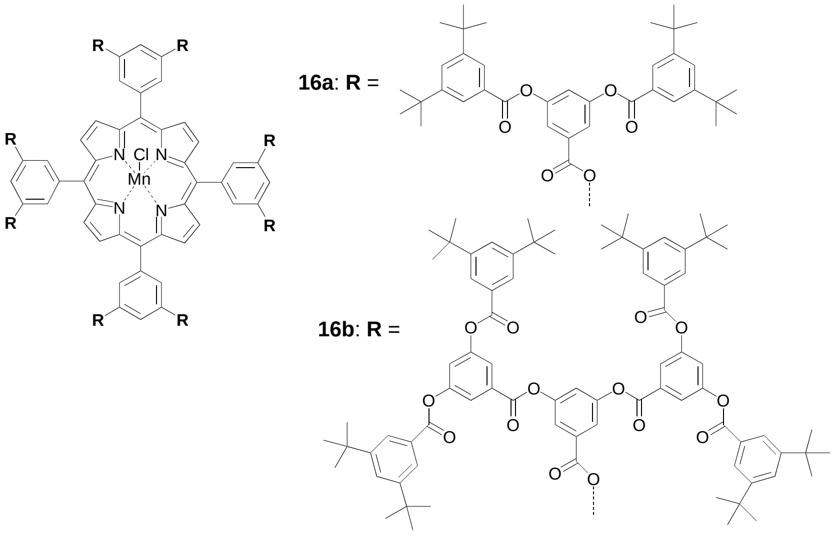
in all the systems, thus under these conditions no effect of this difference on the catalytic activity was expected. Indeed the activity of the dendritic catalysts G0–G2 was very similar. However, a marked drop in activity was observed when G3 was used as the catalyst. The size of this dendritic system results in a change in spatial structure around the catalytic core from planar to globular. The decrease in reaction rate is proposed to be because of a decrease in steric accessibility, with G3 thus acting more like a core-functionalized dendrimer.

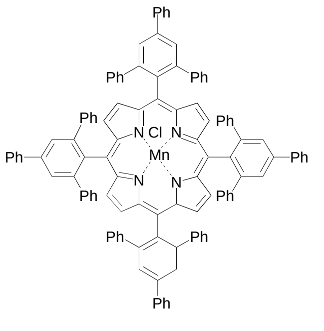
This encapsulation effect was further studied by determination of the substrate selectivity using substrates of different sizes. Dienophiles with different tail lengths were applied in a 1:1 molar ratio to react with cyclopentadiene in the presence of catalyst. The smaller dienophile reacted slightly faster than the bulkier one for all the catalysts studied (non-dendritic parent complex, G1-Cu(OTf)$_2$, and G3-Cu(OTf)$_2$). More importantly, G3-Cu(OTf)$_2$ ($k_{rel} = 1.18$) displayed higher substrate selectivity than G1-Cu(OTf)$_2$ ($k_{rel} = 1.05$).

## 3.4. Manganese-Catalyzed Epoxidation

Introduction of dendritic wedges on metalloporphyrins results in core-functionalized dendrimers in which the porphyrin unit is shielded from the bulk solution. These type of systems were mainly prepared to mimic the microenvironment effect of hemoproteins since this plays a crucial role in dioxygen binding. Suslick et al. used steric shielding of the porphyrin unit to establish regio- and shape-selective catalysis.[55] Eight bulky G1 and G2 poly(aryl ester) dendrons were connected to the porphyrin core to give the manganese(III)-porphyrin complexes **16**. These bulky catalysts have been tested as regioselective epoxidation catalysts, using iodosylbenzene as the oxygen donor, employing nonconjugated dienes that differ in steric hindrance. The dendritic epoxidation catalysts show greater preference for the least hindered double bond than less sterically hindered porphyrins do: 1,4-octadiene epoxidation of the terminal C=C bond is four times more selective using **16b**. A similar effect, but less pronounced, was observed for a moderately hindered (2′,4′,6′-OMeC$_6$H$_4$)Mn$^{III}$-porphyrin.

Epoxidation of 1-alkenes is generally slower than that of the more electron-rich internal alkenes, but steric effects can reverse this trend; up to threefold higher selectivities for 1-alkenes compared to internal alkenes have been observed when using the dendritic catalysts. Remarkably, there was no significant rate difference between parent and dendrimer-encapsulated catalysts. Molecular modeling studies showed that, although access from "above" is completely restricted by the dendrimer branches on both faces of the porphyrin, significant cavities at the "sides" of the porphyrin plane exist which permit the entry of the substrates. Compounds **16a** and **16b** have larger pockets (ca. 7–10 Å) than the double pocket 5,10,15,20-tetrakis(2′,4′,6′-triphenylphenyl)porphyrin **17** (~4 Å), which is fully consistent with the higher selectivity obtained using **17**.[56]





**17**

## 4. Enantioselective Transition Metal Catalysis using Dendrimers

Chirality in dendritic architectures has been reviewed in a recent "Concepts" article by Meijer et al.[57] The traditional concepts of chirality for small molecules are not sufficient to explain the chiroptical properties of some of the chiral dendrimers. Some hypotheses have been proposed, but more detailed studies on novel systems are required to confirm these ideas.

Seebach et al.[58] classified the several ways to introduce chirality in a dendrimer:

1) It can have a chiral core (Figure 6a).
2) The chirality can be introduced at the periphery (Figure 6b).
3) Chiral branching units can be used (Figure 6c).
4) Constitutionally different branching units can be attached to a chiral core (Figure 6d).

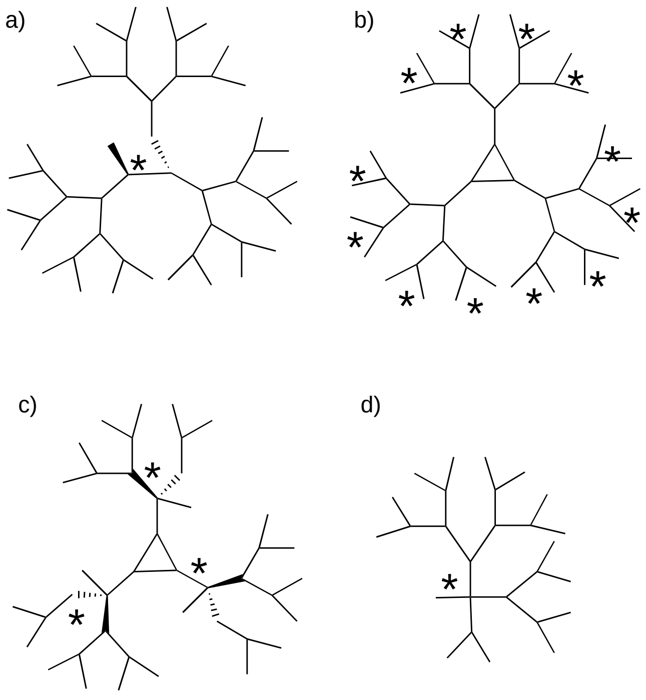


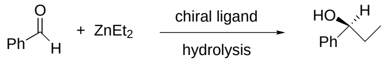
Figure 6. Schematic picture of the positions where chirality can be introduced in the framework of dendrimers.

Moreover, one can prepare systems that combine these types of chirality. Some examples show that the local chirality in the core of a dendrimer can result in a cryptochiral dendrimer that exhibits no optical activity. Also, in systems that are functionalized at the periphery with chiral groups, the optical rotation can strongly depend on the number of end groups. Generally, the rigidity of the system and the dense packing of chiral groups can have a huge impact on the stereochemical properties. For enantioselective transition metal catalysis using chiral dendritic catalysts these factors are likely to be of similar importance. In the field of enantioselective dendrimer catalysis, several reports have appeared and are summarized in ref. [10d].

