Transition Metal Catalysis Using Core-Functionalized Carbosilane Dendrimers.
van Oosterom, G.E.

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Dendrimers are well-defined macromolecules that are extremely suited to be functionalized with transition metal catalysts. The dendrimeric part can add several functions to the catalysts, strongly depending on the design concept and the specific reaction that is catalyzed. Moreover, the obtained systems are generally much larger than the substrates and products providing an intrinsic solution for the homogeneous catalyst separation problem. In the last decade considerable progress has been made in the development of novel dendrimeric catalysts. In this chapter the different concepts and progress in transition metal dendrimeric catalysis will be reviewed and discussed. Furthermore, an outline of the current work as described in this thesis is provided.
1.1 Introduction

Dendrimers (derived from the Greek words *dendron* (tree) and *meros* (part)) are highly branched macromolecules having precisely defined molecular structures (see Figure 1) that are obtained via an iterative sequence of reaction steps. This new class of macromolecules, which has been pioneered by Vögtle,[1] Tomalia,[2] Newkome,[3] and Fréchet,[4] has inspired many chemists in several fields. The initial focus has been on the efficient synthesis and characterization of dendrimers.[5] The progression of new and better analytical techniques such as high field NMR spectroscopy, 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 (inside-outwards), and the convergent route making wedges that can be connected to a core in the last step of the synthesis (outside-inwards).[5a] 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 material 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 research groups are exploring the use of this property for the development of sophisticated drug delivery systems. Often host-guest complexes based on dendrimers have 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-diagnostics, gene delivery vectors, and unimolecular micelles.[6, 9]

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

### 1.1.1 Dendrimeric transition metal catalysts: the new generation?

In order 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 an
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 multi-arm 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.\[11\]

Dendrimeric 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 dendrimeric 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, dendrimeric catalysts can provide systems that:

1) 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 due to a reduced accessibility.\[13\] Organic polymers show solvent dependent swelling properties that can strongly influence the catalytic performance.

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

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

4) allow fine-tuning of their catalytic centers via precise ligand design (advantage of homogeneous catalysts).

5) require relatively low metal loading (advantage of homogeneous catalysts compared to heterogeneous catalysts).

In first instance dendrimeric 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 dendrimeric framework depend on the location of the functional group within the structure. One should distinguish periphery-functionalized (of a dendrimer or a dendrimeric wedge), core-functionalized and focal point-functionalized (on a dendrimeric 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.

![Diagram of catalytic centers](image)

**Figure 1.** Catalytically active transition metal complexes can be attached to the periphery (a) and the core (b) of a dendrimer, and at the focal point (c) and the periphery of a dendrimeric 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 for example core-functionalized systems 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-PPh₂) and 4 M of catalysts ((dendrimer-PPh₂)₂Pd). 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 via a bimetallic mechanism, the dendrimeric catalysts might show better performance than the monomeric species. [14] On the other hand, several deactivation mechanisms operate via a bimetallic mechanism, i.e. 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 especially benefit from the site isolation created by the environment of the dendrimeric structure. Site isolation effects in dendrimers can be beneficial for other functionalities and general reviews
on this topic have recently appeared.[17] For catalytic reactions that are deactivated by excess ligand or in cases that a bimetallic deactivation mechanism is operative, core-functionalized systems can specifically prevent such deactivation pathway, whereas periphery-functionalized systems might suffer from relative low activity. Core-functionalized dendrimeric catalysts may benefit from the local 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 (MW 20000 D, 1 active site) compared to 1 g L\(^{-1}\) (MW 20000 D, 20 active sites)). On the other hand, for core-functionalized systems the solubility of the dendrimeric catalyst can be tuned by changing the end groups.

1.1.2 Dendrimeric 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 has been mainly on polymeric membranes applied in enzymatic reactions. The membrane materials have been improved significantly ever since, and nowadays nanofiltration membranes suitable to retain relatively small compounds are commercially available (e.g. mass cut-off 400 D). Two forms of leaching have to be considered using dendrimeric transition metal catalysts in membrane reactors: leaching of the dendrimeric catalyst through the membrane and metal leaching from the dendrimer (and further leaching through the membrane). For practical applications the overall retention of the (dendrimeric) catalyst must be extremely good in order 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 TON) than those for high value-added fine chemicals). In Figure 2 the theoretical activities of dendrimeric catalysts are given using different retention factors.

If a dendrimeric catalyst has a retention of 0.95 only 25% of the catalyst remains in the reactor after the reactor has been flushed with 30 times its volume. To obtain a catalyst system that remains in the reactor over a prolonged period of time a retention of at least 0.999 is required.

Kragl pioneered the use of dendrimers in catalytic continuous processes using membranes. Initially he used soluble polymeric catalysts in a continuous membrane reactor for
Figure 2. Schematic representation of the use of dendrimeric catalysts in a continuous membrane reactor (top), and theoretical relative concentrations of (dendrimeric) catalysts ($C_r$) with various retention factors versus number of residence times ($N_r$) in a continuous process.

the enantioselective addition of Et₂Zn to benzaldehyde.[19] The polymer was retained almost completely (>0.998), and a high turnover number was obtained using this set-up compared to a batch reactor. Dendrimers are particularly suited for application in this type of reactors due to their globular morphology.[2b] So far only a few examples appeared in the literature describing the use of dendrimeric catalysts in continuous systems and they will be discussed in the next sections (i.e., sections 2.2, 2.3, and 2.7).

