# ‘Dialyzable’ Carbosilane Dendrimers as Soluble Supports in Organic Synthesis:

## Proof of principle, application and diafiltration performance

‘Dialyseerbare’ Carbosilaan Dendrimeren als Oplosbare Dragers in Organische Synthese:

‘Proof of Principle’, toepassing en gedrag bij diafiltratie

(met een samenvatting in het Nederlands)

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# Preface

Organic and organometallic synthesis is traditionally performed by solution phase procedures. The homogeneity of these reactions mixtures has several advantages in terms of, *e.g.*, kinetics, mixing and the application of analytical methods. In the last decades high-throughput screening has been developed in order to explore the synthesis of libraries of small, pharmaceutically interesting molecules (*i.e.* API's, active pharmaceutical ingredients). Solution phase chemistry appeared to be difficult to apply in a parallel, high-throughput setup, since it usually requires rather complicated or time-demanding workup procedures (*e.g.* extraction, filtration). The use of Solid Phase Organic Synthesis (SPOS), initially developed for the preparation of peptides in the early 1960s by Merrifield, allowed high-throughput experimentation to evolve into a widely applied method for the synthesis of large numbers of organic compounds and libraries thereof.[1-3] Over the years many reports described the application of the SPOS procedure for the synthesis of peptides and related compounds, such as poly- or oligonucleotides, polysaccharides, polyamides and bioconjugates.[4-9] The application of solid supports as organic synthesis support for (monomeric) low molecular weight compounds is described more recently as well.[10-13]

In order to overcome the disadvantages originating from the heterogeneous nature of SPOS, soluble synthesis supports have been developed (*i.e.* Liquid Phase Organic Synthesis, LPOS).[14-19] These soluble supports, mainly polymers like (modified) polyethylene glycol, polyvinyl alcohol and crosslinked polystyrene (*e.g.* *J*anda*J*el™), are successfully used, but their loading capacity is rather low and the irregularity of these supports makes application of spectroscopic analysis still not straightforward. The introduction of dendritic supports[20,21] resulted in the availability of highly regular soluble supports that can easily be analyzed using standard spectroscopic techniques like NMR spectroscopy. Several different types of dendrimers for various applications (*i.e.* not only supported synthesis) have been developed over the years, *e.g.*, polyamidoamines (PAMAM),[22] polypropylene imines (PPI),[23] polybenzyl ethers (Fréchet type),[24] polyaliphatic esters,[25] polyester amides (Newkome type),[26,27] and carbosilane dendrimers.[28-30] The size and shape of the dendrimers make it possible to separate molecularly supported scaffolds from reaction mixtures using simple filtration techniques. Studies using different types of filtration membranes proved that dendrimer-supported materials are retained efficiently by these membranes.[31-36]

Many of the dendrimers were initially tested and used as catalyst supports.[20,37,38] The chemical nature of carbosilane dendrimers in particular makes them very robust under the harsh reaction conditions that are often applied in catalytic reactions. In the last years, many reports describing the application of carbosilane dendrimer-supported catalysts were published. *Chapter 1* gives an overview of the recent developments, until 2009, in this field. Besides an introduction, the chapter describes catalysts that are covalently bound to the carbosilane dendritic supports, either at the periphery or at the core or branching points. These dendritic catalysts are divided into phosphine-based and non-phoshine-based dendritic catalysts. For all described dendritic catalysts their application and activity is evaluated. The structural properties of the dendritic catalysts, like the peripheral density and rigidity of the dendritic structure, appeared to influence the activity of the catalysts, resulting in either a negative or positive 'dendritic' effect. The developments described for the application of dendrimer supports in catalysis can also be applied to other applications, *e.g.* to supported organic syntheses. The requirements needed for catalyst supports, like recyclability, nanofiltration, inertness, and robustness, are also required for supported organic synthesis with soluble supports. The expertise in the use of carbosilane dendrimers as catalyst supports can therefore be combined with the general experiences in SPOS and LPOS for the development of carbosilane dendrimers as soluble supports for organic synthesis.

The primary aim of the work describe in this thesis was to develop the application of carbosilane dendrimers as soluble supports in organic synthesis. An initial study towards this application was presented earlier.[39] In this thesis additional results will be described in order to benchmark this proof of principle. Besides, a more extended study towards the application of dendritic support in SPOS methodologies will be described. A second aim of the work was to gather more information regarding the behavior of the carbosilane dendrimers during diafiltration experiments. To this end the correlation between the structure of the dendritic core – flexible, rigid, core density – and the performance during the filtration procedures is of interest.

The synthesis of pyridine derivatives using standard solution phase synthetic procedures is often rather difficult due to the number of purification steps required to obtain the pure compounds. Changing to dendrimer-supported synthesis can result in easier reaction procedures and higher purities, due to the possibility to use easy filtration techniques for purification. In a previous study the modification of 3-bromopyridine moieties using dendritic

supports was investigated.[39] In *Chapter 2* this study is expanded with the modification of 2-bromopyridine moieties. The proven method to attach these moieties to the dendritic periphery makes use of lithiation chemistry, which can be challenging in the presence of the chlorosilane end groups of the carbosilane dendrimers. For the modification of supported pyridines, reaction procedures that make use of metal-catalyzed coupling reactions, like the palladium-catalyzed Suzuki and Negishi reactions, were studied. In order to establish reaction sequences for the stepwise modification reactions, test reactions with trimethylsilyl groupings as mimic for the dendrimers were performed. The obtained procedures were then applied in the dendrimer-supported chemistry. In the synthetic procedures, passive dialysis was chosen as purification method for the separation of the supported synthesis scaffolds as well as the separation of the aimed products after release from the dendritic supports.

In order to get a better understanding of the behavior of the dendrimers during dialysis and diafiltration procedures, a series of structurally different carbosilane dendrimers was studied. *Chapter 3* describes the synthesis of several new rigid carbosilane dendritic structures in order to be able to compare their filtration behavior to more conventional flexible dendrimers. Based on a previous study,[32] dendrimers with phenyl groupings at their core were selected for this study. The synthesis of these dendrimers proceeded via polylithiation reactions, which were studied and optimized in detail. Using the optimized procedures, the synthesis of a series of rigid core molecules, rigid dendritic wedges, and rigid carbosilane dendrimers was achieved, in addition to the synthesis of dendrimers in which a rigid core is combined with flexible dendrons.

The new carbosilane dendrimers were used to investigate the filtration behavior of dendrimers in a diafiltration setup. In *Chapter 4* the loading of these dendrimers with two different coloring agents (ferrocene and Dispere Red 1) is described, which has allowed for these dendrimers to be detected during the diafiltration experiments. The colored dendrimers were further investigated in order to get a better understanding of their size, shape and behavior in solution, using, *e.g.*, molecular modeling, GPC and UV/Vis spectroscopy. The diafiltration experiments were performed using the colored dendrimers and a selection of membranes with varying molecular weight cut-off (MWCO). The results from this study will allow one to select an optimal combination of a dendritic support structure and a filtration membrane for particular LPOS application.

The most common and well-known solid supports for SPOS are based on a polystyrene (PS) backbone to which different linker-groupings are connected. For example, the original Merrifield resin consists of a PS resin which was partly chloromethylated.[1] In order to be able

to compare the application of carbosilane dendrimers as synthesis support to SPOS and LPOS methodologies, *Chapter 5* describes the synthesis of carbosilane dendrimers with a number of typical SPOS-type linker groupings at their periphery. Three different linkers were selected for this purpose, *i.e.* the benzylbromide linker (comparable to the Merrifield resin),[1] the REM linker[40,41] and the DEAM linker.[42] The linker-modified dendrimers were used as support for the stepwise synthesis of a series of small, pharmaceutically interesting molecules, based on piperidine and piperazine building blocks, using a standard supported synthesis procedure that includes the attachment of a molecular scaffold, its chemical modification, and the release of the reaction product. One of the observed advantages of this dendrimer-based procedure as compared to SPOS is the ease of characterization of the functionalized dendritic species after every modification step, due to the solubility of the supports.

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# Chapter 1

## Polycarbosilane Dendrimers - Molecular Supports and Containers for Homogeneous Catalysis and Organic Synthesis

*Since the first publications on the use of carbosilane dendritic scaffolds as supports for organometallic catalysts in 1994, this field has been explored extensively. Compared to the more conventional polymeric and dendritic supports, carbosilane dendrimers display several advantages when dealing with their synthesis and application as carriers for catalysts. In this chapter an overview of the catalytic reactivity of recently developed metallodendrimers is presented with a focus on the effect of the dendritic scaffold on the catalytic activity and recycling of the nano-sized metallodendrimers by nano-filtration techniques. Furthermore, an outlook is given for the use of carbosilane dendrimers as soluble supports for organic synthesis since this field of research is dealing with some of the same requirements for supports as encountered in their applications as supporting catalysts.*

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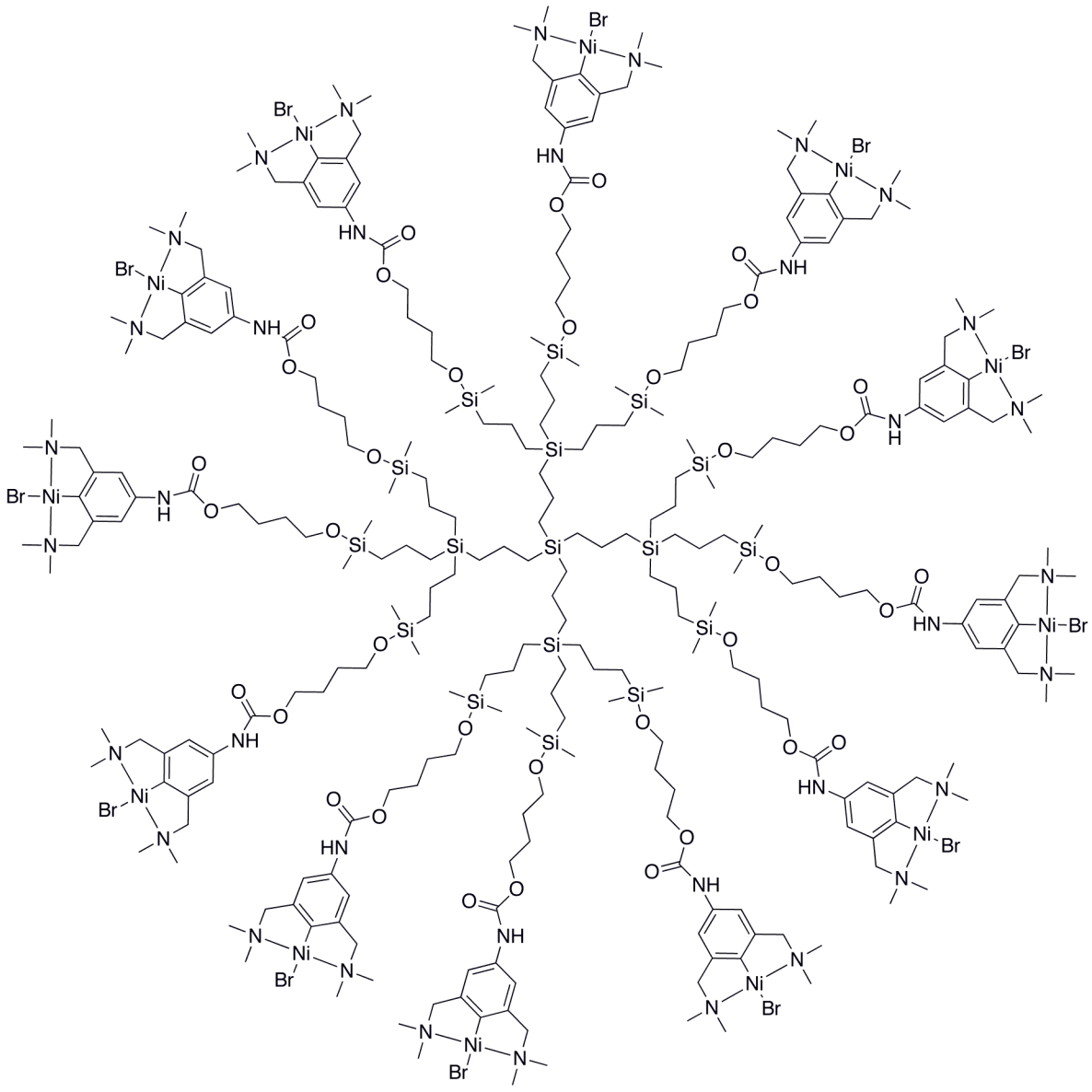
## 1.1 Introduction

The attachment of catalytic species to support materials is a widely applied method to combine the advantages of homogeneous and heterogeneous (supported) catalysis. The commonly used organic supports are insoluble polymeric materials, which have been developed with great success for solid phase organic synthesis and have a long history and importance. Obvious difficulties with these materials are their restricted loading capacity, the wettability issues, the often restricted accessibility of active (supported) sites, their reactivity or incompatibility towards reactive reagents, such as organometallics, and last but not least their high polydispersity. The use of soluble support materials can solve some of these problems, and for this reason soluble dendrimers have been explored as supports for homogeneous catalysts. Some of the advantages of dendrimers over many other types of macromolecules are their well defined structures and low polydispersity, good solubility in common organic solvents, and the presence of well-defined end-groups for the anchoring of catalytic species, all of which facilitate analysis of the (loaded) dendrimers often with atomic precision.

During the last decade, several reviews appeared describing the use of dendrimers as soluble supports for catalysts.[1-11] Among these, the silicon-based carbosilane dendrimers assume a special position because of their structural robustness and stability towards highly reactive reagents. These are important prerequisites for any derivatization of the dendritic structure as well as for the introduction of the catalytic metal sites, *vide infra*. Carbosilane dendrimers derive their kinetic and thermodynamic stability from the relatively high dissociation energy (306 kJ/mol) and low polarity of the Si-C bond.[1] The first demonstration of the potential of these unique properties has been the successful synthesis of a carbosilane dendrimer **1** functionalized at its periphery with catalytically active NCN-pincer nickel catalysts (NCN = $[C_6H_3(CH_2NMe_2)_2\text{-}2,6]^-$).[12] Due to its molecular size, which is about 2 nm, such catalytic species can be separated from the reaction solutions by nanofiltration, which in principle opens the way for recycling of the catalyst as well as for continuous use of such catalysts in membrane reactors.



**1**

Carbosilanes are particularly attractive dendrimers because of the degree of control one has over the sites where the catalytic species can be attached to the dendrimer scaffold. Figure 1 shows various possibilities for this attachment: (A) on the periphery of a dendrimer or dendron; (B) at the core or at the focal point; (C) at the branching points, or (D) as dendrimer-encapsulated nanoparticles.[3] However, the last possibility is not applicable to carbosilane dendrimers, since interactions between the catalyst and the scaffold are unlikely because of the absence of internal metal-coordinating moieties. However, the high degree of branching which originates from the use of silicon as the core atom and branching points, makes these carbosilane dendrimers very suitable for use as carriers for catalytic species.

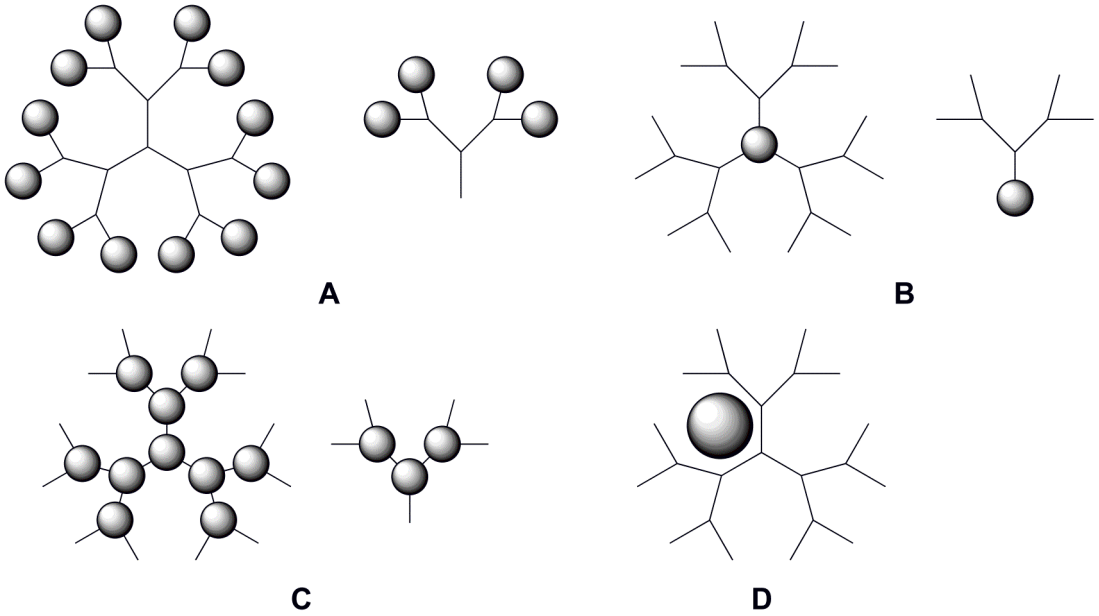



**Figure 1:** Schematic representation of different binding modes of catalytic species to a (carbosilane) dendritic (i.e., dendrimers or dendrons) architecture. (A) At the periphery; (B) at the core; (C) at the branching points; (D) as encapsulated nanoparticles.[3]

Since dendritic architecture can be designed with a high degree of control, features such as mutual proximity of catalytic sites (e.g., mutual deactivation or cooperativity effects) and secondary coordination (sphere effects) by the catalyst-surrounding dendritic organic mass can be implemented in a controlled fashion.[13-15] The sizes of the carbosilane dendrimers (larger than 2 nm) and their low polydispersities enable application of (nano)filtration methods with commercially available membranes. In fact, dendrimers with sizes in the range of 2.5 to 3.0 nm are already suitable for nanofiltration.[15] Other types of catalytic dendrimers that have been used in nanofiltration set-ups, include, for example, porphyrin-functionalized pyrimidine dendrimers, which were used as recyclable photosensitizers for the oxidation of various olefinic compounds.[16] For applications in continuous catalytic processes retentions of at least 99.99% are required in order to obtain a catalyst system that remains in the reactor for a prolonged period of time.[17]

Several reactor designs and membrane types have been developed for the separation of soluble, catalytic, carbosilane dendrimers from the product stream.[3,18-26] Membrane technology can be performed either batch-wise or in continuous-flow membrane reactors, using micro-, ultra-, nano-, diafiltration or reverse osmosis. Passive dialysis is used batch-wise, since it utilizes the difference in concentrations of the reactants and product on either

side of the membrane (see Figure 2). In continuous-flow membrane reactors, reactants and products, but not the dendrimer catalyst, are transported through the membrane by applying an external force like air pressure. Dijkstra et al. reviewed the different types of continuous-flow membrane reactors used with dendrimer catalysts.[19]

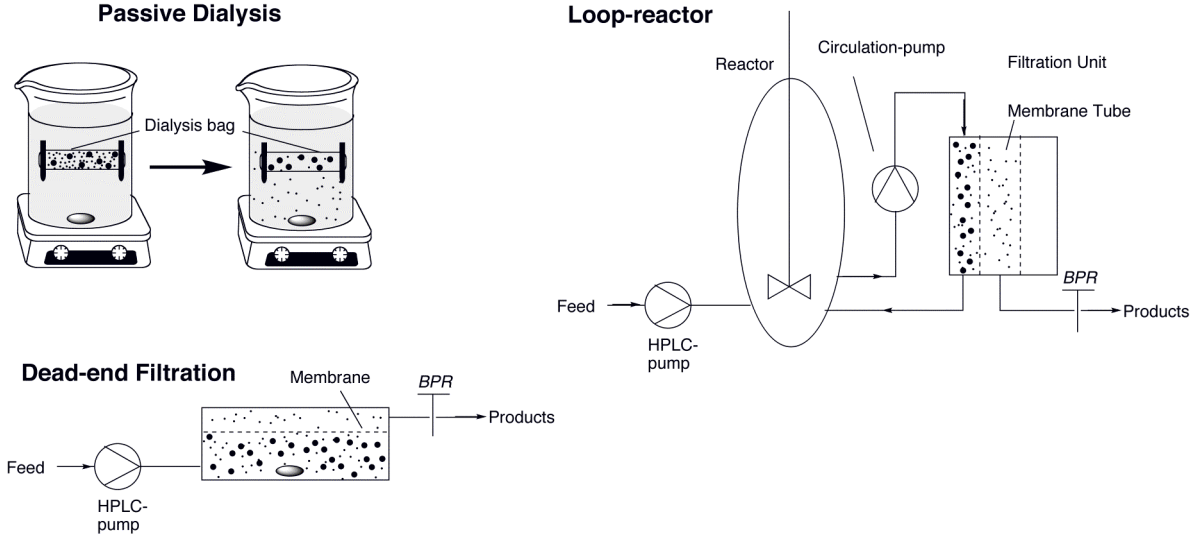



**Figure 2:** Schematic representation of different combinations of reactors and (nano)filtration methods (*BPR* = Back-Pressure Regulator).[19]

Different kinds of membranes, prepared from polymeric as well as ceramic materials, have been developed. They need to be solvent resistant, and preferably able to withstand industrially important solvents such as tetrahydrofuran (THF), dimethylformamide (DMF), dimethylsulfoxide (DMSO), *N*-methylpyrrolidone (NMP) and dichloromethane (DCM). Most currently available polymeric membranes, however, still show some incompatibility problems with these conditions. Ceramic membranes, on the other hand, overcome some of these problems, but suffer from brittleness and are still more expensive. Vankelecom et al. nicely reviewed the field of solvent resistant nanofiltration techniques.[26]

In this chapter we review the use of carbosilane dendrimers in catalysis research, including different derivatives with covalently bonded metal catalysts and different types of catalysis in which they have been used. Multiple uses of such relatively expensive carrier molecules, whose synthesis is labor intensive, will be of importance when it comes to industrial applications. Most of the catalytic species that have been covalently attached to dendrimers are simple mimics of the catalysts used in the corresponding homogeneous catalytic processes and are based on either phosphine or other ligand donor systems. In each section of this chapter, a brief overview of the synthesis and structural aspects of the respective dendrimer

catalysts is presented first, followed by a discussion of the catalytic processes in which they have been applied. Special attention is given to filterability, cooperativity effects, solvent compatibility, recyclability, secondary coordination sphere effects, etc. The chapter closes with a concise overview of the use of the newly developed, soluble carbosilane dendrimers as carrier molecules for multistep supported organic synthesis. It is particularly noted that many requirements that are so important for the successful use of soluble dendrimer catalysts in homogeneous catalysis are encountered in this application again. These include the number and proximity of active sites, solvent and reagent compatibility, as well as inertness and filterability of the dendrimer supports.

## 1.2 Carbosilane Dendrimers with Covalently Bound Catalysts

The common method for the introduction of catalytic species onto a dendrimer scaffold is attachment of the catalyst directly to the periphery of the preformed dendrimer. In this way, well-defined multi-catalyst structures can be obtained, in which the activity of each site can be easily compared to that of the corresponding monomeric analogue. The effects of the presence of dendritic mass around each active metal center, as well as proximity effects of neighboring metal centers, are often reflected in the catalytic reactivity that is observed. This reactivity (selectivity) can be either unchanged, increased or lowered with respect to its monomeric analogue, i.e., either a positive or negative *dendritic effect* is observed. In addition to the peripherally-functionalized dendrimers, dendrimers that are core-functionalized with a catalyst have also been reported. The large dendritic mass surrounding the single catalytic site in such dendrimers can cause a site-isolation effect, leading to the formation of a microenvironment around the metal center that influences its catalytic properties. Two main groups of catalysts covalently bonded to dendrimer scaffolds include those with phosphine-based dendrimer ligands and those with “other” (non-phosphine-based) dendrimer ligands.

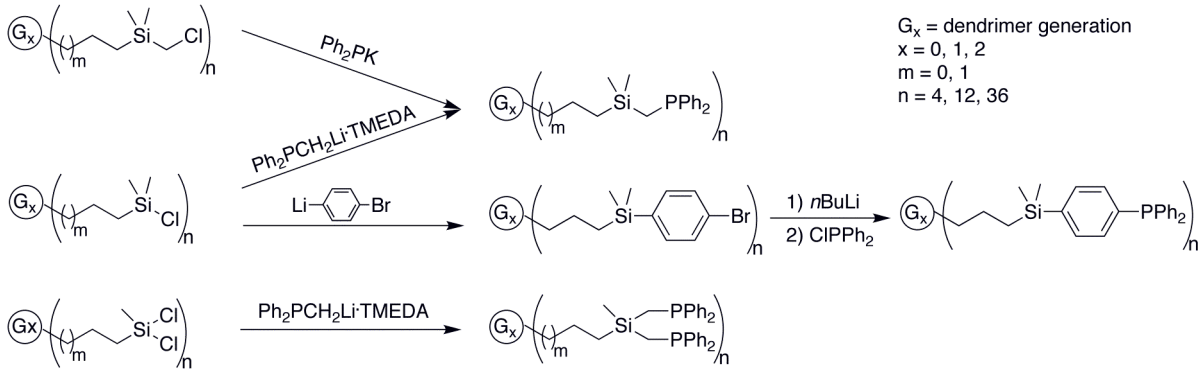
### *1.2.1 Synthesis and structural aspects of phosphine-based dendrimer catalysts*

Phosphine ligands are widely used in homogeneous catalysis to stabilize complexes and to direct activity and selectivity. Many mono- and polydentate phosphine ligands have been synthesized and used in, for example, palladium and platinum complexes, yielding homogeneous catalysts for a plethora of reactions. One way to make these catalysts recyclable and applicable in continuous catalytic processes is to connect them to a soluble support, i.e. to

create dendrimers with sizes in the range of 2-3 nm which allows their separation from the reaction solutions by nano- or diafiltration techniques.

For the synthesis of phosphine-based dendrimer catalysts, mainly carbosilane dendrimers comprising silicon atoms at the core and at the branching points with ethane-diyl- or propane-1,3-diyl-spacers have been used, although other types of connectivities between the silicon centers are also known. The synthesis of alkyl-based carbosilane dendrimers of low polydispersities has been extensively studied[27] and these are now available for many applications. As these dendrimers have relatively well-defined structures, spectroscopic techniques such as NMR are applicable for the study of their structural features in solution. In addition to these, other dendritic species have also been developed in which a carbosilane wedge (i.e., dendron) is connected to a non-carbosilane core. Examples are the silsesquioxane cores with carbosilane dendrons studied by Cole-Hamilton et al. and Morris et al.[28-33]

In most cases, the phosphine ligands, most frequently diphenylphosphino groups, are first anchored covalently to the periphery of the dendrimer scaffold and then converted into the corresponding phosphine-metal complexes. The phosphine groups can be connected to the carbosilane dendrimer either directly, or via a linking moiety, a tether, such as a benzylic group or aliphatic chain.[34-36] The generally applied method for direct attachment involves the use of a lithiated phosphine, which is quenched with the chlorosilane dendrimer end-groups (see Reaction Scheme 1)[35] In some cases (not shown), a hydrosilylation reaction was used to connect the phosphine ligands to the allylic or vinylic end-groups of the dendrimer scaffold.[29]




(1)

In general, introduction of phosphine ligands in the last step of the synthetic sequence reduces the chance of losing or damaging the sensitive and expensive phosphanyl functions during the synthesis of the dendrimer scaffold. The attachment of a phosphine group via a tether to a

dendrimer periphery can be performed in two ways. Either the tether is first connected to the dendrimer and then loaded with the phosphine groups, or it is first attached to the phosphine, followed by connecting the tether to the dendrimer surface. In the latter case the tether-phosphine unit can be perfectly tuned for the formation of both the ligand and the phosphine-metal complex site, since dendrimer effects are less likely to play a role.

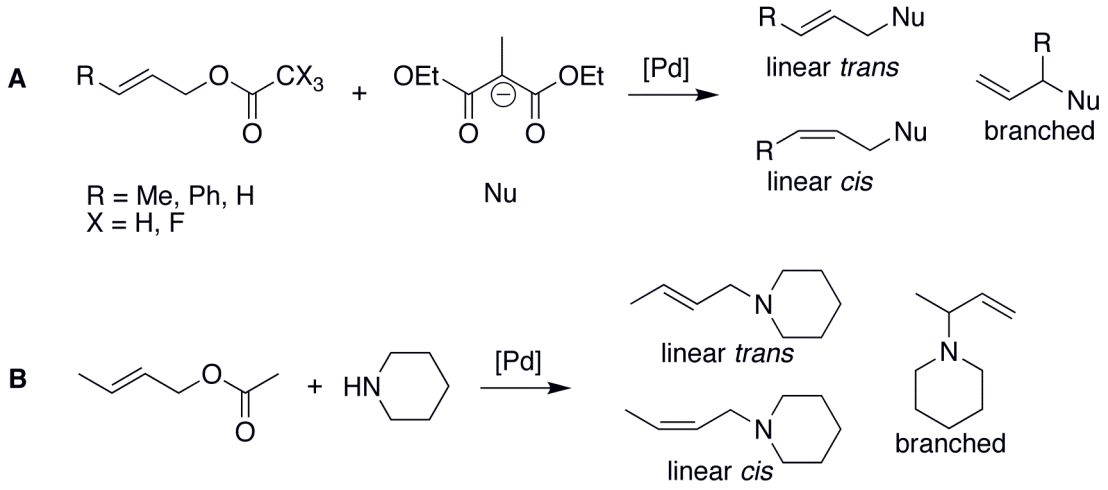
### *1.2.2 Catalytic reactivity of phosphine-based dendrimer catalysts*

Phosphine-based dendrimer catalysts have been tested in a wide variety of catalytic reactions. This section deals with a comparison between their reactivity and selectivity with those of their monomeric analogues.

#### 1.2.2.1 Allylic substitution

Palladium phosphine complexes are excellent catalysts of allylic substitution or alkylation reactions. Van Leeuwen et al. reported on the synthesis and catalytic activity of several carbosilane dendrimers functionalized with phosphine-palladium units.[37-39] Peripheral phosphine-functionalized carbosilane dendrimers up to the second generation were synthesized by the reaction of peripheral chlorosilyl-functionalized dendrimers with [(diphenylphosphino)methyl]lithium·TMEDA,[37,38] yielding dendrimers containing one or two diphenylphosphanyl groups per end-group (see Reaction Scheme 1). The palladium complexes were formed by subsequent reaction of the phosphine functionalized dendrimers with either [PdClMe(COD)] or $[PdCl[(\eta^3\text{-}C_3H_7)]_2$. Dendrimers with one $PPh_2$ end-group per Si-branching point formed trans-complexes when reacted with [PdClMe(COD)], whereas dendrimers with two $PPh_2$ end-groups per Si-branch point formed cis-complexes, i.e. the latter end-groups were acting as bidentate ligands. The resulting metallodendrimers were tested as catalysts in allylic alkylation and amination reactions (Reaction Scheme 2 A and B, respectively), both in batch and continuous processes.[37] It was found that the number of phosphine units per dendrimer end-group had some influence on the activity and selectivity. The dendrimer catalyst containing bidentate ligands appeared to be more active in both the allylic amination reaction between crotyl acetate and piperidine and the allylic alkylation reaction between crotyl acetate and sodium 2-methylmalonate. The selectivity in the allylic alkylation reactions was hardly influenced by the dendrimer size and number of phosphine end-groups, whereas in the allylic amination reaction the selectivity induced by bidentate ligands was slightly different from that of the monodentate ligands. The size of the dendrimer scaffold hardly affected the catalytic activity, which makes these dendrimers suitable

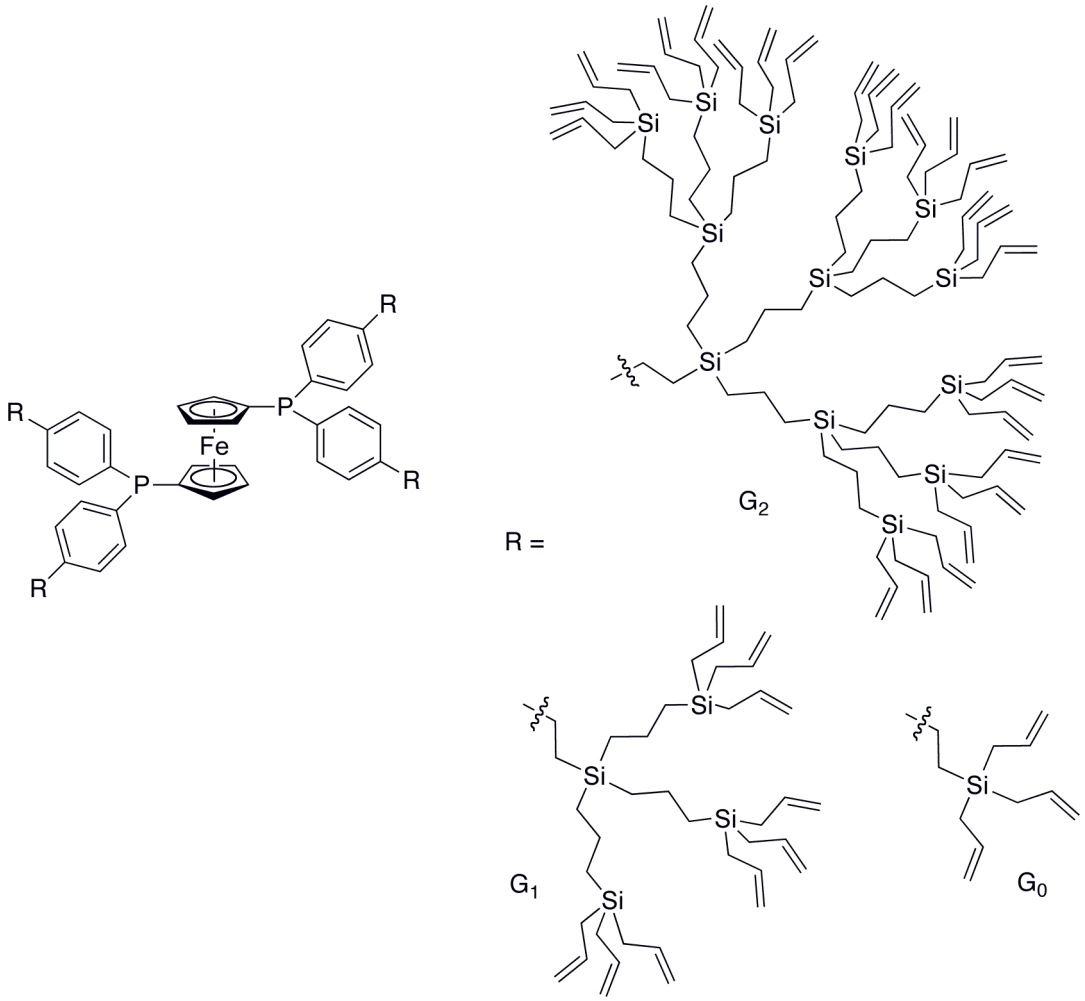
supports. It also enables their application in continuous-flow membrane reactors, as indicated by the retention of up to 99.7% obtained for the second generation dendrimer catalyst in dichloromethane during the allylic alkylation reaction. The preservation of activity with increasing dendrimer generation also indicates that all catalytic sites act as independent catalysts even when steric crowding at the periphery increases, as is the case for higher generation dendrimers. However, the test of dendrimer catalysts in continuous processes, resulted in a rapid drop of the yield of allylic substitution reactions, rather than in leaching of the dendrimer catalyst (as was demonstrated by previous retention studies[38]). Since this drop in yield was ascribed to catalyst deactivation, dendrimers with an ethanediyl tether between the terminal silicon and the phosphorus atom, i.e. with $SiCH_2CH_2PPh_2$ end-groups, were prepared and tested. This seemingly subtle change in the tether length positively influenced the stability of the catalytic systems and although the yield of the reaction products still decreased to some extent, decomposition of the catalysts was not observed in continuous allylic amination reactions. Combining these results with those obtained from previous retention studies, the retention of the dendrimer catalyst with ethanediyl tether was estimated to be 98.5-99%.




(2)

The synthesis of 1,1'-bis(diphenylphosphino)ferrocene (dppf) ligands having dendrons connected to the para-positions of the phenyl groups yielded carbosilane dendrimers with a bidentate phosphorus ligand at its core **2**.[39] The dendrons of up to the third generation, were converted to the corresponding bisphosphine palladium complexes by reaction with $[PdCl_2(MeCN)_2]$. The complexation of the ligand in a bidentate cis fashion, forming similar palladium complexes as dppf allowed comparison of the catalytic activity between dendritic

and palladium-dppf complexes. For catalytic experiments, the dendritic ligands were first reacted with crotylpalladium chloride dimer to form dppf-like palladium complexes, which were then used in the palladium-catalyzed allylic alkylation of 3-phenyl-1-allyl acetate with diethyl sodium-2-methylmalonate (Reaction Scheme 2A; R = Ph; X = H) and were all found to be active and producing mainly the linear *trans*-product. A decrease in reaction rate was observed, when using the higher generation dendrons, especially on going from the second to the third generation. This was ascribed to a decreased mass transport of the reagents through the dendrimer shell surrounding the catalytic site. However, the selectivity for the branched product increased with increasing generation, probably because the increased steric bulk of the dendrimer shell caused hindering of the nucleophile attack on the palladium-allyl. As another reason for these different selectivities a gradual change in the apolar microenvironment created by the carbosilane dendrons was also suggested.




**2**

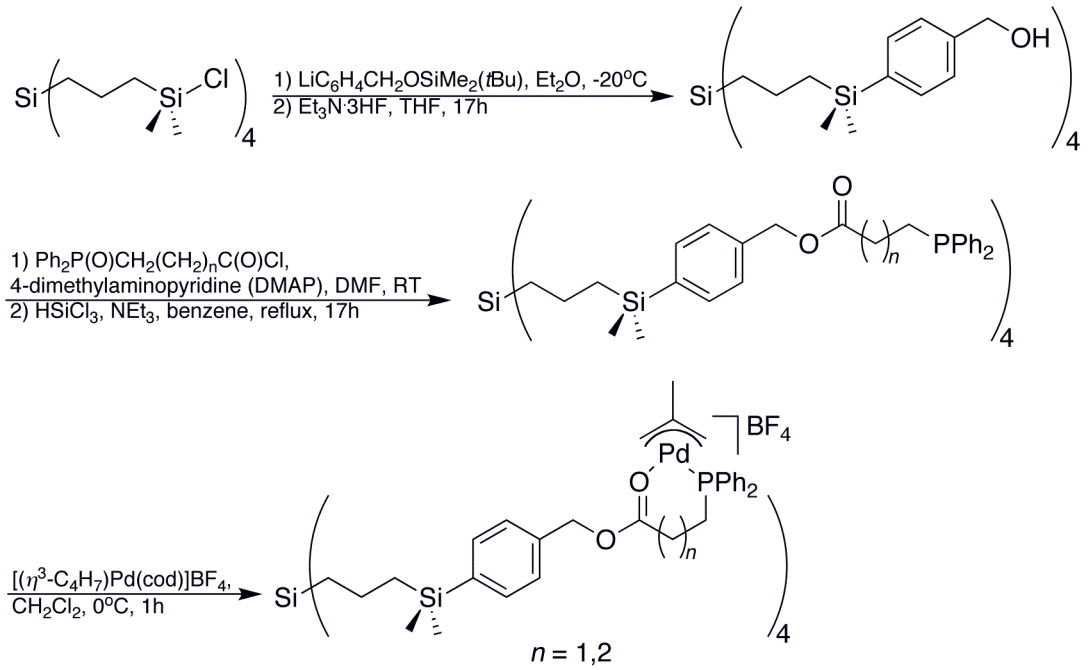
### 1.2.2.2 Hydrovinylation

Carbosilane dendrimers with phosphine palladium complexes at the periphery were also tested in hydrovinylation processes. Van Koten's and Vogt's groups described the synthesis of monomeric and dendrimeric carbosilanes functionalized with various ω-(diphenylphosphino) carboxylic acid ester end-groups (Reaction Scheme 3).[40] The palladium complexes of these ligands were successfully applied in the palladium-catalyzed hydrovinylation of styrene. The monomeric model compounds showed higher activity than the corresponding $G_0$ dendrimer catalysts and became more active with increasing Pd-P,O ring size. However, while almost complete isomerization occurred in the batch-wise processes, when hydrovinylation reactions with dendrimer complexes were carried out in a continuously operated nanofiltration membrane reactor with $G_0$-$Pd_4$ catalyst, hardly any isomerization or formation of other side products were observed. This can be ascribed to the shorter contact times between the catalyst, reagents and products in the continuous set up.

In addition to the easy separation when using dendrimer catalysts, this decreased amount of isomerized product in the product stream is an important advantage over the non-supported or batch-wise reactions. However, as the $G_0$-$Pd_4$ catalyst showed only modest retention in the membrane reactor, a loss of catalytic species during the reaction occurred, resulting in lower catalysts concentrations and corresponding lower conversions. In addition, formation of palladium black, which was observed on the membrane surface, probably accelerated the decrease in catalyst activity. Consequently, higher generations of these dendrimer catalysts were prepared and tested in order to overcome the low retention of $G_0$-$Pd_4$.[41] As expected, the retention of dendrimer catalyst increased when going from the zeroth to the first generation, but the time dependent product formation resembled the one found for the $G_0$ catalyst.

Furthermore, although the selectivity of the hydrovinylation reaction also increased, deactivation of the dendrimer catalysts was again observed. This deactivation was ascribed to easier double or multiple phosphine complexation to the palladium, probably due to the increased proximity of neighboring phosphino end-groups resulting from the flexibility of dendrimer arms. Formation of these diphosphine complexes leads to a lack of free (available) ligand in the catalytic solution, which results in the formation of palladium black and thereby catalyst deactivation. NMR studies suggested that deactivation of the dendrimer palladium catalysts took place during the catalysis, since freshly prepared solutions contained only pure monophosphine complexes. Since the deactivation process is similar in both batch and

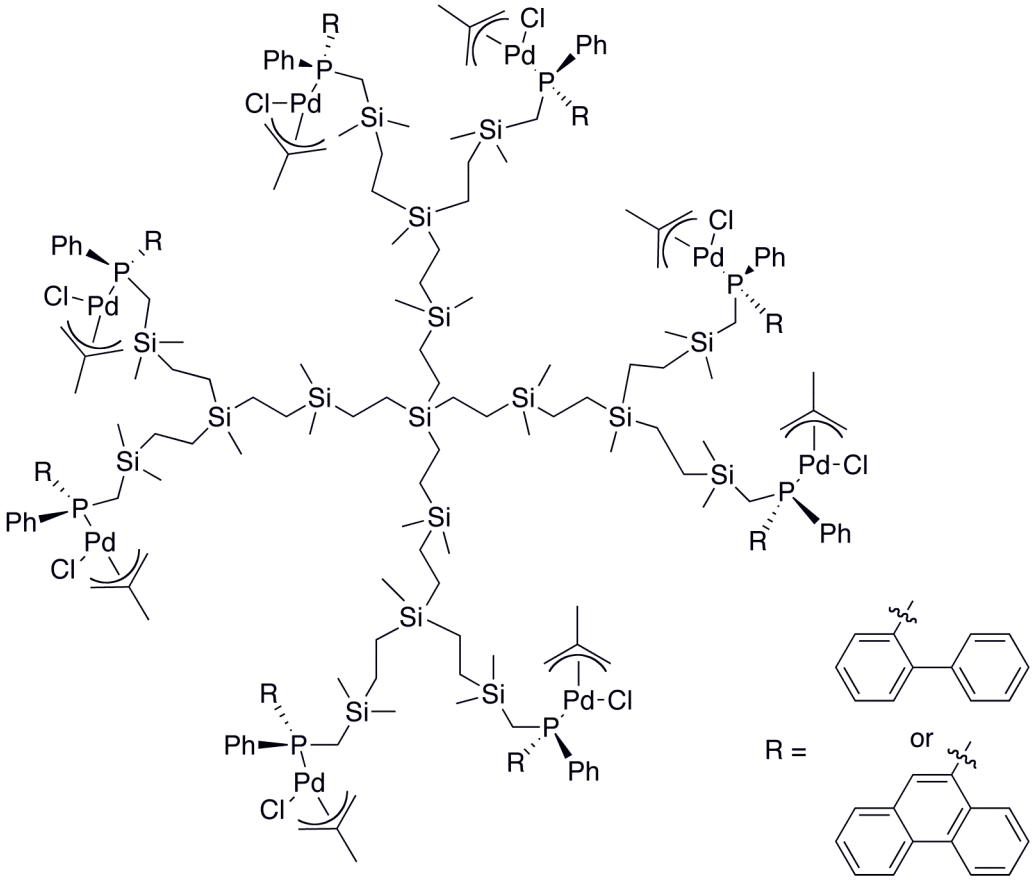
continuous processes, but different total turnover numbers are reached, it can be excluded that deactivation is correlated to the amount of converted styrene or to the amount of passed solvent.[41]




(3)

Rossell et al. synthesized palladium-functionalized carbosilane dendrimers of up to the third generation with peripheral P-stereogenic monophosphines **3**.[42] These dendrimer catalysts were formed by a reaction of dinuclear $[Pd(\mu\text{-}Cl)(\eta^3\text{-}2\text{-}MeC_3H_4)]_2$ with carbosilane dendrimers having chiral monophosphines (with either 2-biphenylyl or 9-phenanthryl substituents) at their periphery, thereby grafting the dendrimer surface with $[PdCl(\eta^3\text{-}2\text{-}MeC_3H_4)]$ units. The activity of these catalysts was tested in the asymmetric hydrovinylation of styrene to give 3-aryl-1-butenes and related derivatives, and compared to those of two chiral, monomeric model compounds. It was found that activity, product selectivity, and enantiomeric excesses (ee) depended strongly on both the nature of the phosphine and the halide abstractor used. For the first generation dendrimer carrying 2-biphenylylphosphine ligands, the best results were obtained by using Na[BArF] (BArF = $\{B[3,5\text{-}(CF_3)_2C_6H_3]_4\}^-$) as activator instead of $AgBF_4$. The best results in terms of ee (79% towards the S-isomer) were obtained with the third generation dendrimer-palladium catalyst. Furthermore, all generations of dendrimer catalysts with 9-phenanthryl substituents (activated with $AgBF_4$) were extremely active but did not induce any enantioselectivity. Surprisingly, the second generation of this dendrimer catalyst, when activated with Na[BArF], yielded mainly the (R)-

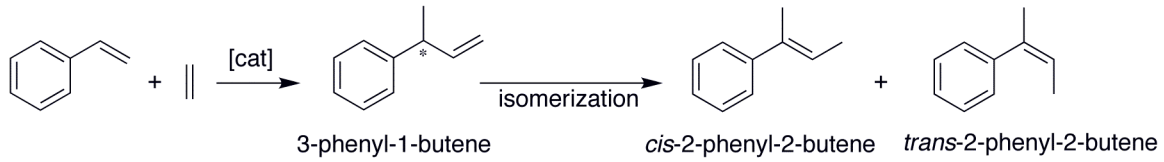
3-phenyl-1-butene isomer, in contrast to the first generation which mainly produced the (S)-3-phenyl-1-butene, similar to all other dendrimer systems studied. When, in the case of dendrimer catalysts with 2-biphenylylphosphine ligands, the solvent was changed from $CH_2Cl_2$ to supercritical $CO_2$, selectivities and ee values comparable to those obtained in the previous studies were observed, although the activities were somewhat lower.[43] In general, no clear dendrimer effect was observed for these systems. The hydrovinylation reactions were performed in autoclaves, not membrane reactors, so that no conclusions about the retention of dendrimer catalysts could be provided.