### 4.1. Periphery-Functionalized Chiral Dendritic Catalysts

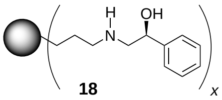
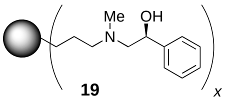
#### 4.1.1. Diethylzinc Addition

Meijer et al. used poly(propylene imine) dendrimers, that were functionalized with chiral amino alcohol ligands, for the $Et_2Zn$ addition to benzaldehyde (Scheme 9).[59] Preliminary results using **18** and **19** are given in Table 3, showing high yields of 1-phenylpropanol for all generations. Moderate enantioselectivities were obtained for the smaller dendritic catalysts and the *ee* decreased with increasing generation number: upon using G5 almost no selectivity was observed, which was proposed to be a result of the dense packing of the chiral end groups at the periphery. Presumably, this leads to several "frozen-in" conformations (this was also observed for the "dendritic box"[8, 60]), which is directly related to the presence of different catalytic sites. Introducing spacers between the dendrimer surface and the chiral functionalities to minimize steric interactions might solve this problem.[57]

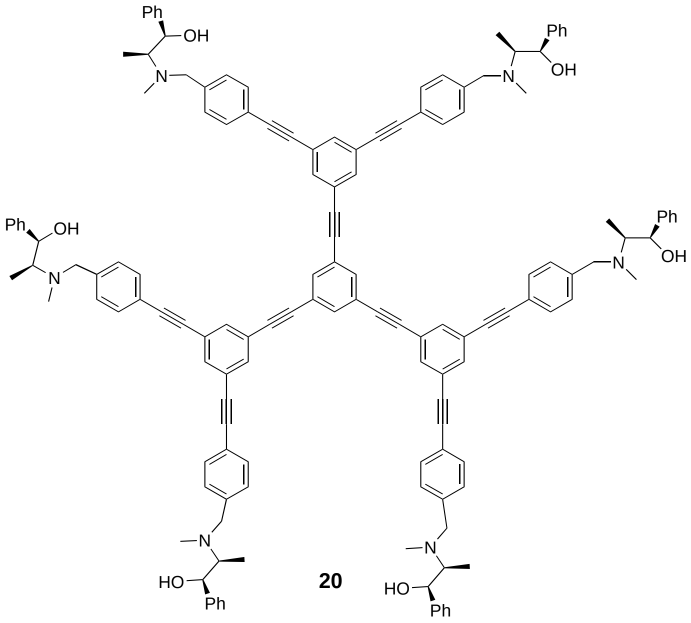


Scheme 9. The diethylzinc addition to benzylaldehyde yielding optically active secondary alcohols.

Table 3. The use of modified poly(propylene imine) dendritic catalysts **18** and **19** for the addition of diethylzinc to benzaldehyde.

| Number of end groups (*x*) |  **18** | |  **19** | |
|---|---|---|---|---|
| | Yield [%] | *ee* [%] | Yield [%] | *ee* [%] |
| 1 | 82 | 36 | 86 | 27 |
| 2 | 75 | 36 | 77 | 25 |
| 4 | 54 | 11 | 86 | 25 |
| 8 | 58 | 6 | 64 | 24 |
| 16 | 63 | 13 | 57 | 18 |
| 32 | 49 | 10 | 70 | 18 |
| 64 | 57 | 7 | 68 | 18 |

Poly(amido amine) dendrimers were functionalized with four and eight chiral amino alcohol groups.[61] In the presence of these chiral ligands, enantioselective addition of $Et_2Zn$ to various *N*-diphenylphosphinylimines was examined. With *N*-diphenylphosphinylbenzaldimine as the substrate the monomeric parent ligand gave 92% *ee*, whereas the dendritic catalysts showed only moderate enantioselectivities (43% *ee* for G0 and 30–39% *ee* for G1). The reaction rates also decreased for the larger systems. Thus a similar effect was observed for these systems as for those of Meijer et al.;[59] the high local concentration of chiral active sites leads to a diminishing of the overall enantioselectivity of the reactions. In a subsequent paper it was reported that similar ligands linked to a more rigid dendrimer **20**[62] gave enantioselectivities similar to the parent compound in the addition reaction of $Et_2Zn$ to *N*-diphenylphosphinylimines and at similar rates. In **20** the chiral ligands are effectively separated by the rigid



**20**

backbone yielding systems that do indeed have independent catalytic sites.

Seebach et al. prepared G0 and G1 poly(phenyl benzyl ether) dendrimers functionalized with three or six terminal $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs; for the structure of the TADDOLs see Scheme 10).[63] The $Ti(OCHMe_2)_2$ complexes of these TADDOLs were applied in the catalytic nucleophilic addition of $Et_2Zn$ to benzaldehyde. The yields are generally lower than for mononuclear Ti-TADDOLates, but the enantioselectivity of the reaction for (*S*)-1-phenylpropanol was high for all the systems used (94 % *ee* for the largest dendritic catalyst compared to 96–98 % *ee* for the other systems). The dendritic catalysts could be separated from the reaction mixture on a silica column, but reuse was not reported.

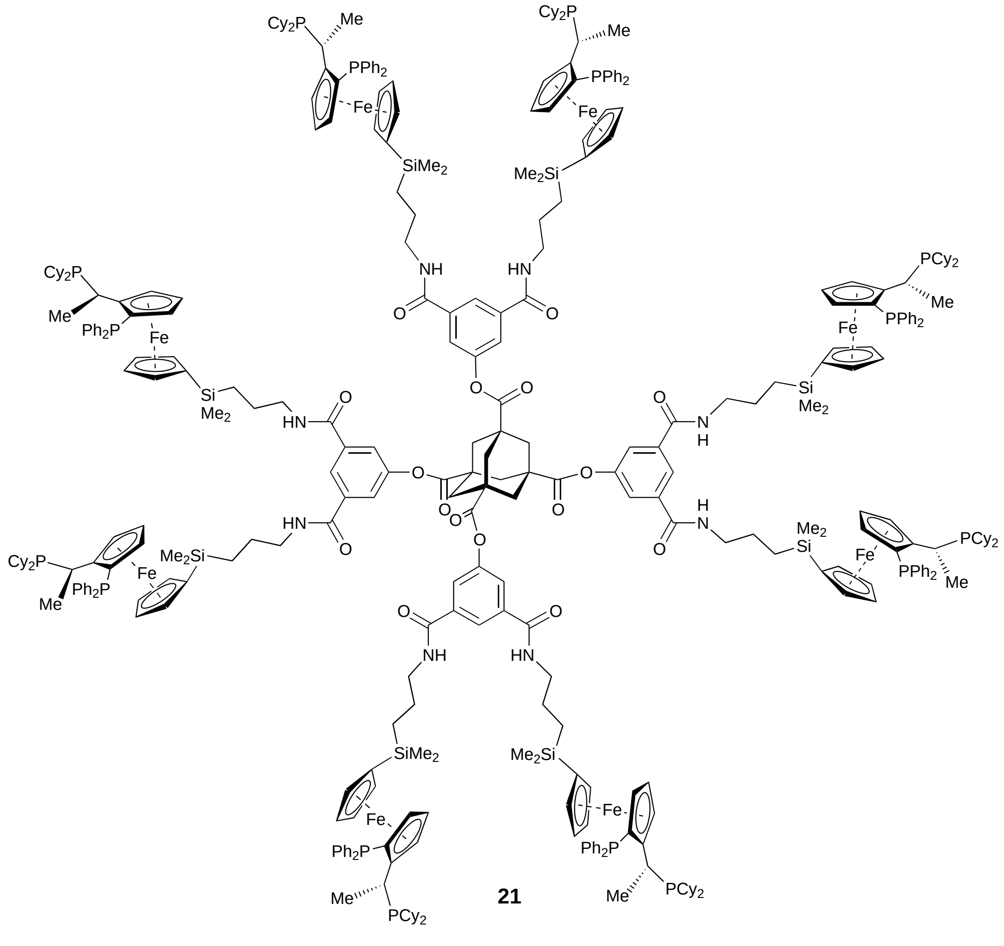
### *4.1.2. Rhodium-Catalyzed Hydrogenation*