This chapter is divided in the following topics: periphery-functionalized dendrimers, core-functionalized dendrimers, enantioselective dendrimeric 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.

1.2 Periphery-functionalized dendrimeric catalysts

1.2.1 Terpolymerization of ethene, propene, and CO

The first dendrimeric 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, i.e. precipitation of the polymer on the reactor wall. Using the dendrimeric catalyst under comparable conditions this was reduced to 3% only. A possible explanation is that in the dendrimeric 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 in turn may lead to fouling).

1.2.2 Nickel-catalyzed Kharasch addition

Another early example of a dendrimeric catalyst was reported by Van Leeuwen, Van der Made, and Van Koten, who functionalized G0 (generation zero) and G1 carbosilane dendrimers with up to twelve NCN pincer-nickel(II) groups (1a in Figure 3).[10a] These dendrimers were applied as catalysts for the Kharasch addition of CX to alkenes (Scheme 1). The relative catalytic activity of the dendrimeric catalyst was slightly lower than that of the monomeric parent compound; 80 % of the activity was found for G0 (four Ni centers) and 70 % for G1 (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.

\[
\text{CX}_3\text{Y} + \text{catalyst} \rightarrow \text{YX}_2\text{C}
\]

Scheme 1. The Kharasch addition reaction (X = halogen; Y = H, halogen, or CF₃).

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 due to the high local concentration of nickel centers. In a subsequent paper this effect was studied in more detail using dendrimers with different spacer lengths.[21] An even larger decrease in activity was observed on using larger dendrimeric 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 TOF increased from 39 for 1b to 85 for 1c). It was proposed that the catalyst deactivation was caused by an interaction between neighboring Ni⁰/Ni³ sites, which obviously is more pronounced in systems were surface congestion is larger. Alternatively one might propose that local high radical concentrations lead to termination and Ni³ 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 dendrimeric wedges that were functionalized at the periphery with up to four NCN pincer-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. 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 for 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 interactions 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 periphery and backbone and the palladium complexes (2) were prepared by the addition of \([\text{Pd(CH}_3\text{CN})_4](\text{BF}_4)_2\)[26] (Figure 4). These systems catalyze the electrochemical reduction of \text{CO}_2 to \text{CO}, and the rates and selectivities observed for the dendrimeric systems were comparable to 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.

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 catalysts 3a containing six CpFe\(^1\) (arene) complexes (Figure 5) indeed were as efficient as single site complexes in the redox-catalyzed reduction of nitrite and nitrate to ammonia.[28]
Figure 4. A palladium complex of dendrimer 2 having phosphine branching units

Figure 5. The star shaped (3a) compounds having electrochemically active iron centers for the redox-catalyzed reduction of nitrite at the periphery compared to the dendrimeric systems (3b).

1.2.3 Palladium-catalyzed coupling reactions

Several research 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 diphenylphosphine groups at the periphery (4) by Reetz et al. via a double phosphination of the amines with diphenylphosphine and formaldehyde (Figure 6).[29] Transition metal complexes 4a to 4d have been prepared in which the dendrimer-N-(CH$_2$PPh$_2$)$_2$ groups act as bidentate ligands. 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 forming stilbene as the product (Scheme 2). Interestingly, the
dendrimers showed larger turnover numbers than the monomeric parent compounds, which was ascribed to the higher thermal stability of the dendrimeric palladium complexes. Palladium black formation was only observed when the monomeric species was used. The catalytic activity using 50% palladium loading (M:L = 1:4) was similar to systems with 100% loading. After the reaction the dendrimeric 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.

Heterobimetallic complexes 4e have also been prepared. Half of the diphosphine ligands were used for complexation with palladium after which the other 50% were made to react with nickel (Figure 6). This strategy resulted in a statistical distribution of the metal atoms on the dendrimer surface. No catalysis using these systems has been reported so far, but interesting properties can be expected for a reaction in which a heterobimetallic mechanism is operative.\[30\]

Reetz and Kragl reported the use of these phosphine based dendrimeric 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

![Scheme 2](image)

**Scheme 2.** The palladium-catalyzed Heck reaction of bromobenzene and styrene.

![Figure 6](image)

**Figure 6.** Peripheral phosphine-functionalized G3 DAB-dendrimer 4 and its metal complexes.
Scheme 3. The palladium-catalyzed allylic substitution reaction (Nu = nucleophile).

of 10212 g mol$^{-1}$). Although the dendrimer stayed in the reactor, some palladium leaching was observed. Metal-ligand dissociation results in low molecular weight Pd species that will be washed out of the reactor. During the reaction leaching was compensated by addition of allyl palladium chloride to the feed solution. Applying G3 4b in palladium-catalyzed allylic substitution (see Scheme 3) the continuous reactor could be operated for over 60 residence times with a conversion of up to 12%, but the product was obviously contaminated with palladium. Better results were obtained using in situ prepared Pd complexes of a G4 dendrimer (calculated molecular weight 20564 g mol$^{-1}$ for 100% palladium loading of the 32 diphosphines). After 100 residence times, the conversion had decreased from 100% to ~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). A solid conclusion about the effect of the dendrimeric catalyst used requires more experiments.