**3**

In 2002, the group of Benito and Rossell used the same ligand system as Van Leeuwen and his coworkers, with diphenylphosphino-terminated carbosilane dendrimers containing one or two $PPh_2$ groups per dendrimeric arm (see Reaction Scheme 1). These ligands were palladated and platinated and the palladium complexes were tested in the batch-wise hydrovinylation of styrene (Reaction Scheme 4).[44] Comparable monomeric systems were also synthesized, in which one or two phosphine groups were present per end-group. The activity of the dendrimer catalysts appeared to be lower than that of the monomeric analogues and the

polynuclear complexes containing four or eight catalytic end-groups were more active than the dendrimer catalysts of Van Koten/Vogt containing eight or twelve terminal bidentate P,O-coordinating atoms at the periphery.[41] Moreover, a good selectivity towards 3-phenyl-1-butene was observed.

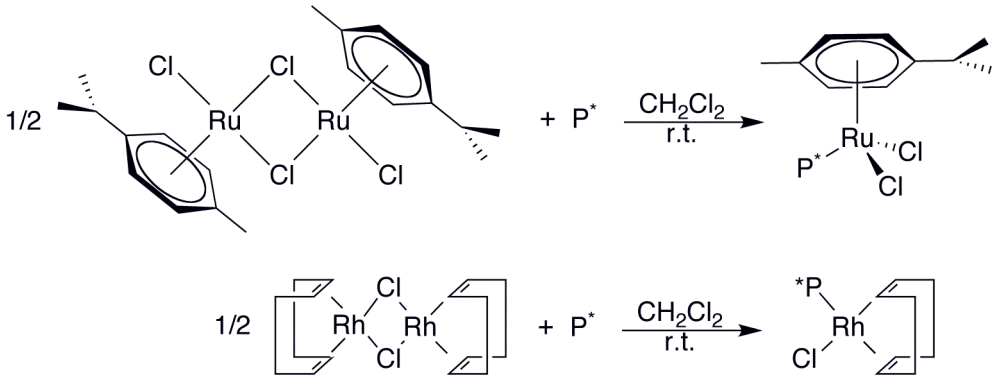



(4)

### 1.2.2.3 Hydrogenation and transfer hydrogenation

Recently, rhodium and ruthenium catalysts with carbosilane dendrimers containing P-stereogenic monophosphine ligands prepared by Rossell et al., were used in hydrogenation reactions.[45] The same ligand system was also used in the hydrovinylation reaction, but for this purpose it was metallated with rhodium or ruthenium using either [RhCl(cod)] (cod = cyclooctadiene) or [$RuCl_2$(p-cymene)], respectively (see Reaction scheme 5 where $P^*$ = carbosilane dendrimer, as depicted in Reaction Scheme 3, functionalized with (S)-$CH_2$PPh(2-biphenylyl). The rhodium complexes were tested in the hydrogenation of dimethyl itaconate and the relationship between the size/generation and its catalytic properties was investigated. Going from the model compound to the first generation dendrimer the activity decreased, probably due to the decreased accessibility of the metal centers in the dendrimer species. The ee value was zero in all cases.

The ruthenium complexes were tested in the transfer hydrogenation of acetophenone. A positive dendrimer effect was observed, since the zeroth generation dendrimers were slightly more active than the model compounds, although the enantiomeric excesses were low and appeared to be hard to reproduce.

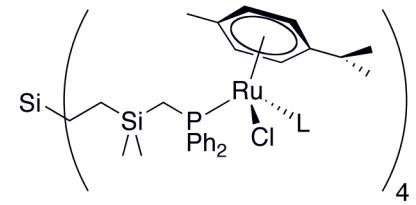



(5)

In 2003, the same group reported on the synthesis of neutral and cationic diphenylphosphino rhodium- and iridium-containing dendrimers up to the second generation.[46] The dendrimer ligands contained one or two diphenylphosphino groups per dendrimer arm and were reacted with $[MCl(cod)]_2$ (M = Rh, Ir) to form neutral or cationic catalytic species. The products were tested as catalysts in the hydrogenation of 1-hexene and the results obtained with the neutral dendrimer rhodium(I) were compared to those obtained with mononuclear and dinuclear rhodium complexes, showing a higher activity for the dendrimer catalysts. However, there was also a slight decrease in turnover frequency for the higher generations of dendrimer species. The cationic rhodium(I) metallodendrimer was less active than the cationic monomeric analogue, but it showed higher activity than the neutral species of the same generation. The first generation iridium(I) metallodendrimer showed comparable results to those of the rhodium one. However, these results were irreproducible, which was attributed to the low solubility of iridium(I) dendrimers under the reaction conditions applied.

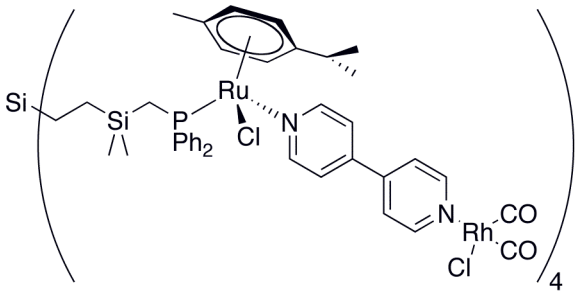
Dendrimer catalysts bearing phosphine ligands on the periphery, synthesized by the groups of Van Leeuwen and Rossell (see Reaction Scheme 1), were also tested in the transfer hydrogenation reactions, e.g. reduction of cyclohexanone to cyclohexanol.[47] 'Single' and 'double' metallic-layered dendrimers containing ruthenium complexes were prepared from diphenylphosphino ligands (see structures **4** and **5**) where in the double layered dendrimers one metal site functioned as a branching point. In preliminary catalytic studies with mononuclear ruthenium complexes an increase in activity was observed when the reaction was performed in refluxing propan-2-ol compared to the reaction at room temperature. It also appeared that neutral complexes were more active than the corresponding cationic ones. Under the same conditions, the single-layered dendrimer complexes showed lower activities

than the mononuclear analogues, pointing to a negative dendrimer effect. Furthermore, among the first generation compounds, the neutral compounds were more active than the corresponding cationic analogues, following the same trend that was found for the mononuclear complexes. The double metallic-layered dendrimers were unstable and could not be tested.




L = py, 4-CNpy, 4,4'-bipy

**4**

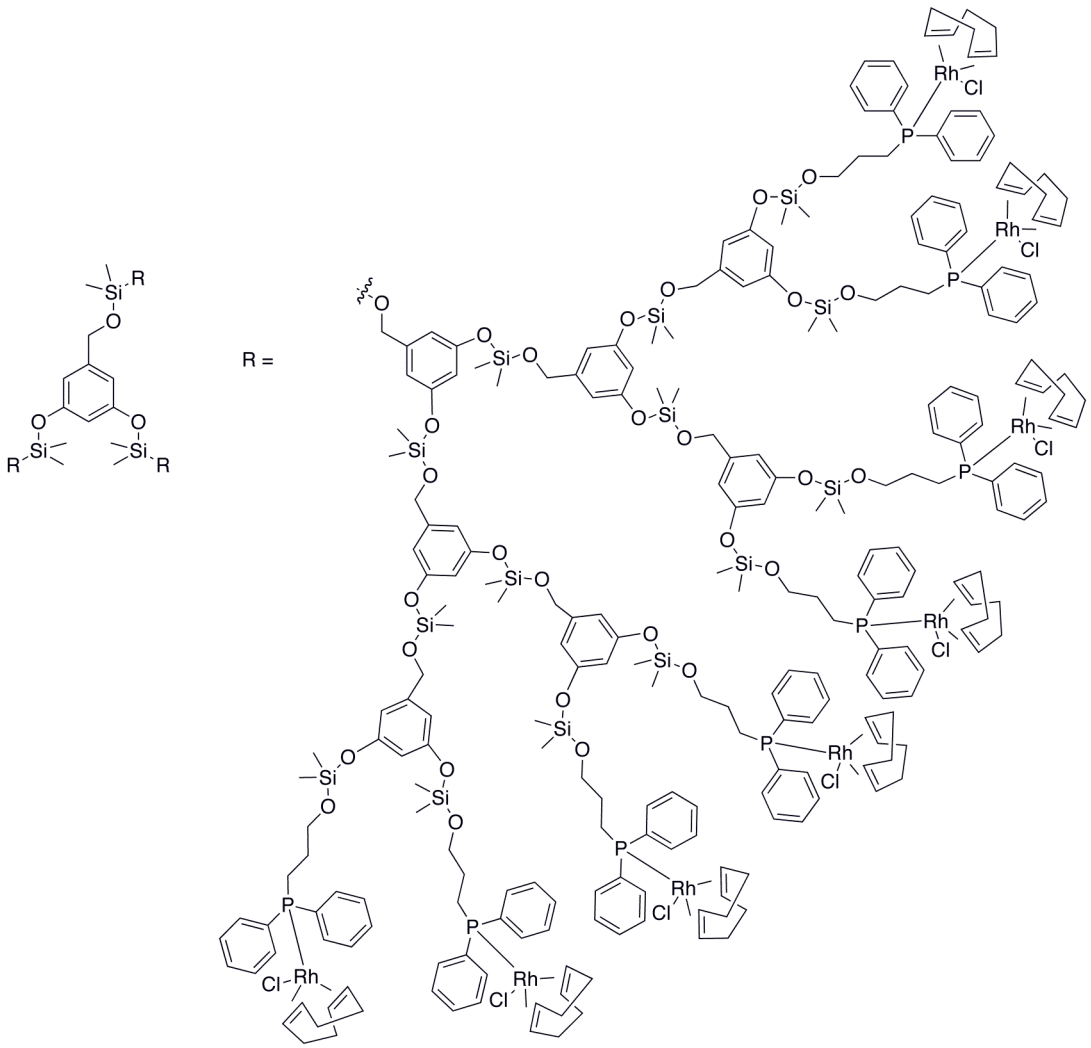



**5**

A different system was developed by Kakkar and co-workers, who synthesized a dendrimer with a dimethylsilyl-linked 3,5-dihydroxybenzyl alcohol scaffold, containing diphenylphosphino end-groups.[48] By reaction with [RhCl(cod)], catalytic species **6** was obtained that appeared to be active in the hydrogenation of 1-decene. The catalytic activity was found to be slightly dependent on the dendrimer generation and reaction time, giving higher activity for higher generation, i.e. showing a positive dendrimer effect.[48,49] All dendrimer catalysts showed an increasing activity with time. In addition, while with the first generation dendrimer nearly full conversion was reached after 5 hours, the same was achieved with the third generation already after 2 hours. However, it should be noted that the number of Rh(I) centers at the periphery of metallodendrimers increases with increasing generation, and therefore causes the higher turnover frequencies (TOFs) per dendrimer catalyst, not per single Rh-center. Furthermore, when these results were compared with those obtained for Rh(I)-supported tri(alkyl)phosphine dendrimers which were prepared earlier[50] and in which the catalytic sites were distributed throughout the dendrimer scaffold, higher TOFs were observed for metallodendrimers with peripherally-supported catalytic sites. These differences can be explained by both steric factors (diphenylphosphine ligands are shielding the Rh-center more than trialkylphosphine ligands) and differences in electronic density at the metal centers.

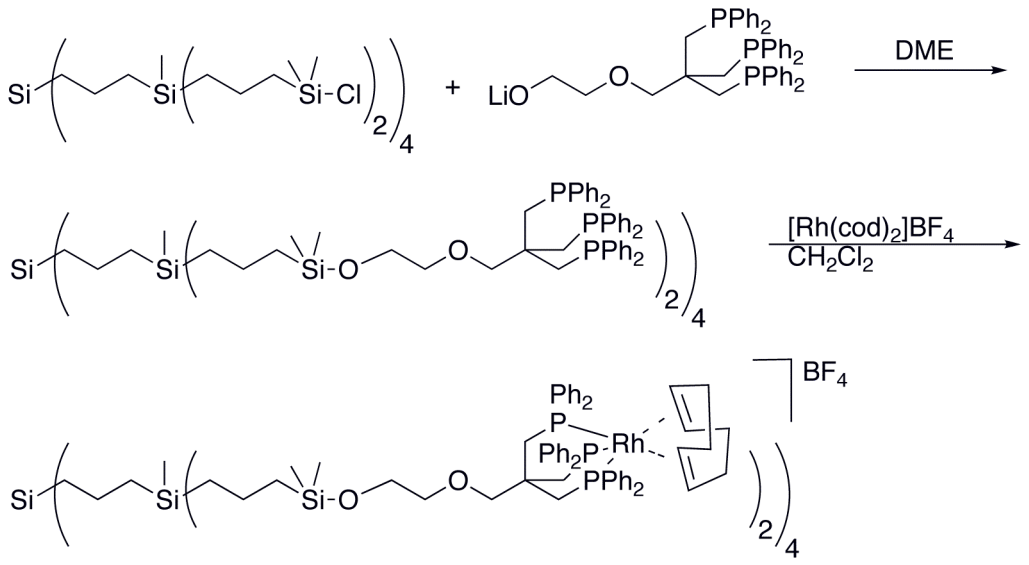
Recovery of metallodendrimer catalysts and their suitability for recycling were also investigated. It was found that recycled catalysts retained their efficiency and, surprisingly, an increase in activity was observed upon recycling.[49] In addition to this, it was also found that

during the dendrimer synthesis, the use of uncontrolled reaction conditions (i.e. a multi-step (2-, 4- or 6-step procedures) reaction without dropwise addition or control of temperature) led to the formation of hyperbranched carbosilane polymers.[48] These polymers were also tested in hydrogenation of 1-decene, giving good conversion rates, with reaction times as low as 0.5 h for the 2- and 4-step hyperbranched polymers.[49] In the case of the 6-step hyperbranched polymer, the catalytic activity increased gradually during the catalysis, as in the case of the metallodendrimers. This difference in behavior was explained by suggesting that the large 6-step hyperbranched polymer was almost a single species organometallic dendrimer, since its MALDI-TOF spectrum showed only one extremely dominant peak (in contrast to the lower generation hyperbranched polymers that consisted of mixtures of organometallic macromolecules present in equal amounts). As a consequence, it behaved more like a typical metallodendrimer catalysts.[49]




**6**

Findeis and Gade synthesized mononuclear model compounds and the corresponding dendrimers with tripodal trisphosphine ligands at their peripheries, which were then transformed into the corresponding rhodium complexes (Reaction Scheme 6).[51] Mononuclear molybdenum complexes were also prepared, but these were not tested as catalysts. In contrast to the dendrimers described earlier, these tripodal trisphosphine ligands were first connected to a tether moiety, forming a ligand-tether combination, which was then connected to the periphery of the dendrimer scaffold and subsequently metallated using $[Rh(cod)_2]BF_4$. The catalytic properties of these metallodendrimers in hydrogenation of styrene and 1-hexene were the same as those of the monomeric catalysts. However, since the catalysts were connected to the dendrimer scaffold, they were robust enough to withstand several sequential recycling steps. This robustness also allowed a complete analysis of these dendrimer catalysts, which confirmed their uniformity (i.e., low polydispersity).

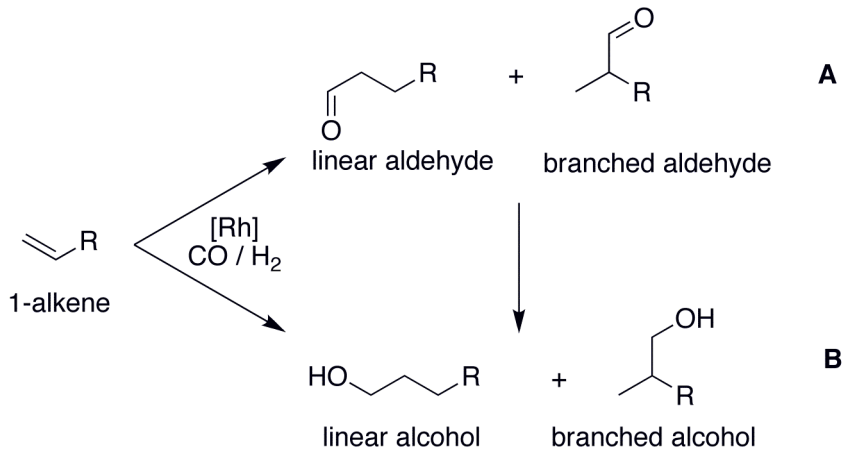



(6)

### 1.2.2.4 Hydroformylation and hydrocarbonylation

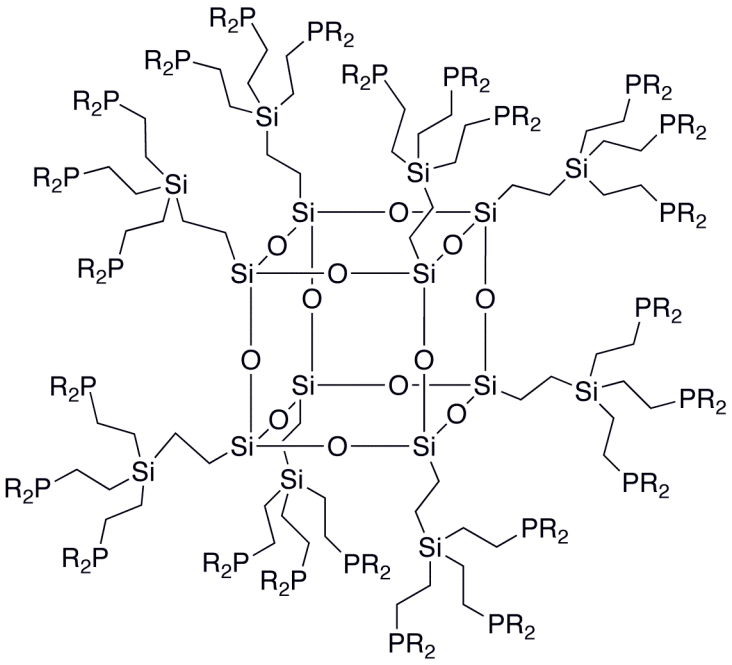
The diphenylphosphino-functionalized carbosilane dendrimers of Reaction Scheme 1, were also applied as catalysts in hydroformylation reactions by both Van Leeuwen and Cole-Hamilton et al.[28-31,35] Van Leeuwen investigated dendrimers comprising silicon atoms at the core and branching points, and ethanediyl- or propane-1,3-diyl- spacers, which were functionalized with diphenylphosphino end-groups at the periphery. These ligands were metallated with $[Rh(acac)(CO)_2]$ and the resulting dendrimer-phosphino rhodium complexes were tested in the hydroformylation of 1-octene (A) and hydrocarbonylation of 1-alkenes (B) in Recation Scheme 7.[35,52] These dendrimer catalysts showed the same selectivity as the

mononuclear analogues, however, their activity depended on their size and flexibility. Those with more flexible $C_3$-spaces in the backbone generally gave higher conversions than the more compact ones containing the $C_2$-spacers. Furthermore, the $C_3$-dendrimer monophosphine rhodium catalysts showed a decrease in activity with increasing dendrimer generation. The difference between the catalysts derived from the dendrimers with monodentate and bidentate end-groups was apparent, since the latter gave slower reactions. A similar difference was also observed for the mononuclear rhodium parent compounds. In all cases similar proportions of linear-to-branched products (7:3) were obtained.




(7)

Cole-Hamilton et al. described the synthesis of diphenyl- and dialkyl-phosphino-containing carbosilane dendrimers based on a polyhedral silsesquioxane core, with up to 48 phosphino end-groups (**7**).[28-32] The first and the second generation diphenyl- and diethyl-phosphino-containing dendrimers were successfully applied as ligands for the synthesis of metallodendrimer rhodium catalysts which were then tested in hydroformylation and hydrocarbonylation reactions of 1-octene. In the hydroformylation reaction, the use of the first and the second generation diphenylphosphino dendrimer ligands resulted in high linear-to-branched ratios (up to 14:1). However, on changing from the first to the second generation ligand a drop in reaction rate by a factor of 2 was noted, probably due to increased steric hindrance at the periphery of the more bulky second generation ligand.




**7**

In the hydrocarbonylation reactions of alkenes (hex-1-ene, oct-1-ene, non-1-ene, prop-1en-2-ol (Reaction Scheme 7, *vide supra*), the linear-to-branched ratios of the resulting products were slightly higher (3.1:1) with the dendrimer ligands than with free triethylphosphine (2.4:1).[29,32] Depending on the nature of the phosphine end-groups and the complexity of the dendrimer scaffold, differently functionalized dendrimers showed different properties during the catalytic experiments. For example, hexyl and ethyl functionalized phosphines (compared to methyl phosphines) and longer alkanediyl spacers between the branching points in the dendrimer scaffold gave higher solubilities and therefore more homogeneous systems. The generation of the dendrimers did not seem to affect the selectivity of the hydroformylation reaction. However, the branching pattern did show a large influence on the reaction rate, in a way that the amount of peripheral functional groups and the length of the bridges between the phosphines in the dendrimers appeared to be the determining factors for the reactivity of the corresponding rhodium catalysts.

### *1.2.3 Synthesis and structural aspects of non-phosphine-based dendrimer catalysts*

In addition to carbosilane dendrimers with phosphine ligands, the synthesis and reactivity of many other dendrimer systems functionalized with ligands with different donor atoms, e.g. nitrogen containing ligands, have been investigated. The first prepared and tested

metallodendrimer catalyst was reported by Van Koten et al. in 1994.[12] This system contained the so-called NCN-pincer metal catalysts connected to the periphery of a carbosilane dendrimer via spacer moieties. The ATRA (atom-transfer radical addition) catalysis, such as mononuclear [NiX(NCN)] for addition of $CCl_4$ to activated alkenes had been developed earlier by the Van Koten group[12,53,54] and was found to function equally well on the dendrimer scaffold. Following this report, many other metallodendrimer catalysts containing multiple catalytic sites at the periphery of carbosilane as well as non-carbosilane dendrimers have been described.[1-11]

In general, two approaches to the introduction of catalytic metal-ligands are known. They follow strategies similar to those described earlier for the introduction of phosphine-based ligands to a carbosilane dendrimer scaffold. According to one approach, the metal can be introduced at the end of the synthesis of the carbosilane poly-ligand scaffold, which requires novel ways for polyfunctionalization of the carbosilane dendrimer periphery since many of these donor atoms have weaker coordination power than the phosphorus-donor atom in a triorganophosphine. In the other approach, the metal-ligand unit can be synthesized before connecting the complex to the periphery of the dendrimer, which has the advantage that the most sensitive step in the synthesis can be carried out separately from the synthesis of the dendrimer support which allows working with pure metal-ligand units.

As with the chemistry of phosphine-based ligands, metal-ligand units have been either put onto the periphery of dendrimers or modified by attachment of one or various dendrons to the ligand(s) of the metal-ligand complex. For example, cyclopentadienyl ring(s) of metallocenes or half-sandwich complexes have been functionalized with dendrons,[55] resulting in the formation of dendritic catalysts that are functionalized either at the dendrimer core or at the focal point of the dendrons (see for example structures **10** A and B). The post-synthesis modification of the focal point of a dendron allows for incorporation of more reactive cores, which can be useful for the chemistry of both dendrimers and hyperbranched polymers.[55] Furthermore, when a dendron is attached to a well-known ligand system, the stability of the catalyst can be increased, making the catalyst more robust towards water and air.

In most cases, dendrimers are used as supports for catalytic species themselves. However, examples are also known in which the periphery of a dendrimer is functionalized with anionic cocatalytic species, such as $-[B(C_6F_5)_3]^-$ units, which during catalysis are applied as

counteranions of actual cationic catalytic species (see Structure **9**).[56] Another possibility is attachment of species that function as initiators, e.g. in radical or atom transfer radical (ATR) polymerization reactions, which in certain cases can lead to the formation of multi-arm starpolymers.[57-61]

### *1.2.4 Catalytic reactivity of non-phosphine-based dendrimer catalysts*

Various non-phosphine-based metallodendrimer systems described above have been applied as catalysts in a variety of different reactions. In this section, the activity of these systems is described and compared to their mononuclear analogues.

#### 1.2.4.1 Aldol condensation

The catalytic activity of metal complexes of the so-called ECE-pincer ligands (ECE = $[C_6H_3(CH_2E)_2\text{-}2,6]^-$ where E = $NR_2$, $PR_2$, $AsR_2$, OR, SR) has been explored intensively.[20,62-65] The first example in which twelve NCN-pincer Ni halide moieties were connected via linkers to a carbosilane dendrimer scaffold[12] and tested as a catalyst in a Kharasch addition reaction involving atom-transfer radical addition (ATRA) was described in 1994. Moreover, it was also shown that the resulting metallodendrimer had a suitable size for use in a membrane reactor. Later, NCN-pincer palladium halide units were connected directly, without a linker, to hyperbranched-polycarbosilane supports (see Figure 3) and tested in the aldol condensation of benzaldehyde and methyl isocyanoacetate as a model reaction.[66] The activities observed were comparable to those of the analogous single-site palladium catalyst, while the size of the structures allowed their purification by dialysis to obtain metallodendritic polymer with a low enough polydispersity to allow its application in a continuous membrane reactor.

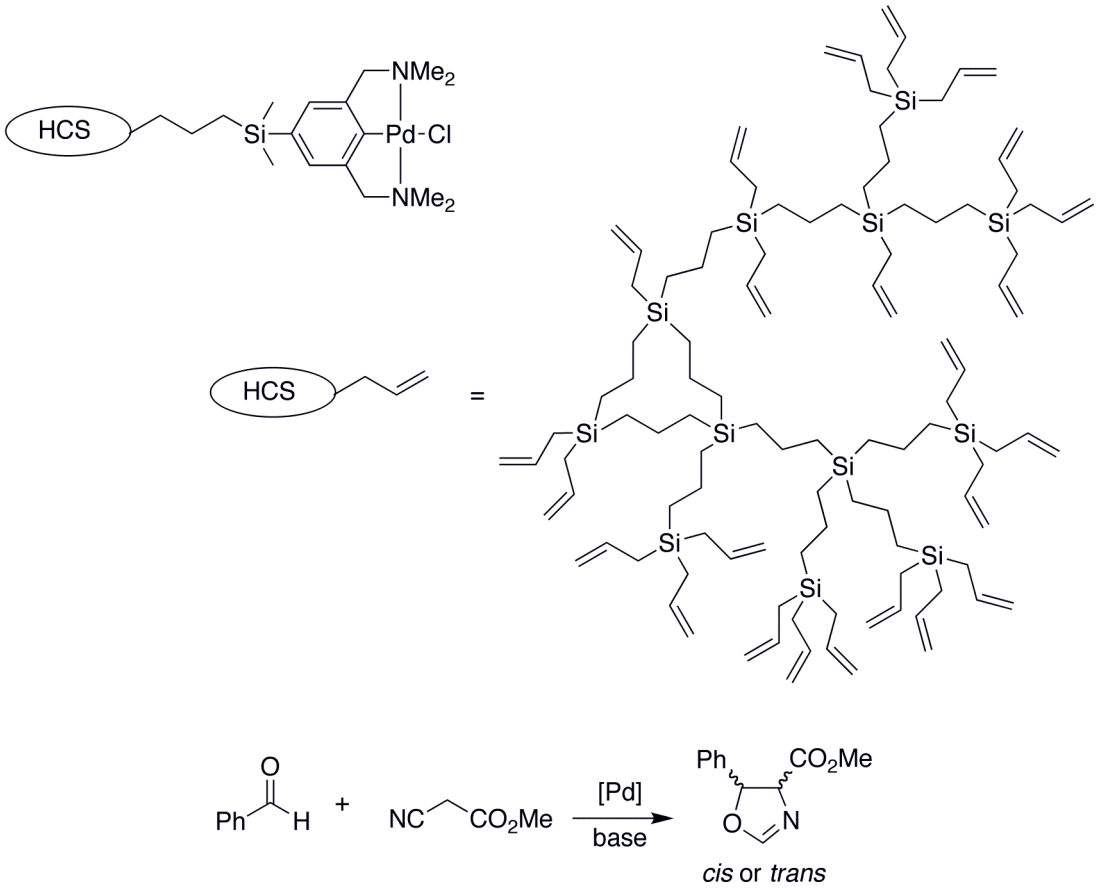



**Figure 3:** One of Van Koten/Frey metallodendrimer catalysts in which the metal catalyst is connected to a hyperbranched carbosilane dendritic scaffold and used for aldol condensation of benzaldehyde and methyl isocyanoacetate.[66]

In 2001, the same group reported on the synthesis of macrocyclic structures in which a dendrimer scaffold was functionalized with monoanionic C,N-chelating ligands.[67] On palladation of these ligands the formation of dimeric structures occurred which in the case of the first and second generation dendrimers led to the formation of several stereoisomers. These could originate from dimer formation between [CN-PdCl] complexes of different branches, sections or wedges (intramolecular), or even different dendrimers (intermolecular) (see Figure 4).

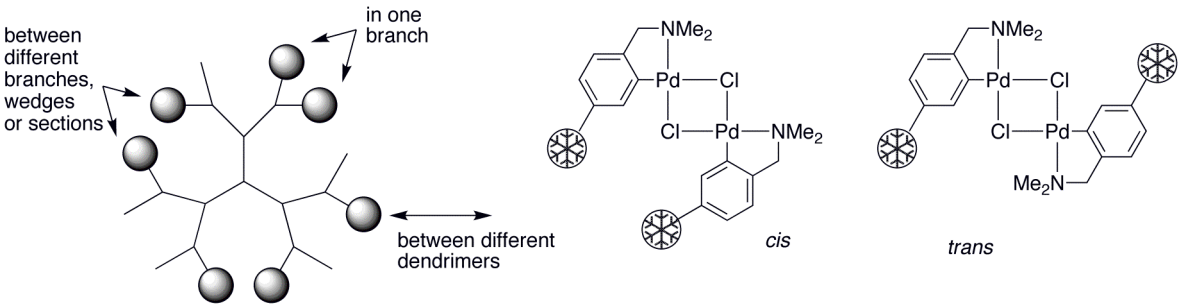


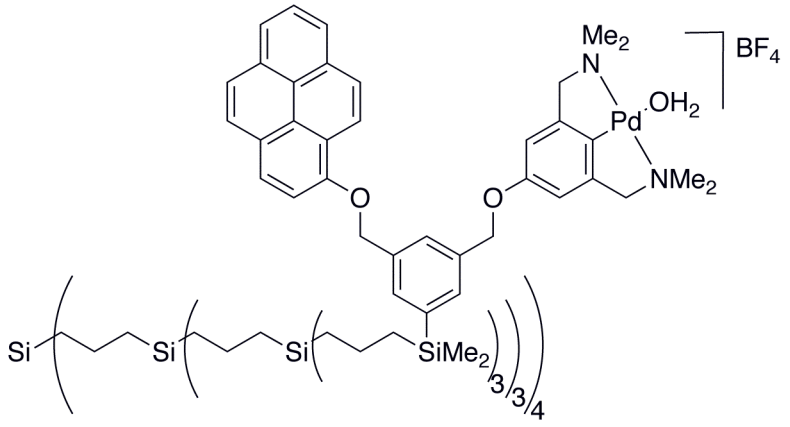

**Figure 4:** Schematic representation of the formation of stereoisomeric dendrimer dimmers in cyclopalladated CN-derivatized carbosilane dendrimers.[67]

Upon addition of pyridine, the single-site, mononuclear pyridine adducts of these macromolecular constructs were formed and used as catalysts for the aldol condensation of benzaldehyde and methyl isocyanoacetate. Abstraction of the halide anion yielded the polycationic analogues, which were used in subsequent catalytic experiments without palladium black formation. This indicated an increased stability of the polycationic palladium-dendrimer species as compared to the mononuclear palladium complexes. It was also observed that a metallodendrimer system which had a more rigid skeleton or a higher degree of peripheral crowding was less active in the aldol condensation reaction, also causing a slight change in the cis/trans ratio of the oxazoline product.

In addition to these, other mononuclear and dendrimer systems with cage-like structures were also prepared.[68] In these structures, the catalytic NCN-pincer palladium complexes were encapsulated within carbodiazasilane cages, forming mononuclear macrocycles. These cages could be connected to each other via a central core molecule, yielding a multicage dendrimer structure containing three macrocycles. Interestingly, in the same catalytic aldol condensation reaction, the dendrimer (multicage) cationic derivative appeared to be more active than the mononuclear analogues.

Pyrenoxy-based NCN-pincer palladium molecular tweezers were attached to carbosilane dendrimers of up to the second generation (see Structure **8**).[69] Aldol condensation reactions between methylisocyanoacetate and aromatic aldehydes, catalyzed by the monomeric pincer palladium species with and without pyrenoxy ligands and the metallodendrimers were compared. For the monomeric series it was found that the presence of pyrenoxy groups in the catalyst increased initial reaction rates by a factor of two. One of the reasons for this could be that pyrenoxy groups stabilize one or more of the transition states or intermediates in the

catalytic cycle. On the other hand, dendrimer catalysts caused a dramatic fourfold drop in the reaction rate compared to the monomeric analogue, probably due to steric crowding, which makes the catalytic sites less accessible. However, the *cis/trans* ratio of the resulting products was not dependent on the nature of the catalyst used. Although these metallodendrimers are large enough to be used in the continuous processes, no details on this aspect have been reported.



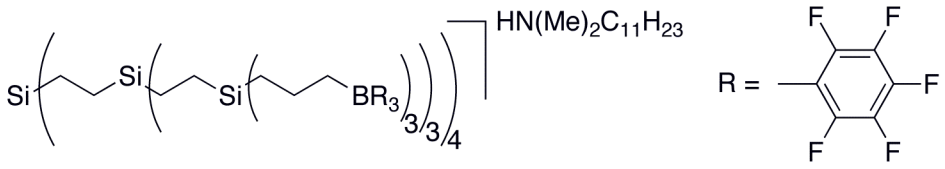

**8**

### 1.2.4.2 Polymerization

The metallocene-catalyzed polymerization of α-olefins allows production of polymers with new architectures and properties. The active species during this catalysis is cationic metallocene stabilized by a non-coordinating anion. This contact ion pair is formed by treating the neutral metallocene with an activating cocatalyst, such as methyl aluminoxane (MAO) or perfluorophenylborane, $B(C_6F_5)_3$. In most cases, the metallocene (in the catalytic site) is connected to the supporting dendrimer. However, Mager et al. described a study of the polymerization properties of metallocene-cation-anion pairs in which the anions were embedded in an extremely sterically crowded environment by using a carbosilane dendrimer's periphery.[56] The resulting steric hindrance led to weaker coordination of the anions that were less nucleophilic thus leading to their increased stability. This made the system suitable for use even in cases of very sterically demanding ion pairs.

Polyanionic carbosilane dendrimers functionalized with $-[B(C_6F_5)_3]^-$ groups on their periphery up to the second generation were also synthesized (see Structure **9**). The stable ammonium salts of these dendrimers were tested in olefin polymerization with various zirconocene catalysts and they all showed high activities. Other advantages of these systems are their high

stability during polymerization (no decrease in activity was observed) and the possibility to use aliphatic solvents such as hexane.

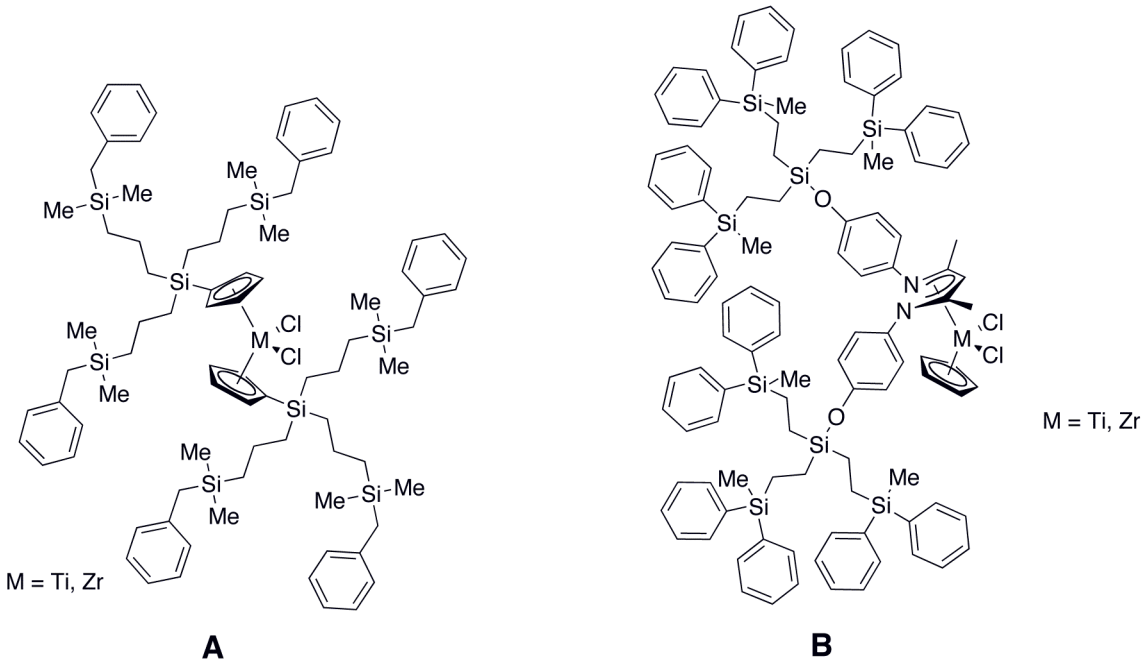



**9**

The De Jésus group described several dendrimer-catalyst systems that were active in the polymerization of α-olefins. The difference between these systems and those described above was in the way the dendrimer scaffold was connected to the catalytic center, which either involved the focal point of a dendron, or the periphery of the dendrimer. The system described by Andrés et al., contained organometallic complexes at the focal point of a dendron,[55,70,71] for example, the first generation carbosilane dendrons (with $C_3$-linkers) with cyclopentadiene groups at focal points. Subsequent reaction of potassium hydride with these Cp groups yielded the cyclopentadienyl salt that upon reaction with $TiCl_4$ or $ZrCl_4$·2THF in toluene afforded the corresponding metallocene dendrimer **10A**.[55] These metallocene dendrimers were activated with MAO and tested in the polymerization of both ethylene and propylene. Compared to the simple metallocene catalyst [$MCp_2$], the activity of the titanium Cp-dendron catalyst was lower by one order in the polymerization of ethylene, whereas the corresponding zirconium catalyst showed no decrease in activity. Comparable results were obtained earlier for carbosilanes with $C_2$ linkers, although for these systems a decrease in activity of about 30% was observed for the zirconocene compound.[71]

The dendrimer metallocene zirconium catalysts were also used for propylene polymerization where their activity was found to be comparable to that of the monomeric analogue. The second and the third generation catalysts could not be synthesized, probably because of steric issues or because appropriate reaction conditions were not found.[55] In another study, a β-diketiminato ligand was chosen as the focal point of dendrons[70] and the reaction of dendritic (and non-dendritic) β-diketimines with half-sandwiched titanium and zirconium complexes ($\eta^5$-$CpMCl_3$) in the presence of triethylamine as Lewis acid yielded mixed cyclopentadienyl(β-diketiminato)metal complexes **10B**. Both non-dendritic and dendritic complexes were activated with MAO and applied in ethylene polymerization experiments where the metallodendrimer catalysts showed a slightly increased activity compared to their

non-dendritic analogues. Nevertheless, their performance was still far from that of the well-established metallocene complexes ($\eta^5$-$Cp_2MCl_2$; M = Ti, Zr).[55,71]

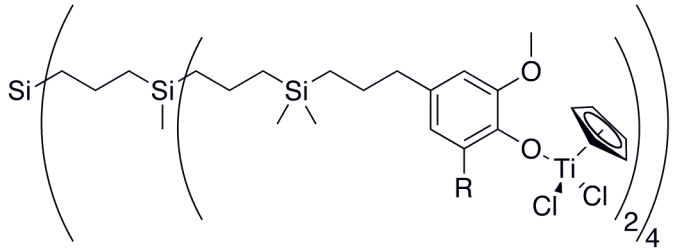



**10**

Arévalo et al. reported on carbosilane dendrimers with monometallic cyclopentadienyl-aryloxy metal complexes at their periphery.[72,73] Various titanium and zirconium derivatives of 4-allyl-2-methoxyphenol or 4-allyl-2,6-dimethoxyphenol precursors **11**, were synthesized and tested in the polymerization of ethylene. In addition to dendrimers in which [-$OTiCl_2Cp$] groups were placed para to the aliphatic (dendrimer) substituent, systems with the same groups positioned ortho to the aliphatic chain were also prepared. However, the catalytic activity of these complexes was found to be very low or negligible after activation with MAO. In general, systems having OMe group(s) ortho to the [-$OTiCl_2Cp$] group yielded high molecular weight polyethylene with low polydispersity. Probably the proximity of ortho-OMe groups allows for additional electronic stabilization of active species, resulting in a higher propagation rate. The use of either monometallic or metallodendrimer catalysts did not affect the polymerization activity, but metallodendrimer catalysts yielded polymers with higher crystallinity.

Furthermore, a difference in activity was observed between fresh and aged toluene solutions of the dendrimer titanium complexes. When activated with MAO, the fresh solutions behaved as moderately active systems, while the aged ones were very active. It was suggested that this

could be ascribed to the occurrence of dendrimer aggregation processes. The aggregates showed high hydrodynamic volumes and low polydispersities, which was confirmed by the relaxation times distribution that showed only one dynamic process with a narrow distribution. When peripheral [$TiCl_2Cp$] units were replaced with [$TiCl_2Cp^*$] or [$MClCp_2$] (M = Ti, Zr) groups or when 2-allyl-6-methylphenol was incorporated as a ligand (yielding complexes with peripheral units ortho to the aliphatic chain) no aggregation of the resulting metallodendrimer was observed on solution aging. These results show that steric and/or electronic effects induced by different ligands or organometallic units can have a large effect on the synthesis and catalytic activity of the resulting metallodendrimeric catalysts.

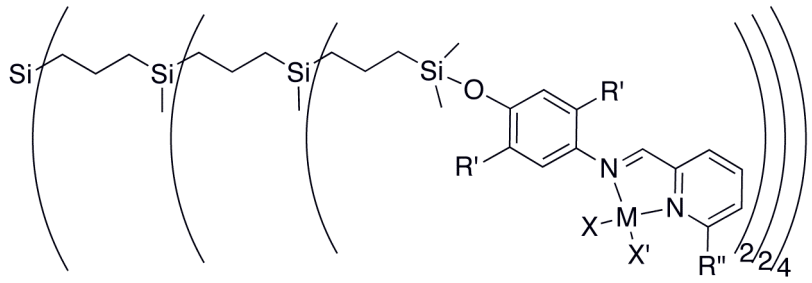



R = OMe, H

**11**

Benito et al. synthesized a series of monomeric complexes and dendrimers with peripheral N,N'-iminopyridine chelating ligands, **12**.[74-76] Neutral and cationic palladium derivatives of these dendrimer ligands were prepared and the cationic complexes were tested in copolymerization reactions.[74] The cationic palladium compounds were found to be active catalysts for the alternating syndiospecific copolymerization of CO and 4-tert-butylstyrene, producing mainly syndiotactic polyketones due to a chain-end-controlled mechanism. Changing the ligand by adding methyl substituents to the aryl ring increased activity of the palladium catalysts, whereas addition of a methyl group ortho to the coordinating N-atom of the pyridine ring deactivated the catalyst completely by steric hindrance. In contrast to other dendrimer catalysts, the presence of a dendrimer support appeared hardly relevant in terms of the stability of catalytic species. The catalytic performance was, however, found to be dependent on the dendrimer generation, which influenced the microstructure of the copolymerization products. Higher generations showed superior activities, i.e. a positive dendrimer effect, but at the same time produced shorter and less stereoregular copolymer chains.

Nickel derivatives of the same N,N'-iminopyridine chelating dendrimer-ligand system **12**, were studied as catalysts for the polymerization of ethylene.[75,76] When activated with MAO under mild reaction conditions, these catalytic systems were active for both oligomerization and polymerization of this monomer. Their catalytic activity and selectivity depended on the ligand structure and dendrimer generation similar to the previously described palladium catalysts. Steric protection of the axial coordination sites by addition of methyl substituents to the aryl ring increased the polymerization and oligomerization activities, while a methyl group in the 6-position of the pyridine ring hindered the equatorial coordination sites and thereby reduced activities. It turned out that production of ethylene insertion products (oligomer for high generation vs. polymer for low generation), as well as the oligomer chain-length distribution, the branching density, molecular weight and polydispersity of the polymers could be regulated by selecting the dendrimer generation. Catalysts derived from higher generation dendrimers produced polyethylene polymers with lower degrees of branching but with higher molecular weights in cases where polymers were formed. In addition, they showed higher oligomerization activities. A combination of steric pressure on the growing chains and microenvironmental protection of the polymerization catalytic species by higher generation dendrimers, may explain these results.[76]

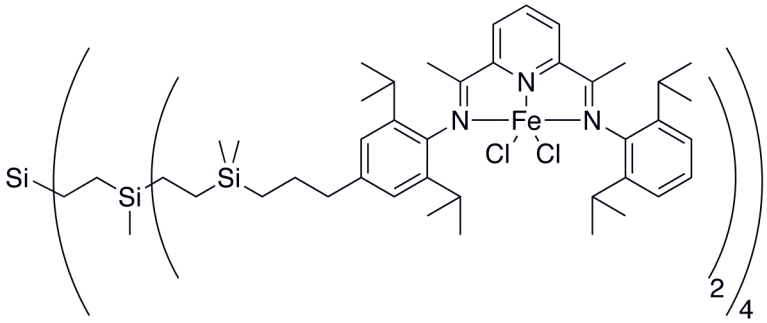



R' = H, Me
R" = H, Me
M = Pd; X = Cl, Me; X' = Cl, NCMe
M = Ni; X = Br; X' = Br

**12**

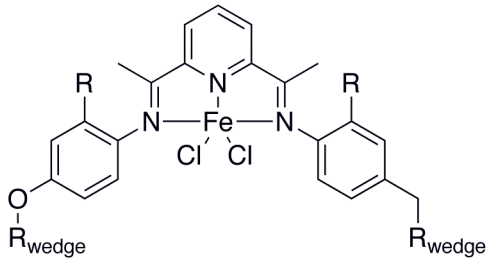
Iron containing metallodendrimer catalysts for polymerization of ethylene were synthesized and tested by Li and coworkers.[77] Metallodendrimers, containing four or eight (2,6-bis(imino)pyridyl)iron(II) dichloride end-groups were prepared starting from a Si-H terminated carbosilane dendrimer. The ligands were connected to the dendrimer periphery by hydrosilylation, followed by complexation with $FeCl_2 \cdot 4H_2O$ (**13**). After activation with modified MAO, catalysts with a low Al/Fe molar ratio (e.g. Al/Fe = 500) showed much higher activity in ethylene polymerization and produced higher molecular weight polymers

than the mononuclear analogues. However, activities of mononuclear and dendrimer catalysts were comparable for the system with a higher Al/Fe ratio (e.g. Al/Fe = 1500), although dendrimer catalysts still produced higher molecular weight polyethylenes with higher melting temperatures. Thus, it seems that steric crowding in dendrimer iron catalysts controls the chain transfer mechanism during ethylene polymerization, indicating a positive dendrimer effect.