Togni et al. reported dendritic catalysts based on chiral ferrocenyl diphosphine ligands. Using different cores they obtained systems with 3, 6, 8[64] (complex **21**) 12, 16,[65] and 24[66] "Josiphos" units (Cy = cyclohexyl). Rhodium complexes of these systems were obtained by stirring one equivalent of ligand with $[Rh(cod)_2]BF_4$ in dichloromethane. These complexes were used as precursors in the hydrogenation of dimethylitaconate (conditions: 1 mol % rhodium, methanol, 1 bar $H_2$ pressure). Remarkably, all the reactions went to completion in 20 min and all the dendritic catalysts gave 98 % *ee* or higher, which is comparable with mononuclear Rh-Josiphos complexes (99 % *ee*). In the lower generations no significant steric interactions between the catalytic sites are expected. The observed high enantioselectivity for the largest dendritic systems, however, clearly suggests that also in these systems the catalysts work as independent sites without significant obstruction by steric congestion. Preliminary nanofiltration experiments indicated that **21** could be completely retained, but catalysis in a continuous process using **21** has not been reported.

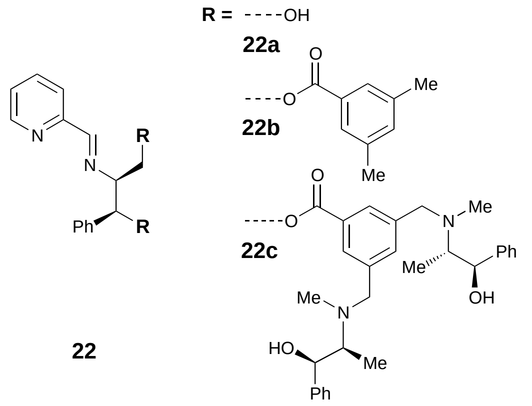
## 4.2. Core-Functionalized Chiral Dendritic Catalysts

Brunner introduced the term "dendrizymes" for core-functionalized transition metal catalysts developed for enantioselective catalysis.[67] Diphosphine and diimine ligands were coupled to the focal point of chiral dendritic branches to create a chiral pocket around the transition metal.

The "dendrizyme" **22a**–**22c** were used in the $Cu^I$-catalyzed cyclopropanation of styrene and a slight increase from < 2 % *ee* to about 10 % *ee* on changing from parent



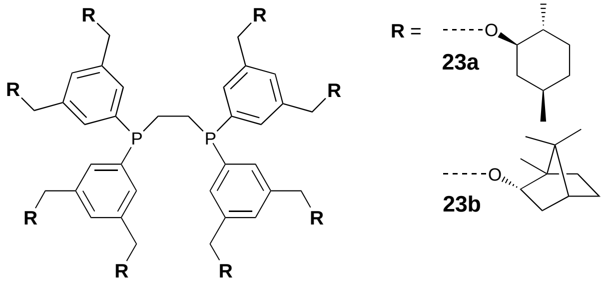
**21**



**22**

pyridine aldimine **22a** to **22b** was observed showing that the chiral pocket slightly enhances the enantioselectivity of the reaction. Further expansion with a second layer of chiral substituents (**22c**) did not result in higher *ee* values.[68]

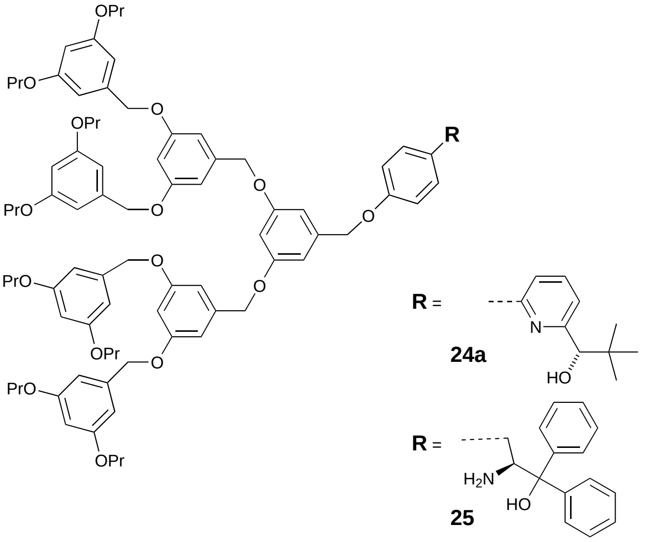
Two-layer chiral diphosphine dendrizymes such as **23** were synthesized by a divergent route.[67, 69] As the chiral functionalities around the P atoms varies, a modification of the enantioselectivity in asymmetric reactions was anticipated. However, only poor enantioselectivities have been reported for all the reactions tested so far (hydrogenation, hydrosilylation, allylation, and Grignard cross-coupling). A lack of rigidity in the outer layer of chiral groups was held responsible for these low enantioselectivities. Detailed kinetic studies were performed to investigate the effect of different dendritic branches on the reaction rate of the hydrogenation of acetamidocinnamic acid. Remarkably, the expanded ligand system **23a** resulted in a faster hydrogenation catalyst than the parent ligand 1,2-bis(diphenylphosphanyl)ethane (dppe). No clear explanation has been given, but the rate of catalyst formation might be involved. The catalysts were prepared in situ, and dppe showed an incubation time whereas the mixture with ligand **23a** immediately started to consume $H_2$. Only a relatively small change in the structure of the dendritic wedge, a 2,5-substituted analogue of **23b** (which contains 3,5-substituted wedges), resulted in a hydrogenation catalyst that was 300 times slower.[70] Blocking of the catalytic site by *ortho* substituents on the P phenyl ring was proposed to cause this lower activity.