Figure 7. G2 Pd(allyl)Cl-complex 5 was used as catalyst in a continuous membrane reactor and the G2 carbosilane dendrimer 6 was used to measure the retention (98.1%).

Transition Metal Catalysis Using Functionalized Dendrimers
Several research groups reported the synthesis of carbosilane dendrimers functionalized with phosphine ligands. These systems can be synthesized via a reaction with silicon chloride end groups (after hydrosilylation with HSiCl\textsubscript{3},\textsubscript{3} of the terminal allyls) or via direct phosphination of the alkene. Van Leeuwen et al. reported carbosilane based dendrimeric catalysts with terminal mono- (-SiMe\textsubscript{2}CH\textsubscript{2}PPh\textsubscript{2}) and diphosphine (-SiMe(CH\textsubscript{2}PPh\textsubscript{2})\textsubscript{2}) groups. The largest dendrimer (G2) contained 36 terminal monodentate phosphines. Allyl palladium complexes of these ligands were formed upon the addition of [\((\eta^3-C_3H_5)PdCl\)\textsubscript{2}]. The bidentate ligands gave well-defined complexes like those observed for the DAB systems whereas the dendrimers with the monodentate phosphines formed a mixture of complexes, differing in ring size (-P-Pd-P-dendrimer-). All complexes were active in the palladium-catalyzed allylic alkylation using sodium diethyl methylmalonate as the nucleophile (batch reaction). 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 dendrimeric catalyst 5 should be much higher since its molecular volume is three times larger (see Figure 7). Therefore, leaching of dendrimeric catalyst cannot account for the observed drop in activity. This suggests that the catalyst decomposed or leached through the membrane probably via small soluble metal clusters that were dissociated from the dendrimer. The similarity of these observations with those of Reetz show that the practical application of dendrimeric 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.

1.2.4 Palladium-catalyzed hydrogenation

Pd\textsuperscript{II}Cl\textsubscript{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-crosslinked polystyrene, and heterogeneous palladium catalysts. High activity in the hydrogenation of cyclopentadiene was found for 4 compared to the corresponding monomeric complex and the polystyrene-bound catalyst (Figure 8). 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\textsubscript{2}O\textsubscript{3}), however, were still more active than the dendrimeric catalyst. Remarkably, excellent selectivity to cyclopentene was obtained on using the dendrimeric catalyst based on 5 in the hydrogenation of cyclopentadiene. This is due to the relatively slow
successive hydrogenation of cyclopentene as can be clearly seen in the graph (slower hydrogen uptake); no explanation for this selectivity has been given. Although Pd/C and Pd/Al₂O₃ where more active catalysts the reaction was not selective; the rates of hydrogen uptake remained unchanged after conversion of cyclopentadiene to cyclopentene, yielding cyclopentane as the product.

In the hydrogenation of 1,3-cyclooctadiene, dendrimeric 4-PdCl₂ showed much higher rates than monomeric [PhN(CH₂PPh₂)₂PdCl₂]. The reaction was most efficient in ethanol while it was very slow in DMF. This is interesting since the dendrimeric 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 substantiates this accessibility. In contrast, the polystyrene-immobilized system has the catalytic sites buried partially within its structure resulting in a bad performance using DMF as the solvent. The heterogeneous dendrimeric catalyst could be recycled via centrifugation and showed only a slight decrease in activity in consecutive reactions.

Scheme 4. Hydrogenation of cyclopentadiene.

Figure 8. Schematic time courses of H₂ uptake in the hydrogenation of cyclopentadiene for various Pd catalysts.
1.2.5 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 dendrimeric backbone on the catalytic performance was studied by comparing dendrimeric ligands 7a-c (see Figure 9: conditions toluene, 80 °C, 20 bar CO/H₂).[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). Reetz et al. reported preliminary results on the rhodium-catalyzed hydroformylation using the multiphosphine DAB dendrimer (4) as the ligand and they also observed similar activities and selectivities as that of the parent ligand.[29] The monodentate analogues of the phosphine-functionalized carbosilane dendrimers (with the (–SiMe₂CH₃PPh₂) end groups) showed a decrease in activity for the more congested systems. By changing these steric properties the structure of the peripheral rhodium complexes also changed since metal complexes were 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 PAMAM poly(amido amine) branches 8

![Scheme 5. Rhodium-catalyzed hydroformylation of alkenes.](image)

**Figure 9.** The influence of steric congestion on the Rh-catalyzed hydroformylation studied using homogeneous carbosilane dendrimers (7) and immobilized PAMAM dendrimers (8).
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 complexes, which were tested in catalytic alkene hydroformylation. Using styrene as a substrate, the G0-G2 dendrimeric 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 due to variation in spacer length.[38b] From comparison of the catalytic activity of these ligands they concluded that steric congestion indeed lowered the activity. This is in contrast with the results obtained with the homogeneous dendrimeric systems. A detailed study using both systems under similar conditions should be performed before any conclusions can be drawn. The re-usability 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.