**13**

A similar (2,6-bis(imino)pyridyl)iron(II) dichloride complex containing different dendritic wedges in the para-positions of aryl rings has been developed by Moss et al.[78,79] Both carbosilane and poly(benzylphenylether) wedges were attached via ether linking groups to the ligand system, followed by complexation with $FeCl_2 \cdot 4H_2O$ (**14**). The resulting complexes were activated with MAO (Al/Fe = 400) and tested in the catalytic oligomerization of ethylene to higher 1-alkenes. The activity of the catalysts appeared to be unrelated to the type of dendritic wedges attached, however, the size of the wedges slightly influenced the catalyst activity in a positive way.

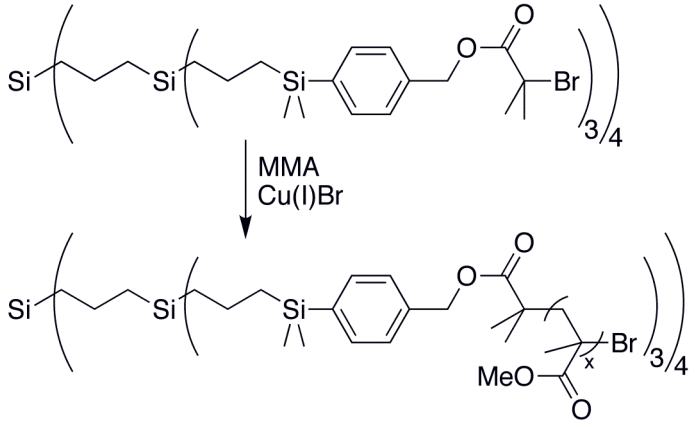



R = H, Me
$R_{wedge}$ = $Br(CH_2)_4SiMe_2Ph$, $Br(CH_2)_4Si((CH_2)_3SiMe_2Ph)$

**14**

The use of the zeroth and the first generation carbosilane dendrimers functionalized with 2-bromoisobutyryl end-groups as initiators in the copper(I) bromide/N-(n-octyl)-2-pyridylmethanimine-mediated living-radical polymerization of methyl methacrylate (MMA) was studied by Van Koten et al. (Reaction Scheme 8).[60,61] The star polymers formed during

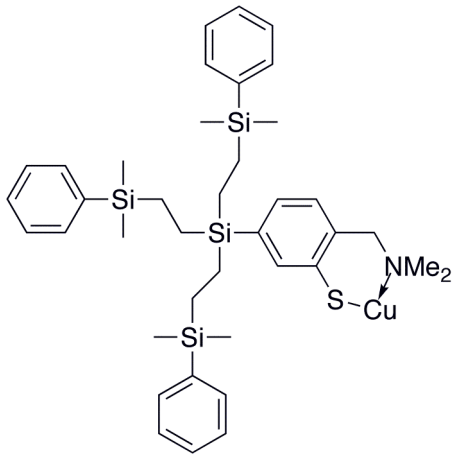
this polymerization had narrow molecular weight distributions (PDI < 1.3) and $M_n$ close to theoretical values predicted by the amount of monomer consumed. The polymerization rates were lower than those produced by the monomeric analogue tested, probably because of initial intramolecular termination reactions (star-star couplings).




(8)

### 1.2.4.3 Michael addition

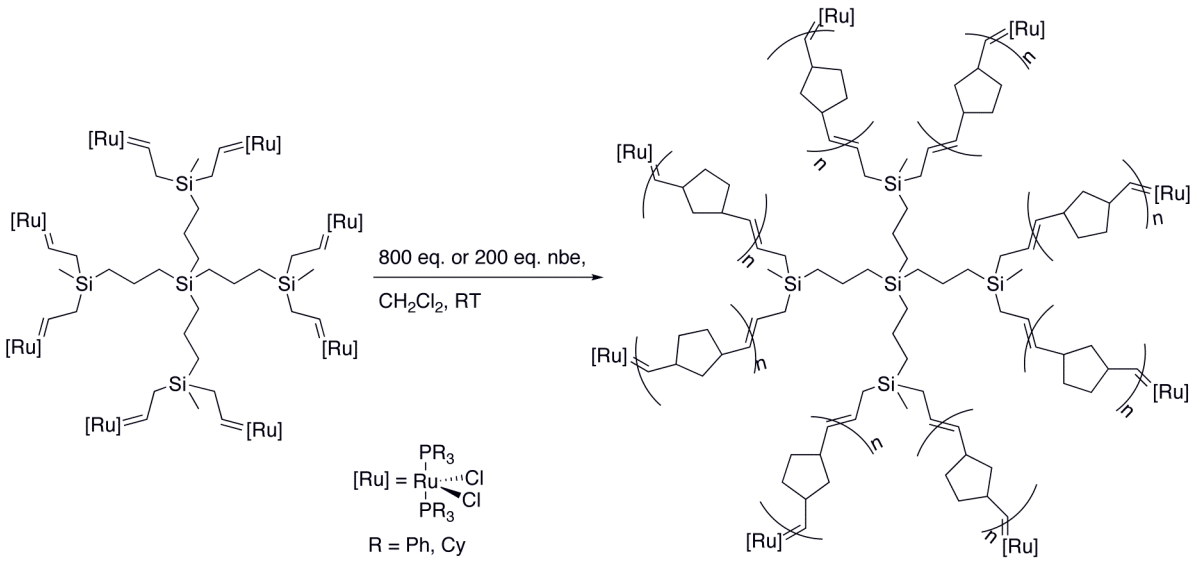
Soluble copper(I) catalysts were developed for the 1,4-addition of diethyl zinc to 2-cyclohexenone by Van Koten's group.[80] ortho-Aminoarenethiolatocopper(I) catalyst was prepared and attached to a zeroth generation carbosilane dendrimer **15**, obtained by a convergent synthetic method. The resulting catalyst was tested in both polar and apolar solvents and showed excellent activity. Its solubility in apolar solvents opens possibilities for a wider variety of substrates that are not soluble in conventional (polar) solvents to be used in this type of reaction. Compared to the unsupported analogue, a clear positive dendrimer effect was observed, since the supported catalyst was more robust towards water and air, had increased solubility in most common organic solvents, and comparable (or even higher) catalytic activity. Furthermore, the increased stability and size of the dendrimer catalyst will allow its separation by nanofiltration, for which higher generations homologues will have to be synthesized.



**15**

### 1.2.4.4 Ring-opening metathesis polymerization (ROMP)

Beerens et al. synthesized metallodendrimers for catalytic ring-opening metathesis polymerization (ROMP) of norbornene by coupling of ruthenium complexes to low generation carbosilane dendrimers via an olefin metathesis reaction.[57-59] Phosphine ligands were used for stabilization of these complexes, but since these ligands were not a part of the dendrimer support, these systems are considered as non-phosphine-based dendrimer ligands. The obtained initiators showed very high activities for the ROMP of norbornene (Reaction Scheme 9) yielding multi-arm star polymers in a controlled manner. The activity and selectivity of the catalysts were comparable to those of their mononuclear analogues.[57]



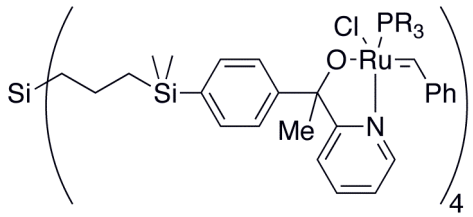

(9)

In addition to several different ruthenium complexes, aryloxy-tungsten complexes were also anchored to small carbosilane dendrimers.[59] These complexes also showed high activities,

yielding, after complete conversion of monomer, high molecular weight branched star polymers by a further dismutation reaction. This reaction, which caused the coupling of two dendrimeric units, was followed by elimination of two metal centers from the dendrimer surface and formation of unidentified multi-tungsten species. A probable reason for this phenomenon may be the high activity of tungsten-alkylidene dendrimer relative to that of the corresponding ruthenium systems.

### 1.2.4.5 Ring-closure metathesis

In addition to the ring opening metathesis polymerization, ring-closure metathesis can also be catalyzed by metallodendrimer catalysts. In the Van Koten group, Si-Cl terminated carbosilane dendrimers were functionalized by using organolithium or organomagnesium reagents.[34] Furthermore, polylithiation of the 4-bromophenyl-functionalized dendrimers yielded valuable starting materials for further functionalization, e.g. to pyridyl alcohols, which could be used as ligands for the formation of ruthenium complexes **16**. Dendrimer ligands were prepared using both the zeroth and the first generation carbosilane dendrimers, of which only the smallest ones were metallated and tested in the ring-closure metathesis of diethyl diallylmalonate. The activity of the dendrimer catalyst was found comparable to that of the unimolecular catalyst system, so that after 30 min 100% conversion was achieved. In another experiment, the catalyst solution was separated from the reaction mixture by nanofiltration through a membrane (molecular weigh cut-off 400), the reaction was stopped after reaching a 20% conversion and catalyst decomposition was observed, which was ascribed to deactivation by the membrane surface. This clearly shows that the development of membranes that are resistant to organic solvents and reagents is still an interesting and very important issue.



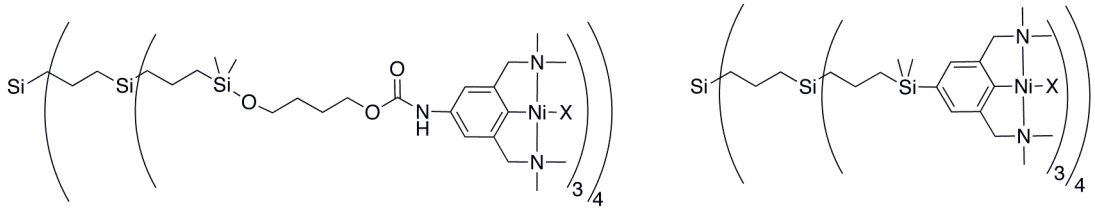

R = *i*Pr, *c*Hex

**16**

### 1.2.4.6 Atom-transfer radical addition (Kharasch addition)

The first attempt to close the gap between homogeneous and heterogeneous catalysis by the use of dendritic supporting scaffolds involved the synthesis of a nanosized dendrimer-

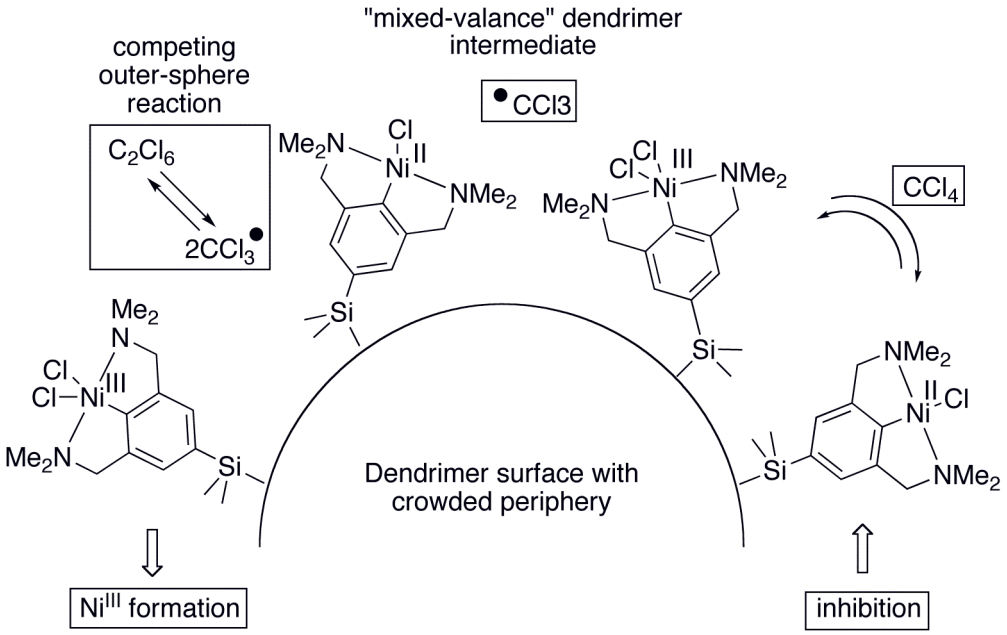
supported homogeneous catalyst that would allow performance of a reaction under homogeneous conditions and separation of the catalyst by nanofiltration from the resulting product. Toward this end, various NCN-pincer nickel(II) halide catalysts[14,15,81] were grafted onto carbosilane dendrimer scaffolds (see for example catalyst **1)** and successfully applied in the Kharasch addition reaction. Initially the NCN-pincer ligands were connected to the dendrimer periphery via a relatively long linker (A), but later the grafting was directly onto the Si-centers (B) (see Structures **17**). An obvious difference between these two types of catalysts is in the accessibility of the nickel centers.




**A** **B**

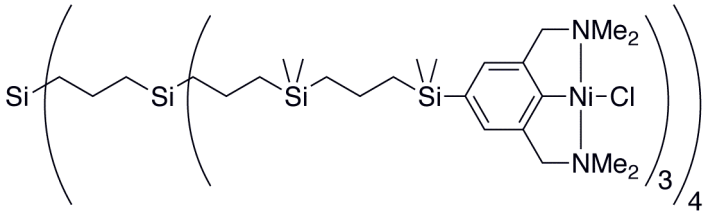
**17**

Both types of catalysts were tested in the Kharasch addition of $CCl_4$ to methyl methacrylate and it was observed that catalytic activity per nickel site of higher generation dendrimers **17 B** (up to 36 NCN-pincer nickel halide units) decreased dramatically compared to the same generation of dendrimer **17 A** and the mononuclear analogues. This was explained by suggesting that in the more congested metallodendrimer **17 B**, more densely packed nickel centers enabled an intramolecular redox deactivation reaction shown in Reaction Scheme 10. This 'proximity effect' is more pronounced in the dendrimer catalysts of the type **17 B**, since in this design, in the absence of extended linker, the nickel centers are in closer proximity to each other.




(10)

To overcome this deficiency, dendrimers with more elongated arms have been synthesized by changing the degree of branching within the dendrimer scaffold. In these species (see Structure **18**[15]), the distance between the nickel centers was considerably increased, which resulted in improved catalytic efficiencies (less intramolecular deactivation) that ultimately approximated the activity of the mononuclear analogue. Consequently, in this study a case of negative cooperation of the catalytic sites in a metallodendrimer could be studied in great detail.



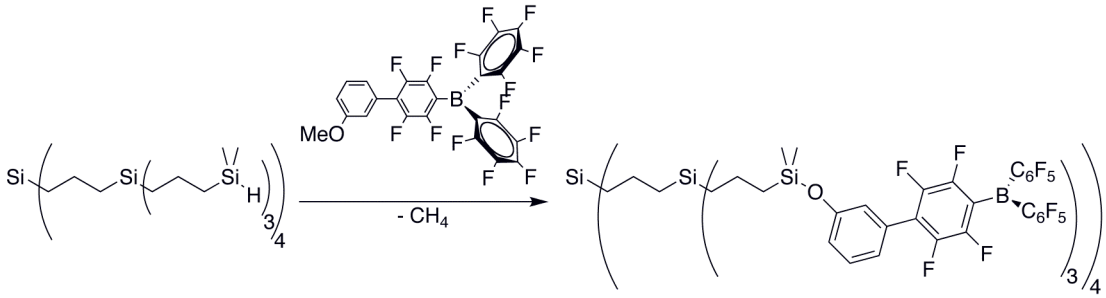

**18**

The metallodendrimer catalysts for the Kharasch addition were also applied in membrane reactors. Already the first generation catalysts (without linker; diameter ~2.5-3 nm) showed high retentions in ultrafiltration membrane reactors and could be applied in continuous-flow reactors with no significant leaching of catalyst through the membrane. However, the formation of purple nickel(III)-containing precipitates revealed the ‘proximity effect’ as well

as effects arising from the membrane surface. This leads to lower catalytic efficiencies and irreversible formation of inactive, very stable NCN-pincer Ni(III) sites.

### 1.2.4.7 Hydrosilylation

A series of dendrimers capped with -$C_6F_4B(C_6F_5)_2$ end-groups were synthesized by Piers et al.[82] In contrast to the borate dendrimers discussed above, these borane dendrimers have not been fully investigated and applied yet. They were prepared via a self-catalyzed silylation reaction of the hydrosilane dendrimer end-groups with appropriate aryl ether containing the -$C_6F_4B(C_6F_5)_2$ group (see Reaction Scheme 11), in which the borane functions as its own catalyst. The dendrimers differed in the number of end-groups at the periphery from 4 for the zeroth generation to 8 or 12 for the second generation dendrimers. They were tested as catalysts for the hydrosilylation reaction of acetophenone using triethylsilane and were found to be only slightly less active than $B(C_6F_5)_3$ itself. The more crowded second generation dendrimer containing 12 end-groups showed a somewhat lower reaction rate compared to the other two dendrimer systems, but it was still an effective catalyst under the conditions applied. These results suggest that all boron centers of these dendrimers acted independently.

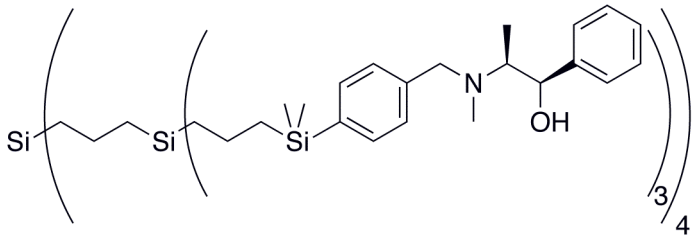



(11)

### 1.2.4.8 Enantioselective addition of dialkylzincs to aldehydes

Sato et al. synthesized carbosilane dendrimers loaded with up to 12 units of chiral β-amino alcohols, yielding a chiral, dendrimer catalyst **19**.[83] These catalysts were tested in the enantioselective addition of various dialkylzinc compounds to aldehydes, and were found to efficiently catalyze the formation of enantiomerically enriched sec-alcohols with ee values of up to 93%. In earlier work, analogues with more rigid dendrimeric chiral ligands were synthesized and tested.[84,85] The ee values obtained in these studies were somewhat lower or comparable to the ee values obtained with the carbosilane dendritic catalysts, but in the more rigid dendrimer catalysts the chiral sites were more isolated and working independently. The authors proposed that flexibility of the carbosilane dendrimer catalysts enables interaction

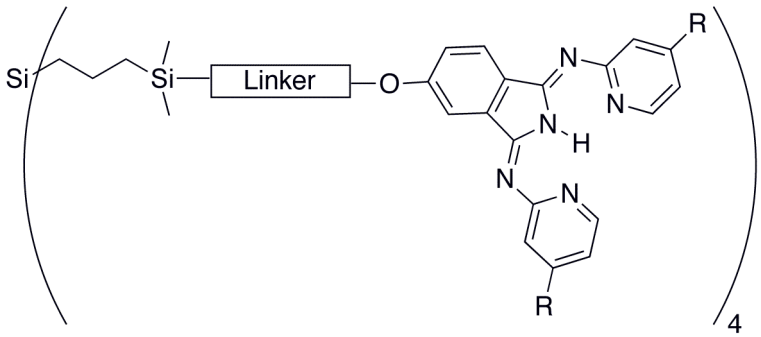
between the chiral sites and thereby the formation of products with high enantioselectivities.[83] The activities of both the zeroth and the first generation dendrimer catalysts and of a dimeric model compound (with a $-Si(Me)_2(CH_2CH_2)(Me)_2Si-$ spacer between the two chiral β-amino alcohol units) were reported. However, no comparison or benchmarking with reactions of the chiral β-amino alcohol itself has been made.




**19**

### 1.2.4.9 Hydrogenation

Metal-phosphine complexes are commonly used as catalysts for hydrogenation of alkenes. Recently, Gade et al. reported the synthesis of a new, non-phosphine based class of molecular hydrogenation catalysts, which were also connected to different types of dendron and dendrimer scaffolds (**20**).[86,87] The monomeric palladium complexes of these so-called BPI-ligands (1,3-bis(2-pyridylimino)isoindolate) were applied to the hydrogenation of olefins. Unfortunately, catalytic studies with dendritic catalysts have not been reported yet.

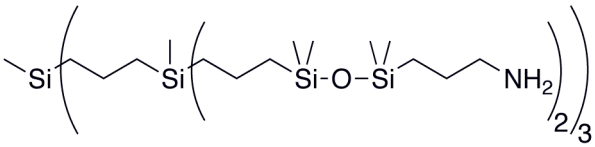



**20**

One of the problems encountered with phosphorus-ligand-based metal complexes is their sensitivity towards oxidation when exposed to air, which results in limited recycling possibilities. However, the dendrimer versions of the BPI-palladium complexes appeared to

be thermally and kinetically more stable than the well-established phosphine containing catalysts. This increased stability of dendrimer BPI-palladium complexes opens the possibility for application of these catalytic species in, for example, continuous hydrogenation processes.

Feng et al. described the synthesis of a carbosilane dendrimer with peripheral aminopropyl groups (**21**) and the corresponding platinum and palladium complexes (prepared by reaction with $H_2PtCl_6 \cdot 6H_2O$ or $PdCl_2 \cdot 2H_2O$).[88,89] The palladium complex (no information on the Pd to N molar ratio was provided) was tested in hydrogenation reactions of several organic compounds (e.g. styrene, allyl alcohol and acetophenones) and appeared to be an effective catalyst for the reduction of both the C=C and the C=O bonds of the substrates tested. The palladium dendrimer complex appeared to be far more active than monomeric $PdCl_2 \cdot 2H_2O$ at the same palladium concentration. In addition to this, the monomeric catalyst caused palladium plating during the reaction. An explanation for this increase in activity of the dendrimer catalyst may be the possible formation of coordinatively unsaturated palladium sites during the catalysis, which does not occur with the monomeric catalyst. It was found that dendrimer catalysts could be reused without any loss in activity. However, no details were given on their recyclability.




**21**

## 1.3 Supported Organic Synthesis on Soluble Carbosilanes

In addition to the use of carbosilane dendrimers as soluble supports for homogeneous catalysts, it is also possible to apply them as supports for supported organic synthesis (SOS). Since the introduction of the well-known Merrifield resins in the 1960's,[90] insoluble solid supports or soluble polymeric supports have been widely used in Solid Phase Organic Synthesis (SPOS). For this, precisely defined soluble supports will have several advantages, such as more homogeneous reaction mixtures leading to more linear reaction kinetics and higher reaction rates. Furthermore, standard spectroscopic methods (e.g., NMR-spectroscopy) can be applied to make monitoring of single reaction steps easier. Carbosilane dendrimers are perfect candidates for this purpose, since they are chemically inert, good anchors for several

reactive molecules, can be separated from small molecules by simple filtration, i.e. reused after isolation by various kinds of separation techniques, and can withstand harsh reaction conditions.[91] As a consequence, the development of peripherally-functionalized carbosilane dendrimers opened various possibilities for the application of dendrimer ligands as soluble supports for SOS.[34,92]

A general approach to SOS consists of three subsequent steps: attachment of the substrate to the dendrimer support, modification of the substrate into the target molecule, and release of the product from the support (see Figure 5). In addition to this, subsequent recycling of the soluble dendrimer support is possible after its separation from the product solution (see Figure 2).

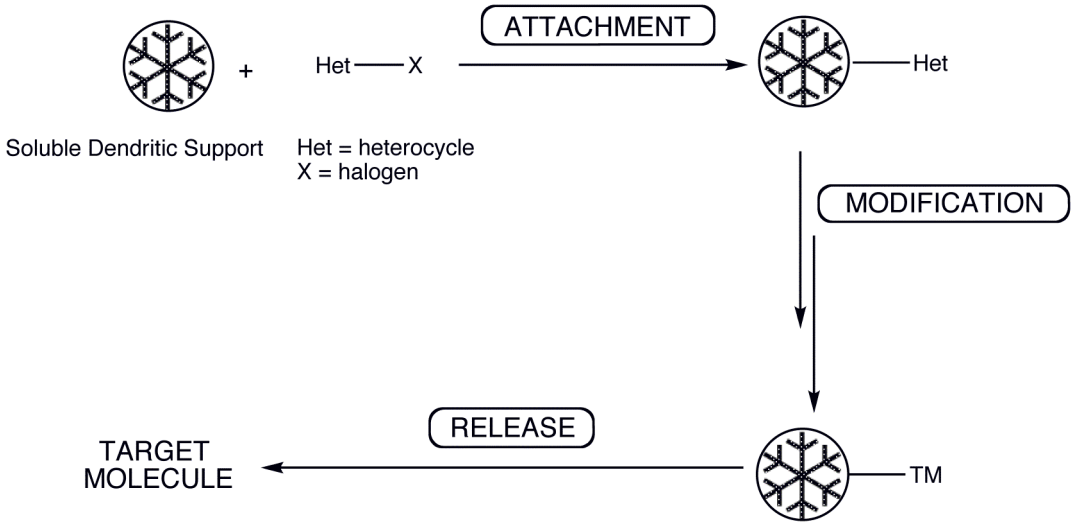
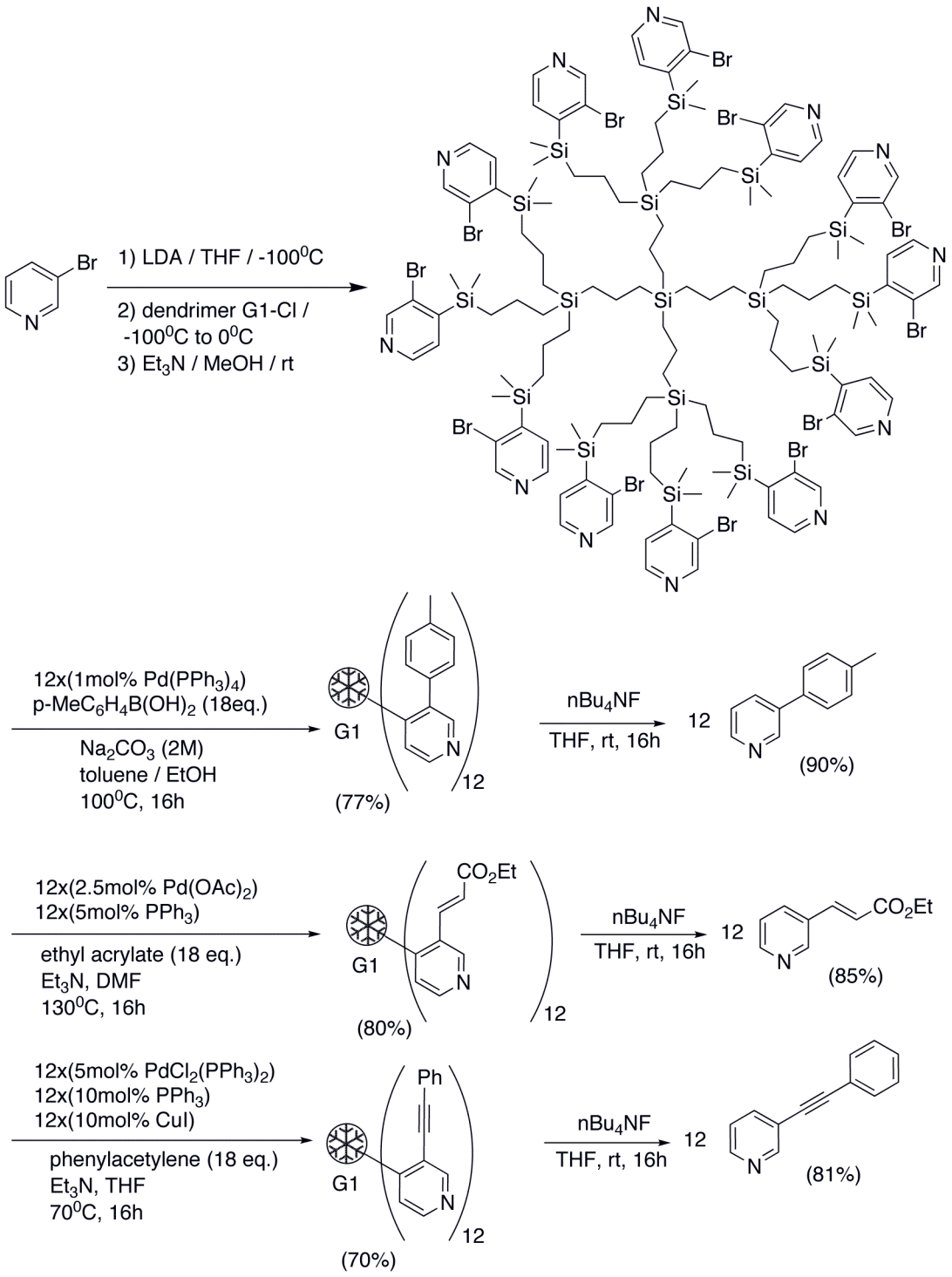



**Figure 5:** General scheme of the process for use of dendrimers as soluble supports in supported organic synthesis.[93]

Recently, in the group of Klein Gebbink, the use of carbosilane dendrimers as soluble supports for organic synthesis has been further advanced.[93] Already second generation dendrimers were shown to be large enough to separate from reaction mixtures by dialysis. This enabled purification after each step of the reaction sequence and thus provided cleaner products. Different types of reactions have been performed, including lithiations and palladium catalyzed C-C coupling reactions. With the loading of dendrimers with pyridine moieties, stepwise modification of the periphery, and release of the products from it, a proof of principle of this technique has been provided (see Reaction Scheme 12).




(12)

Furthermore, in order to obtain an even better diafiltration performance, carbosilane dendrimers with more rigid or shape-persistent cores have been developed as soluble supports. With increased rigidity of the core, membranes with larger pores sizes can be used, which allows higher filtration rates, throughput of products and reactants without loss of dendrimeric support.[19]

## 1.4 Conclusions and Outlook

This chapter describes the current state of the use of carbosilane dendrimers and dendrons as supports for homogeneous catalysts, with active sites located either in their cores or focal points, or at the periphery in the end-groups. The inertness of the carbosilane dendritic scaffold to most of the reagents that are required for the synthesis of metal-ligand complexes as well as its solubility makes carbosilane dendrimers excellent carrier molecules for homogeneous catalytic systems. Via a proper choice of alkane-diyl chains connecting the Si-branching points, the rigidity and solubility of these scaffolds can be tailored, i.e. $C_2$–linkers lead to a more rigid, often less soluble (more crystalline) carbosilane backbone than $C_3$–linkers. Furthermore, lower generation dendrimers already have sizes that make them suitable for separation from the product solutions by nanofiltration techniques and for use in continuous reaction set-ups. Due to this property, the use of dendrimer catalysts in automated processes is a research area that is explored by many groups (reviews on this topic have been published[4,94]). In addition, the development of membranes that are resistant to organic solvents and reagents is still an interesting and very important field.

Fundamental studies have revealed that with a proper not too dense coverage of the dendrimer periphery, each catalytic site can function as if it were an independent catalyst. It was also found that a too high catalyst site density in various types of reactions can lead to severe lowering of the catalytic performance of the metallodendrimer catalysts (negative cooperative effect), although the opposite (positive cooperative effects) has been observed as well. Approaches aimed at reducing this site density by decreasing the degree of branching of dendrimer scaffold near the periphery to regain the activity of the single catalyst site are also described. It should be noted that for the future development of this field it will be necessary that the homogeneous catalyst on the dendrimer scaffold has considerable robustness to make multiple use possible. It goes without saying that recycling is only economical for processes that require higher concentrations of homogeneous catalysts, which is often the case in the synthesis of fine chemicals and special products. Many of the catalytic species described make use of phosphine ligands, which are connected directly or via linker moieties to the dendrimer scaffold. The performance of these dendrimer catalysts is often comparable to that of the mononuclear analogues.

With these developments, systems are now in hand that combine favorable properties of homogeneous catalysts, such as activity, selectivity and well defined structural features, with some of those properties that are specific for heterogeneous catalysts, such as recyclability, easy engineering of complex systems, high total turn over numbers and last but not least an easy, eventually continuous, separation of the catalyst from the product solution. Accurate and easy characterization combined with easy purification and catalyst recycling are advantages that were not achieved with other catalytic systems yet. A possible application of these properties might be in membrane bags to compartmentalize the dendrimer catalyst in the reaction mixture. Through permeation (driven by reverse osmosis) the catalyst and reactants can interact with each other but the catalyst can still be removed easily from the reaction mixture. This approach which can be extended to applications in, for example, mini reactors, is currently being investigated by the research group of Klein Gebbink and others. This method opens a route to the so-called tandem- or cascade-catalysis with one, two or a number of nano-sized, compartmentalized dendrimer catalysts present in a single reaction mixture.

The developments described for the application of dendrimer supports in catalysis can also be applied to supported organic syntheses. The requirements needed for catalyst supports, e.g. recyclability, nanofiltration, inertness, robustness, are also required for supported organic synthesis with soluble supports. This new field of application of carbosilane dendrimers has been opened only recently but it already shows promise for the near future.

Finally, it should be also noted that almost all the described dendrimer catalysts consist of catalytic species covalently bonded to the carbosilane scaffolds. However, recent developments have provided systems, in which the catalyst is non-covalently bonded to the core of a core-shell dendrimer species.[9,95-102] The systems developed by Van Koten et al. comprise a non-covalently bonded metal catalyst which is charged with an anionic tether and a core-shell dendrimer carrier/container that has a polycationic core. The dendrimer container-metal catalyst assembly forms itself by ion exchange and is primarily held together by Coulombic forces. The dendrimers used for this purpose are based on carbosilane core molecules, functionalized with polybenzyl aryl ether dendrons. One of the advantages of this system lies in the fact that catalytic species are bonded strongly enough to prevent leaching, but at the same time can easily be removed from the dendrimer container. These recent developments open new ways for application of carbosilane dendrimers as recyclable supports for various catalysts for a wide variety of reactions.[95-101]

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# Chapter 2

## The Application of Carbosilane Dendrimers as Soluble Supports for the Stepwise Modification of 2-Bromopyridine Moieties

*Solids Phase Organic Synthesis (SPOS) is a widely applied method in both chemical and pharmaceutical industries and academia. Besides many advantages, SPOS shows several shortcomings due to its heterogeneous nature. Changing to Liquid Phase Organic Synthesis (LPOS), and especially using structurally very regular dendritic supports, overcomes many of the disadvantages related to the insolubility of the supports in the reaction media. At the same time separation of the supported products from the reaction mixture after using (large) excesses of reagents is still straightforward using nanofiltration techniques, resulting in products of high purity. The application of carbosilane dendrimers as soluble supports for organic synthesis is described here, by means of the challenging modification of 2-bromopyridine moieties. In analogy to previous studies, procedures using TMS as a mimic for the carbosilane dendrimers were first developed, which served as starting point for the dendrimer supported modifications. Based on this experience, several 2-bromopyridine moieties were connected directly to the dendrimers without the use of linking groupings, using lithiation chemistry, resulting in synthesis scaffolds in yields up to 68%. These scaffolds were used in various modification reactions (e.g. C-C linker reactions). Both the dendritic starting materials and the modified dendrimers were purified using passive dialysis techniques to remove any remaining reagents, prior to following reaction steps. The modified intermediates were obtained in yields varying from 64 to 88%. After purification the products were released from the dendrimers. Although in general all three steps (attachment, modification, release) were performed as expected, the yields were rather low compared to standard SPOS methodologies. As an additional proof, and in order to show another advantage of carbosilane dendrimer compared to PS-supports (i.e. chemical resistance), the synthesis of a dendrimer containing activated peripheral groupings was investigated. For this purpose the 2-bromopyridine moieties at the dendrimer's periphery were reacted with tributyltin chloride, resulting in an activated dendrimer in 82% yield. The resulting activated scaffold was successfully used for the synthesis of a supported bipyridine moiety using C-C coupling reactions, in which full conversion was reached. Choosing appropriate substrates and reaction conditions, this methodology can be expanded for the synthesis of libraries of small molecules, e.g. oligopyridines.*

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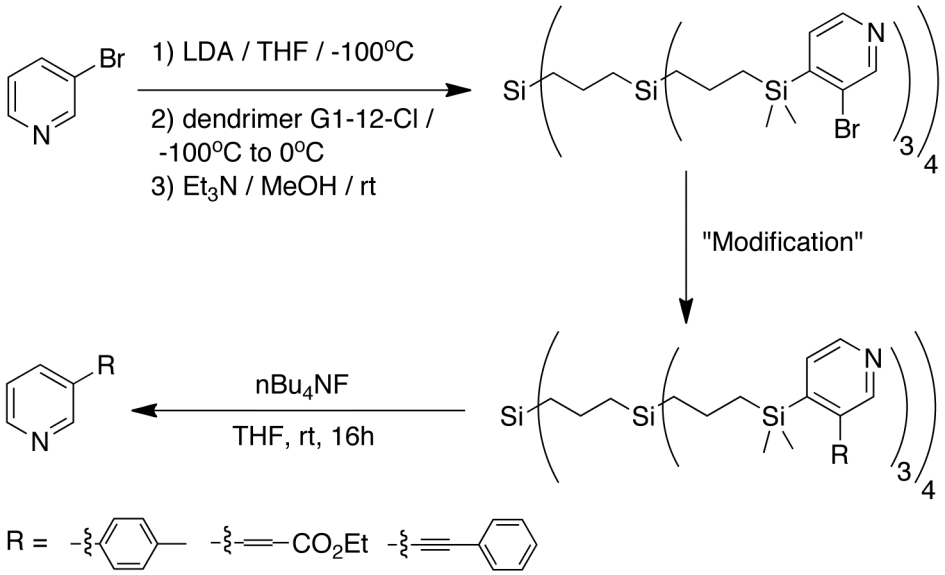
## 2.1 Introduction

Solid phase organic synthesis (SPOS) is a widely applied method since its introduction for peptide synthesis in the 1960's by Merrifield.[1] Among the many applications of SPOS, the use of insoluble resins as support for the synthesis of small (pharmaceutically interesting) molecules has become a well established tool in both organic chemistry and pharmaceutical research, opening ways for high-throughput investigations.[2-7] Classical, solution phase synthesis of these small molecules often involves many (challenging) reaction steps, resulting in low overall yields due to necessary purification methods in order to obtain high purity products. SPOS has several advantages compared to this solution phase approach, like high yielding reaction steps by using large excesses of reagents and the ease of purification using filtration techniques. Compared to classical solution phase chemistry, several disadvantages also exist for SPOS, which are mainly due to the heterogeneous character of the supports. These disadvantages include solvatation problems, non-linear reaction kinetics and the lack of *in situ* spectroscopic analyses. Changing to Liquid Phase Organic Synthesis (LPOS) through the use of soluble synthesis supports, like *e.g.* *J*anda*J*el™, partly solves the problems of SPOS.[8-13] Yet, other drawbacks are introduced upon the use of many soluble supports, *e.g.* low loading capacity of the polymers. In order to increase the loading capacity of soluble synthesis supports, hyperbranched polymers and dendrimers have been proposed as supports in organic synthesis.[14-18] Dendrimers, and in particular carbosilane dendrimers, were initially explored as catalyst supports[19-24] and later also as supports in organic synthesis.[14,15,18,25-28] Compared to other kinds of dendritic structures, carbosilane dendrimers present several additional advantages, such as their high kinetic and thermal stability (due to the relatively strong Si-C bonds[29]), high solubility in organic solvents, good accessibility, and high inertness towards organic and organometallic reagents. Furthermore, the purification of supported materials by means of nanofiltration or dialysis techniques has been well described for carbosilane and carbosilane-based dendritic supporting materials.[27,28,30-32]

In order to further explore the scope of carbosilane dendrimers as synthesis supports, we have set out to investigate the supported synthesis of pharmaceutically interesting small molecules. One class of these small molecules consists of pyridine derivatives, which are known for their presence in many natural product skeletons, pharmacophores and also in ligands for transition metals. SPOS methods for the (palladium-catalyzed) synthesis of pyridine derivatives starting from a pyridine-functionalized support are not widely described in literature.[33-36] In a previous

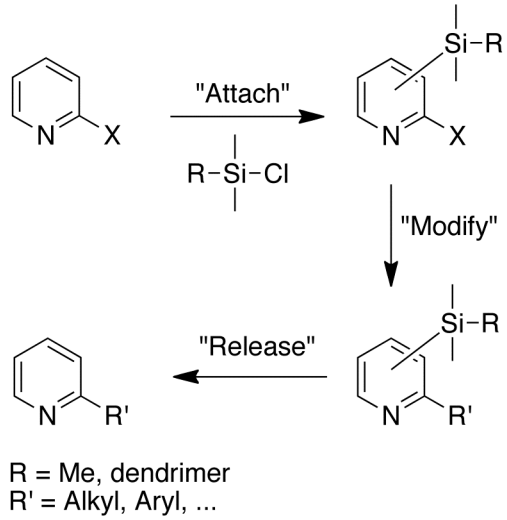
study we have examined the dendrimer-supported modification of 3-bromopyridine moieties (Scheme 1).[27] Especially pyridines substituted at the 3-position are known to be part of pharmaceutically interesting compounds like nicotine derivatives. Work up procedures in conventional synthesis routines towards such compounds are very demanding, which makes these modification reactions using synthesis supports very illustrative.[37] Modification of bromopyridines generally involves very sensitive and challenging reaction steps, like lithiation and Grignard chemistry, and metal-catalyzed C-C or C-heteroatom coupling reactions (*e.g.* Suzuki-Miyaura,[38,39] Sonogashira,[40,41] and Buchwald-Hartwig coupling[42,43]). Performing these types of reactions using carbosilane dendrimers as supports has previously provided us with information about the possibilities and limitations of the application of these carbosilane dendrimers as supports in organic synthesis (Scheme 1).[27]




**Scheme 1.** Dendrimer-supported modification of 3-bromopyridine.[27]

Here, we present a study aimed at extending the dendrimer-supported modification of pyridine moieties towards the modification of 2-halo-pyridine fragments. These 2-halo-pyridines are interesting as building blocks for the synthesis of natural products and pharmaceutically interesting compounds, as well as for the synthesis of ligands for transition metals like oligopyridines, all of which require demanding work up procedures in the case of non-supported synthesis methods. Previous investigations of the supported modification of the 3-bromopyridine scaffold showed that reactions using a TMS-substituted mimicking system served to develop synthetic methods for the application in dendrimer-supported modification reactions.[27] Here, we have followed a similar approach. Methods for the attachment of a TMS group to a 2-bromopyridine moiety, followed by modification of the

obtained TMS-substituted 2-bromopyridine moiety, and the subsequent traceless cleavage of the TMS-pyridine bond were initially evaluated and subsequently translated to dendrimer-supported attach-modify-release protocols (Scheme 2). Next, by using these protocols and carbosilane LPOS supports, a small library of modified pyridines was prepared, that comprises compounds with pyridine-pyridine, pyridine-aryl and pyridine-heteroatom connections. The use of passive dialysis and nanofiltration techniques in these syntheses was investigated to allow the use of reagent excesses and dendrimer-supported scaffold purification.




**Scheme 2.** Dendrimer-supported modification of 2-halo-pyridines.

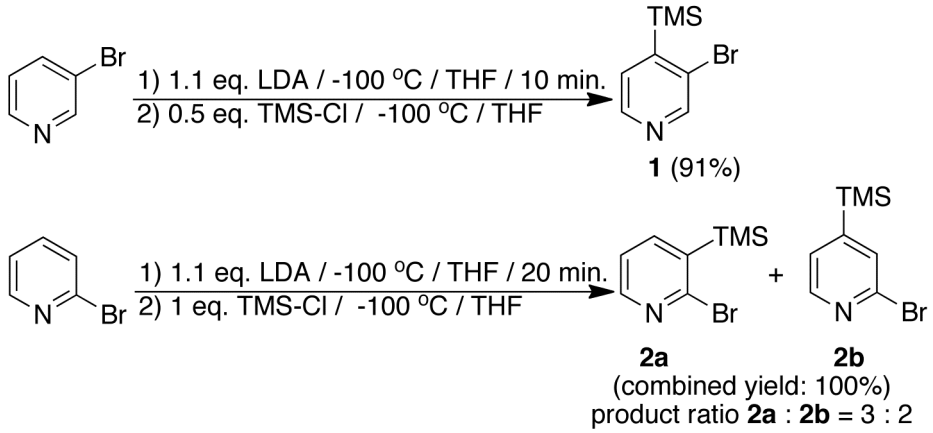
## 2.2 Results

The starting point of our investigations on the dendrimer-supported modification of 2-halopyridines was the functionalization of carbosilane dendrimers with these 2-halopyridine moieties at their periphery. In analogy to the previously reported method for the dendrimer-supported modification of 3-bromopyridines,[27] a TMS-substituted mimicking system for the attach-modify-release procedures was first investigated and used to develop synthetic methods for the application in the dendrimer-supported modification of 2-halopyridines. For this purpose the methods for attachment of these 2-halopyridines to a chlorosilane moiety and thereby the modification (or activation) of pyridine moieties at specific ring positions was explored. Several approaches for the functionalization of carbosilane dendrimers with 2-halopyridine moieties were investigated, followed by a number of modification reactions (C-C and C-heteroatom coupling reactions) and release of the coupled products from the dendritic supports. Furthermore, the functionalization of dendritic supports with activated

peripheral groupings was explored, together with their use in the step-wise supported synthesis of oligopyridines moieties.

*2.2.1 Introduction of trimethylsilyl groups*

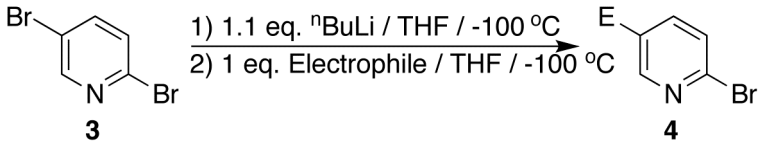
The attachment of a trialkyl-chlorosilane moiety (trimethylsilyl chloride or carbosilane dendrimer) to 3-bromopyridine was earlier accomplished via the selective monolithiation of 3-bromopyridine at the 4-position via C-H activation by freshly prepared lithium diisopropyl amine (LDA) at –100 °C.[27] Trimethylsilyl chloride (TMS-Cl) was added at the same temperature after 10 min, yielding 3-bromo-4-trimethylsilyl-pyridine (**1**), in which the bromine functional group is still available for further modification reactions (Scheme 3). Compound **1** was obtained in 91% yield, based on the amount of TMS-Cl used.[27] In analogy to this methodology, the selective monolithiation of 2-bromopyridine was investigated. Lithiation of 2-bromopyridine with freshly prepared LDA at –100 °C, followed by the addition of TMS-Cl after 20 min at the same temperature, resulted in the formation of a mixture of 3- and 4-trimethylsilyl substituted 2-bromopyridine (**2a** and **2b**) in a 3:2 ratio, in a combined yield of 100% based on TMS-Cl (Scheme 3). Attempts to optimize the reaction to yield one isomer selectively by changing the reaction conditions (*e.g.* reaction times, temperatures, amounts) did not improve this ratio of products.