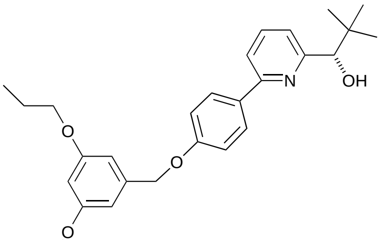


**23**

### 4.2.1. Diethylzinc Addition

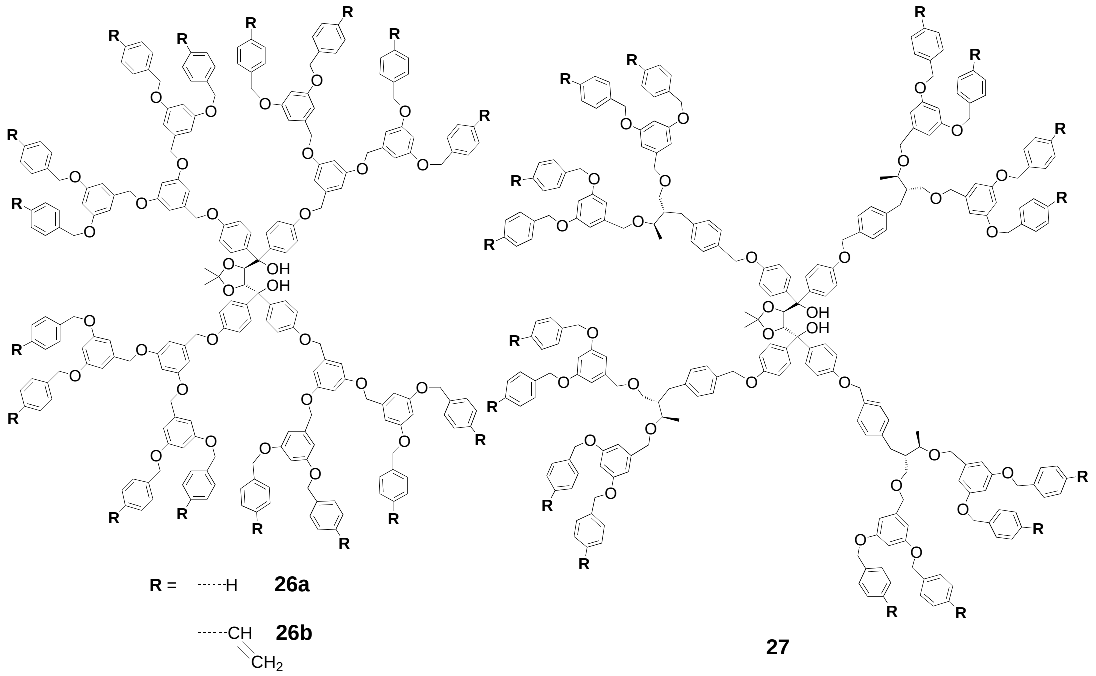
The group of Bolm reported asymmetric catalysis using focal-point-functionalized Fréchet-type wedges. Similar to the chiral parent compound, dendritic catalysts such as **24a** were catalytically active in diethylzinc additions to benzylaldehyde yielding optically active secondary alcohols (Scheme 9).[71] Enantiomeric excesses were only slightly lower (85–86% *ee*) than those of the parent pyridyl compound (5 mol% catalyst; 88% *ee*). The chiral amplification using **24b** was also studied. Using 5 mol% of **24b**, which was 76% enantiopure, resulted in a 84% *ee* for the product. The observed positive nonlinear effect is similar to that observed for the reference pyridyl compound. For larger dendritic systems such nonlinear effects might not be observed since the formation of complexes with a metal:ligand ratio of 1:2 is involved, but experiments with such systems have not been reported.





**24b**

Seebach et al. described the synthesis of dendrimers with TADDOLs as asymmetric active sites in the core.[72] Achiral Fréchet-type wedges of G0 to G4 were coupled to the *para* positions of the four phenyl groups of the TADDOL core (**26**, Scheme 10).[72b] Styrene-functionalized derivatives of these systems have been prepared for immobilization purposes (**26b**). Interestingly, this group also reported TADDOL ligands such as **27**, functionalized with both the *R*,*S* (shown) as well as the *S*,*R* chiral wedges. The molar rotation value of the chiral dendrimers was not significantly affected by the size or by the chirality of the wedges.



Scheme 10. G2 dendrimers with TADDOL ligands at the core for homogenous reactions (**26**) and for immobilization with styrene functionalized derivatives (**26b**). The dendrimer **27** contains chiral wedges.

The Ti-catalyzed enantioselective nucleophilic addition of $Et_2Zn$ to benzaldehyde was studied using these dendritic catalysts. The dendrimers with achiral branches gave slightly slower reaction rates and a small decrease in enantioselectivity with increasing generation number (G0 to G3) was observed. A large drop in both the activity and selectivity was observed for the largest system G4. On going from G3 to G4, the structure changes from roughly planar to globular and densely packed which provides an explanation for the drop in catalytic activity. This is a similar effect to that observed for the copper-catalyzed Diels–Alder reaction reported by Chow et al.[54] (see Section 3.3). The chiral branches in **27** did not significantly affect the rates and selectivities of the addition reaction. This was probably because the distance between the central catalytic site and the stereogenic centers of the branches is too large.

The TADDOL-cored dendrimers were immobilized by copolymerization[72a] of styryl-substituted TADDOLs in cross-linked polystyrene using divinylbenzene and TADDOL-centered dendrimers with peripheral styryl groups (**26b**, Scheme 10) as cross-linkers. These ligands were coordinated to Ti by exchange with $Ti(OCHMe_2)_4$ and their activities and enantioselectivities in the $Et_2Zn$ addition to benzaldehyde were then evaluated. As shown before, the branches of the dendritic catalyst (**26b**) have only a minor influence on the selectivity of the homogeneously catalyzed reaction.[73] Using the immobilized systems *ee* values comparable to the homogeneous systems were obtained (98% versus 96% *ee*). However, using polymers with a high TADDOLate content (thus higher cross-linking) resulted in much lower enantioselectivities. This effect was proposed to be the result of "frozen-in" conformations of the ligand. The immobilized dendritic catalysts did not perform better when higher generation dendrimers were used, but generally the activities of the dendritic immobilized systems were between those of the polymer-bound analogues and the homogeneous counterparts. This confirms the hypothesis that catalytic sites within the polymer beads show intermediate accessibility.[72a]

The selectivity drops considerably with the introduction of spacers between the Ti-TADDOLates and the styryl-functionalities of **26** which might be caused by a less control of the active site and the swelling properties of the polystyrene beads.[74] All the polymeric systems were recycled in 20 consecutive reactions by decanting/filtration and subsequent washing with toluene. The dendritic polymer showed the highest enantioselectivity of 98:2 in 20 sequential runs.

### 4.2.2. *Asymmetric Borane Reduction*

Optically active amino alcohols were attached to the focal point of dendritic branches (G0 to G3), and the resulting ligands (**25** $\hat{=}$ G2) were employed in asymmetric borane reductions.[75] Compared to the parent catalyst (87% *ee*) slightly higher enantioselectivities (88–91% *ee*) and good yields were obtained for various generations using acetophenone as a substrate. The highest *ee* values (up to 96%) for the reduction of $\alpha$-chloroacetophenone were observed using the catalyst based on G2. The slightly lower selectivity of the G3 was proposed to be an effect of steric hindrance whereas the smaller systems (G0 and G1) are less efficient because of their flexibility.

### 4.2.3. *Titanium-Catalyzed Asymmetric Allylation*

Yoshida et al. prepared chiral 1,1′-binaphthol derivatives having poly(benzyl ether) wedges at the 6,6′-positions.[76] The molecular optical rotation was identical for all generations, which is in agreement with the presence of a single chiral group. From circular dichroism (CD) spectroscopy it was concluded that the chiral environment of the binaphthol remained unchanged for all systems. In titanium-catalyzed asymmetric allylation of aldehydes the enantioselectivity decreased only slightly for the larger dendritic catalysts (92 – 88 % *ee* compared to 87 % for the parent (*R*)-binaphthol).