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 as the products. Interestingly, the dendrimeric catalyst with 24 PEt\(_2\) end groups was slightly more selective for the linear product (l:b = 3.1) compared to the monomeric ligand PEt\(_3\) (l:b = 2.4), whereas for the other dendrimeric catalyst the selectivity was lower. It was suggested that this higher selectivity was due to a subtle steric control over the reaction.

1.2.6 Rhodium-catalyzed Hydrogenation

In the research group of Kakkar, dendrimers having phosphines as branching point were synthesized via acid-base hydrolysis of aminosilanes with alcohols (Figure 10).[39] The synthesis of these dendrimeric 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 reactions that form the dendrimer. The Rh\(^{1}\) metallo-dendrimers were catalytically active in the hydrogenation of decene, and even the larger system 9 showed only a small decrease in activity compared to the monomeric rhodium complex. Rates around 400 mol mol(Rh)\(^{-1}\) h\(^{-1}\) were obtained in THF at
25°C and 20 bars of hydrogen. After extraction and recrystallization the catalysts were re-used showing an activity of 95 % in the second run. Unfortunately, the catalytic performance of the complexes at the periphery was not compared with those located in the interior.

1.2.7 Palladium-catalyzed hydrovinylilation

Van Koten and Vogt et al. prepared carbosilane dendrimers (10) that were functionalized with hemilabile P,O-ligands at the surface (Figure 11). The palladium complexes of this system are active catalysts in the hydrovinylilation reaction of styrene (Scheme 6), which is 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 dendrimeric 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
Scheme 6. Hydrovinylation of styrene.

Figure 11. Palladium-catalyzed hydrovinylation using carbosilane dendrimers functionalized with P-O-chelates (10).

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 due to decomposition of the catalyst 10. This decomposition was substantiated by the observation of palladium precipitate on the membrane.

1.2.8 Metallocene-catalyzed polymerization

Seyferth synthesized carbosilane dendrimers with 4, 8, and 12 peripheral zirconocene, hafnocene, and titanocene groups.[41] Dendrimer 11 (Figure 12) containing 8 zirconocene
dichlorides was applied in MAO activated olefin (co)polymerization (Table 1) and in silane polymerization. Considerable activity of 11 in the ethylene polymerization and co-polymerization (of two different alkenes) was found (5760 kg polyethylene/mol metal per hour). However, these systems are 10 times less active than monomeric zirconocenes (Kaminsky[42] reported activities as high as 60900 kg (mol metal)$^{-1}$ h$^{-1}$). Hyperbranched polymers based on dimethylvinylsilane were prepared,[41b] which are attractive because in one step large dendrimer-like structures can be obtained. After functionalization of their irregular surface with zirconocenes, they were tested in ethylene polymerization. Unexpectedly, a higher activity (12400 kg mol$^{-1}$ h$^{-1}$) was observed for these hyperbranched polymers than for 11.

![Figure 12. Carbosilane based dendrimeric metallocenes 11 are active catalyst in the polymerization of alkenes.](image)

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

<table>
<thead>
<tr>
<th>Substrate 1</th>
<th>Substrate 2</th>
<th>Activity (kg mol$^{-1}$ h$^{-1}$)</th>
</tr>
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<tbody>
<tr>
<td>Ethylene</td>
<td>5760</td>
<td></td>
</tr>
<tr>
<td>1-Hexene</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Cyclopentene</td>
<td>29</td>
<td></td>
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</table>
1.3 Core-functionalized dendrimeric 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 aiming at 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. In order to demonstrate this difference we performed molecular dynamics calculations of a first-generation (phosphine) core-functionalized and a second-generation focal point-functionalized system.[43] The results are clearly shown in Figure 13 were the structures are plotted. In the core-functionalized dendrimers the phosphine ligand is located at the center of the molecule, thereby being shielded from the exterior by the dendrimeric architecture. In the focal point-functionalized system the phosphine is located closer to the surface of the dendrimer, and the dendrimer is shielding less effectively.

Figure 13. Molecular modelling (dynamics) clearly shows the efficient encapsulation of the phosphine ligand in the core-functionalized wedge (right) compared to the focal point-functionalized system (left).

The specific microenvironment created by dendrimeric structures shows great similarity with 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 were generally not used for transition metal catalysis. Hemoprotein-dioxygen binding, selective recognition of guest molecules and stabilization of for instance iron-sulfur clusters are features in nature that have been studied using these mimics. Dendrimeric 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. Several research groups studied recognition of guest molecules by dendrimeric receptors. With respect to catalysis, core-functionalized systems potentially can mimic enzyme properties.