**Scheme 3.** Modification of 2- and 3-bromopyridine with a trimethylsilyl group.

Next, the monolithiation of 2,5-dibromopyridine (**3**) was investigated, which was described by Parham and Piccirilli for the selective monolithiation of either the 2- or 5-position of **3**.[44] In our case, the selective monolithiation of the 5-position in **3** would leave the 2-position available for modification reactions. For this reaction the reported reaction conditions (0.08 M in THF, 1.1 eq. $^{n}$BuLi, –100 °C, 20 min) were optimized using a series of different

electrophiles, *i.e.* TMS-Cl, dimethyl disulfide, dimethylformamide and benzaldehyde (Scheme 4). After modification of these conditions, the mono-lithiation of **3** at the 5-position in dry THF (0.5 M) at –100 °C using 1.1 eq. of $^{n}$BuLi was accomplished. The time between the lithiation with $^{n}$BuLi and the addition of the electrophile (dissolved in THF in the case of solids) was varied and a reaction time of 1.5 h was found to be optimal. Products **4a-d** were obtained in moderate to high yields (62-95%). The TMS-substituted 2-bromopyridine (**4a**) was obtained in 68% isolated yield.

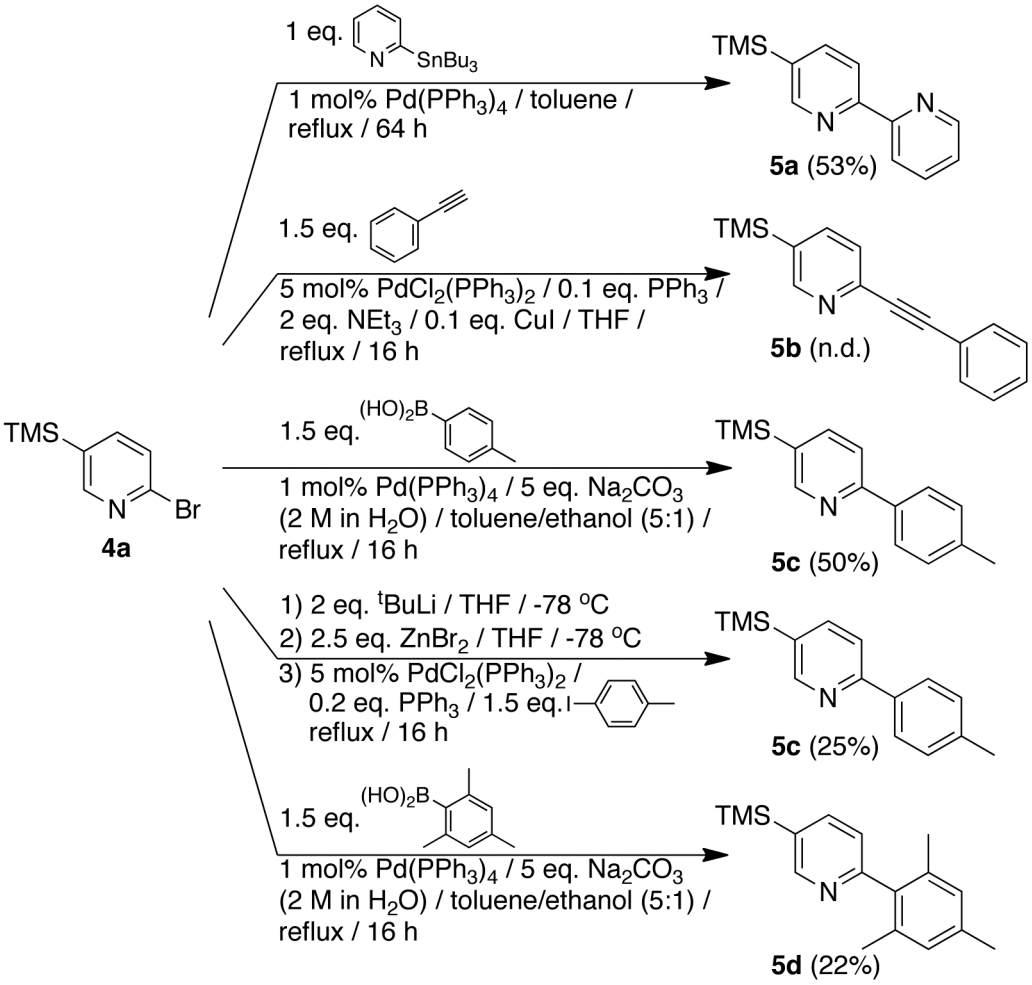



Electrophile = TMS-Cl, MeSSMe, DMF, benzaldehyde.
E = TMS (**4a**, 68%), SMe (**4b**, 62%), C(O)H (**4c**, 75%), C(OH)PhH (**4d**, 95%).

**Scheme 4.** Mono-functionalization of 2,5-dibromopyridine **3** at the 5-position.

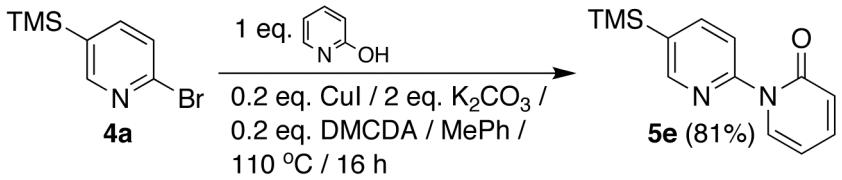
*2.2.2 Modification and release reactions of 5-trimethylsilyl modified 2-bromopyridine*

In a first approach towards pyridine modification, a number of palladium-catalyzed C-C coupling reactions was performed with model compound **4a**, *i.e.* the Suzuki,[27,38,45] Negishi,[46] Sonogashira[27,33,40,41] and Stille[47-49] couplings. These cross-coupling reactions were carried out according to standard literature procedures, as depicted in Scheme 5. After aqueous work up (and purification by column chromatography for **5c** and **5d**), the coupled products **5a-d** were obtained in moderate to high yields. The low yields of **5a**, **5c** and **5d** could be explained by loss of product during workup (*vide infra*, section 3.1).



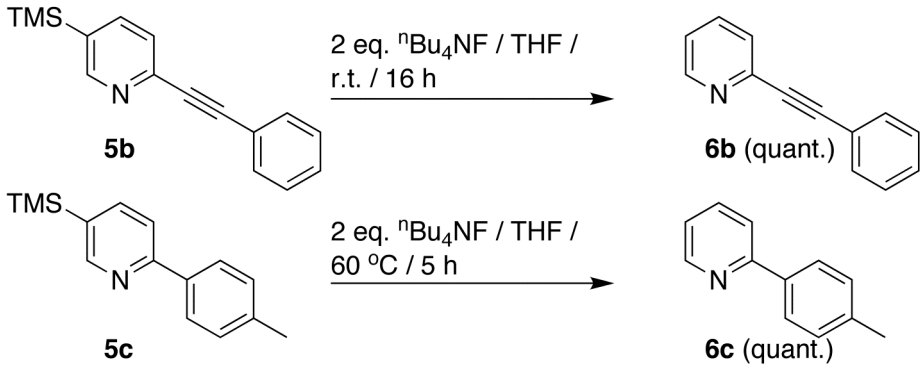

**Scheme 5.** C-C coupling reactions with 2-bromo-5-TMS-pyridine (**4a**).

Besides these C-C coupling reactions, a C-N coupling reaction was performed with **4a**. Using an improved Ullmann-Ukita-Buchwald procedure allows the coupling of aryl halides to 2-hydroxypyridine via a CuI-catalyzed reaction.[50] Following this literature procedure and starting from **4a** resulted in the formation of the desired 1-(2-(5-TMS-)pyridyl)-1*H*-pyridin-2-one (**5e**) in 81 % yield (Scheme 6).




**Scheme 6.** Ullmann-Ukita-Buchwald reaction with **4a** (DMCDA = N,N'-dimethylcyclohexane-1,2-diamine[51]).

With two of the cross-coupled products, *i.e.* the phenylethynyl pyridine **5b** and the *p*-tolyl pyridine **5c**, the traceless removal of the TMS group from the coupled product was tested (Scheme 7). Reaction with 2 equivalents of $^{n}Bu_4NF$ in THF at room temperature overnight for **5b** or at 60 °C for 5 h for **5c** appeared to be sufficient to remove the TMS group completely.[52-54] The products **6b** and **6c** were purified by filtration over a short plug of silica in order to remove the excess of $^{n}Bu_4NF$ and Si-containing moieties and were obtained in quantitative yields.



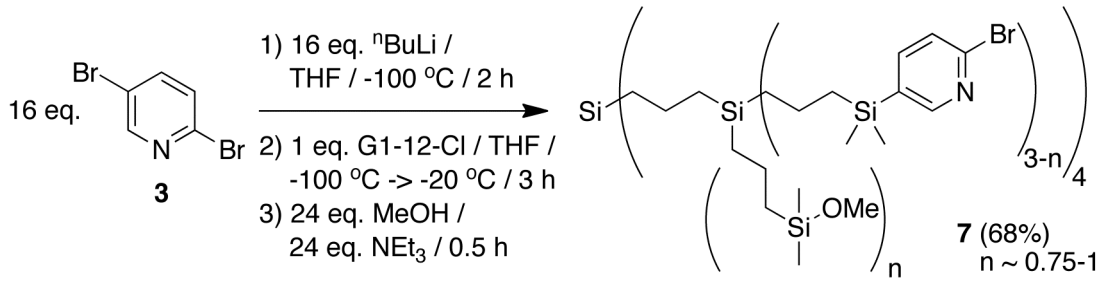

**Scheme 7.** Traceless removal of TMS group.

The synthesis of TMS-substituted 2-bromopyridine **4a** from **3**, followed by several modification and release reactions provided the TMS-based proof of concept for the dendrimer-supported modification of 2-halopyridines. The yields of separate reaction steps (attach, modification, release) at this point were taken as sufficient, in general, and were expected to increase upon the use of dendrimer-supported procedures (due to easier purification methods), although further optimization might be required.

*2.2.3 Attachment of 2-bromopyridines to the periphery of carbosilane dendrimers*

In line with the selective introduction of a TMS-group at the 5-position of 2,5-dibromopyridine (**3**; Scheme 4), we set out to apply this protocol to the 'loading' of chlorosilane-terminated carbosilane dendrimers with 2-bromopyridine moieties. Accordingly, **3** was monolithiated upon treatment with 1 equiv $^{n}BuLi$ in THF at –100 °C for 2 h (instead of 1.5 h in the model reaction; further optimized conditions) and subsequently treated with a solution of the first generation carbosilane dendrimer (G1-12-Cl) containing 12 chlorosilane end groups (16 equiv. of lithiated **3** were used per equiv. dendrimer, *i.e.* 1.3 equiv. of lithiated **3** per dendritic Si-Cl end grouping) at –100 °C (Scheme 8). After allowing the reaction mixture to warm to room temperature, it was treated with $NEt_3$ and MeOH in order to convert any remaining Si-Cl end groupings on the dendrimer into Si-OMe groups.[27] $^{1}H$ NMR analysis

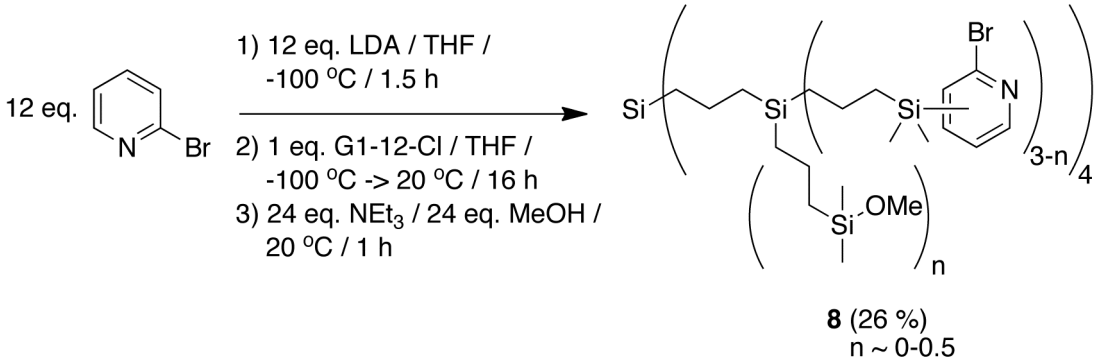
of reaction product **7** showed the presence of both 2-bromopyridine and methoxy end groups on the dendrimer. The relative integrals for these peripheral groupings did not match any meaningful and reproducible degree of pyridine loading of the dendrimer. Comparing the integrals corresponding to the dendrimer backbone and the bromopyridyl groupings, on the other hand, resulted in an estimated amount of 8 pyridyl end groupings per dendrimer, *i.e.* a loading percentage of 67%. Maldi-TOF MS analysis supported this estimated value, showing *m/z* values that correspond with a dendrimer containing 9 bromopyridyl- and 3 OMe-endgroupings. Attempts to increase the degree of loading with bromopyridine groupings, *e.g.* by using larger reagent excesses and longer reaction times, did not result in fully functionalized dendrimers. Crude **7** was purified by passive dialysis and obtained in yields up to 68%.




**Scheme 8.** 2-Bromopyridine loading of G1-12-Cl starting from **3**.

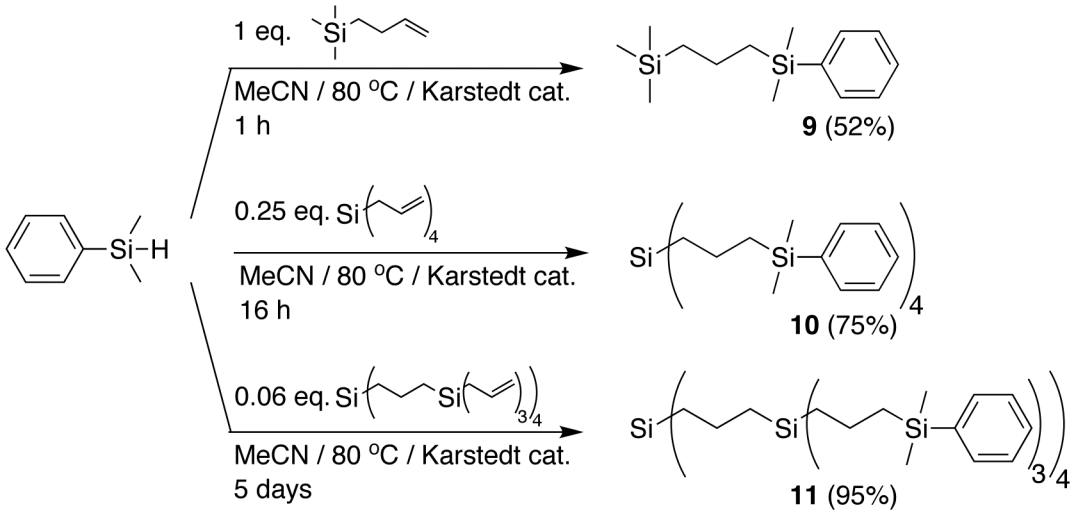
This protocol was repeated several times, each time resulting in carbosilane materials with a different bromopyridine loading. It was therefore decided to investigate other synthetic methods to arrive at fully loaded dendrimers in a reproducible manner. Although the lithiation of 2-bromopyridine with LDA, followed by reaction with the TMS-Cl (*vide supra*) resulted in the formation of a mixture of 3- and 4-TMS substituted bromopyridines **2a** and **2b**, previous studies had shown that this LDA-based procedure is successful for the full functionalization of carbosilane dendrimers with 3-bromopyridines.[27] Indeed, treatment of 2-bromopyridine with LDA, followed by treatment with G1-12-Cl dendrimer and subsequently with $NEt_3$ and MeOH resulted in the formation of functionalized dendrimer **8** containing two different bromopyridyl groups in a ratio of 8:2 (Scheme 9). Purification of the reaction mixture was carried out via passive dialysis, which resulted in a disappointing 26% yield. The degree of dendrimer functionalization was again estimated from the comparison of the relative integrals for the dendrimer backbone and the pyridyl end groups in the $^1$H NMR spectra of the product, and gave an average of 10 bromopyridyl groups per dendrimer. Like in the above-described approach for the synthesis of **7**, the relative integrals for the peripheral OMe- and

bromopyridyl end groups did not match this degree of functionalization. Maldi-TOF MS analysis did show the presence of the fully functionalized dendrimer, containing 12 bromopyridyl end groupings per dendrimer in samples of **8**. Reproduction of the results again appeared to be troublesome.



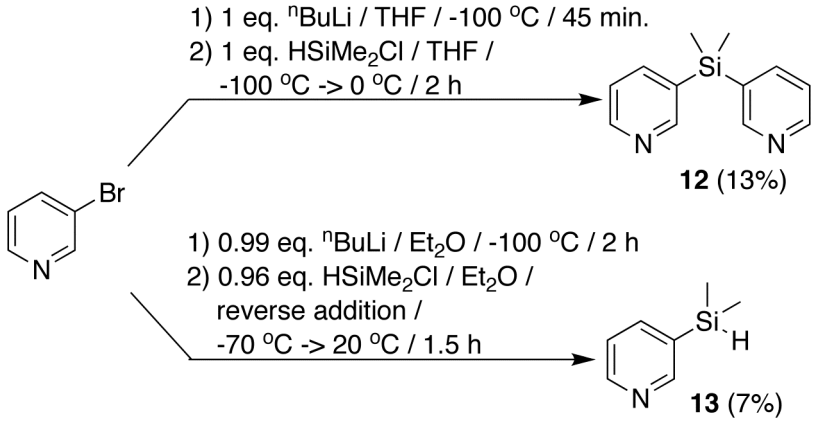

**Scheme 9.** 2-Bromopyridine loading of G1-12-Cl starting from 2-bromopyridine.

Because both lithiopyridine-based routes towards dendrimer-supported 2-bromopyridines were not successful, another approach towards the loading of the dendrimers with peripheral 2-bromopyridine moieties was investigated. Since the synthesis of the carbosilane dendrimers makes use of a sequence of alkylation and hydrosilylation steps, the application of this type of reactions to load the dendrimers was explored. In the dendrimer synthesis the peripheral $SiMe_2Cl$ groupings are introduced via a platinum-catalyzed hydrosilylation reaction on allyl end groupings. In order to investigate the applicability of this reaction to attach an aryl moiety to the dendrimers, some test reactions with commercially available dimethylphenyl silane were performed (Scheme 10). All reactions were performed in dry MeCN in the presence of Karstedt's catalyst ($(C_8H_{18}OSi_2)_3Pt_2$) and heated to 80 °C for at least 1 h for the mono-allyl compound and up to 5 days for the G1-dendrimer, to yield the desired compounds **9**, **10**, and **11** after work up in moderate to high yields. Since in all cases exactly equal amounts of dimethylphenyl silane and allyl-silane groupings were used, the yields could possibly be improved by increasing the amounts of dimethylphenyl silane. The functionalized G1-dendrimer **11** was purified by passive dialysis, whereas **9** and **10** were purified by column chromatography.




**Scheme 10.** Hydrosilylation reactions with dimethylphenyl silane.

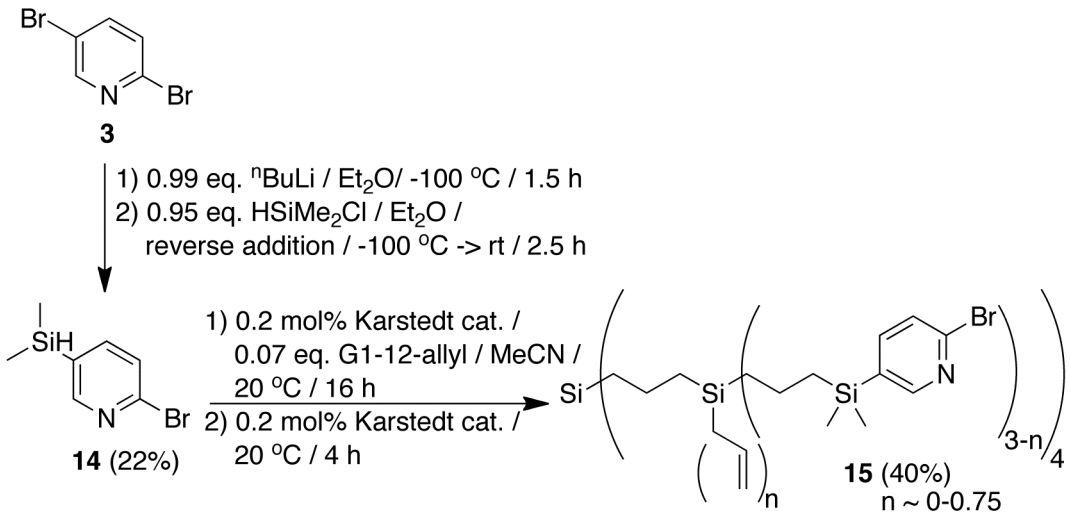
These results encouraged us to apply this protocol to functionalize carbosilane dendrimers with 2-bromopyridine moieties. In order to connect bromopyridine moieties to allyl-terminated dendrimers, the introduction of a dimethylsilyl group on the pyridine ring is required. When 3-bromopyridine was lithiated using $^{n}$BuLi in THF at –100 °C, followed by the addition of $HSiMe_2Cl$ to the mixture according to a literature procedure,[55] the silyl-bridged bispyridine compound **12** was obtained instead of the anticipated 3-$HSiMe_2$-pyridine **13**. Changing the solvent to $Et_2O$ and applying a reverse addition order resulted in the formation of the desired product **13**, albeit in very low yield (Scheme 11). This reaction was not further optimized.




**Scheme 11.** Synthesis of 3-$HSiMe_2$-pyridine.

In order to synthesize the desired 2-bromo-5-dimethylsilyl-pyridine (**14**), the protocol developed to attach a TMS group to **3** was applied. However, lithiation of **3** with $^{n}$BuLi at –100 °C followed by reaction with $HSiMe_2Cl$ did not result in the formation of **14**. Like for the

reaction with 3-bromopyridine, the reverse addition of lithiated **3** to $HSiMe_2Cl$ in $Et_2O$ at –100 °C resulted in the formation of **14**, although it was obtained in low yield after purification by column chromatography (22%; Scheme 12). Pyridylsilane **14** was then attached to the G1-12-allyl dendrimer via a hydrosilylation reaction with the allyl end groupings of the dendrimer in the presence of Karstedt's catalyst (Scheme 12). The reaction mixture was purified by passive dialysis, yielding **15** in 40% isolated yield. On average (*i.e.* results of several experiments) dendrimers containing 9 pyridine moieties at their periphery were obtained using this strategy. In the $^1H$ NMR spectra of **15**, the remaining allyl end groupings were clearly visible, making determination of the degree of functionalization very straightforward. Using more Karstedt catalyst, added in multiple portions in time to the reaction mixture, together with longer reaction times (up to 16 h after each addition of catalyst), resulted in a full functionalization of the G1-dendrimer. This procedure was not further examined and optimized at this point.

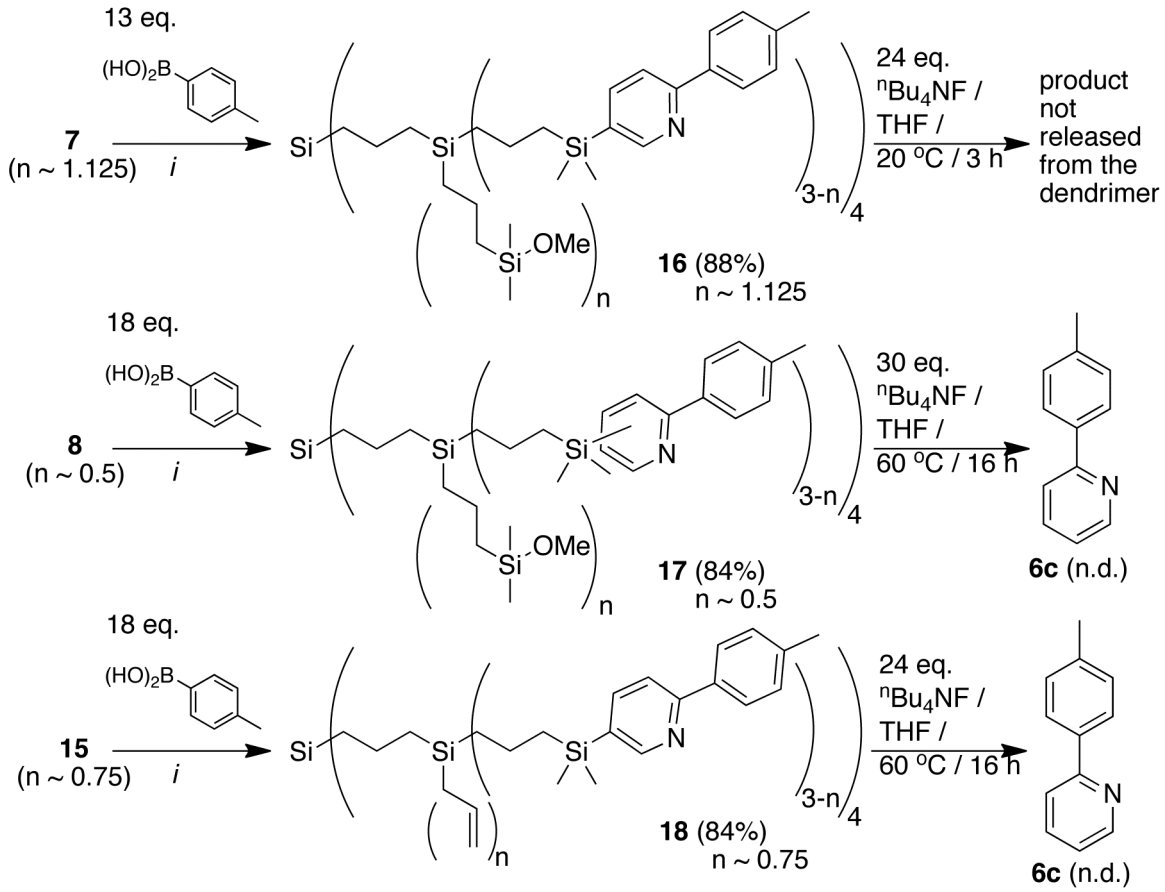



**Scheme 12.** Loading of G1-12-Cl via hydrosilylation.

*2.2.4 Application of the dendrimers as soluble supports in organic synthesis*

With the dendrimers **7**, **8**, and **15** in hand, the supported modification of 2-bromopyridines was investigated. The test reactions performed with TMS-substituted bromopyridine **4a** (*vide supra*) served as a proof of concept for the dendrimer-supported modification reactions and provided the protocols for these reactions. First, the three dendrimer supported 2-bromopyridines **7**, **8**, and **15** were applied as starting material in Suzuki-coupling reactions. In all cases, the Suzuki reaction was performed in the presence of a palladium catalyst using an excess of 1.1-1.5 equiv of *p*-tolyl boronic acid relative to the maximum number of twelve bromopyridine end groupings present (Scheme 13). The dendrimer-supported coupled

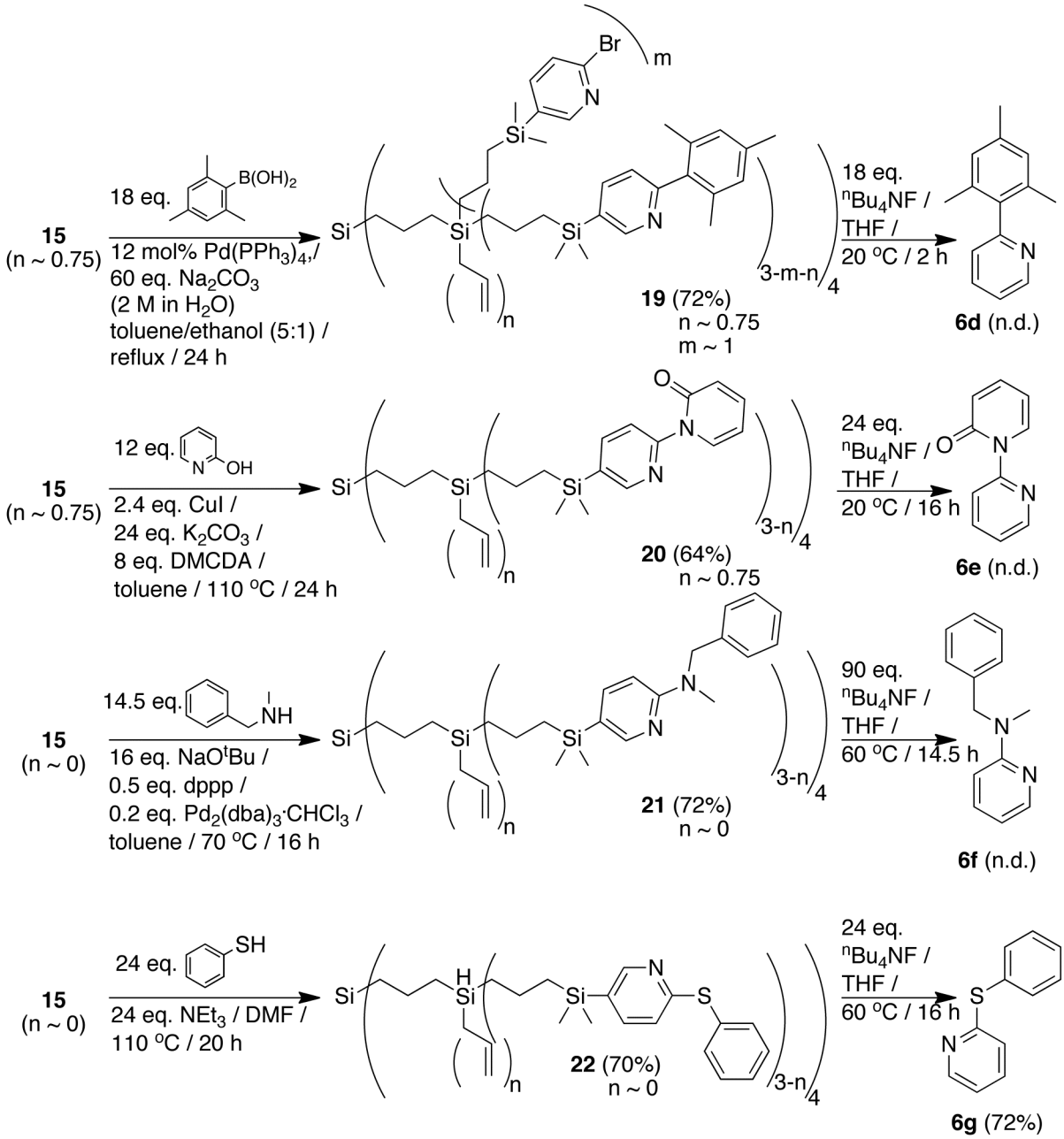
products **16**, **17**, and **18** were purified by passive dialysis and obtained in good yields. The coupled products were then released from the dendrimers by reaction with $^{n}Bu_4NF$ in THF (Scheme 13). Although for the release of a TMS-group ambient reaction temperatures appeared to be sufficient, in case of the dendrimer-supported pyridines reaction temperatures of 60 °C and prolonged reaction times (overnight) were required in order to release the products from the dendrimers. Treatment of **16** with $^{n}Bu_4NF$ was only performed at room temperature and accordingly did not result in release of 2-*p*-tolylpyridine (**6c**) from the dendrimer. Reactions of dendrimers **17** and **18** with $^{n}Bu_4NF$ on the other hand were carried out at 60 °C and did result in release of **6c**. The crude products were obtained together with some remaining dendrimer fragments, formed by reaction with $^{n}Bu_4NF$. Filtration of the crude reaction mixture over a short plug of silica did improve the purity of the product, although some alkyl-fragments were still visible in the NMR spectrum. Therefore the yields of **6c** could not be determined.




*i* = 10-12 mol% $Pd(PPh_3)_4$ / 50-60 eq. $Na_2CO_3$ (2 M in $H_2O$) / toluene/ethanol (5:1) / reflux / 16 h

**Scheme 13.** Dendrimer-supported synthesis of 2-*p*-tolylpyridine **6c**.

To further explore the scope of the carbosilane dendrimers as soluble supports for the modification of 2-bromopyridines, several other coupling reactions were carried out (Scheme 14). Since it was shown that a Suzuki coupling reaction is in principle successful using dendrimeric supports, the same Suzuki coupling reaction of **15** with an excess of the sterically hindered mesityl boronic acid in the presence of a palladium catalyst was examined. This reaction was performed in an analogous manner to the reaction with TMS-substituted bromopyridine **4a** to synthesize **5d** (*vide supra*, Scheme 5) and resulted in the formation of dendrimer **19** in which, next to the allyl groupings, both the coupled product and unsubstituted 2-bromopyridine are present (Scheme 14). The ratio of these end groupings in the dendrimer was estimated from its $^{1}$H NMR spectrum and was found to be 3:5:4 (*i.e.* allyl:mesitylpyridine:2-bromopyridine), respectively. The yield (72%) was calculated in accordance with this ratio and the weight of the isolated product after purification by passive dialysis. Apparently the steric crowding at the dendrimer periphery in combination with the mesityl grouping hampers full substitution of the peripheral bromopyridines. This result correlates to the low yield (22%) obtained for the reaction with 2-bromo-5-trimethylsilylpyridine (**4a**; *vide supra*, Scheme 5). Release of the coupled product from dendrimer **19** was achieved by reaction with $^{n}Bu_4NF$ in THF. Although the reaction was performed at room temperature and for just 2 h, **6d** was released from the dendrimer. Along with the product several alkyl-fragments were formed, which again precluded the determination of the chemical yield of the reaction.




**Scheme 14.** Dendrimer-supported synthesis of small molecules **6d**-**6g**.

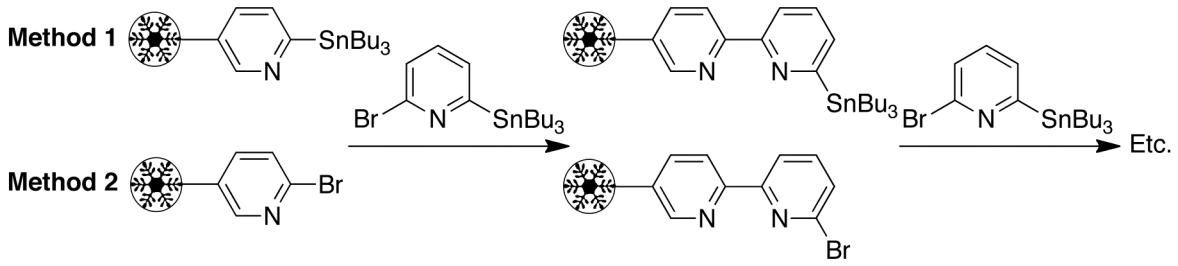
Besides the dendrimer supported C-C coupling reactions also dendrimer-supported C-N and C-S coupling reactions were performed using dendrimer **15**. Following the Ullmann-Ukita-Buchwald coupling reaction[51] (procedure described in section 2.2) and a Buchwald-Hartwig C-N coupling reaction,[56] the 2-bromopyridine moieties attached to dendrimer **15** were used in C-N coupling reactions, resulting in the formation of dendrimers **20** (purified by passive dialysis) and **21** in 64% and 72% yield, respectively (Scheme 14). In both reactions all peripheral 2-bromopyridine moieties were converted into the coupled products. Release of the coupled products **6e** and **6f** from **20** and **21** was carried out by reaction with $^{n}Bu_4NF$ in THF

overnight at room temperature (**20**) or 60 °C (**21**), resulting in both cases in isolation of the desired products **6e** and **6f**, albeit in very low yield. Full purification by filtration over a short plug of silica was only successful for product **6e**.

The non-catalyzed reaction[57] between dendrimer **15** and thiophenol in the presence of triethylamine resulted in formation of dendrimer **22** in 70% yield (full conversion) after purification by passive dialysis (Scheme 14). Release of the product from dendrimer **22** by reaction with $^{n}Bu_4NF$ in THF yielded product **6g** in an estimated yield of 72% (obtained together with some alkyl fragments).

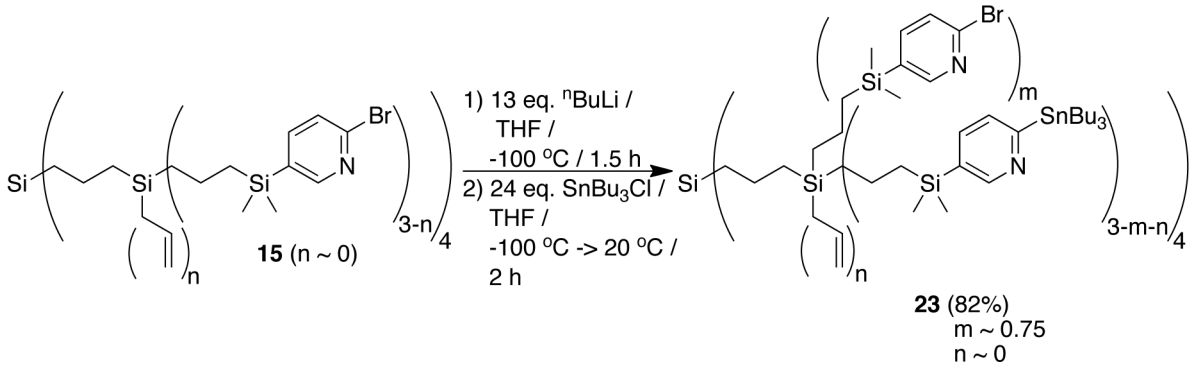
*2.2.5 Carbosilane dendrimers as activated scaffolds for a stepwise synthesis approach*

The wider applicability of the carbosilane dendrimers as soluble synthesis support was explored via the development of a stepwise synthesis approach for the preparation of *e.g.* oligopyridines. Traditional solution phase chemistry to prepare oligopyridines requires many purification steps due to the use of bifunctional pyridines (*i.e.* side-product formation), and is therefore in general very time consuming and low yielding.[58] Changing to a supported synthesis approach for the stepwise synthesis of oligopyridines would simplify the purification procedures and thereby probably increase the overall yield. Oligopyridines can by synthesized via a palladium-catalyzed Stille type cross coupling reaction, which requires the presence of an activated tributyltin group attached to one of the pyridines.[47] This tributyltin group can be attached either to the peripheral pyridine groupings (Method 1) or to the pyridine-moiety that will react with the peripheral bromopyridine moieties (Method 2) (Scheme 15). In this first reaction step peripheral bipyridine groupings will be obtained, which could still have an available functional group (*e.g.* bromide) for further reaction steps towards larger oligopyridines. Both synthetic approaches for the synthesis of these bipyridine moieties were investigated. Method 1 will serve as a test case for the wider investigation of the synthesis of functional groups at the dendrimer's periphery.



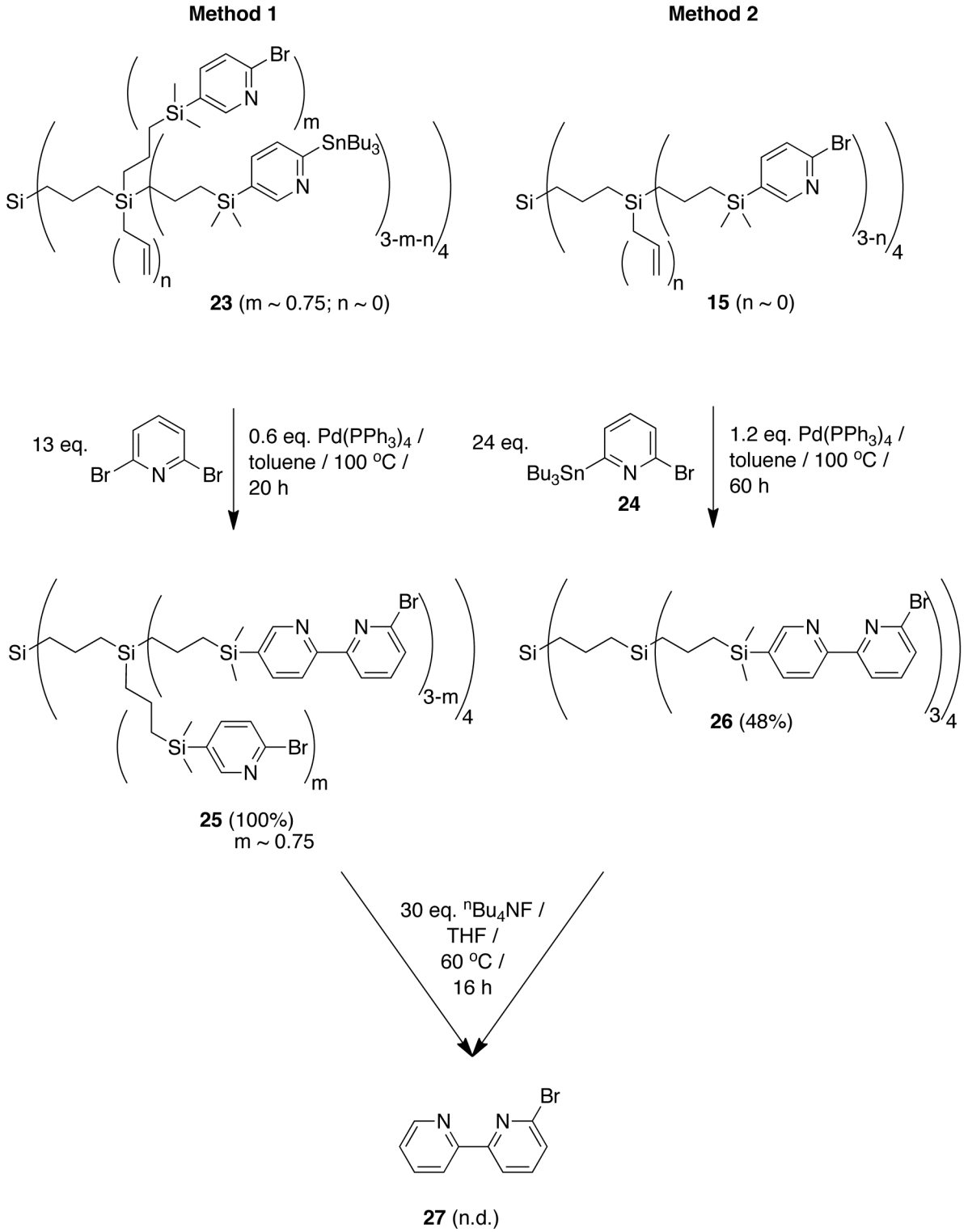

**Scheme 15.** Schematic representation of the dendrimer-supported stepwise synthesis of oligopyridines.

The first step for Method 1 involves the conversion of the peripheral bromopyridine moieties into tributyltin-pyridine moieties. The introduction of these tributyltin groupings at the peripheral pyridines was achieved via lithiation of dendrimer **15** using $^{n}$BuLi at –100 °C, followed by treatment with an excess of $SnBu_3Cl$ after 1.5 h (Scheme 16). The reaction mixture was purified by passive dialysis and the product was obtained in 82% yield. Although no complete conversion was obtained, this dendrimer-supported pyridyl stannane **23** was used as such in further reaction steps.




**Scheme 16.** Functionalization of dendrimer **15** with peripheral tributyltin groups (Method 1).

Using the two different methods as depicted in Schemes 15 and 17, palladium catalyzed Stille coupling reactions were performed to evaluate the supported synthesis of 6-bromo-2,2'-bipyridine using either 2,6-dibromopyridine or 2-bromo-6-tributyltin-pyridine (**24**)[59] as the coupling reagents. In both cases, carbosilane dendritic products were obtained with 6-bromo-2,2'-bipyridine groupings at their periphery (compounds **25** and **26**). The products were not further purified and the yields could only be estimated (100% and 48%, respectively). The coupled products were cleaved from dendrimers **25** and **26** by reaction with excess $^{n}Bu_4NF$ in THF at 60 °C overnight, yielding in both cases the released 6-bromo-2,2'-bipyridine (**27**). However, even after filtration over a short plug of silica, both products could not be purified completely. Therefore the yield of **27** could not be determined.




**Scheme 17.** Dendrimer supported synthesis of 6-bromo-2,2'-bipyridine (**27**).

## 2.3 Discussion

*2.3.1 Optimization of the attach-modify-release procedures*

In order to get more insight into the synthetic procedures required for the application of carbosilane dendrimers as soluble supports for organic transformations on halopyridine

scaffolds, the attachment of halo-pyridines, their modification at the halogen functionality, and the subsequent (traceless) release of the target product were investigated by using trimethylsilyl (TMS) moieties as a 'mimic' of the carbosilane periphery. Starting with the attachment of a TMS group to a 2-bromopyridine moiety, a procedure based on the previous results obtained for the 3-bromopyridines was initially applied.[27] This procedure (*i.e.* lithiation of 2-bromopyridine with fresh LDA, followed by reaction with TMS-Cl) resulted in the formation of a mixture of compounds, in which the TMS group is attached either at the 3- or 4-position of the pyridine ring. Although the formation of a single species would make characterization of the (dendritic) material easier, a differentiation in the attachment, or more general, the formation of a mixture of products in principle does not cause problems in the application of the dendrimers as synthesis supports. As long as the position of the TMS group or the dendrimer at the reaction scaffold, *i.e.* pyridine ring, is not interfering with the subsequent supported modification reactions, it is insignificant on which position at the reaction scaffold the synthesis support is attached, as long as the target products will be released from the TMS groups and dendrimers in a traceless manner. For the proof of principle for the dendrimer-supported synthesis of pyridine derivatives, a single type of peripheral attachment is preferred, because this will exclude any possible influence of the varying attachment modes and result in more straightforward characterization. Therefore, other attachment methods were investigated, starting from 2,5-dibromopyridine. In these methods 2,5-dibromopyridine was either directly lithiated using $^{n}$BuLi followed by reaction with TMS-Cl or the Si-Cl terminated dendrimer,[44] or a dimethylsilyl group was first attached to the lithiated 2,5-dibromopyridine, followed by a hydrosilylation reaction with an allyl-terminated dendrimer (*vide supra*).[55] Both methods resulted in the formation of a single type of attachment, both with the TMS mimic and the dendrimers.

The coupling reactions performed with the 'mimic system' 2-bromo-5-trimethylsilyl-pyridine **4a** resulted in product formation in various yields (Scheme 5). The relatively low yields of products **5a** (Stille coupling, 53%), **5c** (Suzuki and Negishi couplings, 50 and 25%), and **5d** (Suzuki coupling, 22%) could be explained by product loss during workup. In case of **5a**, several extraction steps (acid-base) were performed, while **5c** and **5d** were both further purified by column chromatography. In contrast, **5b** (Sonogashira coupling, quantitative yield) was isolated after a single extraction with ethyl acetate and not further purified. The very low yield for the mesityl-substituted product **5d** can further be explained by the influence of steric hindrance, due to the use of mesityl boronic acid as cross coupling partner. Using excess of reagent, which is also done in the dendrimer-supported synthesis methods,

could improve the yield for this reaction. Furthermore, when comparing the yield of products **5c** prepared by both the Negishi and Suzuki coupling reactions, a difference in yield is observed, which cannot be explained by different workup procedures. Possibly the larger number of reaction steps in the Negishi coupling reaction could influence the isolated yield of the product.

Release of the coupled products from the TMS groups (and later on also the dendrimers) was initially performed with relative small amounts of trifluoroacetic acid or tetrabutylammonium fluoride ($^{n}Bu_4NF$), at room temperature and for relatively short reaction times. This procedure did not result in (complete) release of the products from the TMS-groups or dendrimers. However, from SPOS methodologies it is known that large amounts of an $F^-$-source, long reaction times and higher temperatures are usually necessary to completely cleave the Si-aromatic bonds.[60-62] Indeed, using larger amounts of $^{n}Bu_4NF$, higher temperatures and longer reactions times did significantly increase the level of released product.