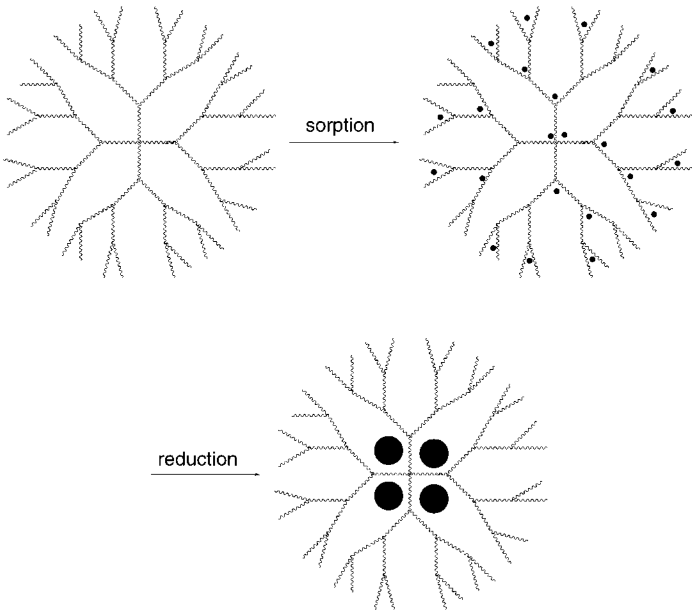
## 5. Metal Nanocomposites in the Dendrimer Interior

So far we have only discussed catalysts in which the metal ions are *coordinated* to appropriate donor atoms such as P, N, O. Recently, a new concept was reported independently by the groups of Crooks,[77] and Tomalia.[78] Hydroxyl-terminated poly(amido amine) dendrimers were found to be excellent templates for the preparation of precise metal nanoclusters within the dendrimer interiors.

Among the potential applications of nanoclusters, catalysis is an important one and metal clusters have been shown to be very active catalysts.[79] However, clusters tend to aggregate into larger (less active) systems under catalytic conditions which complicates the application of these systems. Precise construction of nanocomposites in the cavities of dendrimers might lead to both cluster stability and full control over size and size distribution, while the dendrimer branches still allow substrates access to the catalytically active clusters. Additionally, dendrimers could enhance the solubility of the metal clusters, a result of their solubility in a wide-range of solvents.

$Cu^{2+}$ ions have been extracted into poly(amido amine) dendrimers bearing terminal hydroxyl groups and bind to pairs of the outermost tertiary amine groups. This results for G2-OH, G4-OH, and G6-OH in sorption of 4, 16, and 64 $Cu^{2+}$ ions respectively, as shown by spectrophotometry.[77a] Chemical reduction leads to stable, perfectly soluble nanocluster complexes (Scheme 11). Evidence for the formation of these clusters comes from an immediate color change from dark blue to gold brown, and from the loss of signal in the EPR spectrum upon reduction.[77a, 78] The absorbance bands at 605 and 300 nm disappear and a characteristic peak at 590 nm appears (its exponential shape points to a band-like electronic structure of metal clusters). Metal particle diameters of 1 – 2 nm were found based on transition electron micrographs (TEM), CPK modelling, and optical absorption spectroscopy. Samples of intradendrimer copper clusters remained unaggregated for over 90 days at room temperature in oxygen-free aqueous solutions. Similarly, $Pd^{II}$ and $Pt^{II}$ ions were sorbed into poly(amido amine) dendrimers, and subsequently reduced to yield dendrimer-embedded nanoclusters.[77b] TEM clearly shows that the clusters are monodisperse, roughly spherical, with diameters of 1.3 – 1.6 nm.

Dendrimer-encapsulated Au, Ag, Pd, and Pt metal particles can be prepared by multiple in situ replacement reactions in which the Cu atoms being less noble are exchanged.[80] Such intradendrimer reactions are fast and quantitative. Moreover, the resulting particles are stable, small (1 – 3 nm) and relatively monodisperse. The Ag nanoclusters G6-OH($Ag_{110}$), which were prepared by primary metal-exchange reactions from G6-OH($Cu_{55}$), could be converted further into the more noble G6-OH($Au_{37}$), G6-OH($Pt_{55}$), and G6-OH($Pd_{55}$) by secondary replacement reactions. Using this replacement method, catalytically active encapsulated nanoparticles were prepared.



Scheme 11. Sorption of metal ions and subsequent reduction forming dendrimer-stabilized nanocluster complexes.

The water-soluble and stable composite G4-OH($Pd_{40}$) exhibits high catalytic activity for the hydrogenation of alkenes in water. Turnover frequencies were higher than for water-soluble polymer-bound $Rh^I$ catalysts and comparable to PVP-stabilized colloidal palladium dispersions in water (PVP = poly(vinyl pyrrolidone)). These nanocluster-dendrimer catalysts are sufficiently stable for recycling and reuse. Moreover, choice of the dendrimer generation can control the hydrogenation activity.[77b] The end groups of higher generation dendrimers are more densely packed together resulting in there being less free space in the dendrimer surfaces, which thus give limited access of substrates to the Pd nanoclusters. G6-OH($Pd_{40}$) and G8-OH($Pd_{40}$) show rates of only 10 % and 5 %, respectively, of that for G4-OH($Pd_{40}$). In principle this could add substrate selectivity to the dendrimer. In a subsequent paper[81] dendrimer-encapsulated palladium nanoparticles were applied in fluorous biphasic catalysis.[82] PAMAM dendrimers were functionalized with perfluoropolyether groups by complexation of the carboxylic end groups with the terminal amino groups of the dendrimer. The nanoparticles were active in the catalytic hydrogenation and could be recycled at least 12 times without significant decrease in activity. Moreover, polar substrates were hydrogenated much faster than non-polar substrates, which is a result of the polar microenvironment within the dendrimer. Using these dendritic nanocomposites substrate selectivity can be achieved on the basis of size and polarity.

## 6. Summary and Outlook

The field of dendritic transition metal catalysis is very new, but already numerous examples based on different dendritic backbones functionalized at different locations have appeared. At this stage it is pivotal to focus on the fundamental aspects of dendritic catalysis and many points of interest stated in the introduction have been addressed. Periphery-functionalized dendrimers, which have extremely high local concentrations of catalysts/ligands, can on the one hand lead to more stable catalysts than their monomeric analogues (e.g., in the Heck reaction). On the other hand this high local concentration could promote deactivation and thus lead to lower activities (as observed in the Kharasch addition reaction). To date no examples have been reported in which the catalytic sites at the periphery of a dendrimer showed (chiral) cooperativity; heterobimetallic catalysis using dendritic catalysts has not been studied yet. The dendrimer surface seems to be very suitable for catalytic reaction sequences that require two (or more) metals, and the quest for this highly interesting behavior is still ongoing.

Also the core-functionalized dendrimers have huge potential as transition metal catalysts and the analogy with natural systems is evident. Large dendritic branches positioned around the catalytic site can induce substrate-, regio-, and enantioselectivity, albeit often at the price of lower reaction rates. The precise tuning of the microenvironment (polarity, steric constrains) is still a difficult task, but might provide a tool to enhance the selectivity of a reaction. Construction of molecular recognition sites close to the catalytically active core in combination with the specific microenvironment created by the dendrimer will provide interesting systems that might increase selectivities by using noncovalent interactions, analogous to the working principles of enzymes.

Preliminary results show that dendrimers are suitable supports for transition metal catalysts and the larger systems can be used in continuous processes. Using dendritic catalysts the common problems involved in catalyst recycling can still occur, such as dendrimer or catalyst decomposition, dendrimer leaching, metal leaching and catalyst deactivation. These problems can be solved for most reactions by proper choice of ligands and dendrimer backbone. Whether dendritic catalysis can compete successfully in commercial applications with other systems such as two-phase catalysis remains to be seen. High turnover numbers are required considering the sophisticated dendritic ligands.