1.3.1 Polymerization

The first example of a catalytic reaction at the core of dendrimers was provided by Fréchet using dendrimeric alcoholates such as 12 as macro-initiators for anionic ring-opening polymerization (ROP) of ε-caprolactone (Scheme 7). Usually the alkali metal alcoholates yield low molecular weight (MW) polymers with broad MW distribution in the polymerization of ε-caprolactone. Earlier studies had shown that steric bulk around the

\[ \text{Scheme 7. Polymerization reactions at the focal point of dendrons: anionic ring-opening polymerization of ε-caprolactone (12), and styrene radical polymerization (13).} \]
reaction center leads to suppression of side reactions as well as to a decrease of ‘backbiting’, which is responsible for low MW products. Furthermore, solubility problems usually result in low MW polymers.

The dendrimeric initiators appeared suitable initiators due to their excellent solubility in THF and their steric bulk prevented ‘back-biting’. The G4 alcoholate acts as a highly effective initiator (Scheme 7) producing high MW polymers with a narrow MW distribution (MWD) 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 with 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 reacting with a chain of another growing tip.

Similarly, dendrimeric wedges were designed for the synthesis of living polymers and living block copolymers via controlled radical polymerization. A nitroxy 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 due to irreversible release of the growing chains and slow recombination. This 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.

1.3.2 Copper-catalyzed Diels-Alder reactions

Chow reported the synthesis of a series of poly(alkyl aryl ether) dendrons (G0 to G3; G3 (14) is shown in Scheme 8) functionalized at the focal point with dendrimeric bis(oxazoline) ligands. 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 enzyme-like Michaelis-Menten kinetics. A reversible formation of the Cu-dienophile complex is followed by the rate-limiting conversion to 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 dendrimeric wedges which is more pronounced for the larger systems. Since the dienophile was used in large excess during the catalytic experiments, for all the systems the copper was present as dienophile-complex. Thus under these conditions no effect of this difference on the catalytic activity was expected. Indeed the activity of the dendrimeric catalysts G0 to G2 was very similar. However, a marked drop in activity was observed when G3 was used as catalyst. Presumably, the size of this dendrimeric 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 due to a decrease in steric accessibility, 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 a copper catalyst. The smaller dienophile reacted somewhat faster than the bulkier one for all catalysts studied (non-dendrimeric parent complex, G1Cu(OTf)2, and G3Cu(OTf)2). More importantly, G3Cu(OTf)2 (\(k_{rel} = 1.18\)) displayed slightly higher substrate selectivity than G1Cu(OTf)2 (\(k_{rel} = 1.05\)).

![Scheme 8](image)

**Scheme 8.** Diels-Alder reactions using Cu\[^{II}\]-bis(oxazoline) complexes located at the core of polyether dendrimers.
1.3.3 Manganese-catalyzed epoxidation

Introduction of dendrimeric wedges on metallo-porphyrins result in core-functionalized
dendrimers in which the porphyrin unit is shielded from the bulk solution. This type of system
was 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.[49] Eight bulky G1 and G2 poly(aryl ester)
dendrons were connected to the porphyrin core to give manganese(III)porphyrin complexes 15
(Figure 14).

Figure 14. Dendrimeric metalloporphyrins 15 and 16 used as shape selective oxidation
catalysts.[49]

These bulky catalysts have been tested as regioselective epoxidation catalysts using
iodosylbenzene as the oxygen donor employing non-conjugated dienes that differ in steric
hindrance. The dendrimeric epoxidation catalysts show an increased preference for the least
hindered double bond compared to a less sterically hindered porphyrin: 1,4-octadiene
epoxidation of the terminal C=C bond occurs four times more selective using 15b. A similar
effect, but less pronounced, was observed for a moderately hindered (2',4',6'-OMePh)-Mn
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 dendrimeric
catalysts. Remarkably, there was no significant rate difference between parent and dendrimer-
encapsulated catalysts. Molecular modelling studies showed that, although top access 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 entering of the substrates. 15a and 15b have larger pockets (~7-10 Å) than the bis-pocket (5,10,15,20-tetrakis(2',4',6'-triphenylphenyl)porphyrin) 16 (~4 Å), which is fully consistent with the higher selectivity obtained using 16.[50]

1.4. Enantioselective transition metal catalysis using dendrimers

Chirality in dendrimeric architectures has been reviewed recently.[51] 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[52] was the first to classify the several ways to introduce chirality in a dendrimer: 1) one can have a chiral core (Figure 15a), 2) the chirality can be introduced at the periphery (Figure 15b), 3) chiral branching units can be used (Figure 15c), or 4) constitutionally different branching units can be attached to a chiral core (Figure 15d). Moreover, one can prepare systems that combine these types of chirality. Some examples show that the local chirality at 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 dendrimeric catalysts these factors are likely to be of similar importance. In the field of enantioselective dendrimer catalysis,[10d] several reports have appeared.