### *2.3.2 Considerations on the application of the TMS-protocols to dendrimer-supported synthesis protocols*

For the ultimate application of the dendrimers as synthesis support, a high loading degree is preferred but not necessary. The large dendritic structures will still result in the advantages of supported chemistry (*i.e.* ease of purification by filtration techniques),[14] even if these are not fully functionalized. As long as the remaining 'empty' positions at the dendrimer's periphery do not interfere with subsequent modification reactions, their presence is acceptable. Initially we attempted to reach a full, 100 % loading of the dendrimer's periphery. The procedures using the G1-12-Cl dendrimer (*i.e.* lithiation of a bromopyridine moiety, followed by reaction with G1-12-Cl dendrimer, resulting in dendrimers **7** and **8**)[27] did repeatedly not result in a full dendrimer loading. In the third procedure to functionalize the dendrimers, *i.e.* hydrosilylation of the G1-12-allyl dendrimer using pyridylsilane **14** to form dendrimer **15,**[55] full loading of the dendrimer's periphery was only reached after prolonged reaction times and at high catalyst loadings. This procedure is time consuming and has no major significance for the final application of the dendrimers as support (*i.e.* a high degree of functionalization is preferred, but full functionalization of the dendrimer is not required). Similar results have been described in literature for the synthesis of other carbosilane dendrimers using hydrosilylation reactions.[63-65]

As described above, the coupling reactions using the 'mimic' 2-bromo-5-trimethylsilyl-pyridine **4a** were all moderate to low yielding, partly due to purification using column

chromatography or acid-base extractions. When applying these test reactions in the dendrimer-supported modification of 2-bromopyridine, the low yields of these reactions do therefore not necessarily have to lead to inferior conversions. The use of excesses of reagents when applying these reaction types to dendrimer-supported halopyridines, in combination with size-based purification (dialysis), is expected to lead to higher conversions of the supported scaffold and to a diminished loss of (supported) material.[14,18,27]

The presence of the remaining, unreacted peripheral groupings (*i.e.* chlorosilane groupings converted into Si-OMe groupings for the first two methods;[27] allyl groupings in the third method) can be useful for the determination of the loading degree of the dendrimer. However, the integrals of the signals corresponding to the OMe groupings in the $^1$H NMR spectra of the dendritic products did not match any meaningful degree of loading (*vide infra*). The remaining allyl-groupings, on the other hand, were clearly visible in the $^1$H NMR spectra, and do serve as an internal standard to determine the loading degree of the dendrimer. In subsequent modification reactions of dendrimer **15**, any remaining allyl-groupings did not interfere with the anticipated coupling reactions and these stayed present at the dendrimer periphery. During all reaction steps the allyl-groupings were always clearly visible in the NMR spectra of the products.

*2.3.3 Functionalization of the carbosilane dendrimers with 2-bromopyridine moieties*

Three methods for the attachment of 2-bromopyridine moieties to the dendrimer periphery were investigated (section 2.3). As described above (section 3.2), the initially applied methods (*i.e.* the two procedures starting with the lithiation of a 2-bromopyridine moiety, followed by reaction with G1-12-Cl, and resulting in **7** and **8**) did result in functionalization of the dendrimers, although a full loading was not reached. The remaining reactive chlorosilane end groupings were reacted with MeOH and $NEt_3$ to convert these into less reactive Si-OMe groupings.[27] In the $^1$H NMR spectra (measured both before and after purification by dialysis), the relative integrals corresponding to these Si-OMe end groupings did not match any meaningful degree of dendrimer loading, when compared to the loading degree calculated from the dendrimer-backbone- and pyridyl-integrals. Apparently the presence of the very sensitive and reactive lithiopyridine intermediate together with the very reactive dendritic chlorosilane groupings results in the formation of side-products, in which inter- and intramolecular connections between dendritic arms were formed. Alternatively, intramolecular Si-O-Si bonds could form due to the presence of water upon introduction of MeOH and $NEt_3$. In the $^1$H NMR spectra no additional, unidentified signals were present,

which points indeed to structures comparable to the anticipated functionalized carbosilane dendritic structures, *i.e.* containing the same structural groups.

A third, new method for the functionalization of carbosilane dendrimers with 2-bromopyridine moieties was developed, in which the linking dimethylsilane group is first introduced to the pyridyl moiety (synthesis of **14**), followed by hydrosilylation of this dimethylsilyl-pyridine moiety to an allyl-terminated dendrimer, resulting in **15**. In this procedure the inter- and intramolecular reactions between the dendritic arms can not take place, which indeed results in higher degrees of dendrimer loading. Optimization of the reaction conditions (prolonged reaction times, higher catalyst loading) eventually resulted in full functionalization of the dendrimer with only one type of bromopyridine scaffold at the dendritic periphery.

The purity (*i.e.* the presence of only one specific reactive synthesis scaffold at the dendritic periphery) of dendrimers **7**, **8**, and **15** will be most important in order to synthesize only the target small molecules. The overall yields of the dendrimer functionalization reactions provide insight into the efficiency of the attachment methods. Purified yields were determined based on the amount of dendritic starting material used (*i.e.* G1-12-Cl or G1-12-allyl). In case of the syntheses of dendrimers **7** and **8**, which both start from a bromopyridine, these yields (68 and 26%, respectively) correspond well to the yields based on the amount of bromopyridine used. However, in the synthesis of **15**, the bromopyridine moiety was first converted into **14** in low yield (22%), followed by attachment of **14** to the dendrimer's periphery (40% yield based on the amount of G1-12-allyl), resulting in a much lower overall yield based on bromopyridine (9%). Therefore, for a fair comparison of the three attachment methods, calculation of the yields based on dendritic material will be preferred.[27] With this in mind, both the purities and yields of dendrimer **7**, **8**, and **15** were compared and the preferred method to arrive at the aimed product (*i.e.* dendrimer peripherally functionalized with 2-bromopyridine moieties) seems to be the synthesis of **15** via **14**. The ease of synthesis by using less sensitive intermediates and the possibility for determination of the loading degree by $^{1}$H NMR in the later method contribute to this evaluation.

### *2.3.4 Modification of dendrimer supported 2-bromopyridine and release of the coupled products*

For comparison of the three loading methods, the functionalized dendrimers **7**, **8** and **15** obtained by the reactions described above were applied in the same Suzuki coupling reactions in order to compare the efficiency of modification steps based on the different attachment

methods. All modification reactions resulted in the desired products **16**, **17** and **18** in comparable yields (84-88%) and purities. The conversions of the Suzuki coupling reactions, which were all quantitative, could be determined from the aromatic regions in the $^{1}$H NMR spectra. Release of the product from dendrimer **16** did not result in coupled product **6c**, and since this procedure is quite comparable to the procedure starting from **8** (via **17**), is left out of the comparison of the three methods. Release of products **6c** from dendrimers **17** and **18** did in both cases result in formation of products **6c**, but at the same time the yields could not be determined due to the presence of large amounts of side products that include, *e.g.*, carbosilane fragments formed by the reaction of the dendrimer support itself with $^{n}Bu_4NF$. It seems that reaction with $^{n}Bu_4NF$ not only released the product, but also damaged the dendritic structure. The small carbosilane fragments will not be retained by the dialysis bag and can not easily be separated from the products. Nevertheless, a comparison could be made based on the ease of synthesis and characterization of all reagents and products (*vide supra*, sections 3.2 and 3.3) and the combined yields from the loading and modification steps. Again, the procedure using the allyl-terminated dendrimers appeared to have more potential than the other two procedures and was used in all further dendrimer supported modification reactions.

With the bromopyridine-functionalized dendrimer **15**, the dendrimer-supported synthesis of a series of small molecules was performed using procedures obtained from the TMS-substituted modification reactions. In all cases the modification reactions were successful and the products **19**-**22** were obtained in yields of 64-72% after purification by passive dialysis. Release of the products **6d**-**6g** from dendrimers **19**-**22** in all cases resulted in recovery of the products. However, only in the synthesis of **6g** could the yield be determined (72%, based on the amount of dendrimer **22** started with**)**.

### *2.3.5 Step-wise synthesis of oligopyridines using dendrimers with peripheral functional groups*

In order to test the application of carbosilane dendrimers in multistep syntheses, the dendrimer supported stepwise synthesis of oligopyridines was investigated. As a first step in this approach, the synthesis of 6-bromo-2,2'-bipyridine **27** starting from dendrimer supported 2-bromopyridine **15** was investigated. After the coupling reaction, another functionalized (bi)pyridine moiety will then be available for modification into higher oligopyridines. A well-established method for the synthesis of bipyridines or higher oligopyridines is the palladium catalyzed Stille coupling reaction, which requires the presence of a $SnBu_3$-functional group.[47-49]

Two synthetic approaches for the preparation of 6-bromo-2,2'-bipyridine **27** were investigated. In the first approach (Method 1) the activated $SnBu_3$-grouping was first introduced to the dendrimer's periphery resulting in dendrimer **23**. The introduction of other functional groups at the dendrimer's periphery will also open a wider applicability of these dendrimers as support. Since generally the introduction of reactive groups like tributylstannyl can not be achieved using solid supports like polystyrene due to chemical incompatibility issues, another advantage of dendritic supports compared to SPOS chemistry has been established here. Application of dendrimer **23** in the palladium catalyzed Stille coupling with 2,6-dibromopyridine resulted in formation of dendrimer **25** containing bromo-bipyridine moieties that can be used for further modification into higher oligopyridines by repeating these reaction steps. In the second approach (Method 2), the functional $SnBu_3$-grouping was not attached at the dendrimer periphery. Instead $SnBu_3$-functionalized 2-bromopyridine moiety **24** was connected via a palladium catalyzed Stille coupling to the peripherally functionalized dendrimer **15**, resulting in the formation of another dendrimer supported bromo(bi)pyridine moiety (dendrimer **26**) that could be used for further modification reactions. In both approaches the release of coupled product from the dendritic scaffolds **25** and **26** indeed resulted in formation of **27**. Although the bipyridine products were not completely pure, their presence was confirmed in a test reaction using $FeSO_4$.[66]

When comparing the two approaches, both have some advantages and shortcomings. For example, dendritic starting material **15** used in the first approach is easier to obtain compared to dendrimer **23**, since the latter requires one more reaction step. However, building block **24** used in the second approach is not readily available, whereas 2,6-dibromopyridine used in the first approach is. Therefore, performing both synthetic approaches probably opens ways for further investigation of the dendrimer supported stepwise synthesis of oligopyridines.

## 2.4 Concluding Remarks

We have described a series of experiments to further demonstrate the application of carbosilane dendrimers as soluble support for the synthesis of small, pharmaceutically interesting molecules. As a proof of principle, and in addition to our previous results,[27] the modification of dendrimer-supported 2-bromopyridine moieties was investigated. The required attach-modify-release procedures were optimized using TMS as a small size 'mimic' of the dendrimers before starting the dendrimer-supported modification of bromopyridines. These TMS methods appeared to be very useful, especially for the investigation of procedures

to functionalize the dendrimers. Performing these reactions with easily recoverable, small compounds provided valuable information about the different attachment procedures. However, some problems arising by the use of the carbosilane dendrimers (*e.g.* side-reactions due to the very reactive lithio-pyridine intermediates and the chlorosilane end groupings of the dendrimers) could not have been predicted using the TMS test reactions. The modification steps in the TMS test reactions were indeed useful to serve as example for the dendrimer-supported modification reactions, despite the fact that these dendrimer-supported modifications make use of larger excess of reagents and different work-up procedures (dialysis instead of *e.g.* chromatography).

The initially applied methods for the peripheral functionalization of the dendrimers, *i.e.* via lithiation of bromopyridine and using chlorosilane terminated dendrimers, did not result in satisfactory loading degrees with one specific synthesis scaffold. Development of an improved method, starting from 2,5-dibromopyridine **3** and making use of hydrosilylation chemistry did result in the desired starting material, bromopyridine-functionalized dendrimer **15**. With dendrimer **15**, several modification reactions were performed, which in general were moderate to high yielding and resulted in purified compounds after passive dialysis. Release of the products from the dendritic scaffolds generally revealed the coupled products. By exploration of this synthetic approach (attachment-modification-release) the application of carbosilane dendrimers as soluble synthesis supports has been demonstrated. Although only a proof of principle was presented here, the methodology can be expanded and further optimized. The advantages of supported synthesis (*e.g.* easy purification by dialysis techniques) together with the homogeneous reaction conditions make the carbosilane dendrimers good candidates as soluble supports for libraries of small, pharmaceutically interesting molecules. Furthermore, the inertness and easy characterization of the carbosilane dendrimers encouraged us to attach activated groups to the dendritic periphery. Indeed, attachment of $SnBu_3$-groupings to the dendritic bromopyridine moieties and application of these dendrimers in a Stille type coupling reaction was performed successfully. These results open ways for further exploration of the use of activated dendritic scaffolds in the stepwise, dendrimer-supported synthesis of small molecules.

## 2.5 Experimental Section

All reactions were carried out under an oxygen-free, dry nitrogen atmosphere using standard Schlenk techniques. THF and toluene were dried and distilled over sodium/benzophenone prior to use. Methanol was dried and distilled over $Mg(OMe)_2$ prior to use. MeCN and DMF were dried and

distilled over $CaH_2$ prior to use. Trimethyl silyl chloride was freshly distilled and stored on molecular sieves prior to use. The carbosilane dendrimers[64,65] (G0-4-Cl, G1-12-Cl and G1-12-allyl), 2-(tributylstannyl)pyridine[47] and DMCDA (N,N'-dimethylcyclohexane-1,2-diamine)[51] were prepared according to literature procedures. All other chemicals were used as purchased. $^{1}H$, $^{13}C\{1H\}$ and $^{29}Si\{1H\}$ NMR spectra were recorded on a Varian AS400 or Varian Inova 300 instrument at room temperature unless stated otherwise. Chemical shifts are reported in ppm relative to residual solvent signals. IR-spectra were measured on a Perkin-Elmer Spectrum One FT-IR. Microanalyses were performed by Microanalytisches Laboratorium Dornis & Kolbe, Mülheim a.d. Ruhr, Germany. MALDI-TOF MS spectra were recorded on a Voyager-DE BioSpectrometry Workstation. GC-MS chromatograms and spectra were recorded on a Perkin-Elmer AutoSystem XL (GC) coupled to a TurboMass (MS). Passive dialysis was performed using benzoylated cellulose dialysis tubing (molecular weight cut off 1200 g $mol^{-1}$) purchased from Sigma-Aldrich and rinsed with a dichloromethane/methanol mixture (1:1 (v/v), technical grade) prior to use; technical grade solvents were used for dialysis.

**Lithiation of 2-bromopyridine, synthesis of 2-bromo-3-(trimethylsilyl)pyridine (2a) and 2-bromo-4-(trimethylsilyl)pyridine (2b)**[27]

To a stirred solution of fresh distilled diisopropylamine (0.77 mL, 5.5 mmol) in THF (5 mL) was dropwise added $^{n}$BuLi (1.6 M solution in hexanes, 3.75 mL, 6.0 mmol) at –100 °C. The mixture was stirred for 20 min while keeping the internal temperature below –90 °C. Subsequently, a solution of 2-bromopyridine (0.48 mL, 5.0 mmol) in THF (5 mL) was added dropwise to the mixture. After 20 min stirring at –100 °C, a solution of trimethylsilyl chloride (0.63 mL, 5.0 mmol) in THF (2 mL) was added slowly to the mixture. Subsequently the mixture was allowed to warm to room temperature in 4 h. Brine (10 mL) was added and the product was extracted with EtOAc (3 x 10 mL). The combined organic layers were died over $MgSO_4$, filtered and evaporated to dryness. The residue was further purified by column chromatography using EtOAc:hexane (1:5 (v/v)) as eluent. This procedure resulted in a mixture of 2-bromo-3-(trimethylsilyl)pyridine **2a** and 2-bromo-4-(trimethylsilyl)pyridine **2b** in a ratio of 6:4. Yield: 1.17 g (5.0 mmol, 100 %). $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 8.26 (dt, $^{4}J_{H\text{-}H}$ = 0.90 Hz, $^{3}J_{H\text{-}H}$ = 4.50 Hz, 1 H, 2 x Py$H_6$), 7.66 (dd, $^{4}J_{H\text{-}H}$ = 2.40 Hz, $^{3}J_{H\text{-}H}$ = 7.50 Hz, 0.60 H, Py$H_4$), 7.50 (t, $^{4}J_{H\text{-}H}$ = 0.90 Hz, 0.40 H, Py$H_3$), 7.27 (dd, $^{4}J_{H\text{-}H}$ = 0.90 Hz, $^{3}J_{H\text{-}H}$ = 4.50 Hz, 0.40 Hz, Py$H_5$), 7.19 (dd, $^{3}J_{H\text{-}H}$ = 4.50 Hz, $^{3}J_{H\text{-}H}$ = 7.50 Hz, 0.60 Hz, Py$H_5$), 0.36 (s, 5.40 H, SiC$H_3$), 0.25 (s, 3.60 H, SiC$H_3$).

**General procedure for the selective mono-lithiation of 2,5-dibromopyridine**[44]

A solution of 2,5-dibromopyridine (**3**) in THF (0.5 M) was cooled to –100 °C while stirring. $^{n}$BuLi (1.1 eq, 1.6 M solution in hexanes) was added slowly at –100 °C. The mixture was stirred at –100 °C for 1.5 h and quenched with 1 eq. of the appropriate electrophile. The mixture was allowed to warm to room temperature in 2 h. Brine (5 mL) and water (5 mL) were added and the mixture was extracted

with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*.

**2-bromo-5-(trimethylsilyl)pyridine (4a)**[67]

Starting from **3** (3.02 g, 12.73 mmol), $^{n}$BuLi (8.75 mL, 14.00 mmol) and chlorotrimethylsilane (1.6 mL, 12.73 mmol), crude product **4a** was obtained as a pale yellow colored oil in 86% yield (2.52 g, 10.95 mmol), which was purified by Kugelrohr (bulb-to-bulb) distillation (100 °C), yielding **4a** as a colorless liquid (2.00 g, 8.69 mmol, 68%). $^{1}$H NMR (300 MHz, $CDCl_3$): δ = 8.39 (s, 1 H, Py$H_6$), 7.60 (d, $^{3}J_{H\text{-}H}$ = 7.80 Hz, 1 H, Py$H_4$), 7.43 (d, $^{3}J_{H\text{-}H}$ = 7.80 Hz, 1 H, Py$H_3$), 0.28 (s, 9 H, Si(C$H_3$)$_3$). $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$): δ = 154.5 (Py*C*), 143.5 (Py*C*), 143.4 (Py*C*), 134.4 (Py*C*), 127.9 (Py*C*), –1.3 (Si(*C*H$_3$)$_3$). GC/MS: *m/z* 230 ($M^+$).

**2-bromo-5-(methylthio)pyridine (4b)**[68-70]

Starting from **3** (0.77 g, 3.24 mmol), $^{n}$BuLi (2.23 mL, 3.56 mmol) and dimethyldisulfide (0.29 mL, 3.24 mmol), **4b** was obtained as a red colored oil in 62 % yield (0.41 g, 2.00 mmol). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, $^{3}J_{H\text{-}H}$ = 2.40 Hz, 1 H, Py$H_6$), 7.42-7.36 (m, overlapping, 2 H, Py$H_3$ and Py$H_4$), 2.47 (s, 3 H, SC$H_3$). $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$): δ = 148.03 (Py*C*), 138.60 (Py*C*), 137.05 (Py*C*), 135.49 (Py*C*), 128.10 (Py*C*), 16.10 (*C*H$_3$). GC/MS: *m/z* 204 ($M^+$).

**6-bromopyridine-3-carbaldehyde (4c)**[71]

Starting from **3** (0.58 g, 2.47 mmol), $^{n}$BuLi (1.7 mL, 2.72 mmol) and dimethylformamide (0.19 mL, 2.47 mmol), **4c** was obtained as a pale yellow colored solid, in 75% yield (0.37 g, 1.85 mmol). $^{1}$H NMR (300 MHz, $CDCl_3$): δ = 10.07 (s, 1 H, C(O)*H*), 8.81 (d, $^{4}J_{H\text{-}H}$ = 2.40 Hz, 1 H, Py$H_6$), 7.80 (dd, $^{4}J_{H\text{-}H}$ = 2.40 Hz, $^{3}J_{H\text{-}H}$ = 8.10 Hz, 1 H, Py$H_4$), 7.66 (d, $^{3}J_{H\text{-}H}$ = 8.10 Hz, 1 H, Py$H_3$). $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$): δ = 189.77 (*C*(O)H), 152.81 (Py*C*), 148.58 (Py*C*), 137.80 (Py*C*), 130.86 (Py*C*), 129.30 (Py*C*). GC/MS: *m/z* 186 ($M^+$).

**(6-bromopyridin-3-yl)(phenyl)methanol (4d)**[72]

Starting from **3** (0.63 g, 2.67 mmol), $^{n}$BuLi (1.9 mL, 3.04 mmol) and benzaldehyde (0.27 mL, 2.67 mmol), **4d** was obtained as a yellow colored oil, although not pure, in an estimated yield of 95% (0.67 g, 2.54 mmol). $^{1}$H NMR (300 MHz, $CDCl_3$): δ = 9.92 (s, 1 H, O*H*), 8.18 (d, $^{4}J_{H\text{-}H}$ = 2.4 Hz, 1 H, Py$H_6$), 7.49 (dd, $^{4}J_{H\text{-}H}$ = 2.4 Hz, $^{3}J_{H\text{-}H}$ = 8.4 Hz, 1 H, Py$H_4$), 7.34, (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 1 H, Py$H_3$), 7.27-7.31 (m, 5 H, Ar*H*), 5.72 (s, 1 H, C(OH)*H*). $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$): δ = 148.51 (Py*C*), 142.93 (Ar*C*), 140.56 (Py*C*), 139.46 (Py*C*), 137.32 (Py*C*), 128.86 (Ar*C*), 128.12 (Py*C*), 128.00 (Ar*C*), 126.65 (Ar*C*), 73.19 (*C*H(OH)). GC/MS: *m/z* 263 ($M^+$, 83%).

**5-(trimethylsilyl)-2,2'-bipyridine (5a)**[47]

To a solution of 2-bromo-5-(trimethylsilyl)pyridine **4a** (0.92 g, 4.0 mmol) and 2-(tributylstannyl)pyridine (freshly prepared, 1.47 g, 4.0 mmol) in toluene (12 mL) was added $Pd(PPh_3)_4$ (60 mg, 40 μmol) and the mixture was heated at 120 °C for 64 h. The resulting red mixture was allowed to cool to room temperature and the volatiles were removed *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (20 mL) and the organic layer was washed with aqueous HCl (4 M, 4 x 10 mL). The combined aqueous layers were added dropwise to aqueous ammonia (10wt%, 50 mL) containing ice for internal cooling. The resulting oil was extracted from the aqueous layer with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were washed with aqueous ammonia (10wt%, 10 mL) and once with water (10 mL) and evaporated to dryness, yielding the product **5a** as a red colored oil. Yield: 0.48 g (2.1 mmol, 53%). $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.73 (s, 1 H, Py*H*), 8.64 (d, $^4J_{H\text{-}H}$ = 4.20 Hz, 1 H, Py*H*), 8.35 (dd, $^3J_{H\text{-}H}$ = 7.80 Hz, $^2J_{H\text{-}H}$ = 16.20 Hz, 2 H, Py*H*), 7.88 (d, $^3J_{H\text{-}H}$ = 7.80 Hz, 1 H, Py*H*), 7.75 (t, $^3J_{H\text{-}H}$ = 7.80 Hz, 1 H, Py*H*), 7.23 (t, $^3J_{H\text{-}H}$ = 7.80 Hz, 1 H, Py*H*), 0.28 (s, 9 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): δ = 156.51 (Py*C*), 156.39 (Py*C*), 153.60 (Py*C*), 149.42 (Py*C*), 142.30 (Py*C*), 137.08 (Py*C*), 135.45 (Py*C*), 123.93 (Py*C*), 121.28 (Py*C*), 120.48 (Py*C*), –1.07 (Si*C*$H_3$).

**2-phenylethynyl-5-(trimethylsilyl)pyridine (5b)**

A mixture of **4a** (0.5 g, 2.17 mmol), phenylacetylene (0.33 g, 3.25 mmol), triphenyl phosphine (56.9 mg, 0.217 mmol), triethyl amine (0.44 g, 4.34 mmol), copper(I) iodide (41 mg, 0.217 mmol) and $PdCl_2(PPh_3)_2$ (76.1 mg, 0.108 mmol) in dry THF (10.8 mL) was heated at 70 °C overnight. The mixture was allowed to cool to room temperature and water (10 mL) was added. The product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The product **5b** was obtained as a dark brown colored oil, together with some aromatic side product. Yield: 0.83 g. $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.68 (s, 1 H, Py*H*), 7.76 (dd, $^4J_{H\text{-}H}$ = 1.80 Hz, $^3J_{H\text{-}H}$ = 7.80 Hz, 1 H, Py*H*), 7.58 (m, 2 H, Ar*H*), 7.49 (m, 3 H, Ar*H*), 7.35 (m, 5 H, Ar*H*, side product), 7.24 (s, 1 H, Py*H*), 0.31 (s, 9 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): δ = 154.39 (Py*C*), 143.69 (Py*C*), 141.53 (Py*C*), 135.09 (Ar*C*, side product), 132.81 (Py*C*), 132.38 (Ar*C*), 129.28 (Ar*C*), 128.67 (Ar*C*), 126.71 (Py*C*), 122.59 (Ar*C*), 90.24 (Py-*C*≡C-Ar), 89.60 (Py-C≡*C*-Ar), –1.09 (Si*C*$H_3$). GC/MS: *m/z* 252 ($M^+$, 78%).

**2-*p*-tolyl-5-(trimethylsilyl)pyridine (5c)**

Two methods were investigated for the synthesis of **5c**:

Method A, Suzuki coupling:

To a solution of **4a** (0.48 g, 2.09 mmol) in a mixture of toluene:ethanol (5:1 (v/v), 12.5 mL) were added 4-tolylboronic acid (0.43 g, 3.14 mmol), $Na_2CO_3$ (2 M in water, 5.2 mL, 10.5 mmol) and $Pd(PPh_3)_4$ (24 mg, 20.9 μmol). The mixture was heated at 90 °C overnight and allowed to cool to

room temperature. Water (10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with $NaHCO_3$ (saturated solution in water, 10 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography using EtOAc:hexane (20:80 (v/v)) as eluent, yielding the product **5c** as a white solid. Yield: 0.25 g (1.03 mmol, 50%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.76 (m, $^4J_{H-H}$ = 1.00 Hz, 1 H, Py*H*), 7.91 (d, $^3J_{H-H}$ = 8.40 Hz, 2 H, Ar*H*), 7.87 (dd, $^3J_{H-H}$ = 8.00 Hz, $^4J_{H-H}$ = 2.00 Hz, 1 H, Py*H*), 7.69 (dd, $^3J_{H-H}$ = 8.00 Hz, $^4J_{H-H}$ = 0.80 Hz, 1 H, Py*H*), 7.30 (d, $^3J_{H-H}$ = 8.00 Hz, 2 H, Ar*H*), 2.41 (s, 3 H, C$H_3$), 0.33 (s, 9 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 157.38 (Py*C*), 153.46 (Py*C*), 142.82 (Py*C*), 139.73 (Ar*C*), 136.19 (Ar*C*), 133.44 (Py*C*), 129.91 (Ar*C*), 127.21 (Ar*C*), 120.22 (Py*C*), 21.64 (*C*H$_3$), –0.97 (Si*C*H$_3$). Microanalysis Calc. for $C_{15}H_{19}NSi$ (241.40): C, 74.63; H, 7.93; N, 5.80; Si, 11.63. Found: C, 73.79; H, 7.90; N, 5.74; Si, 11.90. GC/MS: *m/z* 241 ($M^+$).

Method B, Negishi coupling:

To a solution of $^t$BuLi (1.5M in pentane, 2.9 mL, 4.34 mmol) in THF (5 mL), cooled to –78 °C, was added dropwise **4a** (0.5 g, 2.17 mmol) as a solution in THF (5 mL). The resulting mixture was stirred for 1 h at –78 °C. $ZnBr_2$ (1.22 g, 5.43 mmol) in THF (5 mL) was added dropwise at –78 °C. The mixture was stirred for 1 h at –78 °C and then the cooling bath was removed and the mixture was stirred at room temperature for 1 h. Subsequently $PdCl_2(PPh_3)_2$ (76 mg, 0.11 mmol), triphenyl phosphine (114 mg, 0.434 mmol) and 4-iodotoluene (0.71 g, 3.26 mmol) were added. The resulting mixture was heated at reflux overnight and subsequently allowed to cool to room temperature. Brine (10 mL) and water (10 mL) were added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography using EtOAc:hexane (20:80 (v/v)) as eluent, yielding the product **5c** as a white crystalline solid. Yield: 0.13 g (0.54 mmol, 25%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.76 (m, $^4J_{H-H}$ = 1.00 Hz, 1 H, Py*H*), 7.91 (dd, $^3J_{H-H}$ = 8.00 Hz, $^4J_{H-H}$ = 2.00 Hz, 2 H, Ar*H*), 7.84 (dd, $^3J_{H-H}$ = 8.00 Hz, $^4J_{H-H}$ = 2.00 Hz, 1 H, Py*H*), 7.68 (dd, $^3J_{H-H}$ = 7.80 Hz, $^4J_{H-H}$ = 1.00 Hz, 1 H, Py*H*), 7.28 (dd, $^3J_{H-H}$ = 8.00 Hz, 2 H, Ar*H*), 2.41 (s, 3 H, C$H_3$), 0.33 (s, 9 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 157.53 (Py*C*), 153.79 (Py*C*), 142.33 (Py*C*), 139.39 (Ar*C*), 136.57 (Ar*C*), 133.11 (Py*C*), 129.75 (Ar*C*), 127.03 (Ar*C*), 119.94 (Py*C*), 21.54 (*C*H$_3$), –1.04 (Si*C*H$_3$). GC/MS: *m/z* 241 ($M^+$).

**2-mesityl-5-(trimethylsilyl)pyridine (5d)**[73]

To a solution of **4a** (0.5 g, 2.17 mmol) and mesityl boronic acid (0.53 g, 3.26 mmol) in a degassed mixture of toluene and ethanol (5:1 (v/v), 13 mL) were added $Pd(PPh_3)_4$ (25 mg, 21.7 μmol) and $Na_2CO_3$ (2 M in water, degassed, 5.4 mL, 10.86 mmol). The mixture was heated at 100 °C while vigorously stirring overnight and subsequently allowed to cool to room temperature. Water (20 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were

dried over $MgSO_4$, filtered and evaporated to dryness. The product **5d** was purified by column chromatography using EtOAc:hexane (20:80) as eluent. Yield: 0.13 g (0.48 mmol, 22 %). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.80 (m, 1 H, Py*H*), 7.86 (m, 1 H, Py*H*), 7.20 (m, 1 H, Py*H*), 6.95 (s, 2 H, Ar*H*), 2.33 (s, 3 H, C$H_3$), 2.05 (s, 6 H, C$H_3$), 0.37 (s, 9 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 160.13 (Py*C*), 153.66 (Py*C*), 141.23 (Py*C*), 137.72 (Ar*C*), 137.25 (Py*C*), 135.63 (Ar*C*), 132.27 (Py*C*), 128.24 (Ar*C*), 121.07 (Ar*C*), 21.09 (*C*$H_3$), 20.17 (*C*$H_3$), –1.19 (Si*C*$H_3$). GC-MS: *m/z* 269 ($M^+$).

**1-(5-(trimethylsilyl)pyridin-2-yl)pyridin-2(1*H*)-one (5e)**[50]

A solution of **4a** (0.2 g, 0.87 mmol), 2-hydroxypyridine (83 mg, 0.87 mmol), CuI (33 mg, 0.17 mmol), $K_2CO_3$ (0.24 g, 1.74 mmol) and DMCDA (24 mg, 0.17 mmol) in degassed toluene (10 mL) was stirred at 110 °C for 16 h. After cooling to room temperature, $CH_2Cl_2$ (20 mL) was added and the solution was filtered to remove the insoluble contents. The combined organic layers were washed with water (3 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. Yield of **5e**: 0.17 g (0.71 mmol, 81%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1 H, Ar*H*), 7.78 (m, 3 H, Ar*H* and 2 x Py*H*), 7.27 (m, 1 H, Ar*H*), 6.50 (d, $^3J_{H\text{-}H}$ = 9.20 Hz, 1 H, Py*H*), 6.16 (m, 1 H, Ar*H*), 0.23 (s, 9 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 162.01 (Ar*C*(O)), 152.88 (Py*C*), 152.06 (Py*C*), 142.69 (Py*C*), 140.04 (Ar*C*), 135.91 (Ar*C*), 134.79 (Py*C*), 121.78 (Ar*C*), 120.40 (Ar*C*), 106.10 (Py*C*), –1,49 (Si*C*$H_3$). GC-MS: *m/z* 244 ($M^+$).

**2-phenylethynylpyridine (6b)**[52-54,74]

To a solution of impure **5b** (0.36 g, theoretical maximum 1.43 mmol) in THF (10 mL) was added $^n$Bu$_4$NF (1M in THF, 2.86 mL, 2.86 mmol) and the mixture was stirred overnight at room temperature. $NaHCO_3$ (saturated solution in water, 10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was dissolved in EtOAc and filtered over a short plug of silica, yielding the product **6b** together with an aromatic side product. Yield: 0.29 g (theoretical maximum 1.62 mmol, 113%). $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, $^3J_{H\text{-}H}$ = 4.80 Hz, 1 H, Py*H*), 7.61 (m, 5 H, Py*H* and Ar*H*), 7.49 (m, 1 H, Ar*H*), 7.43 (m, 1 H, Ar*H*), 7.35 (m, 5 H, Ar*H*, side product), 7.22 (m, 1 H, Py*H*). GC/MS: *m/z* 179 ($M^+$).

**2-*p*-tolylpyridine (6c)**[52-54,75]

A solution of **5c** (48.7 mg, 0.202 mmol) and $^n$Bu$_4$NF (1 M solution in THF, 0.4 mL, 0.4 mmol) in THF (10 mL) was heated at 60 °C for 5 h and subsequently stirred at room temperature overnight. Aqueous saturated $NaHCO_3$ solution (10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was dissolved in EtOAc and filtered over a short plug of silica, yielding pure product **6c**

(weight of product too low to determine). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.68 (dd, $^{4}J_{H\text{-}H}$ = 1.00 Hz, $^{3}J_{H\text{-}H}$ = 4.80 Hz, 1 H, Py*H*), 7.90 (dd, $^{3}J_{H\text{-}H}$ = 8.20 Hz, $^{4}J_{H\text{-}H}$ = 1.80 Hz, 2 H, Ar*H*), 7.72 (m, 2 H, Py*H*), 7.28 (dd, $^{3}J_{H\text{-}H}$ = 8.60 Hz, $^{4}J_{H\text{-}H}$ = 0.60 Hz, 2 H, Ar*H*), 7.21 (m, 1 H, Py*H*), 2.41 (s, 3 H, C$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$): δ = 157.62 (Py*C*), 149.62 (Py*C*), 139.44 (Ar*C*), 137.30 (Py*C*), 136.57 (Ar*C*), 129.84 (Ar*C*), 127.15 (Ar*C*), 122.18 (Py*C*), 120.72 (Py*C*), 21.58 (*C*$H_3$). GC/MS: *m/z* 169 ($M^+$).

**2-bromo-5-G1(OMe)-pyridine, Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$(5-$C_5H_3$N-2)Br)$_3$}$_4$ (7)**

To a solution of 2,5-dibromopyridine **3** (3.83 g, 16.16 mmol) in THF (32 mL) was slowly added $^{n}$BuLi (1.6 M solution in hexanes, 10.10 mL, 16.16 mmol) at –100 °C. The mixture was stirred for 2 h at –100 °C. A solution of G1-12-Cl (Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$Cl)$_3$}$_4$, 1.96 g, 1.01 mmol) in THF (5 mL) was added dropwise to the mixture at –100 °C and the mixture was allowed to warm to –20 °C in 3 h. Triethylamine (3.36 mL, 24.24 mmol) and methanol (1.0 mL, 24.24 mmol) were added and the mixture was stirred for 0.5 h and allowed to warm to room temperature. Water (20 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 500 mL) overnight, yielding the product **7** as a brown oil. NMR analysis indicated a loading of 8 pyridines per dendrimer (dendrimer loading is varying per batch; on average 8-9 pyridines per dendrimer). Yield: 1.95 g (0.67 mmol, 68%). $^{1}$H NMR (300 MHz, $CDCl_3$): δ = 8.32 (s, 8 H, Py$H_6$), 7.55 (d, $^{3}J_{H\text{-}H}$ = 7.20 Hz, 8 H, Py$H_4$), 7.41 (d, $^{3}J_{H\text{-}H}$ = 7.20 Hz, 8 H, Py$H_3$), 3.45 (s, 20 H, OC$H_3$, overlap with remaining MeOH-peak), 1.23 (m, 32 H, $CH_2CH_2CH_2$), 0.85 (m, 4 H, C$H_2$SiOMe), 0.75 (m, 16 H, C$H_2$SiPy), 0.47 (m, 40 H, SiC$H_2$), 0.21 (s, 48 H, SiC$H_3$Py), 0.05 (s, 8 H, SiC$H_3$(OMe)). $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$): δ = 154.61 (Py*C*), 143.82 (Py*C*), 143.59 (Py*C*), 133.59 (Py*C*), 127.96 (Py*C*), 50.89 (O*C*$H_3$), 20.42 (*C*$H_2$), 19.28 (*C*$H_2$), 18.70 (*C*$H_2$), 18.04 (*C*$H_2$), 17.50 (*C*$H_2$), –2.85 (Si*C*$H_3$Py), –3.15 (Si*C*$H_3$OMe). MALDI-TOF-MS (Indoleacrylic acid): *m/z* 3018.97 ($M^+$, calc 3017.55 (dendrimer containing 9 pyridine groupings)).

**2-bromo-3/4-G1(OMe)-pyridine, Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$(3/4-$C_5H_3$N-2)Br)$_3$}$_4$ (8)**

To a solution of fresh distilled diisopropylamine (0.66 mL, 4.70 mmol) in THF (5 mL) was dropwise added $^{n}$BuLi (1.6 M solution in hexanes, 2.93 mL, 4.70 mmol) at –100°C. After stirring for 30 min, a solution of 2-bromopyridine (0.45 mL, 4.70 mmol) in THF (5 mL) was added dropwise at –100 °C. The temperature was maintained for another 1.5 h followed by the addition of a solution of G1-12-Cl (Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$Cl)$_3$}$_4$, 0.76 g, 0.39 mmol) in THF (5 mL) at –100 °C. The mixture was allowed to warm to room temperature overnight and methanol (0.38 mL, 9.39 mmol) and $NEt_3$ (1.30 mL, 9.39 mmol) were added. After stirring for an additional hour at room temperature, water (20 mL) was added and the product was extracted with EtOAc (3 x 20 mL) and washed with brine (20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The product

was further purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 900 mL) overnight, yielding the product **8** as a yellow oil (0.32 g, 0.10 mmol, 26%). NMR analysis indicated a loading of 10 pyridines per dendrimer, connected either at the 3- or 4- position (8:2) of the pyridine ring (dendrimer loading is varying per batch). The expected remaining OMe-groups were not visible in the NMR spectrum anymore. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.28 (br s, 10 H, Py*H*), 7.65 (m, 10 H, Py*H*), 7.49 (br s, 2 H, Py*H*), 7.20 (m, 8 H, Py*H*), 1.29 (m, 28 H, $CH_2CH_2CH_2$), 1.19 (m, 4 H, $CH_2CH_2CH_2$), 0.97 (m, 20 H, $CH_2$SiPy), 0.77 (m, 4 H, $CH_2$SiOMe), 0.52 (m, 40 H, Si$CH_2$), 0.34 (s, 60 H, Si$CH_3$Py), 0.23 (s, 12 H, Si$CH_3$(R)). MALDI-TOF-MS (Indoleacrylic acid): *m/z* 3390.86 ($M^+$, calc 3395.41 (dendrimer containing 12 pyridine groupings)).

**(3-(dimethyl(phenyl)silyl)propyl)trimethylsilane (9)**

A solution of commercial trimethylallylsilane (2 mL, 12.6 mmol), commercial dimethylphenylsilane (1.7 g, 12.6 mmol) and Karstedt's catalyst in MeCN (10 mL) was heated at 80 °C for 1 h. After cooling to room temperature, water (10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The product **9** was purified by column chromatography using EtOAc:hexane (1:4 (v/v)) as eluent. Yield: 1.65 g (6.59 mmol, 52%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.59 (m, 2 H, Ar*H*), 7.42 (m, 3 H, Ar*H*), 1.48 (m, 2 H, $CH_2CH_2CH_2$), 0.91 (t, $^3J_{H\text{-}H}$ = 8.20 Hz, 2 H, $CH_2CH_2CH_2$), 0.65 (t, $^3J_{H\text{-}H}$ = 8.20 Hz, 2 H, $CH_2CH_2CH_2$), 0.34 (s, 6 H, Si($CH_3$)$_2$), 0.04 (s, 9 H, Si($CH_3$)$_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 139.89 (Ar*C*), 133.73 (Ar*C*), 128.92 (Ar*C*), 127.90 (Ar*C*), 21.48 ($CH_2$), 20.44 ($CH_2$), 18.65 ($CH_2$), –1.29 (Si($CH_3$)$_3$), –2.66 (Si($CH_3$)$_2$). GC-MS: *m/z* 235 ($M^+$–$CH_3$).

**G0-dimethylphenyl, tetrakis(3-(dimethyl(phenyl)silyl)propyl)silane, Si{$(CH_2)_3SiMe_2(C_6H_5)$}$_4$ (10)**[25]

A solution of tetraallylsilane[64,65] (Si($CH_2CH{=}CH_2$)$_4$, 0.60 g, 3.13 mmol), commercial dimethylphenylsilane (1.7 g, 12.6 mmol) and Karstedt's catalyst in MeCN (10 mL) was heated at 80 °C overnight. After cooling to room temperature, water (10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The product was purified by column chromatography using EtOAc:hexane (1:4 (v/v)) as eluent, yielding the product **10** as a pale yellow oil. Yield: 1.73 g (2.35 mmol, 75%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.53 (m, 8 H, Ar*H*), 7.37 (m, 12 H, Ar*H*), 1.34 (m, 8 H, $CH_2CH_2CH_2$), 0.81 (t, $^3J_{H\text{-}H}$ = 8.20 Hz, 8 H, $CH_2CH_2CH_2$), 0.53 (t, $^3J_{H\text{-}H}$ = 8.20 Hz, 8 H, $CH_2CH_2CH_2$), 0.27 (s, 24 H, Si$CH_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 139.89 (Ar*C*), 133.66 (Ar*C*), 128.87 (Ar*C*), 127.86 (Ar*C*), 20.71, 18.69, 17.53 (3 x $CH_2$), –2.71 (Si$CH_3$). MALDI-TOF-MS (9-Nitroanthracene): *m/z* 844.73 ((M + Ag)$^+$, calc 844.31).

**G1-dimethylphenyl, $Si\{(CH_2)_3Si((CH_2)_3SiMe_2(C_6H_5))_3\}_4$ (11)**

A solution of G1-12-allyl ($Si\{(CH_2)_3Si(CH_2CH=CH_2)_3\}_4$, 0.59 g, 0.62 mmol), commercial dimethylphenylsilane (1.36 g, 9.98 mmol) and Karstedt's catalyst in MeCN (10 mL) was heated at 80 °C for 5 days. After cooling to room temperature, water (10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. Yield (crude): 1.45 g (0.60 mmol, 95%). The product **11** was purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 400 mL) overnight. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.48 (m, 24 H, Ar*H*), 7.32 (m, 36 H, Ar*H*), 1.33 (m, 24 H, $CH_2CH_2CH_2$), 1.25 (m, 8 H, $CH_2CH_2CH_2$), 0.78 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 24 H, $CH_2CH_2CH_2$), 0.53 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 40 H, $CH_2CH_2CH_2$), 0.23 (s, 72 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 139.82 (Ar*C*), 133.64 (Ar*C*), 128.88 (Ar*C*), 127.86 (Ar*C*), 20.75, 18.75, 18.23, 17.95, 17.55 (5 x $CH_2$), –2.65 ($SiCH_3$).

**Di-(3-pyridyl)-dimethylsilane (12)**[76]

To a solution of 3-bromopyridine (3.94 g, 24.9 mmol) in THF (50 mL) was added dropwise $^n$BuLi (1.6 M in hexanes, 15.6 mL, 24.9 mmol) at –100 °C. After 45 min stirring at –100 °C, chlorodimethylsilane (2.77 mL, 24.9 mmol) was added at –100 °C. The mixture was allowed to warm to 0 °C in 2 h. Water (20 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The product **12** was purified by column chromatography using EtOAc:hexane (20:80 (v/v)) as eluent. Yield: 0.71 g (3.31 mmol, 13%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 2 H, Py$H_2$), 8.57 (m, 2 H, Py$H_6$), 7.72 (dt, $^3J_{H\text{-}H}$ = 8.80 Hz, $^4J_{H\text{-}H}$ = 2.00 Hz, 2 H, Py$H_4$), 7.24 (m, 1 H, Py$H_5$), 0.58 (s, 6 H, $Si(CH_3)_2$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 154.51 (Py$C_2$), 150.68 (Py$C_6$), 142.08 (Py$C_4$), 132.25 (Py$C_3$), 123.66 (Py$C_5$), –2.65 ($Si(CH_3)_2$). GC-MS: *m/z* 214 ($M^+$).

**3-pyridyl-dimethylsilane (13)**[55]

To a solution of 3-bromopyridine (5.30 g, 33.54 mmol) in $Et_2O$ (33 mL) was added dropwise $^n$BuLi (1.6 M in hexanes, 20.75 mL, 33.21 mmol) at –100 °C. After 2 h stirring at –100 °C, the suspension was transferred via cannula to a solution of chlorodimethylsilane (3.6 mL, 32.20 mmol) in $Et_2O$ (10 mL) at –70 °C. The mixture was allowed to warm to room temperature in 1.5 h, yielding a yellow suspension which was washed with water (3 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The product **13** was purified by column chromatography using EtOAc:hexane (20:80 (v/v)) as eluent. Yield: 0.32 g (2.33 mmol, 7%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 1 H, Py$H_2$), 8.55 (d, $^3J_{H\text{-}H}$ = 4.80 Hz, 1 H, Py$H_6$), 7.77 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 1 H, Py$H_4$), 7.22 (t, $^3J_{H\text{-}H}$ = 6.80 Hz, 1 H, Py$H_5$), 4.42 (sept, $^3J_{H\text{-}H}$ = 3.60 Hz, 1 H, Si*H*), 0.33 (d, $^3J_{H\text{-}H}$ = 4.00 Hz, 6 H, $Si(CH_3)_2$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 154.51 (Py$C_2$), 150.41 (Py$C_6$), 142.05 (Py$C_4$), 132.65 (Py$C_3$), 123.54 (Py$C_5$), –3.84 ($Si(CH_3)_2$). GC-MS: *m/z* 137 ($M^+$).