Generally, positioning of the catalytic sites and their spatial separation are determined by the geometry of the dendrimer and are very important for the performance of the catalyst. This is especially true for dendritic catalysts with chiral ligands at the periphery. In the near future more examples of dendritic transition metal catalysts are required to substantiate this principle for a broad range of reactions. Ideally we would like to accumulate enough information and synthetic knowledge to implement the dendritic framework in the rational design of new catalyst systems. Dendritic systems functionalized with different catalytic sites at several well-defined locations can potentially be used for tandem reactions. Also the assembly of dendritic catalysts into larger aggregates[7, 83] and systems organized on surfaces will have a bright future in high precision nanotechnology. Multistep reactions using these "nanofactories" are getting closer to the sophisticated natural systems such as the multiprotein respiratory assembly.

After submitting this manuscript several interesting reports on dendritic catalysis appeared, and references to these are included.[84]

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[1] E. Buhleier, W. Wehner, F. Vögtle, *Synthesis* **1978**, 155–158.

[2] a) D. A. Tomalia, H. Baker, J. Dewald, M. Hall, C. Kallos, S. Martin, J. Roeck, J. Ryder, P. Smith, *Polym. J. Tokyo* **1985**, *17*, 117–132; b) D. A. Tomalia, A. M. Naylor, W. A. Goddard III, *Angew. Chem.* **1990**, *102*, 119–157; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138–175.

[3] a) G. R. Newkome, Z.-Q. Yao, G. R. Baker, V. K. Gupta, *J. Org. Chem.* **1985**, *50*, 2003; b) G. R. Newkome, Z.-Q. Yao, G. R. Baker, V. K. Gupta, P. S. Russo, M. J. Saunders, *J. Am. Chem. Soc.* **1986**, *108*, 849–850.

[4] a) C. J. Hawker, J. M. J. Fréchet, *J. Chem. Soc. Chem. Commun.* **1990**, 1010–1013; b) K. L. Wooley, C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1991**, *113*, 4252–4261; c) J. M. J. Fréchet, *Science* **1994**, *263*, 1710–1715.

[5] a) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendritic Molecules*, Wiley-VCH, Weinheim, **1996**; b) J.-P. Majoral, A.-M. Caminade, *Chem. Rev.* **1999**, *99*, 845–880; c) F. Vögtle, *Top. Curr. Chem.* **1998**, *197*.

[6] A. W. Bosman, H. M. Janssen, E. W. Meijer, *Chem. Rev.* **1999**, *99*, 1665–1688.

[7] A. P. H. J. Schenning, C. Elissen-Román, J. W. Weener, M. W. P. L. Baars, S. J. van der Gaast, E. W. Meijer, *J. Am. Chem. Soc.* **1998**, *120*, 8199–8208.

[8] J. F. G. A. Jansen, E. M. M. den Brabander-van der Berg, E. W. Meijer, *Science* **1994**, *266*, 1226–1229.

[9] O. A. Matthews, A. N. Shipway, J. F. Stoddart, *Prog. Polym. Sci.* **1998**, *23*, 1–56.

[10] a) J. W. J. Knapen, A. W. van der Made, J. C. de Wilde, P. W. N. M. van Leeuwen, P. Wijkens, D. M. Grove, G. van Koten, *Nature* **1994**, *372*, 659–663; b) H.-F. Chow, T. K.-K. Mong, M. F. Nongrum, C.-W. Wan, *Tetrahedron* **1998**, *54*, 8543–8660; c) M. A. Hearshaw, A. T. Hutton, J. R. Moss, K. J. Naidoo in *Advances in Dendritic Macromolecules, Vol. 4* (Ed.: G. R. Newkome), JAI Press, Greenwich, **1999**, pp. 1–60; d) D. Seebach, P. B. Rheiner, G. Greiveldinger, T. Butz, H. Sellner, *Top. Curr. Chem.* **1998**, *197*, 125–164.

[11] D. A. Tomalia, P. R. Dvornic, *Nature* **1994**, *372*, 617–618.

[12] A silica particle of 10 μm (a lower limit for a slurry reactor) loaded with 1% of rhodium contains approximately $10^{12}$ metal atoms.

[13] Other solutions to this problem have been reported, for instance grafting of linear polymers carrying catalytic sites to silica spheres (12 nm) (T. Jongsma, H. van Aert, M. Fossen, G. Challa, P. W. N. M. van Leeuwen, *J. Mol. Catal.* **1993**, *83*, 37–50). Note that the primary particles, which form larger conglomerates, like dendrimers contain up to 1000 metal (Rh) atoms.

[14] a) *Catalysis by Di- and Polynuclear Metal Cluster Complexes* (Eds.: R. D. Adams, F. A. Cotton), Wiley-VCH, New York, **1998**; b) M. E. Broussard, B. Juma, S. G. Train, W.-J. Peng, S. A. Laneman, G. G. Stanley, *Science* **1993**, *260*, 1784–1788.

[15] a) M. Ulman, R. H. Grubbs, *J. Org. Chem.* **1999**, *64*, 7202–7207; b) S. Mukhopadhyah, G. Rothenberg, D. Gitis, Y. Sasson, *J. Org. Chem.* **2000**, *65*, 3107–3110.

[16] a) L. A. van de Kuil, D. M. Grove, R. A. Gossage, J. W. Zwikker, L. W. Jenneskens, W. Drenth, G. van Koten, *Organometallics* **1997**, *16*,

4985–4994; b) A. W. Kleij, PhD Thesis, University of Utrecht (The Netherlands), **2000**.

[17] S. Hecht, J. M. J. Fréchet, *Angew. Chem.* **2001**, *113*, 76–94; *Angew. Chem. Int. Ed.* **2001**, *40*, 74–91.

[18] K. K. Sirkar, P. V. Shanbhag, A. S. Kovvali, *Ind. Eng. Chem. Res.* **1999**, *38*, 3715–3737.

[19] U. Kragl, C. Dreisbach, *Angew. Chem.* **1996**, *108*, 684–685; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 642–644.

[20] J. J. Keijsper, P. W. N. M. van Leeuwen, A. W. van der Made, EP 0456317, **1991**; Shell Int. Research, US 5243079 **1993** [*Chem. Abstr.* **1992**, *116*, 129870].

[21] A. W. Kleij, R. A. Gossage, J. T. B. H. Jastrzebski, J. Boersma, G. van Koten, *Angew. Chem.* **2000**, *39*, 179–181; *Angew. Chem. Int. Ed.* **2000**, *39*, 176–178.

[22] R. A. Gossage, J. T. B. H. Jastrzebski, J. van Ameijde, S. J. E. Mulders, A. J. Brouwer, R. M. J. Liskamp, G. van Koten, *Tetrahedron Lett.* **1999**, *40*, 1413–1416.

[23] "Membrane reactors for dendritic catalysts": U. Kragl, *1st International Dendrimer Symposium* (Frankfurt, Deutschland), **1999**.

[24] G. van Koten, J. T. B. H. Jastrzebski, *Polym. Mater. Sci. Eng.* **1997**, *77*, 75–76.

[25] G. van Koten, J. T. B. H. Jastrzebski, *J. Mol. Catal. A* **1999**, *146*, 317–323.

[26] A. Miedaner, C. J. Curtis, R. M. Barkley, D. L. DuBois, *Inorg. Chem.* **1994**, *33*, 5482–5490.

[27] C. Valerio, S. Rigaut, J. Ruiz, J.-L. Fillaut, M.-H. Delville, D. Astruc, *Bull. Pol. Acad. Sci. Chem.* **1998**, *46*, 309–318.

[28] S. Rigaut, M.-H. Delville, D. Astruc, *J. Am. Chem. Soc.* **1997**, *119*, 11132–11133.