Figure 15. Schematic picture of the positions where chirality can be introduced in the framework of dendrimers.
1.4.1 Periphery-functionalized chiral dendrimeric catalysts

Diethylzinc addition

Meijer used poly(propylene imine) dendrimers that were functionalized with chiral amino alcohol ligands for Et₂Zn addition to benzaldehyde.[53] Preliminary results using 17 and 18 are given in table 2, showing high yields of 1-phenylpropanol for all generations. Moderate enantioselectivities were obtained for the smaller dendrimeric 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 dense packing of the chiral end groups at the periphery. Presumably, this leads to several ‘frozen-in’ conformations (this was also observed for the ‘dendrimeric box’,[8, 54]), 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.[51] Poly(amido amine) dendrimers were functionalized with four and eight chiral amino alcohol groups.[55] In the presence of these chiral ligands, enantioselective addition of Et₂Zn to various N-diphenylphosphinylimines was examined.

For N-diphenylphosphinylbenzaldehyde as substrate the monomeric parent ligand gave 92 % ee, whereas the dendrimeric 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 compared with those of Meijer:[53] the

\[
\text{Ph}^+\text{N}^+\text{Ph}^- + \text{ZnEt}_2 \rightarrow \text{HO}^+\text{Ph}^\text{H}
\]

Scheme 9. The addition of Et₂Zn to benzylaldehyde yielding asymmetric secondary alcohols.

<table>
<thead>
<tr>
<th>Number of end groups (x)</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
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<tr>
<td>1</td>
<td>82</td>
<td>36</td>
<td>86</td>
<td>27</td>
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<td>64</td>
<td>57</td>
<td>7</td>
<td>68</td>
<td>18</td>
</tr>
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</table>
Peripheral amino alcohol ligands of rigid dendrimer 19 act as enantioselective catalysts in the diethylzinc addition to N-diphenylphosphinylimines. A high local concentration of chiral active sites leads to a diminishing of the overall chirality and thus to less enantioselective reactions. In a subsequent paper it was reported that similar ligands were linked to a more rigid dendrimer 19 (Figure 16). These dendrimeric catalysts gave enantioselectivities similar to the parent compound in the addition reaction of Et₂Zn to N-diphenylphosphinylimines at similar rates. In 19 the chiral ligands are effectively separated by the rigid backbone yielding systems that indeed consist of independent catalytic sites.

**Rhodium-catalyzed hydrogenation**

Togni et al. reported dendrimeric catalysts based on chiral ferrocenyl diphosphine ligands (Figure 17). Using different cores they obtained systems with 3, 6, 8 (compound 20), 12, 16, and 24 Josiphos units. Rhodium complexes of these systems were obtained by stirring one equivalent of ligand with [Rh(COD)₂]BF₄ in dichloromethane. These complexes were used as precursors in the hydrogenation of dimethylitaconate using 1 mol% rhodium in methanol at 1 bar hydrogen pressure. Remarkably, all reactions went to completion in 20 minutes and all dendrimeric 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 dendrimeric 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 20 could be completely retained, but catalysis in a continuous process using 20 has not been reported.

1.4.2. Core-functionalized chiral dendrimeric catalysts

Brunner introduced the term ‘dendrizymes’ for core-functionalized transition metal catalysts developed for enantioselective catalysis.\[61\] Diphosphine and diimine ligands were coupled to the focal point of chiral dendrimeric branches in order to create a chiral pocket around the transition metal.

N-chelates 21a to 21c (Figure 18) were used in Cu\textsuperscript{1}-catalyzed cyclopropanation of styrene and a slight increase from < 2 % ee to ~10 % ee on going from parent pyridine aldimine 21a to 21b was observed showing that the chiral pocket slightly enhances the enantioselectivity of the reaction. Further expansion with a second layer of chiral substituents (21c) did not result in higher enantioselectivities.\[62\]

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**Figure 17.** A dendrimeric backbone functionalized with 8 ‘Josiphos’ ligands is active in rhodium-catalyzed enantioselective hydrogenation.
Two-layer chiral diphosphine dendrizes such as 22 were synthesized via a divergent route.[61, 63] 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 ee's. Detailed kinetic studies were performed to study the effect of different dendrimeric branches on the reaction rate of the hydrogenation of acetamidocinnamic acid. Remarkably, the expanded ligand system 22a resulted in a faster hydrogenation catalyst than the parent ligand 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 22a directly started to consume H₂. Only a relatively small change in the structure of the dendrimeric wedge, a 2,5-substituted analogue of 22b (which contains 3,5-substituted wedges), resulted in a hydrogenation catalyst that was 300 times slower.[64] Blocking of the catalytic site by ortho-substituents on the P-phenyl ring was proposed to cause this lower activity.

Diethylzinc addition

The research group of Bolm reported asymmetric catalysis using focal point-functionalized Fréchet type wedges (Figure 19). Similar to the chiral parent compound, dendrimeric catalysts such as 23a were catalytically active in diethylzinc additions to benzylaldehyde yielding optically active secondary alcohols (Scheme 9).[65] 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 23b was also studied. Using 5 mol% of 23b, which was 76% enantiopure, resulted in a 84% ee for the product. The observed
positive non-linear effect is similar to that observed for the reference pyridyl compound. For larger dendrimeric systems such non-linear effects

\[
\begin{align*}
&\text{Figure 19. Chiral focal point-functionalized poly(benzyl ether) dendrimers prepared by Bolm.}[65, 69]
\end{align*}
\]

might not be observed since the formation of complexes with a metal to ligand ratio of 1:2 is involved, but experiments with such systems have not been reported.