**2-bromo-5-dimethylsilyl-pyridine (14)**[55]

To a solution of 2,5-dibromopyridine **3** (1.97 g, 8.32 mmol) in $Et_2O$ (16.5 mL) was added dropwise $^{n}$BuLi (1.6 M in hexanes, 5.14 mL, 8.23 mmol) at –100 °C. After 1.5 h stirring at –100 °C, the suspension was transferred via cannula to a solution of chlorodimethylsilane (0.9 mL, 7.9 mmol) in $Et_2O$ (10 mL) at –100 °C. The mixture was allowed to warm to room temperature in 2.5 h. Water (20 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The product **14** was purified by column chromatography using EtOAc:hexane (20:80 (v/v)) as eluent and obtained together with some side-product, only visible in the $^{13}$C NMR spectrum (isomer?). Yield: 0.40 g (1.85 mmol, 22%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H, Py*H*$_6$), 7.60 (dd, $^{3}J_{H\text{-}H}$ = 7.60 Hz, $^{4}J_{H\text{-}H}$ = 2.00 Hz, 1 H, Py*H*$_4$), 7.41 (dd, $^{3}J_{H\text{-}H}$ = 8.00 Hz, $^{4}J_{H\text{-}H}$ = 0.80 Hz, 1 H, Py*H*$_3$), 4.38 (sept, $^{3}J_{H\text{-}H}$ = 3.80 Hz, 1 H, Si*H*), 0.32 (d, $^{3}J_{H\text{-}H}$ = 4.00 Hz, 6 H, Si(C*H*$_3$)$_2$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$): δ = 154.75 (Py*C*), 151.19 (Py*C*), 143.99 (Py*C*), 143.71 (side product), 142.88 (side product), 141.12 (side product), 140.38 (side product), 131.44 (Py*C*), 129.48 (side product), 127.78 (Py*C*), 120.00 (side product), –4.09 (Si*C*H$_3$). GC-MS: *m/z* 216 ($M^+$).

**2-bromo-5-G1(allyl)-pyridine, Si{(CH$_2$)$_3$Si((CH$_2$)$_3$SiMe$_2$(5-C$_5$H$_3$N-2)Br)$_3$}$_4$ (15)**

A solution of G1-12-allyl (Si{(CH$_2$)$_3$Si(CH$_2$CH=CH$_2$)$_3$}$_4$, 0.74 g, 0.92 mmol), **14** (2.59 g, 11.98 mmol) and Karstedt catalyst ((C$_8$H$_{18}$OSi$_2$)$_3$Pt$_2$, 2 wt% Pt solution in xylenes, 0.5 g, 26 μmol) in MeCN (5 mL) was stirred at room temperature overnight. An additional amount of Karstedt catalyst ((C$_8$H$_{18}$OSi$_2$)$_3$Pt$_2$, 2 wt% Pt solution in xylenes, 0.5 g, 26 μmol) was added and the mixture was stirred for 4 more hours at room temperature. The solvent was removed *in vacuo* and the residue was purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 600 mL) for 48 h, yielding the product **15** as a brown oil. NMR analysis indicated an average loading of 9 pyridines per dendrimer (dendrimer loading is slightly different for each batch). Yield: 1.24 g (0.37 mmol, 40%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 9 H, Py*H*), 7.58 (d, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 9 H, Py*H*), 7.43 (d, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 9 H, Py*H*), 5.69 (m, 3 H, CH$_2$C*H*=CH$_2$), 4.74 (m, 6 H, CH$_2$CH=C*H*$_2$), 1.47 (m, 6 H, C*H*$_2$CH=CH$_2$), 1.25 (m, 26 H, CH$_2$C*H*$_2$CH$_2$), 0.78 (t, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 18 H, C*H*$_2$SiPy), 0.50 (m, 34 H, SiC*H*$_2$), 0.23 (s, 54 H, SiC*H*$_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$): δ = 154.40 (Py*C*), 143.61 (Py*C*), 143.38 (Py*C*), 133.39 (Py*C*), 127.75 (Py*C*), 119.31 (CH$_2$*C*H=CH$_2$), 113.10 (CH$_2$CH=*C*H$_2$), 20.21 (*C*H$_2$SiPy), 19.97 (CH$_2$*C*H$_2$CH$_2$SiPy), 18.50 (CH$_2$*C*H$_2$CH$_2$), 17.80 (Si*C*H$_2$), 17.29 (Si*C*H$_2$CH$_2$), –3.03 (Si*C*H$_3$). $^{29}$Si{$^{1}$H} NMR (60 MHz, $CDCl_3$): δ 0.27 (*Si*$_{core}$+*Si*$_{inner}$), –3.55 (*Si*-Py). Microanalysis Calc. for C$_{111}$H$_{174}$Br$_9$N$_9$Si$_{14}$ (9 pyridine groupings, 2746.96): C, 48.53; H, 6.38; N, 4.59; Br, 26.18; Si, 14.31. Found: C, 48.39; H, 6.36; N, 4.52; Br, 26.18; Si, 14.39.

**2-*p*-tolyl-5-G1(OMe)-pyridine, Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$(5-$C_5H_3N$-2)$C_6H_4CH_3$)$_3$}$_4$ (16)**

To a solution of 2-bromo-5-G1(OMe)-pyridine **7** (7.5 pyridines, 0.58 g, 0.204 mmol) and 4-tolyl boronic acid (0.57 g, 2.71 mmol) in a degassed toluene:ethanol mixture (5:1 (v/v), 12.2 mL) were added $Pd(PPh_3)_4$ (23.5 mg, 20 μmol) and $Na_2CO_3$ (2 M solution in water, degassed, 5.1 mL, 10.17 mmol). The mixture was heated at 90 °C for 16 h and allowed to cool to room temperature. Water (20 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with $NaHCO_3$ (saturated aqueous solution, 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 500 mL) for 2 h, yielding the product **16** as a brown oil. NMR analysis indicated an average loading of 7.5 pyridyl groupings per dendrimer. Yield: 0.52 g (0.18 mmol, 88%). $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.70 (s, 7.50 H, Py*H*), 7.87 (d, $^3J_{H\text{-}H}$ = 6.30 Hz, 15 H, Ar*H*), 7.73 (m, 7.5 H, Py*H*), 7.61 (m, 7.5 H, Py*H*), 7.25 (m, 15 H, Ar*H*), 3.44 (s, 6 H, OC$H_3$), 2.38 (s, 22.5 H, ArC$H_3$), 1.32 (m, 32 H, $CH_2CH_2CH_2$), 0.81 (m, 24 H, $CH_2$SiOMe and $CH_2$SiPy), 0.55 (m, 40 H, SiC$H_2$), 0.24 (m, 55 H, SiC$H_3$Py), –0.07 (s, 6 H, SiC$H_3$(OMe)).

**Release of 2-*p*-tolylpyridine (6c) from 16**[52-54]

To a solution of **16** (0.496 g, 0.14 mmol) in THF (10 mL) was added $^n$Bu$_4$NF (1.0 M solution in THF, 3.37 mL, 3.37 mmol). The mixture was stirred at room temperature for 3 h. $NaHCO_3$ (saturated aqueous solution, 10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water and dried over $MgSO_4$, filtered and evaporated to dryness. The product was isolated by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 400 mL) overnight, yielding a residue from the beaker solution which was filtered over a short plug of silica, yielding a residue of 0.04 g. $^1$H NMR analysis of this residue did not show released **6c**. $^1$H NMR analysis of the solution obtained from the inside of the dialysis bag indicated the presence of the starting material, the loaded dendrimer.

Bag: $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.72 (br s, 7.50 H, Py*H*), 7.90 (br s, 15 H, Ar*H*), 7.75 (br s, 7.5 H, Py*H*), 7.63 (br s, 7.5 H, Py*H*), 7.26 (br s, 15 H, Ar*H*), 2.40 (br s, 22.5 H, ArC$H_3$), 1.35 (m, 32 H, $CH_2CH_2CH_2$), 0.83 (m, 24 H, $CH_2$SiOMe and $CH_2$SiPy), 0.56 (m, 40 H, SiC$H_2$), 0.26 (m, 48 H, SiC$H_3$Py), 0.03 (s, 13 H, SiC$H_3$(OMe)).

**2-*p*-tolyl-3/4-G1(OMe)-pyridine, Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$(3/4-$C_5H_3N$-2)$C_6H_4CH_3$)$_3$}$_4$ (17)**

To a solution of **8** (0.30 g, 88 μmol) and 4-tolyl boronic acid (0.216 g, 1.59 mmol) in a degassed toluene:ethanol mixture (5:1 (v/v), 6.4 mL) were added $Pd(PPh_3)_4$ (12.3 mg, 10.6 μmol) and $Na_2CO_3$ (2 M solution in water, degassed, 2.65 mL, 5.3 mmol). The mixture was heated at 100 °C for 20 h and allowed to cool to room temperature. The product was purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 500 mL) overnight, yielding the product **17**, although not completely pure and not fully loaded, as a yellow oil. Yield: 0.26 g (theoretical maximum 79.9 μmol,

84%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.56 (br s, 10 H, Py*H*), 7.79 (m, 12 H, Py*H*), 7.24 (m, 20 H, Ar*H*), 7.17 (m, 28 H, Py*H* and Ar*H*), 2.34 (s, 30 H, C$H_3$), 1.20 (m, 32 H, $CH_2CH_2CH_2$), 0.78 (m, 4 H, $CH_2$SiOMe), 0.45 (m, 60 H, $CH_2$SiPy and Si$CH_2$), 0.22 (m, 12 H, Si$CH_3$(OMe)), –0.07 (s, 60 H, Si$CH_3$Py). $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$): δ = 165.23 (Py*C*), 148.65 (Py*C*), 143.82 (Py*C*), 140.28 (Ar*C*), 138.08 (Py*C*), 132.86 (Py*C*), 129.59 (Ar*C*), 128.87 (Ar*C*), 128.68 (Ar*C*), 126.99 (Py*C*), 121.31 (Py*C*), 21.45 ($CH_3$), 21.37 ($CH_2$), 18.66 ($CH_2$), 18.16 ($CH_2$), 17.91 ($CH_2$), 17.39 ($CH_2$), –1.36 (Si$CH_3$).

**Release of 2-*p*-tolylpyridine (6c) from 17**[52-54]

To a solution of **17** (62 mg, 19 μmol) in THF (10 mL) was added $^{n}Bu_4NF$ (1.0 M solution in THF, 0.6 mL, 0.6 mmol). The mixture was stirred at 60 °C overnight and allowed to cool to room temperature. Water (10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness, yielding the product **6c** together with excess of $^{n}Bu_4NF$ (not described in NMR data). Yield: 0.15 g. $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.47 (dd, $^{3}J_{H\text{-}H}$ = 4.80 Hz, $^{4}J_{H\text{-}H}$ = 0.80 Hz, 1 H, Py*H*), 7.71 (d, $^{3}J_{H\text{-}H}$ = 8.40 Hz, 2 H, Ar*H*), 7.54 (m, 2 H, Py*H*), 7.09 (d, $^{3}J_{H\text{-}H}$ = 8.40 Hz, 2 H, Ar*H*), 7.03 (m, 1 H, Py*H*), 2.22 (s, 3 H, C$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$): δ = 156.89 (Py*C*), 148.92 (Py*C*), 138.83 (Ar*C*), 136.95 (Py*C*), 135.93 (Ar*C*), 129.25 (Ar*C*), 126.56 (Ar*C*), 121.74 (Py*C*), 120.25 (Py*C*), 19.87 ($CH_3$). GC-MS: *m/z* 169 ($M^+$).

**2-*p*-tolyl-5-G1(allyl)-pyridine, Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$(5-$C_5H_3N$-2)$C_6H_4CH_3)_3$}$_4$ (18)**

To a solution of 2-bromo-5-G1(allyl)-pyridine **15** (0.50 g, 0.15 mmol) and 4-tolyl boronic acid (0.36 g, 2.65 mmol) in a degassed toluene:ethanol mixture (5:1 (v/v), 10.6 mL) were added $Pd(PPh_3)_4$ (20 mg, 17.7 μmol) and $Na_2CO_3$ (2 M solution in water, degassed, 4.4 mL, 8.84 mmol). The mixture was heated at 100 °C overnight and allowed to cool to room temperature. Water (20 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 500 mL) overnight, yielding the product **18** as a brownish oil. NMR analysis indicated an average loading of 9 *p*-tolylpyridyl groupings and 3 remaining allyl groupings per dendrimer. Yield: 0.35 g (0.12 mmol, 84%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.70 (br s, 9 H, Py*H*), 7.87 (br s, 18 H, Ar*H*), 7.73 (br s, 9 H, Py*H*), 7.61 (br s, 9 H, Py*H*), 7.25 (br s, 18 H, Ar*H*), 5.70 (m, 3 H, $CH_2CH$=$CH_2$), 4.78 (m, 6 H, $CH_2CH$=C$H_2$), 2.39 (s, 27 H, C$H_3$), 1.50 (dd, $^{3}J_{H\text{-}H}$ = 17.60 Hz, $^{4}J_{H\text{-}H}$ = 7.20 Hz, 6 H, C$H_2$CH=$CH_2$), 1.34 (m, 26 H, $CH_2CH_2CH_2$), 0.82 (m, 18 H, C$H_2$SiPy), 0.55 (m, 34 H, Si$CH_2$), 0.24 (s, 54 H, Si$CH_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$): δ = 157.56 (Py*C*), 154.17 (Py*C*), 142.21 (Py*C*), 139.22 (Ar*C*), 136.77 (Ar*C*), 134.98 ($CH_2CH$=$CH_2$), 132.16 (Py*C*), 129.69 (Ar*C*), 126.93 (Ar*C*), 119.69 (Py*C*), 113.12 ($CH_2CH$=$CH_2$), 21.51 ($CH_3$), 20.56 ($CH_2$SiPy), 18.77 ($CH_2CH_2CH_2$SiPy), 18.60 ($CH_2CH_2CH_2$), 17.57 (Si$CH_2$), 17.29 (Si$CH_2CH_2CH_2$), –2.77 (Si$CH_3$).

**Release of 2-*p*-tolylpyridine (6c) from 18**[52-54]

To a solution of **18** (0.03 g, 8.5 μmol) in THF (5 mL) was added $^{n}Bu_4NF$ (1.0 M solution in THF, 0.21 mL, 0.21 mmol). The mixture was stirred at 60 °C overnight and allowed to cool to room temperature. Water (10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated to dryness, yielding the product **6c** together with excess of $^{n}Bu_4NF$. The residue was dissolved in EtOAc and filtered over a short plug of silica. Yield: 0.02 g (theoretical maximum 0.118 mmol, 116%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, $^3J_{H\text{-}H}$ = 4.80 Hz, 1 H, Py*H*), 7.89 (d, $^3J_{H\text{-}H}$ = 8.00 Hz, 2 H, Ar*H*), 7.74 (m, 2 H, Py*H*), 7.28 (d, $^3J_{H\text{-}H}$ = 8.00 Hz, 2 H, Ar*H*), 7.23 (m, 1 H, Py*H*), 2.41 (s, 3 H, C$H_3$). GC-MS: *m/z* 169 ($M^+$).

**2-mesityl-5-G1(allyl)-pyridine (19)**

To a solution of 2-bromo-5-G1(allyl)-pyridine **15** (9 pyridine groupings, 0.10 g, 36.5 μmol) and mesityl boronic acid (0.11 g, 0.66 mmol) in a degassed toluene:ethanol mixture (5:1 (v/v), 2.6 mL) were added $Pd(PPh_3)_4$ (5.1 mg, 4.4 μmol) and $Na_2CO_3$ (2 M solution in water, degassed, 1.1 mL, 2.2 mmol). The mixture was heated at 100 °C for 24 h and allowed to cool to room temperature. Water (20 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 400 mL) overnight, yielding the product **19** as a brownish oil. NMR analysis indicated an average loading of 3 allyl, 5 mesitylpyridyl and 4 unsubstituted pyridyl grouping per dendrimer. Yield: 77 mg (26.2 μmol, 72%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.72 (br s, 4 H, Py*H*), 8.36 (br s, 5 H, Py*H*), 8.17 (br s, 1 H, Py*H*, side product), 7.78 (br s, 4 H, Py*H*), 7.56 (br s, 5 H, Py*H*), 7.41 (br s, 5 H, Py*H*), 7.16 (br s, 4 H, Py*H*), 6.91 (br s, 10 H, Ar*H*), 6.68 (br s, 2 H, Ar*H*, side product), 5.69 (m, 3 H, $CH_2CH$=$CH_2$), 4.78 (m, 6 H, $CH_2CH$=C$H_2$), 4.32 (m, 2 H, side product), 2.31 (s, 15 H, C$H_3$), 1.99 (s, 30 H, C$H_3$), 1.48 (m, 6 H, C$H_2$CH=$CH_2$), 1.33 (m, 26 H, $CH_2CH_2CH_2$), 0.85 (m, 8 H, C$H_2$SiPy), 0.79 (m, 10 H, C$H_2$SiPy), 0.54 (m, 34 H, SiC$H_2$), 0.30 (s, 24 H, SiC$H_3$), 0.24 (s, 30 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 154.47 (Ar*C*), 143.60 (Ar*C*), 143.44 (Ar*C*), 133.39 (Ar*C*), 132.22 (Ar*C*), 132.12 (Ar*C*), 132.02 (Ar*C*), 128.65 (Ar*C*), 128.48 (Ar*C*), 127.74 (Ar*C*), 127.15 (Ar*C*), 21.51 (*C*$H_3$), 20.22 (*C*$H_3$), 18.52, 18.35, 17.78, 17.32, 17.08 (5 x *C*$H_2$), –3.03 (Si*C*$H_3$).

**Release of 2-mestitylpyridine (6d) from 19**[52-54,73]

To a solution of **19** (16.6 mg, 5.6 μmol) in THF (5 mL) was added $^{n}Bu_4NF$ (1.0 M solution in THF, 0.1 mL, 0.1 mmol). The mixture was stirred at room temperature for 2 h. Water (10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were filtered over a short plug of silica twice and evaporated to dryness, yielding the product **6d** together with excess of $^{n}Bu_4NF$ (not reported in NMR data). Yield too low to determine. $^1$H NMR (400 MHz,

$CDCl_3$): δ = 8.10 (s, 1 H, Py*H*), 7.48 (m, 3 H, Py*H*), 7.00 (s, 2 H, Ar*H*), 2.34 (s, 3 H, C$H_3$), 2.13 (s, 6 H, C$H_3$). GC-MS: *m/z* 196 ($M^+$).

**1-(5-(G1)pyridin-2-yl)pyridin-2(1*H*)-one (20)**[50]

A solution of 2-bromo-5-G1(allyl)-pyridine **15** (9 pyridine groupings, 0.1 g, 36.5 μmol), 2-hydroxypyridine (42 mg, 0.44 mmol), CuI (17 mg, 87 μmol), $K_2CO_3$ (0.12 g, 0.87 mmol) and DMCDA (prepared following literature procedure,[51] 41 mg, 0.29 mmol) in degassed toluene (10 mL) was stirred at 110°C for 24 h. After cooling to room temperature, $CH_2Cl_2$ (40 mL) was added and the solution was filtered to remove the insoluble contents. The combined organic layers were washed with water (3 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The product was further purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 400 mL) overnight, yielding the product **20** as a brownish oil. NMR analysis indicated an average loading of 9 substituted pyridine groupings and 3 allyl groups per dendrimer. Yield: 67 mg (23.3 μmol, 64%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.55 (s, 9 H, Ar*H*), 7.85 (s, 18 H, Ar*H* and Py*H*), 7.82 (s, 1 H, Py*H*), 7.35 (t, $^3J_{H\text{-}H}$ = 7.00 Hz, 9 H, Ar*H*), 6.59 (d, $^3J_{H\text{-}H}$ = 9.20 Hz, 9 H, Py*H*), 6.24 (s, 9 H, Ar*H*), 5.70 (m, $^3J_{H\text{-}H}$ = 8.40 Hz, 3 H, $CH_2CH$=$CH_2$), 4.76 (m, 6 H, $CH_2CH$=C$H_2$), 1.49 (m, 6 H, C$H_2CH$=$CH_2$), 1.34 (m, 26 H, $CH_2CH_2CH_2$), 0.82 (t, $^3J_{H\text{-}H}$ = 7.60 Hz, 18 H, C$H_2$SiPy), 0.56 (m, 34 H, SiC$H_2$), 0.25 (s, 54 H, SiC$H_3$).

**Release of 1-(pyridin-2-yl)pyridin-2(1*H*)-one (6e) from 20**[50,52-54]

To a solution of **20** (19 mg, 6.6 μmol) in THF (5 mL) was added $^n$Bu$_4$NF (1.0 M solution in THF, 0.15 mL, 0.15 mmol). The mixture was stirred at room temperature overnight. Water (5 mL) was added the mixture was evaporated to dryness. $CH_2Cl_2$ (10 mL) and water (10 mL) were added and the product was extracted with $CH_2Cl_2$ (2 x 20 mL). The combined organic layers were evaporated to dryness, yielding the product together with excess of $^n$Bu$_4$NF. The product **6e** was further purified by dissolving the residue in EtOAc and filtering over a short plug of silica. This removed the excess of $^n$Bu$_4$NF, but the yield was too low to determine. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1 H, Ar*H*), 7.95 (d, $^3J_{H\text{-}H}$ = 8.40 Hz, 1 H, Py*H*), 7.86 (m, 2 H, Ar*H* and Py*H*), 7.40 (d, $^3J_{H\text{-}H}$ = 7.20 Hz, 1 H, Py*H*), 7.33 (m, 1 H, Ar*H*), 6.64 (d, $^3J_{H\text{-}H}$ = 9.20 Hz, 1 H, Py*H*), 6.31 (t, $^3J_{H\text{-}H}$ = 6.40 Hz, 1 H, Ar*H*). GC-MS: *m/z* 196 ($M^+$ + 24).

**2-methylbenzylamine-5-G1(allyl)-pyridine, Si{$(CH_2)_3$Si(($CH_2)_3$SiMe$_2$(2-*N*-methylbenzylamine-pyridine-5))$_3$}$_4$ (21)**[42]

To a solution of 2-bromo-5-G1(allyl)-pyridine **15** (0.11 g, 40 μmol) in toluene (4.4 mL) were added NaO$^t$Bu (60 mg, 0.67 mmol), 1,3-bis(diphenylphosphino)propane (dppp, 7.9 mg, 19.2 μmol), $Pd_2(dba)_3$·$CHCl_3$ (9.9 mg, 9.6 μmol) and *N*-methylbenzylamine (0.07 mL, 0.58 mmol). The mixture was heated at 70 °C overnight and allowed to cool to room temperature. The mixture was diluted with $Et_2O$ (20 mL) and washed with brine (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered

and evaporated to dryness, yielding the product **21** as a colorless oil. Yield: 0.20 g (29 μmol, 72%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.26 (br s, 12 H, Py*H*), 7.49 (m, $^{3}J_{H\text{-}H}$ = 2.00 Hz, 12 H, Py*H*), 7.28 (br s, 24 H, Ar*H*), 7.22 (br s, 36 H, Ar*H*), 6.49 (br s, 12 H, Py*H*), 4.79 (s, 24 H, C$H_2$), 3.04 (t, $^{3}J_{H\text{-}H}$ = 2.40 Hz, C$H_3$), 1.37 (m, 32 H, $CH_2CH_2CH_2$), 0.78 (m, 24 H, C$H_2$SiPy), 0.58 (m, 40 H, SiC$H_2$), 0.21 (s, 72 H, SiC$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$): δ = 159.13 (Py*C*), 153.04 (Py*C*), 142.56 (Py*C*), 138.78 (Ar*C*), 128.60 (Ar*C*), 127.11 (Ar*C*), 126.97 (Ar*C*), 119.30 (Py*C*), 105.41(Py*C*), 53.03 (*C*$H_2$), 35.99 (*C*$H_3$), 20.90 (*C*$H_2$SiPy), 18.73 ($CH_2CH_2CH_2$SiPy), 17.99 ($CH_2CH_2CH_2$), 17.91 (Si*C*$H_2$), 17.56 (Si*C*$H_2CH_2$), –2.58 (Si*C*$H_3$).

**Release of 2-*N*-methylbenzylamine-pyridine (6f) from 21**[42,52-54]

To a solution of **21** (0.10 g, 32 μmol) in THF (5 mL) was added $^{n}Bu_4NF$ (1.0 M in THF, 1.0 mL, 1.0 mmol). The mixture was stirred at 60 °C for 6.5 h and allowed to cool to room temperature. The reaction mixture was filtered over a short plug of silica and from the NMR spectra it was clear that the product was not cleaved from the dendrimer yet. Fresh THF (5 mL) and $^{n}Bu_4NF$ (1.0 M in THF, 2.0 mL, 2.0 mmol) were added and the mixture was heated at 65 °C for 8 h. After cooling to room temperature, the volatiles were removed *in vacuo* and the residue was filtered over a short plug of silica using $CH_2Cl_2$ as solvent, yielding less than 0.001 g of the product **6f** in a mixture with some alkyl fragments (not described in NMR data). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H, Py*H*), 7.42 (m, 1 H, Py*H*), 7.22-7.15 (m, 6 H, Py*H* and Ar*H*), 6.43 (m, 1 H, Py*H*), 4.72 (br s. 2 H, C$H_2$), 2.98 (br s, 3 H, C$H_3$). GC-MS: *m/z* 198 ($M^+$).

**2-thiophenol-5-G1(allyl)-pyridine, Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$(5-$C_5H_3$N-2)S$C_6H_5$)$_3$}$_4$ (22)**[57]

To a solution of 2-bromo-5-G1(allyl)-pyridine **15** (0.17 g, 85 μmol) in DMF (4 mL) were added $NEt_3$ (0.29 mL, 2.04 mmol) and thiophenol (0.21 mL, 2.04 mmol). The mixture was heated at 110 °C for 20 h and allowed to cool to room temperature. NaOH (1 M in water, 10 mL) was added and the product was extracted with $Et_2O$ (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The product was further purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 400 mL) for 3 h, yielding the product **22** as an oil. Yield: 0.18 g (59.8 μmol, 70%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.41 (br s, 12 H, Py*H*), 7.53 (br s, 24 H, Ar*H*), 7.46 (br s, 12 H, Py*H*), 7.37 (br s, 36 H, overlapping Py*H* and Ar*H*), 6.80 (br s, 12 H, Ar*H*), 5.26 (br s, 0.6 H, C*H*=$CH_2$), 4.75 (br s, 1.4 H, CH=C$H_2$), 1.25 (m, 32 H, $CH_2CH_2CH_2$), 0.73 (m, 24 H, C$H_2$SiPy), 0.50 (m, 40 H, SiC$H_2$), 0.17 (s, 72 H, SiC$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$): δ = 162.20 (Py*C*), 153.66 (Py*C*), 141.92 (Py*C*), 135.11 (Ar*C*), 130.61 (overlapping, 2 x Ar*C*), 129.65 (Py*C*), 129.20 (Ar*C*), 120.61 (Py*C*), 20.30 (*C*$H_2$SiPy), 18.50 ($CH_2CH_2CH_2$SiPy), 18.33 ($CH_2CH_2CH_2$), 17.81 (Si*C*$H_2$), 17.32 (Si*C*$H_2CH_2$), –2.97 (Si*C*$H_3$).

**Release of 2-thiophenyl-pyridine (6g) from 22**[52-54,57]

To a solution of **22** (0.14 g, 45 μmol) in THF (5 mL) was added $^{n}Bu_4NF$ (1.0 M in THF, 1.1 mL, 1.1 mmol). The mixture was stirred at 60 °C overnight and allowed to cool to room temperature. Water and brine were added and the product was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. After filtration over a short plug of silica using EtOAc as eluent, the product **6g** was obtained in a mixture with some alkyl fragments (not described in NMR data). Yield: 73 mg (theoretical maximum 0.39 mmol, 72%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.41 (br s, 1 H, Py*H*), 7.59 (m, 2 H, Ar*H*), 7.45 (t, $^3J_{H\text{-}H}$ = 7.40 Hz, 1 H, Py*H*), 7.41 (m, 3 H, overlapping Py*H* and Ar*H*), 6.99 (t, $^3J_{H\text{-}H}$ = 5.40 Hz, 1 H, Ar*H*), 6.88 (d, $^3J_{H\text{-}H}$ = 8.00 Hz, 1 H, Py*H*). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 161.58 (Py*C*), 149.50 (Py*C*), 136.89 (Py*C*), 135.03 (Ar*C*), 131.04 (overlapping, 2 x Ar*C*), 129.73 (Ar*C*), 129.20 (Py*C*), 121.46 (Py*C*), 119.97 (Ar*C*). GC-MS: *m/z* 186 ($M^+$).

**2-SnBu$_3$-5-G1-pyridine, Si{(CH$_2$)$_3$Si((CH$_2$)$_3$SiMe$_2$(5-C$_5$H$_3$N-2)SnBu$_3$)$_3$}$_4$ (23)**

To a solution of 2-bromo-5-G1(allyl)-pyridine **15** (0.15 g, 46 μmol) in THF (20 mL) was dropwise added $^{n}$BuLi (1.6 M in hexanes, 0.4 mL, 0.61 mmol) at –100 °C. After 1.5 h, $SnBu_3Cl$ (0.3 mL, 1.10 mmol) was added dropwise at –100 °C. The mixture was allowed to warm to room temperature in 2 h. Water (20 mL) and brine (10 mL) were added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 500 mL) overnight, yielding the product **23** as an oil. NMR analysis indicated an average loading of 9 tributyltin groupings and 3 unsubstituted pyridines per dendrimer. Yield: 0.19 g (37.5 μmol, 82%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.76 (s, 9 H, Py*H*), 8.63 (s, 3 H, Py*H*), 8.52 (s, 3 H, Py*H*), 7.70 (s, 3 H, Py*H*), 7.51 (br s, 9 H, Py*H*), 7.34 (d, $^3J_{H\text{-}H}$ = 7.20 Hz, 9 H, Py*H*), 7.18 (s, 3 H, Py*H*), 1.54 (m, $^3J_{H\text{-}H}$ = 7.80 Hz, 54 H, C$H_2$), 1.32 (m, 113 H, C$H_3$ and $CH_2CH_2CH_2$), 1.09 (t, $^3J_{H\text{-}H}$ = 8.20 Hz, 54 H, C$H_2$), 0.85 (t, $^3J_{H\text{-}H}$ = 7.20 Hz, 54 H, C$H_2$), 0.81 (m, 24 H, C$H_2$SiPy), 0.54 (m, 40 H, SiC$H_2$), 0.21 (s, 72 H, SiC$H_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 154.67 (Py*C*), 154.22 (Py*C*), 150.11 (Py*C*), 141.31 (Py*C*), 138.52 (Py*C*), 132.14 (Py*C*), 123.35 (Py*C*), 29.29 ($SnCH_2CH_2CH_2CH_3$), 27.56 ($SnCH_2CH_2CH_2CH_3$), 20.49 (*C*$H_2$), 18.75 (*C*$H_2$), 18.57 (overlapping, 2 x *C*$H_2$), 17.61 (*C*$H_2$), 13.90 ($SnCH_2CH_2CH_2CH_3$), 8.97 ($SnCH_2CH_2CH_2CH_3$), –2.85 (Si*C*$H_3$).

**2-bromo-6-SnBu$_3$-pyridine (24)**[59]

A solution of 2,6-dibromopyridine (1.00 g, 4.22 mmol) in $Et_2O$ (56 mL) was cooled to –50 °C using a liquid nitrogen/ethanol bath. Excess of $^{n}$BuLi (1.6 M solution in hexanes, 5.6 mL, 8.96 mmol) was added dropwise within 3 min to the white suspension at –50 °C. After stirring for 30 min at –50 °C, the temperature was lowered to –60 °C and $SnBu_3Cl$ (2.72 mL, 10.1 mmol) was added dropwise

within 5 min. The temperature was maintained at –60 °C for 30 min and then lowered to –78 °C for an additional hour. The mixture was allowed to warm to room temperature overnight. The white solids were removed by centrifugation and decantation and the solvent was removed *in vacuo*. The product **24** was used in following reaction steps without further purification. GC-MS: *m/z* 390 ($M^+$–Bu).

**G1-bromo-bipyridines 25 and 26, and 6-bromo-2,2'-bipyridine (27)**

Method 1:

**G1-bipyridine-Br, Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$(5-$C_5H_3N$-2)$C_5H_3$Br-6)$_3$}$_4$ (25)**[47]

To a solution of 2-Sn$Bu_3$-5-G1-pyridine **23** (80 mg, 16 μmol) in degassed toluene were added 2,6-dibromopyridine (50 mg, 0.21 mmol) and Pd($PPh_3$)$_4$ (11 mg, 9.5 μmol). The mixture was stirred at 100 °C for 20 h and allowed to cool to room temperature. The product was purified by passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 500 mL) for 6 h, yielding the product **25** as orange oil. NMR analysis indicated the presence of a mixture containing the desired immobilized bipyridine and some pyridyl-based side products. Yield: 60 mg (theoretical maximum 16 μmol, 100%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.76 (br s, 2 H, Py*H*), 8.67 (br s, 5 H, Py*H*), 8.62 (br s, 3 H, Py*H*), 8.53 (br s, 3 H, Py*H*), 8.34 (br s, 5 H, Py*H*), 8.30 (br s, 5 H, Py*H*), 7.83 (br s, 6 H, Py*H*), 7.69 (m, 4 H, Py*H*), 7.61 (br s, 9 H, Py*H*), 7.45 (br s, 8 H, Py*H*), 7.31 (m, 7 H, Py*H*), 7.19 (br s, 5 H, Py*H*), 5.67 (br s, 1 H, C*H*=$CH_2$), 4.72 (m, 2 H, CH=C$H_2$), 1.34 (m, 32 H, $CH_2CH_2CH_2$), 0.80 (m, 24 H, $CH_2$SiPy), 0.52 (m, 40 H, Si$CH_2$), 0.24 (s, 72 H, Si$CH_3$).

**Release of 6-bromo-2,2'-bipyridine (27) from 25**[52-54]

To a solution of **25** (0.12 g, 33.7 μmol) in THF (5 mL) was added $^n$Bu$_4$NF (1.0 M solution in THF, 1.0 mL, 1.0 mmol). The mixture was stirred at 60 °C overnight. Water (10 mL) and brine (10 mL) were added and the product was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was dissolved in EtOAc and after filtration over a short plug of silica the product **27** was obtained in a mixture with some side products, mainly butyl fragments (not described in NMR data). The presence of **27** was confirmed by a test reaction.[67] Yield: 0.14 g. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, $^3J_{H\text{-}H}$ = 4.80 Hz, 1 H, Py*H*), 8.23 (dd, $^3J_{H\text{-}H}$ = 8.00 Hz, $^4J_{H\text{-}H}$ = 3.20 Hz, 2 H, Py*H*), 7.68 (t, $^3J_{H\text{-}H}$ = 7.80 Hz, 1 H, Py*H*), 7.55 (t, $^3J_{H\text{-}H}$ = 7.80 Hz, 1 H, Py*H*), 7.35 (d, $^3J_{H\text{-}H}$ = 8.00 Hz, 1 H, Py*H*), 7.19 (dd, $^3J_{H\text{-}H}$ = 7.20 Hz, $^4J_{H\text{-}H}$ = 4.80 Hz, 1 H, Py*H*).

Method 2:

**G1-bipyridine-Br, Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$(5-$C_5H_3N$-2)$C_5H_3$NBr-6)$_3$}$_4$ (26)**[47]

To a solution of 2-bromo-5-G1(allyl)-pyridine **15** (0.23 g, 82 μmol) in degassed toluene were added 2-bromo-6-Sn$Bu_3$-pyridine **24** (0.88 g, 1.96 mmol) and Pd($PPh_3$)$_4$ (0.11 g, 98 μmol). The mixture was stirred at 100 °C over the weekend and allowed to cool to room temperature. The solvent was removed

*in vacuo* and the residue was purified by repeated passive dialysis using a $CH_2Cl_2$:MeOH mixture (1:1 (v/v), 2 x 500 mL) for 6 h and overnight. The product **26** was obtained as orange oil. NMR analysis indicated the presence of a mixture containing mainly the desired immobilized bipyridine and some pyridyl-based side products. Yield: 0.27 g (theoretical maximum 78 μmol, 48%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.32 (br s, 12 H, Py*H*), 7.77 (br s, 12 H, Py*H*), 7.51 (br s, 7 H, Py*H*), 7.38 (br s, 12 H, Py*H*), 7.26 (br s, 8 H, Py*H*), 7.16 (br s, 12 H, Py*H*), 5.69 (br s, 0.5 H, C*H*=$CH_2$), 4.75 (br s, 1 H, CH=C$H_2$), 1.26 (m, 32 H, $CH_2CH_2CH_2$), 0.77 (m, 24 H, $CH_2$SiPy), 0.50 (m, 40 H, Si$CH_2$), 0.21 (s, 72 H, Si$CH_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 157.43 (Py*C*), 154.41 (Py*C*), 153.53 (Py*C*), 143.56 (Py*C*), 143.39 (Py*C*), 142.39 (Py*C*), 141.69 (Py*C*), 139.26 (Py*C*), 138.26 (Py*C*), 135.10 (Py*C*), 133.37 (Py*C*), 131.50 (Py*C*), 130.94 (Py*C*), 130.16 (Py*C*), 128.31 (Py*C*), 128.21 (Py*C*), 128.10 (Py*C*), 127.70 (Py*C*), 121.59 (Py*C*), 121.17 (Py*C*), 120.62 ($CH_2CH$=$CH_2$), 119.72 ($CH_2CH$=$CH_2$), 20.34 ($CH_2$SiPy), 20.19 ($CH_2CH_2CH_2$SiPy), 18.50 ($CH_2CH_2CH_2$), 17.84 (Si$CH_2$), 17.31 (Si$CH_2CH_2$), –3.03 (Si$CH_3$).

**Release of 6-bromo-2,2'-bipyridine (27) from 26**[52-54]

To a solution of **26** (0.12 g, 33.7 μmol) in THF (5 mL) was added $^n$Bu$_4$NF (1.0 M solution in THF, 1.0 mL, 1.0 mmol). The mixture was stirred at 60 °C overnight. Water (10 mL) and brine (10 mL) were added and the product was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was dissolved in EtOAc and after filtration over a short plug of silica the product **27** was obtained in a mixture with some side products. NMR analysis and weight determination indicated only partial release of product **27** from the dendrimer. The presence of **27** was confirmed by a test reaction.[67] Yield: 85 mg (0.36 mmol, 89%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.66 (m, 1 H, Ar*H*), 7.64 (m, 2 H, Ar*H*), 7.53 (m, 1 H, Ar*H*), 7.44 (m, 2 H, Ar*H*), 7.29 (m, 1 H, Ar*H*).

## 2.6 References and Notes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# Chapter 3

## Synthesis of polyaryl rigid core carbosilane dendrimers for supported organic synthesis

*Carbosilane dendrimers can be used as soluble supports for organic synthesis, since their structure allows separation of excess of reagents from the supported products, eventually yielding products of high purity and in high yield, like in solid phase organic synthesis (SPOS). In previous studies often loss of dendritic material during filtration was observed, due to the rather flexible structure of the conventional dendrimers. In order to improve the diafiltration retention of the carbosilane dendrimers, the synthesis of carbosilane dendrimers based on more rigid core molecules was investigated. Both 1,3,5-tris(4-bromophenyl)benzene **1** and tetrakis(4-bromophenyl)silane **2** were selected on the basis of their rigid structure and suitable functional groups for further functionalization using organolithium chemistry. An optimized halogen lithium exchange (HLE) protocol was developed for the synthesis of **2** via 1-bromo-4-lithiobenzene. This protocol involves reaction of an aryl bromide with n-BuLi at room temperature, followed by partial removal of the solvent by evaporation (~70%, v/v), addition of pentane to promote precipitation of the aryl lithium compound, and centrifugation and removal of the solvent to obtain, after repeating the last two steps once, the wet aryl lithium compound in pure form. This HLE protocol was proven to be effective for mono- and dilithiation, as well as for polylithiation reactions of aryl bromides. Furthermore, the rigid tris(4-bromophenyl)chlorosilane wedge **3** was synthesized to add a rigid generation to the prepared core molecules and bromotriallylsilane **4** was synthesized for the introduction of triallylsilyl moieties on the periphery of the core molecules. With these four building blocks several rigid core carbosilane dendrimers were synthesized, which can be applied as better retainable soluble supports for organic synthesis in a diafiltration set-up.*

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Maaike Wander, Peter J. C. Hausoul, Leo A. J. M. Sliedregt, Bart J. van Steen, Gerard van Koten, Robertus J. M. Klein Gebbink, *Organometallics*, **2009**, *28*, 4406-4415.

## 3.1 Introduction

Since the introduction of Solid Phase Organic Synthesis (SPOS) by Merrifield in the 1960's[1], supported synthesis is a widely applied method in both industrial and academic research. SPOS has several advantages when compared to classical, solution phase organic chemistry, *e.g.* easy separation of the products from the reaction mixture, high yields by using excesses of reagents and ease of automation. Next to their advantages several shortcomings have also been recognized over the years. These include among others solvatation problems and nonlinear reaction kinetics that occur due to the heterogeneity of reaction mixtures. Furthermore, standard spectroscopic analysis techniques (like NMR spectroscopy) can not be applied in a straightforward manner and several commonly used supports show total incompatibility towards highly nucleophilic reagents.

In order to overcome one or some of these drawbacks, several types of alternative synthesis supports have been developed over the years, of which soluble polymeric supports (*e.g.* crosslinked polystyrene, like *J*anda*J*el™,[2] and (modified) polyethylene glycol[3]) are the most widely used.[4-6] The application of these soluble polymeric supports in so-called Liquid Phase Organic Synthesis (LPOS) overcomes some but not all of the disadvantages of SPOS. In general, the loading capacity of the soluble supports is rather low and the application of spectroscopic techniques may not be straightforward. In the last decades, various dendritic materials have been introduced as carrier material, first as supports for catalytic species,[7-12] and later on also as supports for organic synthesis.[13-19] These dendritic supports show several advantages compared to the traditional SPOS and the 'standard' soluble polymeric supports. In general, the loading capacity per gram of dendritic support is quite high, while at the same time the physical properties of dendrimers guarantee a true solution phase reactivity. Furthermore, dendrimer structures are very well defined, which makes it possible to apply spectroscopic methods for analysis during the synthesis of the dendrimers as well as during the application of the dendrimers as supports. Among these dendritic materials carbosilane dendrimers take a special position, not only because of their kinetic and thermodynamic stability, derived from the relatively high dissociation energy (306 kJ/mol) and low polarity of the Si-C bond, but also because of their stability towards highly reactive reagents.[20] The application of dendrimers as catalyst supports involves comparable requirements as to their application in supported synthesis; the experience gained in the field of dendritic catalysts can therefore be translated to the field of supported synthesis. For example, the principle of dendrimer supported catalyst separation from the product stream by nano- or diafiltration

techniques appears to be useful in supported organic synthesis as well. In this way, excess of reagents can be used like in SPOS, and separated from the reaction mixture, eventually yielding products of high purity and in high yield.

Although the development of nano- and diafiltration techniques for dendritic supports is well established nowadays, loss of dendritic material is often observed during the filtration.[11, 21-24] Most dendrimers are not rigid globular molecules and are sensitive to some extent to shear flow, which results in diminished and variable hydrodynamic volumes under filtration conditions. One way to improve filtration retentions is the use of membranes with even smaller molecular weight cut off (MWC) values, unfortunately this will at the same time severely reduce the filtration rates. An alternative approach to improve the filtration performance of dendritic synthesis supports involves the use of more rigid dendritic structures. These rigid dendrimers are likely to have larger hydrodynamic volumes and are less susceptible to structural deformation under shear flow. Overall, this will lead to higher retentions when using membranes with higher MWC values. Previous studies by Van Koten et al. showed that dendrimers in which only the core is rigidified, *i.e.* so-called rigid-core dendrimers, indeed show higher retentions in diafiltration studies.[25]

Here we present the synthesis of several new rigid-core dendrimers. The design of the rigid cores of these dendrimers is based on the previous reports by Van Koten et al.[25] and comprise 1,3,5-tris(4-bromophenyl)benzene **1** and tetrakis(4-bromophenyl)silane **2** (Fig. 1). These core molecules can be substituted on the outer *para*-positions through polylithiation followed by reaction with halogenated dendritic wedges (**3** and **4**), leading to further rigidly extended dendritic structures or to peripherally more flexible structures. Both the synthesis of the building blocks **1 - 4** as well as their use in dendrimer synthesis is reported.

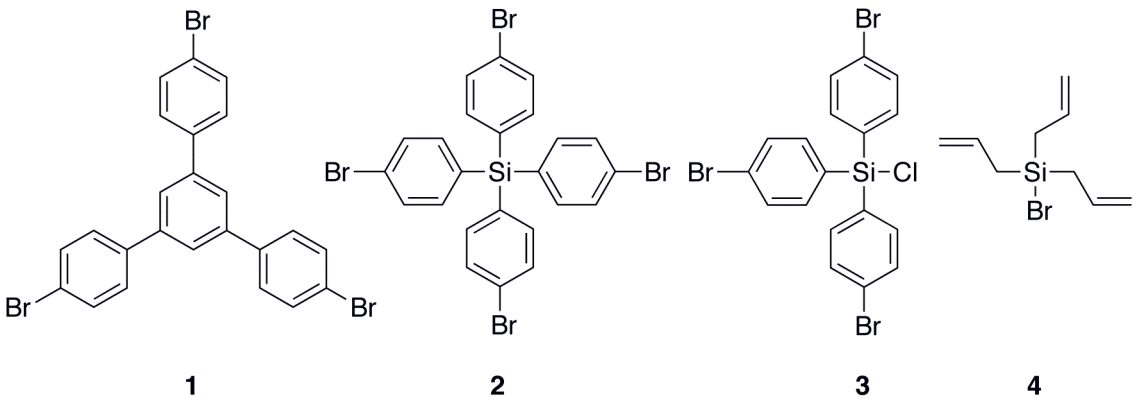


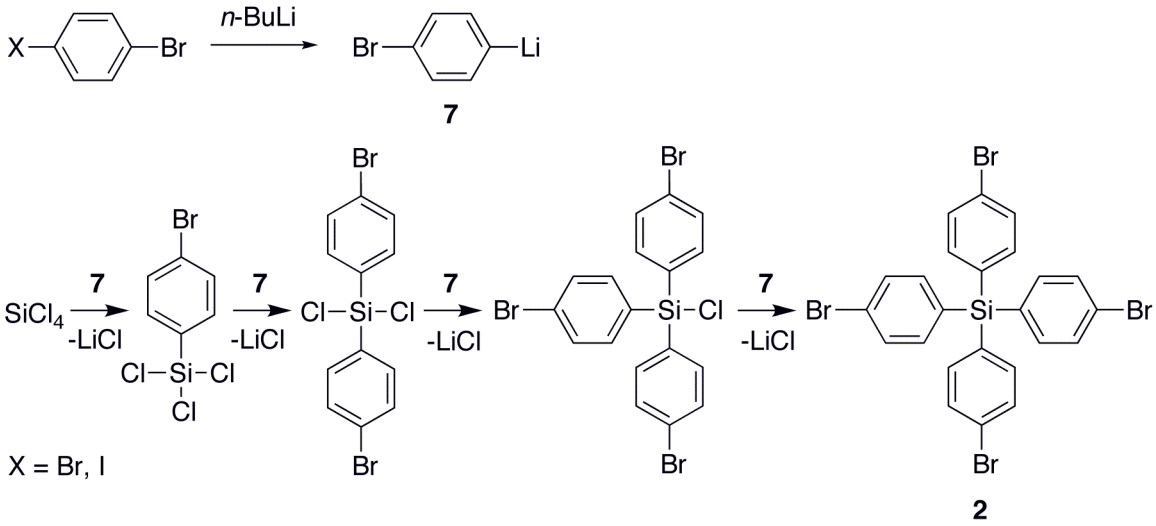

**Figure 1.** Rigid core molecules **1** and **2** and wedges **3** and **4**.

## 3.2 Results

### 3.2.1 Synthesis of rigid core molecules 1 and 2

The synthesis of core molecule 1,3,5-tris(4-bromophenyl)benzene **1** has been described in literature and was performed accordingly, starting from 4-bromoacetophenone using excess $SiCl_4$ at room temperature, yielding **1** in 65% yield.[26-29]

Most of the procedures reported[30-34] for the preparation of core molecule **2** involve the selective monolithiation of a 1,4-dihalobenzene affording 1-bromo-4-lithiobenzene **7**[30,32,35-38] as intermediate. These lithiation reactions were carried out either at lowered temperatures (-10 °C or -78°C) in coordinating solvents or at more elevated temperatures (0°C or room temperature) in non-coordinating solvents, followed by reaction of the lithio intermediate with the appropriate nucleophile, *e.g.* silicon tetrachloride to synthesize **2**. In fact, the synthesis of **2** from **7** and $SiCl_4$ involves a series of consecutive nucleophilic substitutions of which the last one is the most sterically hindered one (Scheme 1).