[29] M. T. Reetz, G. Lohmer, R. Schwickardi, *Angew. Chem.* **1997**, *109*, 1559–1562; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1526–1529.

[30] E. K. van der Beuken, B. L. Feringa, *Tetrahedron* **1998**, *54*, 12985–13011.

[31] N. Brinkmann, D. Giebel, G. Lohmer, M. T. Reetz, U. Kragl, *J. Catal.* **1999**, *183*, 163–168.

[32] D. de Groot, E. B. Eggeling, J. C. de Wilde, H. Kooijman, R. J. van Haaren, A. W. van der Made, A. L. Spek, D. Vogt, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Chem. Commun.* **1999**, 1623–1624.

[33] P. Wijkens, J. T. B. H. Jastrzebski, P. A. van der Schaaf, R. Kolly, A. Hafner, G. van Koten, *Org. Lett.* **2000**, *2*, 1621–1624.

[34] M. Benito, O. Rossell, M. Seco, G. Segales, *Organometallics* **1999**, *18*, 5191–5193.

[35] L. Ropartz, R. E. Morris, G. P. Schwarz, D. F. Foster, D. J. Cole-Hamilton, *Inorg. Chem. Commun.* **2000**, in press.

[36] T. Mizugaki, M. Ooe, K. Ebitani, K. Kaneda, *J. Mol. Catal. A* **1999**, *145*, 329–333.

[37] D. de Groot, P. G. Emmerink, C. Coucke, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Inorg. Chem. Commun.* **2000**, in press.

[38] a) S. C. Bourque, F. Maltais, W.-J. Xiao, O. Tardif, H. Alper, P. Arya, L. E. Manzer, *J. Am. Chem. Soc.* **1999**, *121*, 3035–3038; b) S. C. Bourque, H. Alper, L. E. Manzer, P. Arya, *J. Am. Chem. Soc.* **2000**, *122*, 956–957.

[39] M. Petrucci-Samija, V. Guillemette, M. Dasgupta, A. K. Kakkar, *J. Am. Chem. Soc.* **1999**, *121*, 1968–1969.

[40] N. Hovestad, E. B. Eggeling, H. J. Heidbuechel, J. T. B. H. Jastrzebski, U. Kragl, W. Keim, D. Vogt, G. van Koten, *Angew. Chem.* **1999**, *111*, 1763–1765; *Angew. Chem. Int. Ed.* **1999**, *38*, 1655–1658.

[41] a) D. Seyferth, R. Wyrwa, U. W. Franz, S. Becke (PCT Int. Appl.) WO 9732908, **1997** [*Chem. Abstr.* **1997**, *127*, 263179p]; b) D. Seyferth, R. Wyrwa, WO 9732918, **1997** [*Chem. Abstr.* **1997**, *127*, 263180g].

[42] W. Kaminsky, R. Engehausen, K. Zoumis, W. Spaleck, J. Rohrmann, *Makromol. Chem.* **1992**, *193*, 1643–1651.

[43] J. N. H. Reek, unpublished results.

[44] a) D. K. Smith, F. Diederich, *Chem. Eur. J.* **1998**, *4*, 1353–1361; b) D. Astruc, *C. R. Acad. Sci. Ser. 2* **1996**, *322*, 757–766; c) M. Enomoto, T. Aida, *J. Am. Chem. Soc.* **1999**, *121*, 874–875; d) D.-L. Jiang, T. Aida, *Pure Appl. Chem. A* **1997**, *34*, 2047–2055; e) M. Enomoto, T. Aida, *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 32–42; f) P. Wallimann, P. Seiler, F. Diederich, *Helv. Chim. Acta* **1996**, *79*, 779–781; g) D. K. Smith, F. Diederich, *Chem. Commun.* **1998**, 2501–2502; h) T. Habicher, F. Diederich, V. Gramlich, *Helv. Chim. Acta* **1999**, *82*, 1066–1095; i) P. Weyermann, J.-P. Gisselbrecht, C. Boudon, F. Diederich, M. Gross, *Angew. Chem.* **1999**, *111*, 3400–3405; *Angew. Chem. Int. Ed.* **1999**, *38*, 3215–3219.

[45] a) R. van Heerbeek, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron Lett.* **1999**, *40*, 7127–7130; b) S. C. Zimmerman, Y. Wang, P. Bharathi, J. S. Moore, *J. Am. Chem. Soc.* **1998**, *120*, 2172–2173.

[46] I. Gitsov, P. T. Ivanova, J. M. J. Fréchet, *Macromol. Rapid Commun.* **1994**, *15*, 387–393.

[47] K. Matyjaszewski, T. Shigemoto, J. M. J. Fréchet, M. Leduc, *Macromolecules* **1996**, *29*, 4167–4171.

[48] G. E. Oosterom, R. J. van Haaren, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Chem. Commun.* **1999**, 1119–1120.

[49] G. E. Oosterom, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, unpublished results.

[50] G. E. Oosterom, E. B. de Bruin, E. B. Eggeling, D. Vogt, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, unpublished results.

[51] a) Allylic alkylation reactions: M. Ludwig, S. Strömberg, M. Svensson, B. Åkermark, *Organometallics* **1999**, *18*, 970–975; b) Heck reactions: B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554.

[52] a) M. Kranenburg, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1998**, 25–27; b) R. J. van Haaren, H. Oevering, B. B. Coussens, G. P. F. van Strijdonck, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1999**, 1237–1241.

[53] G. E. Oosterom, S. Steffens, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, unpublished results.

[54] a) H.-F. Chow, C. C. Mak, *J. Org. Chem.* **1997**, *62*, 5116–5127; b) C. C. Mak, H.-F. Chow, *Macromolecules* **1997**, *30*, 1228–1230.

[55] a) P. Bhyrappa, J. K. Young, J. S. Moore, K. S. Suslick, *J. Am. Chem. Soc.* **1996**, *118*, 5708–5711; b) P. Bhyrappa, J. K. Young, J. S. Moore, K. S. Suslick, *J. Mol. Catal. A* **1996**, *113*, 109–116.

[56] B. R. Cook, T. J. Reinert, K. S. Suslick, *J. Am. Chem. Soc.* **1986**, *108*, 7281–7286.

[57] H. W. I. Peerlings, E. W. Meijer, *Chem. Eur. J.* **1997**, *3*, 1563–1570.

[58] a) D. Seebach, J.-M. Lapierre, G. Greiveldinger, K. Skobridis, *Helv. Chim. Acta* **1994**, *77*, 1673–1688; b) D. Seebach, J.-M. Lapierre, K. Skobridis, G. Greiveldinger, *Angew. Chem.* **1994**, *106*, 457–458; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 440–442; c) D. Seebach, G. F. Herrmann, U. D. Lengweiler, B. M. Bachmann, W. Amrein, *Angew. Chem.* **1996**, *108*, 2969–2972; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2795–2797; d) P. Murer, D. Seebach, *Angew. Chem.* **1995**, *107*, 2297–2300; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2116–2119.

[59] M. S. T. H. Sanders-Hoven, J. F. G. A. Jansen, J. A. J. M. Vekemans, E. W. Meijer, *Polym. Mater. Sci. Eng.* **1995**, *210*, 180–182.

[60] J. F. G. A. Jansen, H. W. I. Peerlings, E. M. M. den Brabander-van der Berg, E. W. Meijer, *Angew. Chem.* **1995**, *107*, 1321–1324; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1206–1209.