Seebach described the synthesis of dendrimers with TADDOLs as asymmetric active sites at the core.[66] Achiral Fréchet type wedges of G0 to G4 were coupled to the para-positions of the four phenyl groups of the TADDOL core (25, Figure 20).[66b] Styrene-functionalized derivatives of these systems have been prepared for immobilization purposes (25b). Interestingly, they also reported TADDOL ligands such as 26, functionalized with both the \((R,S)\) (drawn) 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.

The Ti-catalyzed enantioselective nucleophilic addition of \(\text{Et}_2\text{Zn}\) to benzaldehyde was studied using these dendrimeric 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 as observed for the copper-catalyzed Diels-Alder reaction reported by Chow et al.[48] (see section 3.2). The chiral branches in 26 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.
Figure 20. G2 dendrimers with TADDOL ligands at the core for homogeneous reactions (25a) and styrene-functionalized derivatives for immobilization purposes (25b). Dendrimer 26 contains (R,S) chiral wedges.

The TADDOL-cored dendrimers were immobilized by co-polymerization of styryl-substituted TADDOLs in cross-linked polystyrene using divinylbenzene or TADDOL-centered dendrimers with peripheral styryl groups (25b, Figure 20) as cross-linkers. These ligands were co-ordinated to Ti by exchange with Ti(OCHMe$_2$)$_4$ and their activities and enantioselectivities in the Et$_2$Zn addition to benzaldehyde were evaluated. As shown before, the branches of the dendrimeric catalyst (25b) have only a minor influence on the selectivity of the homogeneously catalyzed reaction. Using the immobilized systems ee's 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 was proposed to be the result of 'frozen-in' conformations of the ligand. The immobilized dendrimeric catalysts did not perform better using higher generation dendrimers, but generally the activities of the dendrimeric immobilized systems were in between the polymer-bound analogues and the homogeneous counterparts. This confirms the hypothesis that catalytic sites within the polymer beads show intermediate accessibility. The selectivity drops considerably with introduction of spacers between the Ti-TADDOLates and the styryl-functionalities of 25, which might be caused by a less controlled active site and
from the swelling properties of the polystyrene beads.[68] All polymeric systems were recycled in 20 consecutive reactions via decanting/filtration and subsequent washing with toluene. The dendrimeric polymer showed the highest enantioselectivity of 98:2 in 20 sequential runs.

**Asymmetric borane reduction**

Optically active amino alcohols were attached to the focal point of dendrimeric branches (G0 to G3), and the resulting ligands (Figure 19 shows G2 24) were employed in asymmetric borane reductions.[69] Compared to the parent catalyst that gave 87 % ee, slightly higher enantioselectivities (88-91%) and good yields were obtained for various generations using acetophenone as a substrate. The highest ee values (up to 96 %) for the reduction of α-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 due to their flexibility.

**Titanium-catalyzed asymmetric allylation**

Yoshida prepared chiral 1,1'-binaphthol derivatives having poly(benzyl ether) wedges at the 6,6'-positions.[70] The molecular optical rotation was identical for all generations, which is in agreement with the presence of a single chiral group. From 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 dendrimeric catalysts (92-88 % ee compared to 87 % for parent (R)-binaphthol).

1.5 Metal nanocomposites in the dendrimer interior

So far we have only discussed catalysts in which the metal ions are co-ordinated to appropriate donor atoms like P, N, O. Recently, a new concept was reported independently by the research groups of Crooks,[71] and Tomalia.[72] 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 shown to be very active catalysts.[73] However, clusters tend to aggregate into larger (less active) systems under catalytic conditions which complicates the applications of these systems. Precise construction of nanocomposites in cavities of dendrimers might lead to both cluster stability and full control over size and size distribution, while the dendrimer branches still allow access of substrates to the catalytically active clusters. Additionally,
dendrimers could enhance solubility of the metal clusters due to their solubility in a wide range of solvents.

Scheme 10. Sorption of metal ions and subsequent reduction forming dendrimer stabilized nanocluster complexes.