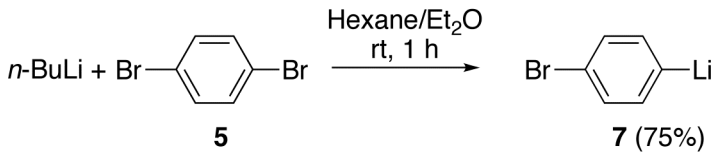

**Scheme 1.** General approach for the synthesis of **2**.

Initially we applied the one-pot procedure developed by Fournier et al.[30] This procedure starts from the monolithiation of (relatively cheap) 1,4-dibromobenzene **5** with 1.025 eq. of *n*-BuLi in $Et_2O$ at -10 °C to form 1-bromo-4-lithiobenzene **7**, which was quenched after 15 min. with $SiCl_4$. Analysis of crude reaction mixtures repeatedly revealed the presence of only small amounts of product **2** and larger amounts of *n*-butyl-substituted silanes. Obviously these are formed by reaction of $SiCl_4$ with unreacted or aggregated[39] *n*-BuLi, pointing to incomplete lithiation of **5**. In order to drive only this lithiation reaction to completion without the formation of undesired side-products, the reaction was performed at -78 °C in $Et_2O$, followed

by the quench with $SiCl_4$ after 15 min. in a one-pot procedure. Analysis of the reaction mixture at -78 °C showed that the first three substitution steps indeed proceed smoothly and only small amounts of *n*-butylsilanes were present. Most interestingly, **2** was never found to be present in reaction mixtures at -78 °C. Only when the reaction mixture was allowed to warm to room temperature after the addition of $SiCl_4$, the presence of traces of **2** could be detected. However, at the same time, again large amounts of mono- and a smaller portion of di-butyl substituted silanes were formed, as was the case for the one-pot reaction performed at -10°C.

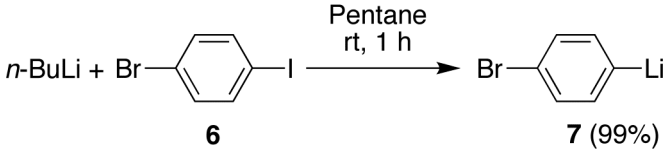
In order to reach the desired fourfold substituted product **2**, we decided to introduce a purification step after the lithiation of **5** with *n*-BuLi in $Et_2O$. Actually after this lithiation reaction, the *para*-bromophenyllithium **7** and *n*-BuBr (and *n*-BuLi) are both dissolved in $Et_2O$ and cannot be separated from each other without engaging in the isolation of **7** as a dry solid which is potentially an explosive material.[38] However, most aryllithium compounds are insoluble in non-coordinating solvents such as pentane,[40] while suspensions of organolithium compounds are far less dangerous than their isolated counterparts.[41] This allows separation by centrifugation of suspensions of the aryllithium material from soluble alkyl halides (and *n*-BuLi) to be carried out safely.[35] The insoluble solids can be washed with fresh solvent (pentane) to remove soluble impurities and then react further as the wetted solids.

Moreover, it appeared that a 1:2 (v/v) mixture of $Et_2O$ and hexane is sufficiently activating to facilitate rapid halogen-lithium exchange (HLE) between *n*-BuLi and **5** at room temperature.[35] After the reaction, which was carried out in a centrifugation vessel (0.6 M scale), excess $Et_2O$ could largely be removed by partial (no more than 70% v/v) evaporation, during which **7** precipitated from solution and a pale white colored suspension was obtained (Scheme 2). Addition of pentane to this suspension, subsequent centrifugation and removal of the supernatant resulted in an almost pure suspension of **7** in pentane. In this way, most of the ethereal solvent and unreacted *n*-BuLi and reaction product *n*-BuBr could be removed, eliminating the various equilibrium reactions leading to the formation of side products. Repeated experiments using this procedure yielded 75% of **7** as a suspended solid in pentane.[42]



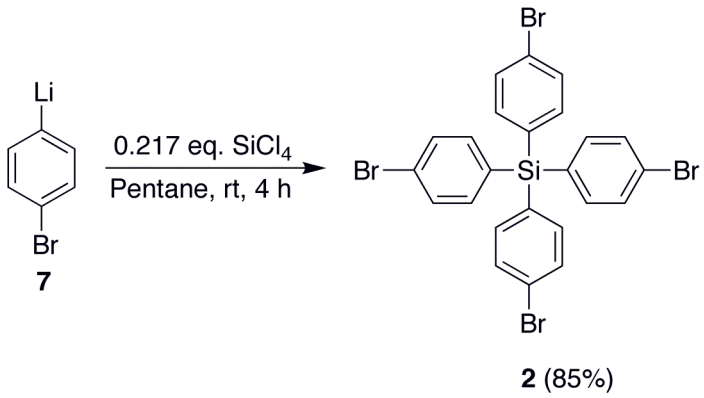

**Scheme 2.** Synthesis of **7** starting from **5**.

The preferred method, however, to arrive at monolithiated *para*-bromophenyllithium involves the reaction of 1-bromo-4-iodobenzene **6** in pentane (0.35 M scale) with a slight excess of *n*-BuLi (1.0017 eq.). This procedure results in precipitation of **7** from the pentane solution as a pale white colored solid (Scheme 3), as was reported earlier by us.[35] After purification by means of solvent replacement, the yield of the reaction reached 99%. Clearly, this procedure is more efficient and less complicated (and risky) than the procedure that uses **5** as starting material.




**Scheme 3.** Synthesis of **7** starting from **6**.

With **7** obtained as a purified suspension in pentane, the synthesis of **2** was first carried out in coordinating solvents such as THF or $Et_2O$, as described above (at low temperatures and by allowing the mixture to warm to room temperature), which still did not yield the fully substituted product **2**, despite the introduced purification step. Since the HLE reaction between *n*-BuLi and **5** in hydrocarbons is a slow process, it could be inferred that the HLE between **7** and an aryl bromide in these solvents is even slower.[43] Therefore, the synthesis of **2** was performed in pentane using a suspension of purified **7** in pentane. The reaction proceeded selectively and yielded the desired (crude) product **2** (Scheme 4). Work-up was achieved by quenching the crude reaction mixture with methanol followed by aqueous work-up and removal of volatile solvent. Purification of **2** was accomplished by dissolving the residue in chloroform and carefully addition of this concentrated solution to ethanol, resulting in the precipitation of **2** as a white crystalline solid, leaving the main side-products (bromobenzene and tris(4-bromopheny)methoxysilane) dissolved in ethanol. Isolated yields up to 85% were obtained and constitute a significant increase with respect to the literature procedures.[30-33]




**Scheme 4.** Synthesis of **2** from purified **7**.

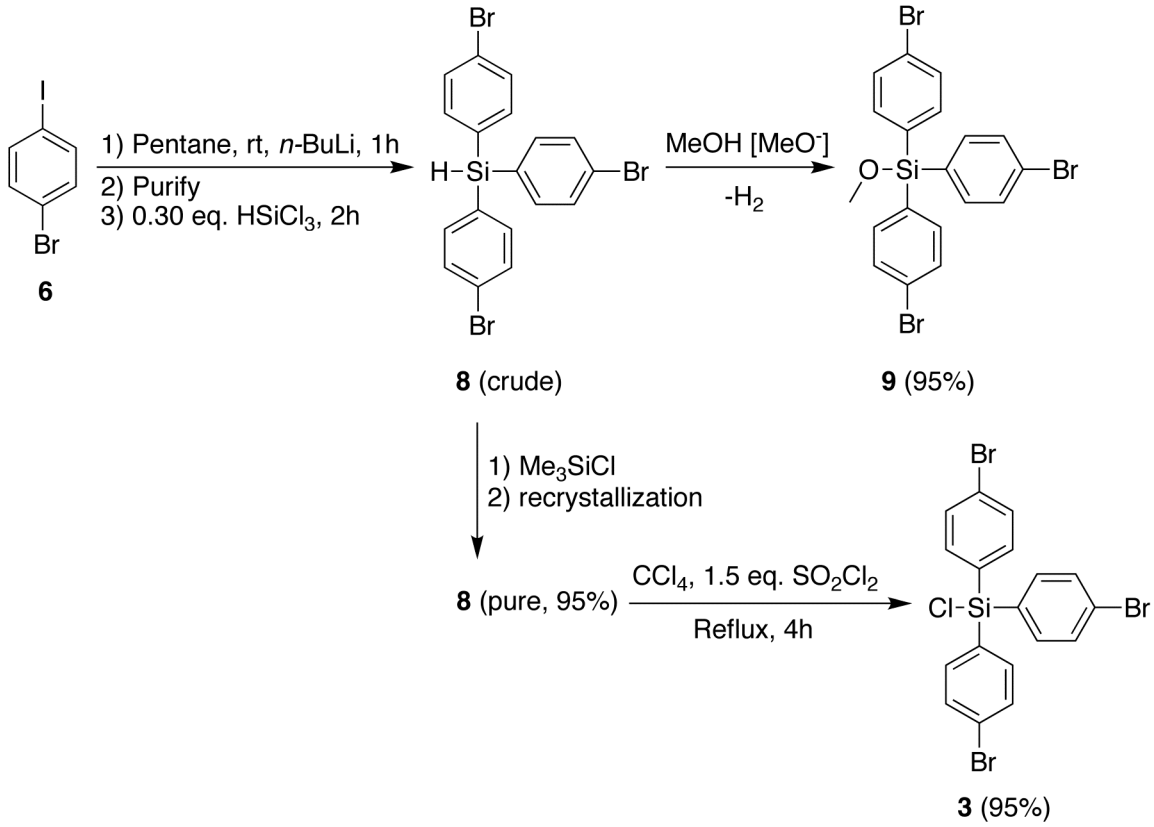
### 3.2.2 Synthesis of tris(4-bromophenyl)chlorosilane wedge 3

A direct, one-step procedure to arrive at the proposed tris(4-bromophenyl)chlorosilane wedge **3** is not available in literature. Tris(4-bromophenyl)silane **8** is a likely precursor to **3**, and its synthesis has been described in literature but uses a rather cumbersome procedure.[44-46] By using a similar approach as used for the preparation of **2**, the synthesis of **8** could be considerably improved.

Starting from 1-bromo-4-iodobenzene **6** and trichlorosilane following the improved procedure as for the synthesis of **2**, work-up of the tris(4-bromophenyl)silane **8** was initially attempted by the addition of methanol to the crude reaction mixture (Scheme 5). In analogy to the synthesis of **2**, this would quench the crude reaction mixture and at the same time serve as a separable solvent to remove the formed lithium chloride from the reaction mixture. However, deprotonation of methanol by the small excess of aryllithium present in the reaction mixture resulted in the formation of lithium methoxide, which can act as a catalyst for the dehydrogenative silylation of methanol.[47] Indeed, upon addition of methanol, rapid evolution of hydrogen gas was observed. After separation of the apolar phase followed by removal of volatile solvents, tris(4-bromophenyl)methoxysilane **9** was obtained as a white solid with isolated yields up to 95% (Scheme 5). Although alkoxysilanes can in general readily be converted to chlorosilanes by the use of electrophilic reagents such as $SOCl_2$, $(COCl)_2$ or acetylchloride,[48,49] refluxing **9** in pure acetyl chloride for one week did not result in any conversion.

In order to prevent the unfavourable formation of **9**, chlorotrimethylsilane was used instead of methanol to quench the crude reaction mixture. The precipitating insoluble lithium salts were removed from the reaction mixture by centrifugation and decantation. The collected supernatant was concentrated to saturation followed by recrystallization from pentane (room

temperature to -40 °C), yielding tris(4-bromophenyl)silane wedge **8** with isolated yields up to 95% (Scheme 5). Halogenation of **8** at its focal point was achieved by treatment of **8** with 1.5 equivalents of $SO_2Cl_2$[50,51] in refluxing $CCl_4$ for four hours, which was sufficient for the quantitative conversion of hydrosilane **8** to chlorosilane **3** (Scheme 5). After removal of all volatiles from the reaction mixture, the crude product was recrystallized from pentane (room temperature to -40 °C), yielding **3** up to 95% as a moisture and air sensitive solid.

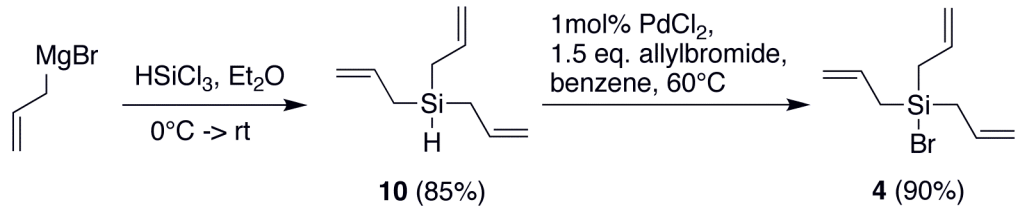



**Scheme 5.** Synthesis of tris(4-bromophenyl)chlorosilane wedge **3**.

### 3.2.3 Synthesis of bromotriallylsilane wedge 4

The synthesis of the bromotriallylsilane wedge **4** was carried out by a two-step procedure, starting with the Grignard synthesis of triallylsilane **10**, which was obtained in 85% yield (Scheme 6).[52] Following an adapted literature procedure,[53,54] treatment of hydrosilane **10** with an excess of 1.5 equivalents of allylbromide in the presence of $PdCl_2$ resulted in the successful synthesis and isolation of bromotriallylsilane **4** (Scheme 6). The excess of allylbromide ensured full conversion and reduced the total reaction time from six to three hours, compared to the literature procedure. After removal of all volatiles from the reaction mixture, crude **4** was purified by flash distillation using a liquid-nitrogen cooled cold trap,

which removed the palladium. Through this procedure **4** was recovered in yields up to 90% as a clear, green colored, volatile and air sensitive liquid.

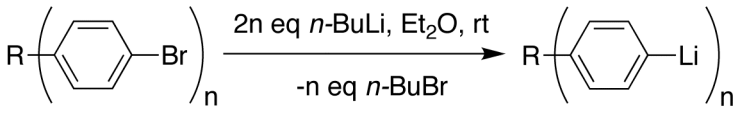



**Scheme 6.** Synthesis of triallylsilane **10** and wedge **4**.

### 3.2.4 Synthesis of rigid dendrimers

In order to couple the halosilane wedges **3** and **4** to the polyaryl bromide cores **1** and **2**, full polylithiation of the core molecules is required. To investigate the required experimental conditions, the commercially available 4,4'-dibromobiphenyl **11** was selected to serve as a model compound. Model compound **11** was treated with four equivalents of *n*-BuLi[55] at ambient temperature and after 15 minutes slow precipitation of the dilithiate was observed (Scheme 7). After 1.5 h reaction time the quantity of dilithiation was determined (by GC-MS analysis of methanol quenched samples of the solid) to be over 99%. Side-reactions such as homo- or hetero-coupling were not observed and attempts to dissolve the obtained solids with excessive equivalents of THF were unsuccessful, indicating the formation of an aryllithium compound.

Similar results were obtained when core **1** was treated with six equivalents of *n*-BuLi at ambient temperature (Scheme 7). Rapid precipitation of the polylithiate was observed and leaving the reaction for one hour was sufficient to reach over 99% trilithiation. Traces of dilithiated species were also detected and remained present even after extended reaction times.

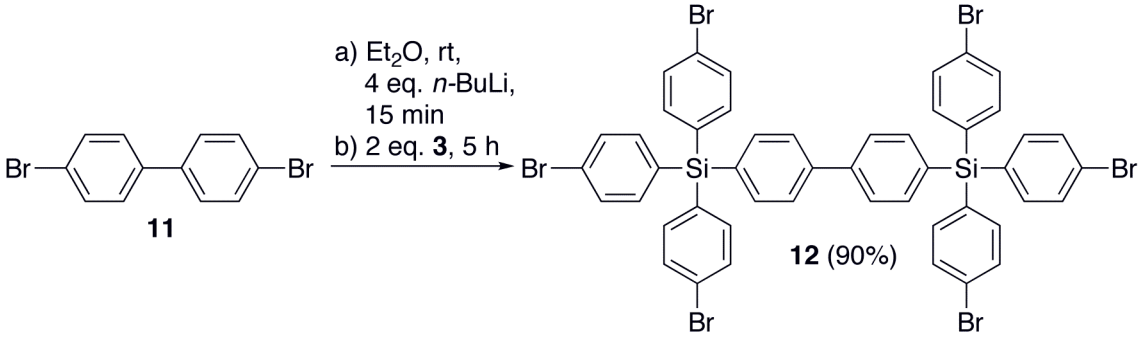



n = 2 (4,4'-dibromobiphenyl, **11**): >99% dilithiation
n = 3 (R = Ph, **1**) : >99% trilithiation
n = 4 (R = Si, **2**) : >97% tetralithiation

**Scheme 7.** Polylithiation of **11**, **1** and **2**.

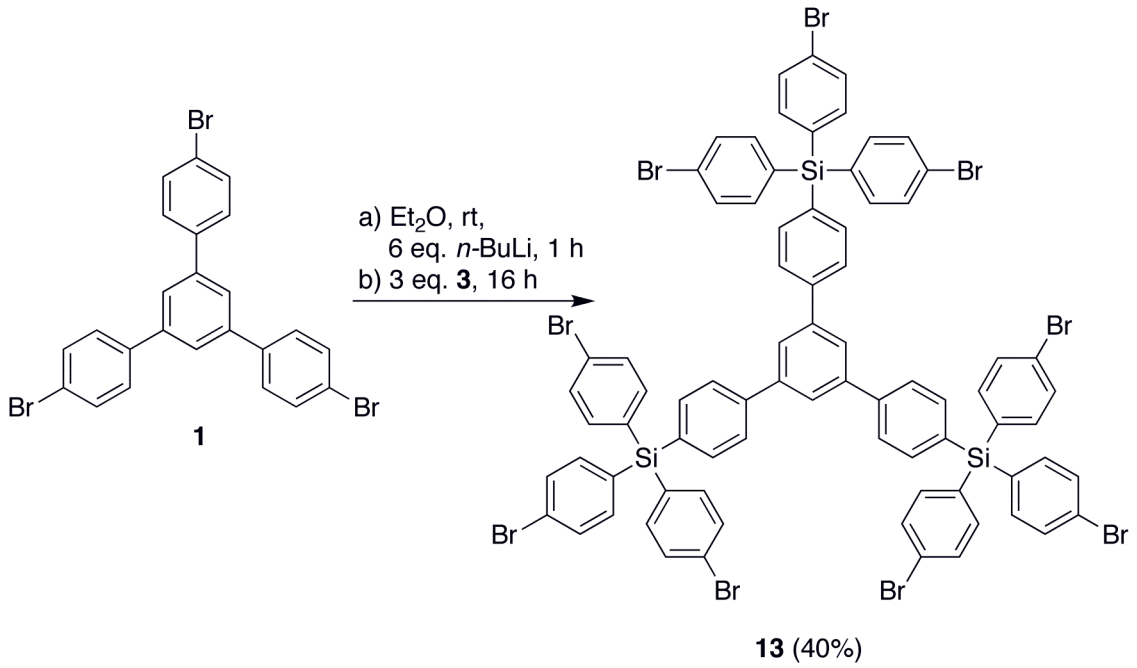
Attempts to polylithiate core **2** using eight equivalents of *n*-BuLi resulted in instant precipitation and analysis revealed a mixture of non-fully lithiated products. Increasing the amount of *n*-BuLi and reaction time only partly improved the degree of lithiation. However,

when the order of addition was reversed, polylithiation of **2** resulted repeatedly in more than 97% tetralithiation with less than 3% trilithiated species as the only side product (Scheme 7). With both the rigid core molecules **1** and **2** and rigid wedge **3** available, the synthesis of rigid dendrimers was attempted by adding a rigid generation (*i.e.* wedge **3**) to the (polylithiated) rigid core molecules **1**, **2** and model compound **11**. Coupling of **3** to an aryllithium compound is in fact the synthesis of a tetraphenylsilane, and the results obtained for the synthesis of **2** clearly demonstrate that this type of reaction should be possible. Again, compound **11** was selected to serve as a model core molecule. Attempts to synthesize G0-dendrimer **12** in pentane (in analogy to the synthesis of **2**) by addition of 2 equivalents of wedge **3** to dilithiated and purified **11** (*i.e.* reverse addition) were unsuccessful, even after extended periods of time. Changing the solvent to the more activating solvent $Et_2O$, the addition of 2 equivalents of **3** to dilithiated **11** resulted in the slow disappearance of the solids (aggregates), indicating that the reaction proceeded (Scheme 8). Leaving the reaction for five hours was sufficient for full conversion after which a clear solution was obtained. After aqueous workup and column chromatography, G0-biphenyl **12** was obtained as a white colored solid in high purity at yields up to 90%.




**Scheme 8.** Synthesis of G0-biphenyl **12**.

The synthesis of G0-triphenylbenzene dendrimer **13** was attempted in a similar way. Using the same procedure starting with the polylithiation and purification of **1**, followed by addition of wedge **3** in $Et_2O$, yielded the crude mixture containing the coupled product **13** in rather low yield, even after a prolonged reaction time of 16 hours (Scheme 9). However, tri-substitution did take place and after column chromatography, **13** was obtained at yields up to 40%. Unfortunately, the synthesis of G0-tetraphenylsilane using the same approach starting from the polylithiation and purification of core **2** followed by addition of wedge **3** was not successful.




**Scheme 9.** Synthesis of G0-triphenylbenzene **13**.

### 3.2.5 Synthesis of the allylsilane periphery

To complete the synthesis of the rigid core carbosilane dendrimers, the introduction of a conventional allylsilane periphery was carried out. In order to test the experimental conditions needed for coupling of wedge **4**, the commercially available allyldimethylchlorosilane **14** was selected to serve as a model compound. Attempts to couple **14** to the polylithiated and purified core molecules **1** and **2** in pentane were unsuccessful (in analogy to the results obtained for the addition of **3** to the cores). This confirms that the polylithiates are, due to strong polydentate interactions and low solubility, essentially unreactive in hydrocarbons and that for coupling to be successful additional solvent activation is required. Therefore, the reactions were performed in $Et_2O$ by reverse addition (*i.e.* addition of **14** to polylithiated **1** or **2**) and proceeded to completion using stoichiometric amounts of **14**. After aqueous work up and removal of all volatiles, dendrimers **15** and **16** were obtained at yields of 95% and 80%, respectively (Fig. 2).

To demonstrate the general applicability of the reverse polylithiation and reverse addition procedures, G0-biphenyl **12** was hexalithiated (confirmed by $^{13}C$ NMR instead of GC-MS[42]), purified and functionalized with **14**, yielding **17** in 90% yield after work up (Fig. 2). Side-reactions such as deprotonation[56] or polymerization of the allylic moieties were not observed, making these coupling reactions essentially quantitative.

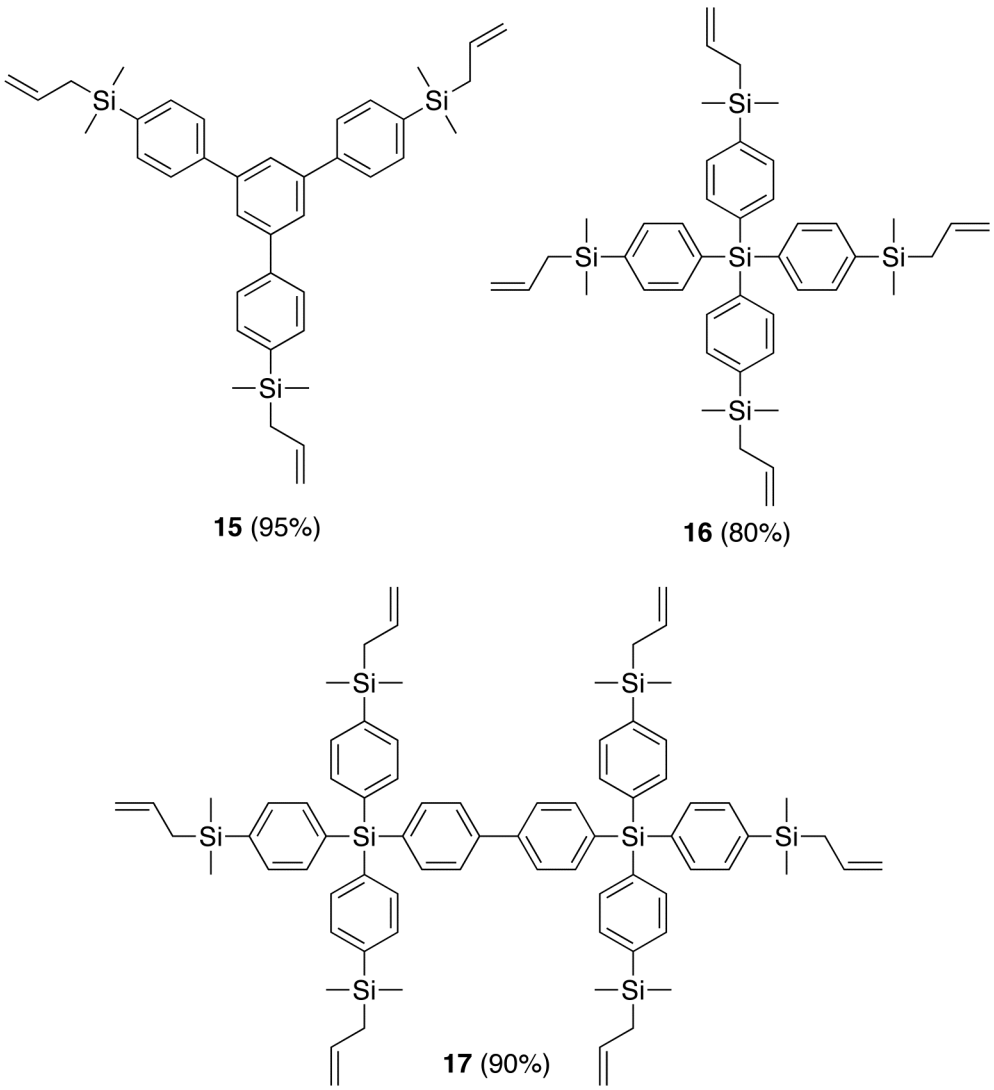
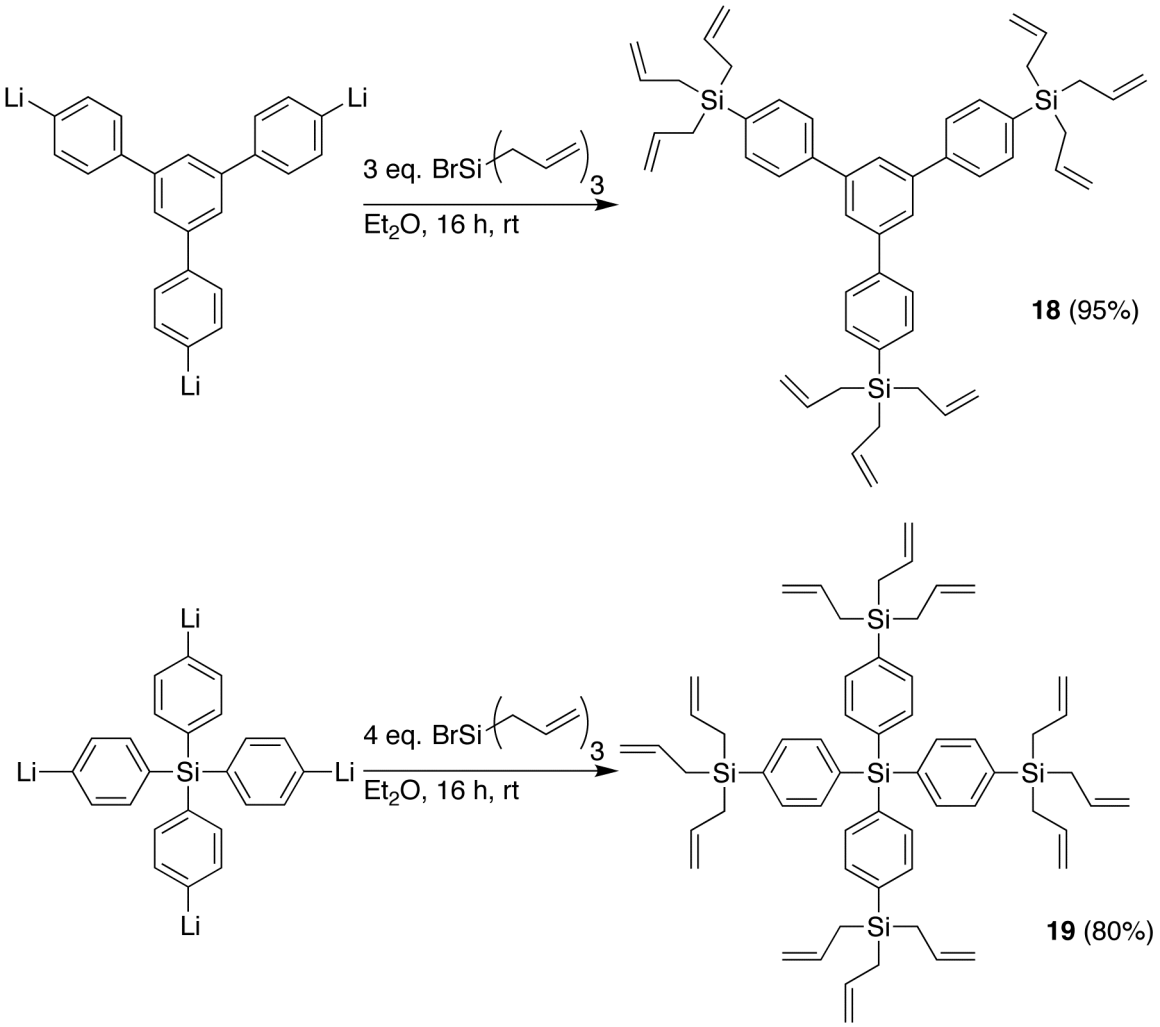


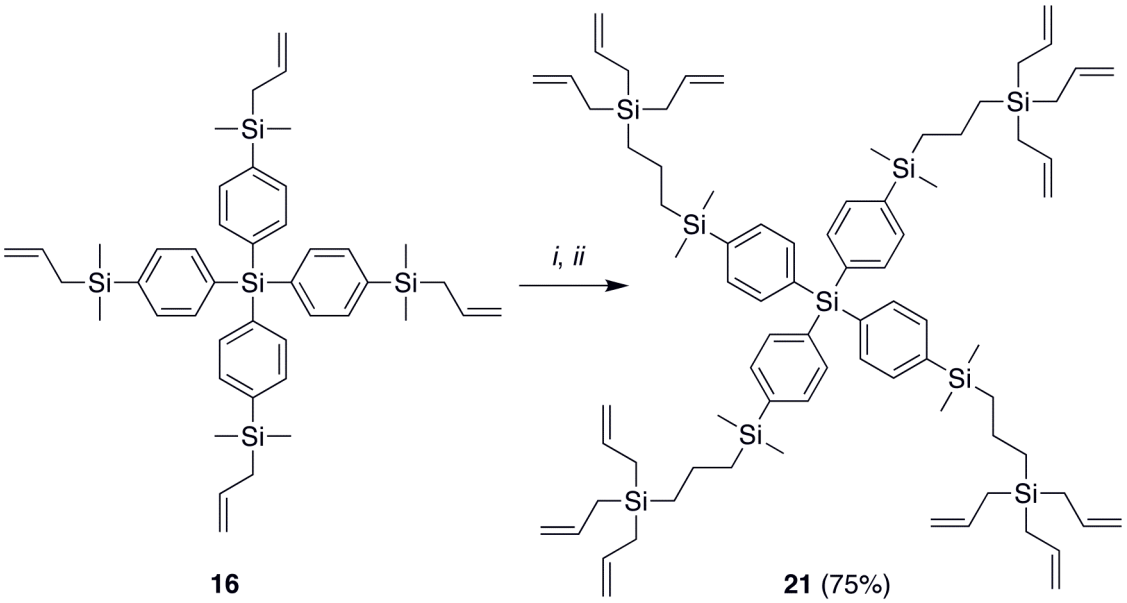

**Figure 2.** Dendrimers **15**, **16** and **17**.

The same synthetic procedure was applied for the addition of wedge **4** to polylithiated and purified core molecules **1** and **2**. However, for the triallylsilyl products **18** (1,3,5-tris(4-[triallylsilyl]phenyl)benzene) and **19** (tetrakis(4-[triallylsilyl]phenyl)silane), the purification procedure, *i.e.* aqueous work up followed by removal of all volatiles, was inadequate to remove the excess of wedge **4**, which is hydrolyzed upon contact with water and condensates as the involatile hexaallyldisiloxane by concentrating the reaction mixture.[57] To overcome this inconvenience, the crude reaction mixture was quenched with methanol, leading to the somewhat more volatile triallylmethoxysilane, which could be removed by applying elevated temperatures and bulb-to-bulb distillation, resulting in dendrimers **18** and **19** in isolated yields of 95% and 80%, respectively (Scheme 10).




**Scheme 10.** Synthesis of dendrimers **18** and **19**.

Finally, to demonstrate that conventional carbosilane dendrimer synthesis[58] is applicable to the new cores, G0-dendrimer **16** was converted to its first generation chlorosilane analog **20**. Hydrosilylation using Lukevics catalyst[59] and trichlorosilane in refluxing THF was performed and monitored by $^{1}$H NMR (Scheme 11). Quantitative conversion was obtained after four hours. Subsequently, the obtained chlorosilane was reacted with 13 equivalents of allylmagnesium bromide and left to react overnight. After aqueous work-up, G1-dendrimer **21** was obtained as a brown colored, viscous liquid. After additional purification by flash chromatography, **21** was obtained as a clear colorless liquid in 75% yield.



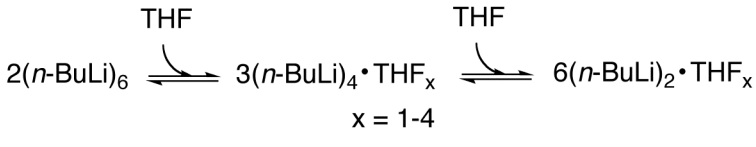

*i* = $(Bu_4N)_2[PtCl_6]$, 4.5 eq $HSiCl_3$, THF, reflux, 4h.
*ii* = 13 eq AllylMgBr, $Et_2O$, 0°C -> rt, 16 h.

**Scheme 11.** Synthesis of G1-dendrimer **21**.

## 3.3 Discussion

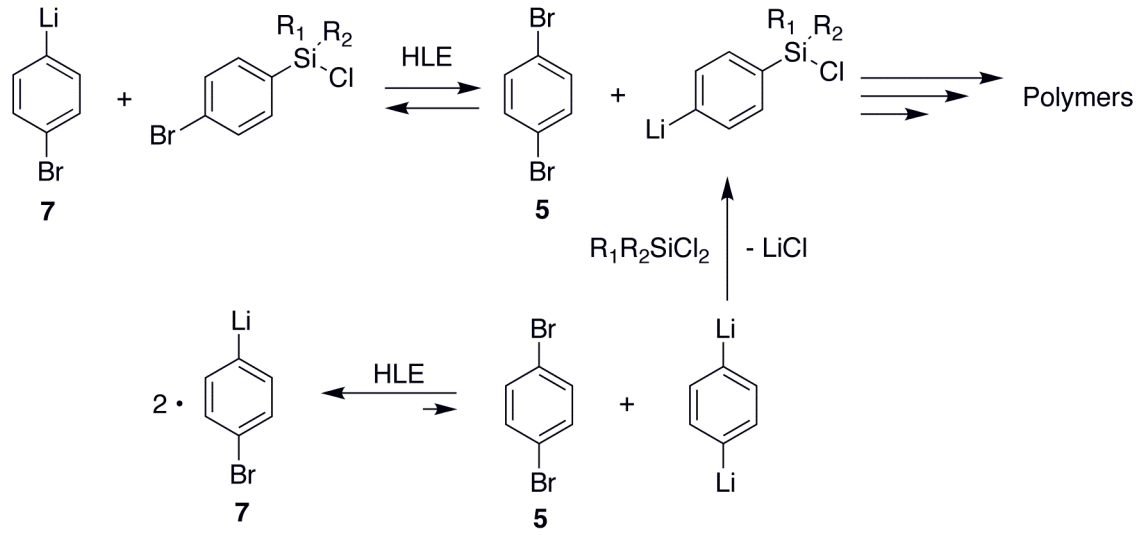
### 3.3.1 Solvents in organolithium chemistry

Activating solvents such as THF and $Et_2O$ are commonly used in combination with organolithium compounds at low temperatures. THF in particular is a strongly activating solvent and side-reactions such as homo-coupling[60-62] and hetero-coupling are readily observed. Herein the oligomer equilibrium (Eq. 1) of *n*-BuLi in HLE reactions plays an important role, since the degree of aggregation can be modified by using either nucleophilic solvents (THF, $Et_2O$) or hydrocarbon solvents.[63-66] In reactions in coordinating solvents such as THF, the equilibrium is shifted towards the lower oligomeric and more reactive forms,[63] resulting in the more readily occurrence of side-reactions. In non-coordination, apolar solvents *n*-BuLi mainly exists in its hexameric form, which is the least reactive, resulting in decreased rates of both the desired reaction and undesired side-reactions. Addition of activating solvent to the hydrocarbon media will selectively increase reaction rates and opens a way for selecting the right solvent system for each reaction.[64] For reactions with aryllithium compounds, comparable equilibria play a role and aryllithium aggregates are present in solution.[39,67,68]




(Eq. 1)

To prevent the occurrence of side-reactions when the reaction is performed in coordinating solvents, the temperature is generally limited to -78°C. During the synthesis of **2**, the reaction of **7** (as a purified suspension in pentane) and $SiCl_4$ in THF or $Et_2O$ at low temperatures produced mainly non-fully substituted products, indicating the need for higher temperatures for full substitution of $SiCl_4$. Therefore, the reaction of **7** (as a purified suspension in pentane) and $SiCl_4$ was carried out in $Et_2O$ at -78°C followed by allowing the reaction mixture to warm to room temperature before further work up. Although the purification of **7** should improve the synthesis of **2**, still traces of butylsilanes were detected and the yield of **2** was still not satisfactory. Analysis of the crude mixture revealed the presence of **5**, even when it was not used as precursor. The cause for this can be attributed to the HLE reaction between **7** and an aryl bromide. Since $Et_2O$ was used as solvent, the reactivity of **7** with respect to HLE is still considerable in every step of the synthesis. All the intermediate chlorosilanes and **2** are essentially aryl bromides and are therefore more or less susceptible to HLE with **7**. The non-fully substituted products, also present as 4-lithiophenylchlorosilanes due to HLE reactions, can react with aryllithiums as well as chlorosilanes and will ultimately lead to the formation of (branched) oligomeric polyphenylsilanes (Scheme 12).




**Scheme 12.** Undesired side-reactions of intermediates in the reaction of $SiCl_4$ with purified **7** in $Et_2O$ at room temperature (HLE = halogen-lithium exchange).

As indicated above, the HLE reaction between *n*-BuLi and **5** in hydrocarbons is a slow process, and it could be inferred that the HLE between **7** and an aryl bromide in these solvents is even slower.[43] Therefore, the synthesis of **2** was performed in pentane at room temperature using the suspension of purified **7** in pentane. The reaction proceeded selectively and yielded the desired product **2** after purification.

### 3.3.2 Halogenation of hydrosilanes

The synthesis of initially proposed (halogenated) wedges **3** and **4** proceeded via the synthesis of the corresponding hydrosilanes tris(4-bromophenyl)silane **8** and triallylsilane **10**. Since these hydrosilanes can not directly be used as building blocks in the proposed dendrimer synthesis, the conversion into the corresponding halosilanes (*i.e.* wedges **3** and **4**) was required. The halogenation of hydrosilanes is commonly performed via a radical substitution mechanism ($S_R2$) using reagents such as $Cl_2$, $PCl_5$, $CCl_4$ or $SO_2Cl_2$, which upon irradiation or heating produce chlorine radicals that can combine with the hydrogen of the hydrosilane.[50,51] In these procedures gaseous hydrochloric acid is evolved and the resulting silyl-radicals react with another chlorine radical to produce the desired chlorosilane. Although radical reactions generally suffer from poor selectivity, they have the distinct advantage of the absence of a hindered transition state.[69] Even the conversion of a sterically hindered hydrosilane proceeded smoothly with $SO_2Cl_2$ in refluxing $CCl_4$, resulting in satisfying yields.[70] Application of this methodology in the conversion of hydrosilane **8** into chlorosilane **3** resulted in quantitative conversion and high yield (95%) after recrystallization.

The conversion of hydrosilane **10** into a corresponding halosilane is more complicated by the presence of its allylic substituents. The common procedures for the chlorination of hydrosilanes rely on the radical substitution mechanism described above, which in case of the triallylsilane wedge **10** will not only lead to halogenation but also to polymerization. Therefore, a more chemo-selective reagent is required which is not reactive towards carbon-carbon double bonds. The synthesis of chlorotriallylsilane from **10**, using the reductive property of the Si-H bond for the reduction of cupric chloride was described by Gossage et al.[71] Although chlorosilanes are the most widely used precursors for substitution by organolithiums, bromosilanes tend to react faster with phenyllithium compounds compared to chlorosilanes, leading to higher conversions. Since full substitution of the phenyllithium cores is required to obtain the desired (monodisperse) dendritic structures, the synthesis of bromotriallylsilane analogue **4** was preferred. Hydrosilanes can efficiently be converted to halosilanes (either direct or via alkoxysilanes) by means of palladium- or nickel-catalyzed

hydrogen-halogen exchange reactions with alkyl or allyl halides.[53,54] Indeed, following this procedure, treatment of **10** with 1.5 equivalents of allyl bromide in the presence of $PdCl_2$ resulted in the high yielding synthesis of **4**.

### 3.3.3 Polylithiation and aggregation

In order to be able to synthesize various rigid dendrimers, full polylithiation of the core molecules **1** and **2** and model compound **11** was required. The polylithiation of polyaryl bromide compounds was investigated, starting with compound **11**. Although *t*-BuLi may appear to be the most appropriate HLE reagent for this reaction, it was not used for practical reasons, *i.e.* the very low temperatures required for this reaction will slow down the HLE reaction substantially.[72,73] Therefore, *n*-BuLi was used at room temperature instead. In order to compensate for the low reaction rates in polylithiation reactions when using *n*-BuLi, double equivalents of *n*-BuLi with respect to the number of aryl bromide groups in the precursor were used to drive the reactions to completion.[55] Indeed, application of this procedure to model compound **11** and core **1** resulted in the full polylithiation at almost quantitative yields. However, in case of core **2**, a mixture of non-fully lithiated products was obtained, even by increasing the amount of *n*-BuLi and reaction time. The cause for these results can be attributed to the aggregation behavior of the organolithium compounds.[68,74-76] Depending on the employed experimental procedure, the order of lithiation and aggregation can be influenced (e.g. as demonstrated by the preparation of hexalithiobenzene[77]). Apparently, in the applied procedure aggregation happened faster than the desired polylithiation reaction and thereby no fully lithiated product was formed. When the order of addition is reversed and the concentration of *n*-BuLi is high at all times, polylithiation is likely to occur faster than aggregation. Applying this to the polylithiation of **2** resulted in tetralithiation in high yield.

The synthesis of rigid dendrimers from the polylithiated cores by addition of a rigid generation (*i.e.* wedge **3**) was first attempted with model compound **11** and wedge **3** in pentane, which did not yield the desired compound. Probably, in this Lewis-base free environment, the lithio-aggregates are very tightly bound and can even become hexameric in nature, leading to a decrease in solubility and reactivity.[78] To increase the reactivity of the aggregates, the same reaction was carried out in $Et_2O$, which weakens the binding of the lithio-aggregates. Indeed, reaction of dilithiated **11** with two equivalents of **3** in $Et_2O$ resulted in the formation of G0-biphenyl **12** in high yield.

Following this procedure starting from trilithiated **1** and wedge **3** resulted in the formation of product **13**, but only in rather low yield. The cause for this partial substitution could be partly attributed to HLE related side-reactions because of the use of the more activating solvent $Et_2O$. Apparently, an impasse has been reached; the activating property of $Et_2O$ needed for increasing the reactivity of the polylithiates is also the cause for an unfavorable side-reaction. However, compound **13** was obtained and could be purified by column chromatography, and no further improvement of yield of the reaction was attempted at this point.

The self-reactivity of the aryl bromide/aryllithium approach together with the strong polydentate interactions of the polylithiates, prevented the formation of the rigid dendrimers derived from the rigid tetraphenylsilane **2** all together. Polylithiation and purification of core **2** followed by addition of wedge **3** did not yield the desired rigid dendritic structure.

## 3.4 Conclusions

In summary, several new rigid-core carbosilane dendrimers have been synthesized. The synthesis and modification of the tetrakis(4-bromophenyl)silane core molecule **2** had to be adapted from literature procedures, due to the self reactivity and poor selectivity of the 1-bromo-4-lithio-benzene intermediate **7**. By choosing rather unconventional reaction conditions, the formation of side products was prevented. Apparently, for the nucleophilic substitution of chlorosilanes by aryllithiums at room temperature, no additional solvent activation is required.

Investigation of the polylithiation reactions with the various bromophenyl core molecules and specifically divalent **11** and trivalent **1** opened the way for the synthesis of new rigid-core dendrimers with different peripheries. Substitution of the polylithiated and purified core molecules **1** and **11** with the rigid wedge tris(4-bromophenyl)chlorosilane **3** were successful only in activating solvents, since the lithio-aggregates are too tightly bound in Lewis-base free environments like pentane. This strong aggregation together with self-reactivity of the aryl bromide/aryllithium approach prevented the coupling of wedge **3** to tetravalent core molecule **2**.