[61] T. Suzuki, Y. Hirokawa, K. Ohtake, T. Shibata, K. Soai, *Tetrahedron: Asymmetry* **1997**, *8*, 4033–4040.

[62] I. Sato, R. Kodaka, T. Shibata, Y. Hirokawa, N. Shirai, K. Ohtake, K. Soai, *Tetrahedron: Asymmetry* **2000**, *11*, 2271–2275.

[63] a) D. Seebach, R. E. Marti, T. Hintermann, *Helv. Chim. Acta* **1996**, *79*, 1710–1740; b) R. Dahinden, A. K. Beck, D. Seebach in *Encyclopedia of Reagents for Organic Synthesis, Vol. 3* (Ed.: L. Paquette), Wiley, Chichester, **1995**, pp. 2167–2170.

[64] C. Köllner, B. Pugin, A. Togni, *J. Am. Chem. Soc.* **1998**, *120*, 10274–10275.

[65] R. Schneider, C. Köllner, I. Weber, A. Togni, *Chem. Commun.* **1999**, 2415–2416.

[66] A. Togni, N. Bieler, U. Burckhardt, C. Köllner, G. Pioda, R. Schneider, A. Schnyder, *Pure Appl. Chem.* **1999**, *71*, 1531–1537.

[67] H. Brunner, *J. Organomet. Chem.* **1995**, *500*, 39–46.

[68] H. Brunner, S. Altmann, *Chem. Ber.* **1994**, *127*, 2285–2296.

[69] a) H. Brunner, J. Fürst, J. Ziegler, *J. Organomet. Chem.* **1993**, *454*, 87–94; b) H. Brunner, J. Fürst, *Tetrahedron* **1994**, *50*, 4303–4310; c) H. Brunner, P. Bublak, *Synthesis* **1995**, 36–38; d) H. Brunner, M. Janura, S. Stefaniak, *Synthesis* **1998**, 1742–1749; e) H. Brunner, G. Net, *Synthesis* **1995**, 423–426.

[70] H. Brunner, J. Fürst, U. Nagel, A. Fischer, *Z. Naturforsch. B* **1994**, *49*, 1305–1306.

[71] C. Bolm, N. Derrien, A. Seger, *Synlett* **1996**, 387–388.

[72] a) P. B. Rheiner, H. Sellner, D. Seebach, *Helv. Chim. Acta* **1997**, *80*, 2027–2032; b) P. B. Rheiner, D. Seebach, *Chem. Eur. J.* **1999**, *5*, 3221–3236.

[73] P. B. Rheiner, D. Seebach, *Polym. Mater. Sci. Eng.* **1997**, *214*, 124–126.

[74] H. Sellner, D. Seebach, *Angew. Chem.* **1999**, *111*, 2039–2041; *Angew. Chem. Int. Ed.* **1999**, *38*, 1918–1920.

[75] C. Bolm, N. Derrien, A. Seger, *Chem. Commun.* **1999**, 2087–2088.

[76] S. Yamago, M. Furukawa, A. Azuma, J.-i. Yoshida, *Tetrahedron Lett.* **1998**, *39*, 3783–3786.

[77] a) M. Zhao, L. Sun, R. M. Crooks, *J. Am. Chem. Soc.* **1998**, *120*, 4877–4878, zit. Lit.; b) M. Zhao, R. M. Crooks, *Angew. Chem.* **1999**, *111*, 375–377; *Angew. Chem. Int. Ed.* **1999**, *38*, 364–365; c) M. Zhao, L. Sun, R. M. Crooks, *Polym. Mater. Sci. Eng.* **1999**, *217*, 28–30.

[78] a) L. Balogh, D. R. Swanson, R. Spindler, D. A. Tomalia, *Polym. Prepr. Am. Chem. Soc. Div. Polym. Chem.* **1997**, *77*, 118–119; b) L. Balogh, D. A. Tomalia, *J. Am. Chem. Soc.* **1998**, *120*, 7355–7356.

[79] a) J. D. Aiken III, R. G. Finke, *J. Mol. Catal. A* **1999**, *145*, 1–44; b) L. N. Lewis, *Chem. Rev.* **1993**, *93*, 2693–2730; c) G. Schmid, *Chem. Rev.* **1992**, *92*, 1709–1727.

[80] M. Zhao, R. M. Crooks, *Chem. Mater.* **1999**, *11*, 3379–3385.

[81] V. Chechik, R. M. Crooks, *J. Am. Chem. Soc.* **2000**, *122*, 1243–1244.

[82] I. T. Horváth, J. Rabai, *Science* **1994**, *266*, 72–75.

[83] a) F. Zeng, S. C. Zimmerman, *Chem. Rev.* **1997**, *97*, 1681–1712; b) S. C. Zimmerman, F. W. Zeng, D. E. C. Reichert, S. V. Kolotuchin, *Science* **1996**, *271*, 1095–1098; c) J. C. M. van Hest, D. A. P. Delnoye, M. W. P. L. Baars, M. H. P. van Genderen, E. W. Meijer, *Science* **1995**, *268*, 1592–1595; d) S. D. Hudson, H.-T. Jung, V. Percec, W.-D. Cho, G. Johansson, G. Ungar, V. S. K. Balagurusamy, *Science* **1997**, *278*, 449–452; e) V. Percec, W.-D. Cho, P. E. Mosier, G. Ungar, D. J. P. Yeardley, *J. Am. Chem. Soc.* **1998**, *120*, 11061–11070; f) H. Frey, *Angew. Chem.* **1998**, *110*, 2313–2318; *Angew. Chem. Int. Ed.* **1998**, *37*, 2193–2197; g) H. Tokuhyse, M. Zhao, L. A. Baker, V. T. Phan, D. L. Dermody, M. E. Garcia, R. F. Peez, R. M. Crooks, T. M. Mayer, *J. Am. Chem. Soc.* **1998**, *120*, 4492–4501.

[84] a) Dendritic ruthenium-based metathesis catalysts: S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, 8168–8179; b) Dendrimers with binaphthol cores for asymmetric diethylzinc addition to aldehydes: Q.-S. Hu, V. Pugh, M. Sabat, L. Pu, *J. Org. Chem.* **1999**, *64*, 7528–7536; c) Dendritic ligands with BINAP cores for enantioselective Ru hydrogenations: Q.-H. Fan, Y.-M. Chen, X.-M. Chen, D.-Z. Jiang, F. Xi, A. S. C. Chan, *Chem. Commun.* **2000**, 789–790; d) Supported dendritic phosphine ligands for Pd-catalyzed Heck reactions: H. Alper, P. Arya, S. C. Bourque, G. R. Jefferson, L. E. Manzer, *Can. J. Chem.* **2000**, *78*, 920–924; e) Phosphorus-based dendrimers for ruthenium- and palladium-catalyzed reactions: V. Maraval, R. Laurent, A.-M. Caminade, J.-P. Majoral, *Organometallics* **2000**, *19*, 4025–4029; f) Vanadium and tungsten polyoxometalate-terminated dendrimers used in catalytic oxidations: H. Zeng, G. R. Newkome, C. L. Hill, *Angew. Chem.* **2000**, *112*, 1841–1844; *Angew. Chem. Int. Ed.* **2000**, *39*, 1771–1774; g) Dendrimer-based titanium-containing xerogels as epoxidation catalysts: J. W. Kriesel, T. D. Tilley, *Chem. Mater.* **2000**, *12*, 1171–1179; h) Asymmetric catalytic ring opening of epoxides indicating cooperative effects using dendritic catalysts: R. Breinbauer, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 3750–3753; *Angew. Chem. Int. Ed.* **2000**, *39*, 3604–3607.