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 was shown by spectrophotometry.[71a] Chemical reduction leads to stable, perfectly soluble nanocluster complexes (Scheme 10). Evidence for the formation of these clusters comes from an immediate color change from dark blue to gold brown, and the loss of signal in the EPR spectrum upon reduction.[71a, 72] 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. 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.[71b] 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 less noble Cu atoms are exchanged.[74] 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 via primary metal-exchange reactions from G6-OH(Cu$_{55}$), could be converted further to the more noble G6-OH(Au$_{37}$), G6-OH(Pt$_{55}$), and G6-OH(Pd$_{55}$) via secondary replacement reactions. Using this replacement method, catalytically active, encapsulated nanoparticles were prepared.
The water-soluble and stable composites G4-OH(Pd40) exhibit high catalytic activity for the hydrogenation of alkenes in water. Turnover frequencies were higher than for watersoluble polymer-bound Rh1 catalysts and comparable to PVP-stabilized colloidal Pd dispersions in water (PVP = poly(vinyl pyrrolidone)). These nanocluster-dendrimer catalysts are sufficiently stable for recycling and re-use. Moreover, proper choice of the dendrimer generation can control the hydrogenation activity.[71b] Higher generation dendrimers have more dense surfaces, which give limited access of substrates to the Pd nanoclusters. G6-OH(Pd40) and G8-OH(Pd40) show rates of only 10 % and 5 %, respectively, of that for G4-OH(Pd40). In principle this could add the function of substrate selectivity to the dendrimer. In a subsequent paper[75] dendrimer-encapsulated palladium nanoparticles were applied in fluorous biphasic catalysis.[76] PAMAM dendrimers were functionalized by complexation of carboxylic acid-terminated perfluoropolyether tails 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 much faster hydrogenated than non-polar substrates, which is due to the polar microenvironment within the dendrimer. Using these dendrimeric nanocomposites substrate selectivity can be achieved on the basis of size and polarity.

1.6 Summary and outlook

The field of dendrimeric transition metal catalysis is very new, but already numerous examples based on different dendrimeric backbones functionalized at different locations have appeared. At this stage it is pivotal to focus on the fundamental aspects of dendrimeric catalysis and many points of interest stated in the introduction have been addressed. Periphery-functionalized dendrimers, which have extreme 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) co-operativity and also heterobimetallic catalysis using dendrimeric 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 as transition metal catalysts have huge potential and the analogy with natural systems is evident. Large dendrimeric 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 non-covalent interactions, on the analogy of the working principles of enzymes.

Preliminary results showed that dendrimers are suitable supports for transition metal catalysts and the larger systems can be used in continuous processes. The common problems involved in catalyst recycling can occur using dendrimeric catalysts, 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 dendrimeric 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 dendrimeric 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 dendrimeric catalysts with chiral ligands at the periphery. In the nearby future more examples of dendrimeric transition metal catalysts are required to substantiate this for a broad range of reactions. Ideally we would like to accumulate enough information and synthetic knowledge to implement the dendrimeric framework in the rational design of new catalyst systems. The field of dendrimeric systems functionalized with different catalytic sites at several well-defined locations can potentially be used for tandem reaction. Also the assembly of dendrimeric catalysts into larger aggregates[7, 77] and systems organized on surfaces will have a bright future in high precision nanotechnology. Multi-step reactions using these nanofactories are getting closer to sophisticated natural systems such as the multiprotein respiratory assembly.

After submitting this manuscript several interesting reports on dendrimeric catalysis appeared, of which the references and brief descriptions were included.[78]

1.7 Aim and outline of the thesis

The aim of the work described in this thesis is the development of core-functionalized dendrimeric catalysts to study the effects of dendrimeric encapsulation on the activity and selectivity of various catalytic reactions. From the enormous variety of types of dendrimeric backbones the carbosilanes were selected for the construction of functional dendrimers and their application in catalysis because of their high thermal and chemical stability, the ease of synthetic variations, and the apolar character of the branches.
In Chapter 2 the effects of the dendrimeric encapsulation on the regioselectivity and activity of the palladium-catalyzed allylic alkylation reaction are described. These effects have been studied using a series of novel ferrocenyl diphosphine ligands at the core of dendrimers. In addition, the utility of the core-functionalized dendrimeric catalysts in a continuous-flow membrane reactor is shown.

Chapter 3 deals with a direct comparison of the catalytic activity and selectivity of ferrocenyl diphosphines ligands located at the core- and at the periphery of carbosilane dendrimers. Palladium complexes of these conceptually different dendrimeric ligands were applied as catalysts in the Grignard cross-coupling and the allylic amination reactions. The application of these core- and periphery-functionalized dendrimeric catalysts in the continuous amination reaction is also examined.

Chapter 4 contains the synthesis of three series of core-functionalized dendrimeric ligands based on the diphosphine backbones dppf and xantphos and on the monophosphine triphenylphosphine. The application of rhodium complexes of these ligands in batchwise and continuous hydroformylation and hydrogenation reactions will be discussed. An highly interesting effect of the dendrimeric encapsulation on the activity and regioselectivity of a bulky substrate is described.

Based on previous work on the Kharasch addition reaction, it can be concluded that the reaction is inhibited when catalytic sites are in close vicinity of each other. Possibly, dendrimeric encapsulation provides site isolation, and thus would circumvent the inhibition due to dimerization. In Chapter 5 we report the preparation of NCN pincer-nickel complexes at the focal point of carbosilane dendrimeric wedges and preliminary catalytic experiments in the Kharasch addition reaction.

References


[12] A silica particle of 10 mm (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). Note that the primary particles, which form larger conglomerates, like dendrimers contain up to 1000 metal (Rh) atoms.


38 Chapter I


Chapter 1