The functionalization of the core molecules to form dendrimers with an allylsilane periphery was performed successfully, using two different wedges **4** and **14**. This demonstrates the possibility of synthesizing dendrimers with new rigid-cores and more flexible peripheries using conventional carbosilane chemistry.

Currently, the physical properties of the rigid core dendrimers are investigated. These studies include measurements of the hydrodynamic volumes or radii of the molecules and molecular modeling studies. Furthermore, diafiltration experiments with both the rigid core dendrimers, as well as the convenient, more flexible carbosilane dendrimers are in progress. With these results more insight in the filtration behavior of the dendrimers will be obtained. The rigid, polyfunctional dendritic scaffolds such as **2**, **3**, **12** and **13** may, in addition, find use in other fields of chemistry such as supramolecular chemistry and polymer chemistry.

## 3.5 Experimental Section

All reactions were carried out at room temperature (unless stated otherwise) under an oxygen-free, dry nitrogen atmosphere using standard Schlenk-techniques. Solvents were dried and distilled over sodium/benzophenone prior to use. 4-Bromoacetophenone, 1,4-dibromobenzene **5**, silicon tetrachloride, trichlorosilane, sulfuryl chloride and allyl bromide were used as purchased. 1-Bromo-4-iodobenzene **6** was purified prior to use via flash chromatography (eluent: pentane). Allylmagnesium bromide and triallylsilane **10** were prepared using literature procedures.[52] Most reactions involving organolithium intermediates were carried out in a flame dried 90 mL centrifugation vessel fitted with a gas inlet adapter.

$^{1}H$, $^{13}C\{^{1}H\}$ and $^{29}Si\{^{1}H\}$ NMR (DEPT sequence) spectra were recorded on a Varian AS400 or Varian Inova 300 instrument. Chemical shifts are reported in ppm relative to residual solvent signals.[79] IR-spectra were measured on a Perkin-Elmer Spectrum One FT-IR. Elemental analyses were performed by Microanalytisches Laboratorium Dornis & Kolbe, Mulheim a.d. Ruhr, Germany. MALDI-TOF MS spectra were obtained with 9-nitroantracene as matrix in combination with silver triflate on a Voyager-DE BioSpectrometry Workstation. GC-MS chromatograms and spectra were recorded on a Perkin-Elmer AutoSystem XL (GC) coupled to a TurboMass (MS).

**1,3,5-Tris(4-bromophenyl)benzene 1**

According to literature procedures[27-29], yielding **1** (1.77 g, 3.25 mmol, 65%) as slightly yellow needle-like crystals. $^{1}H$ NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ = 7.69 (s, 3 H, Ar-H), 7.61 (d, $^{3}J_{H-H}$ = 8.4 Hz, 6 H, Ar-H), 7.53 (d, $^{3}J_{H-H}$ = 8.7 Hz, 6 H, Ar-H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 141.9, 140.0, 132.4, 129.2, 125.3, 122.5. Mp = 263°C (lit.[29]: 263°C).

**1-Bromo-4-lithiobenzene 7 (starting from 5)**

Compound **5** (7.08 g, 30 mmol) was dissolved in a 1:2, v/v mixture of $Et_2O$/hexane solution (50 mL). *n*-BuLi (18.8 mL, 1.6 M in hexanes, 30.08 mmol) was added dropwise at room temperature. The resulting clear yellow solution was left to react for 1 h. Careful, partial evaporation (70 % v/v) of the solvent resulted in the precipitation of **7**. Pentane (35 mL) was added to the remaining suspension and

the resulting mixture was stirred for 5 min. Subsequently, the mixture was centrifuged (5 min. at 2400 rpm). The supernatant was removed via a syringe and the previous steps were repeated once. The yield of the lithiation reaction was estimated[42] to be around 75% (*i.e.* ~23 mmol of **7**). The product (white residue) was not further characterized, but used directly in the following reaction steps.

**1-Bromo-4-lithiobenzene 7 (starting from 6)**

Compound **6** (6.50 g, 23 mmol) was dissolved in pentane (65 mL). To the stirred solution, *n*-BuLi (14.4 mL, 1.6 M in hexanes, 23.04 mmol) was added dropwise at room temperature and left to react for 1 h. The resulting pale suspension was centrifuged (5 min. at 2400 rpm) and the supernatant was carefully removed via a syringe. Fresh pentane (70 mL) was added to the residue. After stirring the suspension for 5 min., centrifugation and supernatant removal were repeated once. The yield of the lithiation reaction was estimated[42] to be around 99% (i.e. ~23 mmol **7**). The product (white residue) was not further characterized, but used directly in the following reaction steps.

**Tetrakis(4-bromophenyl)silane 2**

A solution of $SiCl_4$ in dry pentane (0.2 M, 25 mL, 5.0 mmol) was added dropwise to a suspension of **7** (~ 23 mmol) in pentane (50 mL) (Caution: Exothermic reaction!). The reaction mixture was stirred for 4 h at room temperature and was then quenched with methanol (5 mL). Subsequently the crude reaction mixture was evaporated to dryness. The resulting residue was dissolved in dichloromethane (100 mL) and water (20 mL), followed by addition of a saturated aqueous $NH_4Cl$ solution (2 mL). The aqueous phase was extracted with dichloromethane (2 x 50 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and the filtrate was concentrated to dryness. The residue was dissolved in chloroform (~20 mL) and careful addition of this solution to ethanol (~100 mL) resulted in the precipitation of **2**, which was obtained as a white crystalline solid after decantation of the supernatant and drying of the solids *in vacuo*. Yield: 2.77 g (4.25 mmol, 85%). $^1$H NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ = 7.54 (d, $^3J_{H-H}$ = 8.4 Hz, 8 H, Ar-H), 7.34 (d, $^3J_{H-H}$ = 8.7 Hz, 8 H, Ar-H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 138.0, 131.84, 131.79, 125.8. $^{29}Si\{^1H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -13.52. Mp = 235 °C (lit.[30-33]: 240°C).

**Tris(4-bromophenyl)silane 8**

A solution of $HSiCl_3$ in pentane (0.4 M, 17.5 mL, 7.0 mmol) was added dropwise to a suspension of **7** (~ 23 mmol) in pentane (50 mL) at room temperature (Caution: Exothermic reaction!). The reaction was stirred for 2 h and the resulting suspension was centrifuged (5 min. at 2400 rpm). The clear supernatant was decanted. The remaining solids were washed with fresh pentane (70 mL) and the centrifugation and decantation steps were repeated once. The combined supernatants were quenched with chlorotrimethylsilane (0.5 mL) and concentrated to saturation. Recrystallization from pentane (-40 °C) yielded **8** as colorless crystals. Yield: 3.03 g (6.65 mmol, 95%). $^1$H NMR (300 MHz, $CDCl_3$,

25°C): $\delta$ = 7.53 (d, $^{3}J_{H-H}$ = 8.1 Hz, 6 H, Ar-H), 7.37 (d, $^{3}J_{H-H}$ = 7.8 Hz, 6 H, Ar-H), 5.38 (s, 1 H, Si-H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 137.4, 131.8, 131.2, 125.7. $^{29}Si\{^{1}H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -18.21. IR: ν ($cm^{-1}$) = 2141 (Si-H stretch), 739, 776 (Si-H bend). Mp = 110.5°C (lit.: 110°C)[44-46]. MS: EI+ (70 eV) m/z = 497 (70%). Anal. Calcd. for $C_{18}H_{13}Br_3Si$: C, 43.49; H, 2.64; Si, 5.65. Found: C, 43.56; H, 2.70; Si, 5.72.

**Tris(4-bromophenyl)chlorosilane 3**

To a stirred solution of **8** (2.98 g, 6 mmol) in dry, degassed carbontetrachloride (30 mL) was added sulfuryl chloride (1 mL, 12.3 mmol). The resulting mixture was heated to reflux for 4 h. The evolved gaseous hydrochloric acid was allowed to escape (by bubbling $N_2$ though the mixture) and after completion of the reaction (determined by $^{1}H$ NMR), solvent and excess reagents were evaporated *in vacuo* using a liquid nitrogen cooled cold trap. The solid residue was recrystallized from pentane (-40 °C), yielding **3** as colorless crystals (Stored under a dry nitrogen atmosphere at 4 °C). Yield: 3.03 g (5.70 mmol, 95%). $^{1}H$ NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ = 7.57 (d, $^{3}J_{H-H}$ = 8.4 Hz, 6 H, Ar-H), 7.44 (d, $^{3}J_{H-H}$ = 8.4 Hz, 6 H, Ar-H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 136.9, 132.0, 131.0, 126.8. $^{29}Si\{^{1}H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = 1.48. Mp = 123°C (lit.: 127°C)[44-46]. MS: EI+ (70eV) *m/z* = 530 (100%). Anal. Calcd. for $C_{18}H_{12}ClBr_3Si$: C, 40.67; H, 2.28; Si, 5.28. Found: C, 40.84; H, 2.36; Si, 5.36.

**Bromotriallylsilane 4**

Compound **10** (3.05 g, 20 mmol), allyl bromide (2.6 mL, 30 mmol) and palladium dichloride (~10 mg, ~0.05 mmol) were dissolved in dry benzene (25 mL) and heated to 60 °C. The reaction was stirred for 3 h after which all volatiles were removed *in vacuo* (at room temperature). The resulting liquid was flash-distilled (at 110°C) *in vacuo* using a liquid nitrogen cooled cold trap. The frozen liquid was warmed to room temperature, yielding **4** as a clear, greenish colored, air and moisture sensitive liquid (stored under a dry nitrogen atmosphere at 4 °C). Yield: 4.15 g (18.0 mmol, 90%). $^{1}H$ NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ = 5.79 (m, 3 H, =CH), 5.02 (d, $J_{H-H}$ = 14.95 Hz, 6 H, $=CH_2$), 1.97 (d, $J_{H-H}$ = 7.8 Hz, 6 H, $CH_2$). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 131.6, 116.2, 22.8. $^{29}Si\{^{1}H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = 20.0. Anal. Calcd. for $C_9H_{15}BrSi$: C, 46.75; H, 6.54; Si, 12.15. Found: C, 46.64; H, 6.63; Si, 12.12.

**General procedure for polylithiation of bromophenyl compounds 1, 2, 11 and 12**

The bromophenyl compound **1**, **2**, **11** or **12** (1.0 mmol) was dissolved (partially) in dry $Et_2O$ (75 mL). *n*-BuLi (2 eq. per arylbromide group[55], 1.6M in hexanes) was slowly added dropwise (in case of **2** and **12** reverse addition was performed). Rapid precipitation of the polylithiated compound was observed. After stirring the reaction for 1 h, the resulting suspension was centrifuged (5 min. at 2400 rpm). The

supernatant was removed via a syringe and fresh pentane (70 mL) was added to the residue. The suspension was stirred for 5 min and centrifugation and solvent removal were repeated once. The purified polylithiated compound was obtained as a still submersed white solid. GC-MS analysis of a quenched (with methanol) sample of this solid showed in all cases more than 97% full polylithiation.

**4,4'-Bis[tris(4-bromophenyl)silyl]biphenyl 12**

After polylithiation and purification according to the general procedure outlined above for **11** (0.31 g, 1.0 mmol), the wet solids were suspended in dry $Et_2O$ (80 mL). Compound **3** (1.07 g, 2.0 mmol) was added and the mixture was stirred for 5 h. Subsequently methanol (5mL) was added, followed after 5 min. stirring by water (20 mL). The aqueous phase was separated and extracted with $Et_2O$ (2 x 50 mL). The combined ethereal fractions were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*. Column chromatography of the obtained residue (eluent: $CH_2Cl_2$:hexane 20:80 v/v) yielded **12** as a white solid in high purity. Yield: 1.03 g (0.9 mmol, 90%). $^1$H NMR (300 MHz, $C_6D_6$, 25°C): $\delta$ = 7.60 (d, $^3J_{H-H}$ = 8.4 Hz, 4 H, Ar-H), 7.52 (d, $^3J_{H-H}$ = 8.4 Hz, 4 H, Ar-H), 7.34 (d, $^3J_{H-H}$ = 8.4 Hz, 12 H, Ar-H), 7. 17 (d, $^3J_{H-H}$ = 8.4 Hz, 12 H, Ar-H, overlap with solvent signal). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 142.6, 138.1, 137.0, 132.3, 132.2, 131.8, 127.2, 125.7. $^{29}Si\{^1H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -13.69. MALDI-TOF MS: *m/z*: 1252.34 $[(C_{48}H_{32}Br_6Si_2 + Ag)^+]$ (Calcd. 1252.23). Anal. Calcd. for $C_{48}H_{32}Br_6Si_2$: C, 50.38; H, 2.82; Si, 4.91. Found: C, 50.18; H, 2.74; Si, 4.75.

**1,3,5-Tris{4-[tris(4-bromophenyl)silyl]phenyl}benzene 13**

In analogy to the procedure described above for the synthesis of **12**, compound **1** (0.54 g, 1.0 mmol) was reacted with **3** (1.60 g, 3.0 mmol) in dry $Et_2O$ and the mixture was stirred for 16 h. Following the same work-up, addition of methanol (5 mL) followed by water (20 mL), and extraction of the aqueous layer with $Et_2O$ (2 x 50 mL), afforded a residue from which after column chromatography (eluent: $CH_2Cl_2$:hexane 30:70 v/v) **13** was obtained as a white solid in high purity. Yield: 0.76 g (0.4 mmol, 40%). $^1$H NMR (400 MHz, $C_6D_6$, 25°C): $\delta$ = 7.95 (s, 3 H, Ar-H), 7.64 (d, $^3J_{H-H}$ = 8.4 Hz, 6 H, Ar-H), 7.57 (d, $^3J_{H-H}$ = 8.4 Hz, 6 H, Ar-H), 7.36 (d, $^3J_{H-H}$ = 8.4 Hz, 18 H, Ar-H), 7.21 (d, $^3J_{H-H}$ = 8.4 Hz, 18 H, Ar-H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 143.2, 143.0, 138.1, 137.3, 132.6, 132.3, 131.8, 127.6, 126.2, 125.8. $^{29}Si\{^1H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -13.65. MALDI-TOF MS: *m/z*: 1898.32 $[(C_{78}H_{51}Br_9Si_3 + Ag)^+]$ (Calcd. 1899.50). Anal. Calcd. for $C_{78}H_{51}Br_9Si_3$: C, 52.29; H, 2.87; Si, 4.70. Found: C, 52.32; H, 2.93; Si, 4.75.

**General procedure for the preparation of allyldimethyl- and triallyl derivatives**

The polyaryl bromide compound (1.0 mmol) was polylithiated and purified according to the general procedure described above. The obtained wet polylithiates were suspended in dry $Et_2O$ (80 mL) and

briefly stirred. The appropriate halosilane wedge, either **4** or **14** (1 eq. per aryllithium equivalent in the polylithiated compound), was added to this suspension (*i.e.* reverse addition). The pale suspension converted to a clear solution in a couple of hours and was stirred overnight to ensure full substitution. Subsequently methanol (1 mL) was added and the mixture was briefly stirred, followed by the addition of water (20 mL). The aqueous phase was extracted with $Et_2O$ (2 x 50 mL). The combined ethereal fractions were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*. In the case of the triallylsilyl products the filtrate was dried additionally for several hours by low pressure bulb-to-bulb distillation of volatiles at 60°C.

**1,3,5-Tris([4-(allyldimethylsilyl)phenyl]benzene 15**

Compound **1** (0.54 g, 1.0 mmol) was polylithiated, purified and subsequently reacted with compound **14** (0.44 mL, 0.40 g, 3.0 mmol) according to the general procedures. After work-up and drying *in vacuo*, **15** was obtained as a colorless and highly viscous liquid. After standing for a day the liquid solidified. Yield: 0.57 g (0.95 mmol, 95%). $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 7.84 (s, 3 H, Ar-H), 7.72 (d, $^3J_{H-H}$ = 8.0 Hz, 6 H, Ar-H), 7.67 (d, $^3J_{H-H}$ = 7.6 Hz, 6 H, Ar-H), 5.86 (m, 3 H, =CH), 4.93 (d, 6 H, =$CH_2$), 1.85 (d, $^3J_{H-H}$ = 8.0 Hz, 6 H, $CH_2$), 0.37 (s, 18 H, $CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 142.6, 142.0, 138.2, 134.9, 134.6, 127.0, 125.6, 113.9, 24.0, -3.0. $^{29}Si\{^1H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -4.56. MALDI-TOF MS: *m/z*: 709.14 [$(C_{39}H_{48}Si_3 + Ag)^+$] (Calcd. 709.93). Anal. Calcd. for $C_{39}H_{48}Si_3$: C, 77.93; H, 8.05; Si, 14.02. Found: C, 77.07; H, 9.51; Si, 13.07.

**Tetrakis[4-(allyldimethylsilyl)phenyl]silane 16**

Compound **2** (0.65 g, 1.0 mmol) was polylithiated, purified and subsequently reacted with compound **14** (0.59 mL, 0.54 g, 4.0 mmol) according to the general procedures. After work-up and drying *in vacuo*, **16** was obtained as a white solid. Yield: 0.58 g (0.8 mmol, 80%). $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 7.55 (d, $^3J_{H-H}$ = 7.6 Hz, 8 H, Ar-H), 7.51 (d, $^3J_{H-H}$ = 7.6 Hz, 8 H, Ar-H), 5.79 (m, 4 H, =CH), 4.87 (d, 8 H, =$CH_2$), 1.76 (d, $J_{H-H}$ = 8.0 Hz, 8 H, $CH_2$), 0.28 (s, 24 H, $CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 140.5, 135.9, 135.1, 134.9, 133.3, 113.8, 24.0, -3.2. $^{29}Si\{^1H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -4.65, -14.85. MALDI-TOF MS: *m/z*: 837.13 [$(C_{44}H_{60}Si_5 + Ag)^+$] (Calcd. 837.24). Anal. Calcd. for $C_{44}H_{60}Si_5$: C, 72.46; H, 8.29; Si, 19.25. Found: C, 72.55; H, 8.18; Si, 19.24.

**4,4'-Bis{tris[4-(allyldimethylsilyl)phenyl]silyl}biphenyl 17**

Compound **12** (1.14 g, 1.0 mmol) was polylithiated, purified and reacted with compound **14** (0.88 mL, 0.81 g, 6.0 mmol) according to the general procedures. After work-up and drying *in vacuo*, **17** was obtained as a white solid. Yield: 1.13 g (0.9 mmol, 90%). $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 7.66 (d, $^3J_{H-H}$ = 8.0 Hz, 4 H, Ar-H), 7.63 (d, $^3J_{H-H}$ = 8.0 Hz, 4 H, Ar-H), 7.59 (d, $^3J_{H-H}$ = 7.4 Hz, 12 H, Ar-H), 7.53 (d, $^3J_{H-H}$ = 7.4 Hz, 12 H, Ar-H), 5.79 (m, 6 H, =CH), 4.87 (d, 12 H, =$CH_2$), 1.77 (d, $^3J_{H-H}$ = 8.0

Hz, 12 H, $CH_2$), 0.29 (s, 36 H, $CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 142.3, 140.7, 137.3, 135.9, 135.1, 135.0, 133.5, 133.4, 126.9, 113.8, 24.0, -3.2. $^{29}Si\{^1H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -4.63, -14.69. MALDI-TOF MS: *m/z*: 1367.08 [$(C_{78}H_{98}Si_8 + Ag)^+$] (Calcd. 1368.16). Anal. Calcd. for $C_{78}H_{98}Si_8$: C, 74.33; H, 7.84; Si, 17.83. Found: C, 74.45; H, 8.03; Si, 17.47.

**1,3,5-Tris[4-(triallylsilyl)phenyl]benzene 18**

Compound **1** (0.54 g, 1.0 mmol) was polylithiated, purified and reacted with compound **4** (0.69 g, 3.0 mmol) according to the general procedures. After work-up, bulb-to-bulb distillation *in vacuo* at 60°C was performed for 6 h, followed by flash chromatography (eluent: $CH_2Cl_2$:pentane = 10:90 v/v), yielding **18** as a clear and highly viscous liquid. Yield: 0.72 g (0.95 mmol, 95%). $^1H$ NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 7.82 (s, 3 H, Ar-H), 7.70 (d, $^3J_{H-H}$ = 8.0 Hz, 6 H, Ar-H), 7.64 (d, $^3J_{H-H}$ = 8.0 Hz, 6 H, Ar-H), 5.86 (m, 9 H, =CH), 4.94 (d, 18 H, $=CH_2$), 1.93 (d, $^3J_{H-H}$ = 8.0 Hz, 18 H, $CH_2$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 142.4, 142.2, 135.2, 134.8, 134.1, 127.0, 125.6, 114.8, 20.0. $^{29}Si\{^1H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -7.85. MALDI-TOF MS: *m/z*: 865.11 [$(C_{51}H_{60}Si_3 + Ag)^+$] (Calcd. 865.16). Anal. Calcd. for $C_{51}H_{60}Si_3$: C, 80.89; H, 7.99; Si, 11.13. Found: C, 78.95; H, 7.72; Si 11.61.

**Tetrakis[4-(triallylsilyl)phenyl]silane 19**

Compound **2** (0.65 g, 1.0 mmol) was polylithiated, purified and reacted with compound **4** (0.92 g, 4.0 mmol) according to the general procedures. After work-up, bulb-to-bulb distillation *in vacuo* at 60°C was performed for 6 h, yielding **19** as a sticky white solid. Yield: 0.75 g (0.8 mmol, 80%). $^1H$ NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ = 7.54 (s, 16 H, Ar-H), 5.81 (m, 12 H, =CH), 4.94 (d, 24 H, $=CH_2$), 1.88 (d, $^3J_{H-H}$ = 7.8 Hz, 24 H, $CH_2$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 137.4, 135.9, 135.3, 134.1, 133.9, 114.8, 19.9. $^{29}Si\{^1H\}$ NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -8.01, -14.75. MALDI-TOF MS: *m/z*: 1045.26 [$(C_{60}H_{76}Si_5 + Ag)^+$] (Calcd. 1045.54). Anal Calcd. for $C_{60}H_{76}Si_5$: C, 76.85; H, 8.17; Si, 14.98. Found: C, 76.62; H, 8.09; Si, 14.94.

**G1-tetrakis[4-(allyldimethylsilyl)phenyl]silane 21**

A solution of **16** (0.84 g, 1.0 mmol), trichlorosilane (0.45 mL, 4.5 mmol) and Lukevics catalyst ($(Bu_4N)_2[PtCl_6]$, ~40 mg, ~0.04 mmol) in dry THF (20 mL) was refluxed for 4 h, resulting in quantitative conversion (determined by $^1H$ NMR). All volatiles were removed *in vacuo*, yielding the polychlorosilane intermediate **20** as a viscous, air and moisture sensitive residue. This residue was dissolved in dry $Et_2O$ (20 mL) and the stirred solution was cooled to 0 °C. Fresh prepared allylmagnesiumbromide[52] (0.5 M solution in $Et_2O$, 26 mL, 13 mmol) was added dropwise at 0 °C and the reaction mixture was stirred overnight at room temperature. The resulting suspension was poured out in a saturated aqueous $NH_4Cl$ solution containing ice (~200 mL). After warming to room

temperature, the aqueous phase was separated and extracted with $Et_2O$ (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness *in vacuo*, yielding a brown colored viscous liquid. After purification by flash chromatography (eluent: $CH_2Cl_2$:hexane 10:90 v/v), **21** was obtained as a clear, viscous liquid. Yield: 1.08 g (0.75 mmol, 75%). $^1$H NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ = 7.54 (d, $^3J_{H-H}$ = 7.5 Hz, 8 H, Ar-H), 7.48 (d, $^3J_{H-H}$ = 7.8 Hz, 8 H, Ar-H), 5.75 (m, 12 H, =CH), 4.84 (d, 24 H, $=CH_2$), 1.55 (d, $^3J_{H-H}$ = 7.8 Hz, 24 H, $CH_2$(allyl)), 1.38 (m, 8 H, $CH_2$-$CH_2$-$CH_2$), 0.80 (t, 8 H, allyl$_3$Si-$CH_2$), 0.64 (t, 8 H, Ar$Me_2$Si-$CH_2$), 0.24 (s, 24 H, $CH_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 141.3, 135.9, 134.9, 134.8, 133.2, 113.8, 20.7, 20.0, 18.5, 16.5, -2.7. $^{29}$Si{$^1$H} NMR (60 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = -0.99, -3.66, -14.73. MALDI-TOF MS: *m/z*: 1446.03 [$(C_{80}H_{124}Si_9 + Ag)^+$] (Calcd. 1446.48). Anal. Calcd. for $C_{80}H_{124}Si_9$: C, 71.78; H, 9.34; Si, 18.88. Found: C, 71.65; H, 9.28; Si, 18.77.

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# Chapter 4

## Dye-functionalized Carbosilane Dendrimers: Synthesis, Physical Properties and Application in a Diafiltration Set-up

*Carbosilane dendrimers can be used as supports in organic synthesis, since their dimension allows separation of the (supported) products from the reaction mixture by diafiltration. In order to investigate the performance (based on both retention and filtration rate) of the dendrimers during these diafiltration experiments, several flexible and more rigid dendrimers have been functionalized with two different dyes (i.e. Disperse Red 1 (DR1) and ferrocene (Fc)) at their periphery. The series consists of flexible dendrimers of the zeroth generation (G0-4-DR1* ***2*** *and G0-4-Fc* ***10****; four dye-groups), first generation (G1-4-DR1* ***3****, G1-8-DR1* ***4****, G1-12-DR1* ***5*** *and G1-12-Fc* ***11****; four, eight or twelve dye-groups) and second generation (G2-36-DR1* ***6****; 36 dye-groups), and first and second generation rigid-core dendrimers (G1(RC)-9-DR1 7 and G2(RC)-9-DR1* ***8****; both 9 dye-groups). The dyes allow for the straightforward determination of the retention of the dendrimers during filtration experiments in a diafiltration set-up using membranes with varying mass cut-off values. UV/Vis spectroscopy, GPC and modeling studies were applied to the dye-functionalized dendrimers in order to obtain more information about the size and shape of the dendritic structures. In general an increase of the dimensions of the dendrimers with increasing generation or increasing molecular weight was observed, which was corroborated by the diafiltration experiments. In contrary to the results from the GPC and modeling studies, the first generation Fc-dendrimer* ***11*** *was retained better than its DR1-equivalent* ***5****, which could be explained by the effect that the peripheral ferrocene groupings rigidify the dendrimer. Furthermore, within the series of the flexible first-generation DR1-dendrimers* ***3****–****5****, the lighter dendrimer* ***4*** *is retained better by all membranes than the heavier dendrimer* ***5****, probably due to a number of structural and solvent effects. Furthermore, the higher generation flexible dendrimer* ***6*** *and the more rigid core dendrimers 7 and* ***8*** *showed indeed better retentions by the membranes with higher molecular weight cut-off (MWCO) values, compared to the smaller flexible dendrimers. Together with the higher filtration rates using these membranes, this makes them good candidates for the application as support for organic synthesis. Yet, also first generation dendrimer* ***4*** *represents an interesting candidate, as this dendrimer can be made in relatively few steps, comprises only aliphatic Si-C bonds, and therefore is highly robust. The sacrifice with this dendrimer is a somewhat longer filtration time.*

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## 4.1 Introduction

Since the introduction of Solid Phase Organic Synthesis (SPOS) by Merrifield in the 1960's,[1] supported synthesis is a widely applied method in both industrial and academic research for the synthesis of (pharmaceutically interesting) small molecules. Although SPOS has many advantages (*e.g.* easy purification, high yields) compared to classical, solution phase organic chemistry, also several disadvantages exist (*e.g.* solvatation problems, nonlinear reaction kinetics and difficult spectroscopic analysis). In order to overcome one or some of these existing drawbacks of SPOS, several types of alternative synthesis supports have been developed over the years. Soluble polymeric supports (Liquid Phase Organic Chemistry, LPOS, *e.g. J*anda*J*el™) are the most widely used.[2-6] Besides, various dendritic materials have been introduced as carrier material in the last decades, first as supports for catalytic species,[7-12] and later on also as supports for organic synthesis.[13-19] Among these dendritic materials, carbosilane dendrimers[20,21] take a special position; not only because of their kinetic and thermodynamic stability, originating from the relatively high dissociation energy (306 kJ/mol) and low polarity of the Si-C bond, but also because of their stability towards highly reactive reagents.[22]

The experience gained with the application of dendrimers as catalyst supports combined with the SPOS knowledge, makes carbosilane dendrimers good candidates for application as supports for organic synthesis. The dimensions of the dendrimers allow separation of the dendritic species from the product stream by nano- or diafiltration techniques. In this way, excess of reagents can be used like in SPOS, and separated from the reaction mixture, eventually yielding products of high purity and in high yield.

Although the development of nano- and diafiltration techniques for dendritic supports is well established nowadays, loss of dendritic material is often observed during the filtration.[10,23-26] Most dendrimers are not rigid globular molecules and are sensitive to shear flow, at least to some extent, which results in diminished and variable hydrodynamic volumes under filtration conditions. Previous studies by Van Koten et al. showed that dendrimers in which the core is rigidified, *i.e.* so-called rigid-core dendrimers, show higher retentions in diafiltration studies than their traditional, more flexible counterparts.[27]

Various types of membranes have been used in nano- or diafiltration set-ups.[23,24] In general, the resistance towards the reaction conditions used is not optimal, and membranes that are (solvent) resistant (*e.g.* ceramic) are usually very expensive. Yet, contrary to the application as catalyst support, for the application as support in organic synthesis, using the dendrimers in

stoichiometric amounts, full retention of the dendrimers is not crucial. Filtration in this case is used as a method to remove low molecular weight impurities from the dendrimer supported product. Losing small amounts of dendritic material during the filtration is acceptable, as long as all impurities will be removed at the same time. A balance between fast filtration and high retention has to be found, which will make automation of the processes possible.

Here, we present the functionalization of both flexible and rigid-core[28] carbosilane dendrimers of various generations with two different coloring agents (dyes), namely ferrocene (Fc) and Disperse Red 1 (DR1) (Figure 1). Several physical properties of these dye-functionalized dendrimers were investigated, in order to gain more information about the dimensions and shape of the different dendrimers. DR1 and ferrocene differ in size and shape (*i.e.* DR1 is more rod-shaped whereas ferrocene is more ball-shaped), which will provide more information about the influence of the dimensions of peripheral groupings on the behavior of the dendrimer as a whole. Finally, the diafiltration behavior of the dye-functionalized dendrimers is investigated in relation to their size and shape, using a membrane reactor with membranes of various molecular weight cut-off (MWCO) values.

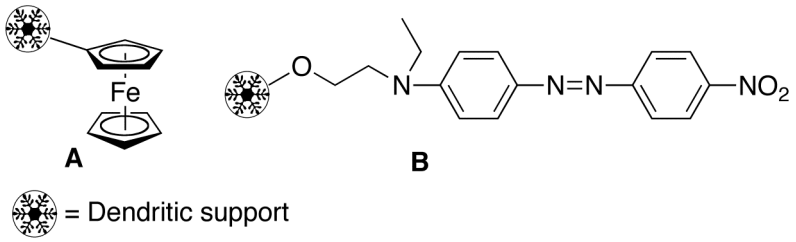



**Figure 1.** Carbosilane dendrimers loaded with the dyes ferrocene (A) and Disperse Red 1 (B).

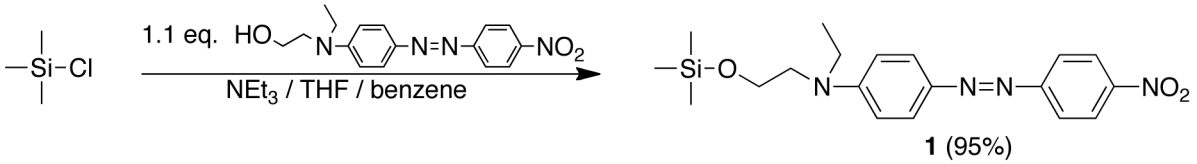
## 4.2 Results

### 4.2.1 Synthetic approach for the dye-functionalized dendrimers

*4.2.1.1 Disperse Red 1*

Disperse Red 1 (DR1) is a frequently used, water-soluble, and pH-responsive dye. Its $\lambda_{max}$ (484 nm) and molar extinction coefficient ($\varepsilon$ = 34,119 $cm^2$ $mmol^{-1}$; experimental values in dichloromethane) make it an interesting and highly sensitive coloring agent for our studies. The hydroxy group of the ethanolamine moiety of DR1 offers a ready anchoring point, although the modification at this point will decrease the water solubility of DR1. A series of different carbosilane dendrimers bearing chlorosilane end groups were reacted with DR1 in the presence of a mild base in order to anchor DR1 to these dendrimers via siloxane bonds. The model compound trimethylsilyl-DR1 **1** (TMS-DR1) was synthesized to serve as a

reference for the DR1-dendrimers (Scheme 1). The chlorosilane grouping of trimethylsilyl chloride was reacted with 1.1 equivalents of DR1 in a mixture of THF and benzene (2:1 (v/v)). The reaction was performed in the presence of $NEt_3$ to scavenge HCl. Leaving the reaction for 1.5 h, followed by quenching the reaction with methanol, resulted in complete conversion, as was confirmed by NMR spectroscopy. Purification by column chromatography resulted in an isolated yield of 95%. TMS-DR1 **1** has an ε of 41,000 $cm^2$ $mmol^{-1}$ at $\lambda_{max}$ = 487 nm in dichloromethane and serves as a better reference for the DR1-dendrimers than DR1 itself (which has a free hydroxyl group, making its solubility and absorption phenomena more solvent dependent[29]).




**Scheme 1.** Synthesis of TMS-DR1 **1**.

In analogy, the synthesis of the simple G0-4-DR1[30] dendrimer was taken as a test case for the synthesis of the other dendrimers. The chlorosilane end groupings of G0-4-Cl were reacted with 1.1 equivalents of DR1 per dendritic arm using the conditions described for the synthesis of **1**. G0-4-DR1 dendrimer **2** was purified by column chromatography, resulting in an overall 55% yield. This result encouraged us to synthesize a complete range of both flexible and rigid-core dendrimers functionalized with DR1 (Figure 2).[31] In all cases complete conversion of the Si-Cl groups was obtained using the same reaction conditions, as indicated by $^1$H NMR analysis, elemental analysis and MALDI-TOF MS. All dendrimers in the G1-series (**3** - **5**) as well as G2-36-DR1 **6** and both rigid-core dendrimers G1(RC)-9-DR1 **7** and G2(RC)-9-DR1 **8** were purified by passive dialysis and were obtained in moderate to high yields (59 - 85%). The relatively low yield for **3** can be explained by its flexible nature, which makes permeation through the dialysis bag induced by shear flow more likely to occur. These synthetic protocols provide us with a series of DR1-functionalized dendrimers that vary in the number of end groupings (DR1 moieties), the degree of branching ('internal density'), and flexibility at the core.

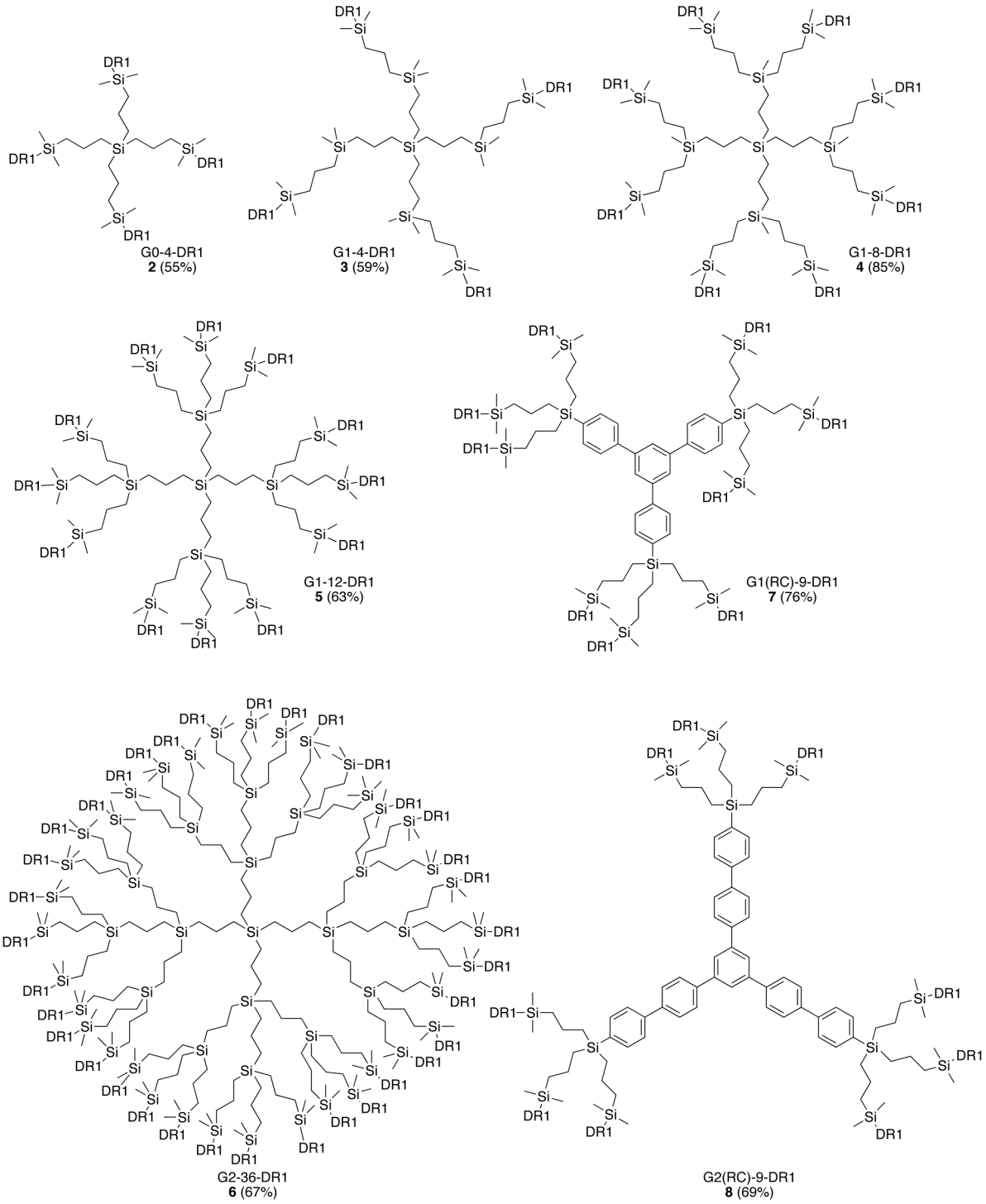
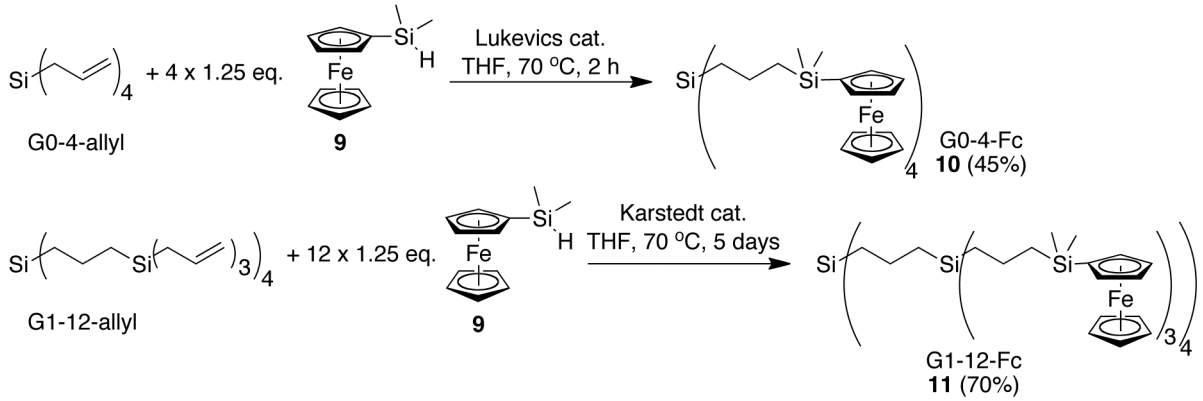



**Figure 2.** DR1-functionalized carbosilane dendrimers **2**-**8**.

*4.2.1.2 Ferrocene*

Ferrocene is a well-known, widely used, and air-stable organometallic compound, with an extinction coefficient $\varepsilon$ = 98.2 $cm^2$ $mmol^{-1}$ at $\lambda_{max}$ = 442 nm (experimental values in dichloromethane). Its aromatic nature makes modification straightforward and results, *e.g.*, in the application as ligand scaffold in the widely used ferrocenyl phosphines.[32] The ferrocene

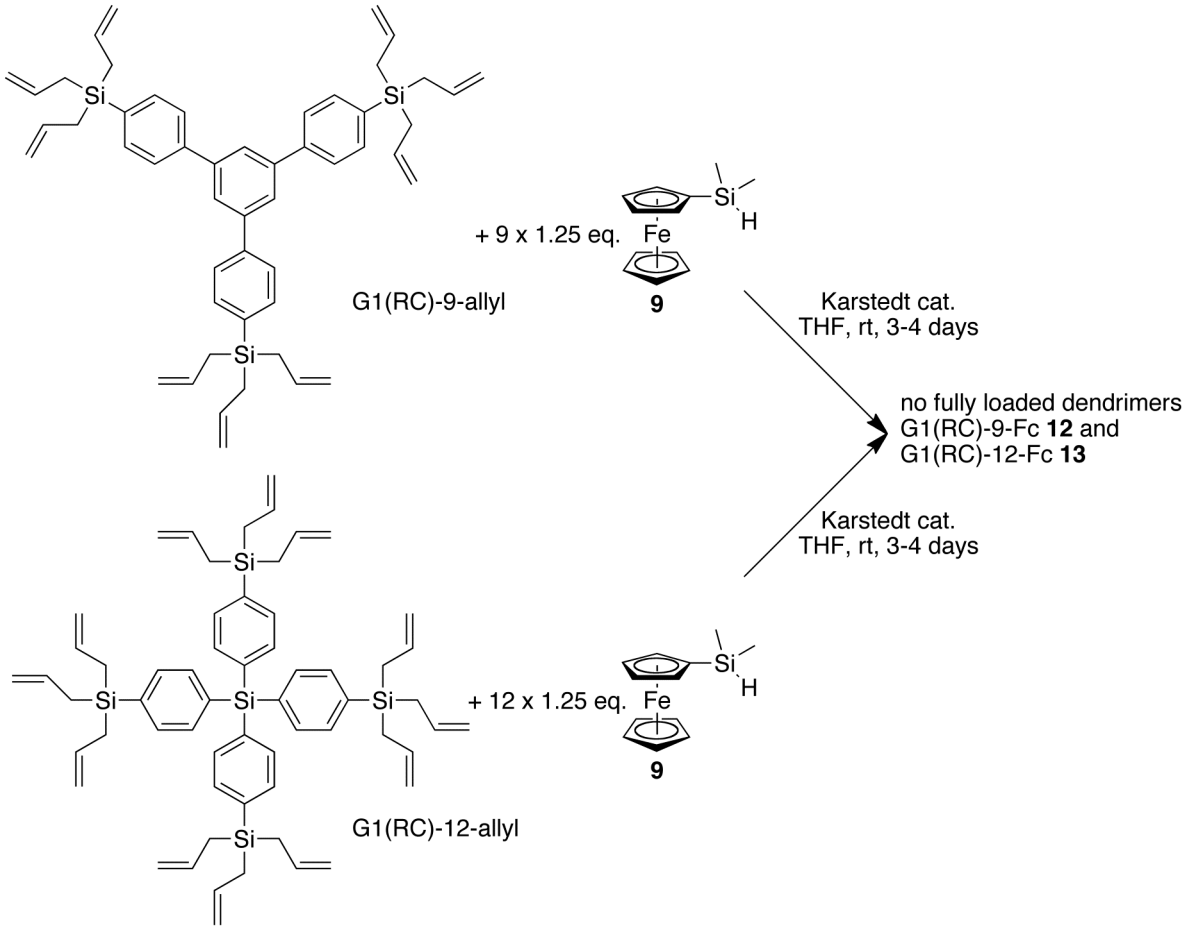
molecule is rather small and spherical, which allows for mimicking the presence of a small, compact molecule at the dendrimer periphery. In addition to the DR1-dendrimers **2 - 8**, which have the more rod-shaped DR1 molecules attached to their periphery, the use of ferrocene as peripheral dye moiety will provide more information about the dependence of the shape of the peripheral groupings on the diafiltration performance of the dendrimers. The loading of the dendrimers with ferrocene (Fc) started with the modification of ferrocene with dimethylsilane.[33-35] To this end, ferrocene was monolithiated using 2 equivalents *t*-BuLi in THF in the presence of *t*-BuOK at –78 °C. After stirring the mixture at this temperature for 1 h, it was added to a solution of chlorodimethylsilane in THF at –40 °C, yielding ferrocenyldimethylsilane **9** as a red oil, together with ferrocene as the only observable side-product after work up. The product was obtained in 86% purity according to GC-MS analysis. Ferrocenyldimethylsilane **9** was attached to both the zeroth (G0-4-allyl) and first (G1-12-allyl) generation carbosilane dendrimer via a hydrosilylation reaction of the allyl groups of the dendrimers in the presence of a platinum catalyst (Lukevics catalyst $(Bu_4N)_2[PtCl_6]$ or Karstedt catalyst $(C_8H_{18}OSi_2)_3Pt_2$), in analogy to the general carbosilane dendrimer synthesis procedure (Scheme 2).[20,21] The addition of 1.25 equivalents of **9** per dendritic arm resulted in full conversion of all allyl groups of both dendrimers, as was confirmed by NMR. The functionalized dendrimers G0-4-Fc **10** and G1-12-Fc **11** were purified either by column chromatography or passive dialysis, resulting in isolated yields of 45% and 70%, respectively.




**Scheme 2.** Functionalization of carbosilane dendrimers with ferrocene.

Unfortunately, in our hands, application of this procedure to functionalize the two rigid-core dendrimers G1(RC)-9-allyl and G1(RC)-12-allyl[28] with ferrocenyl end groupings did repeatedly not result in the formation of the pure, fully loaded dendritic compounds G1(RC)-9-Fc **12** and G1(RC)-12-Fc **13** (Scheme 3). The dendrimers were obtained as complex

mixtures of the product and the starting materials, which made determination of the loading degrees impossible. Because of the incomplete loading of these dendritic materials, it was decided not to include these materials in our further studies.




**Scheme 3.** Attempted synthesis of **12** and **13**.

### 4.2.2 Physical Properties of the Dye-functionalized Dendrimers

*4.2.2.1 UV/Vis Spectroscopy*

As described above, the dyes and thereby the dye-functionalized dendrimers are highly UV/Vis sensitive, which makes UV/Vis spectroscopy an appropriate tool to monitor the retention of the dendrimers during the filtration experiments. UV/Vis spectroscopy was used to determine the extinction coefficients ε (in $cm^2$ $mmol^{-1}$, at $\lambda_{max}$ values of 442-487 nm, see Table 1) of the dye-functionalized dendrimers. For this purpose, solutions of various concentrations of the dendrimers were analyzed by UV/Vis spectroscopy and it was observed that all dendrimers obeyed Lambert-Beer's law, *i.e.* a linear relationship exists between the concentration and absorbance (Figure 3).

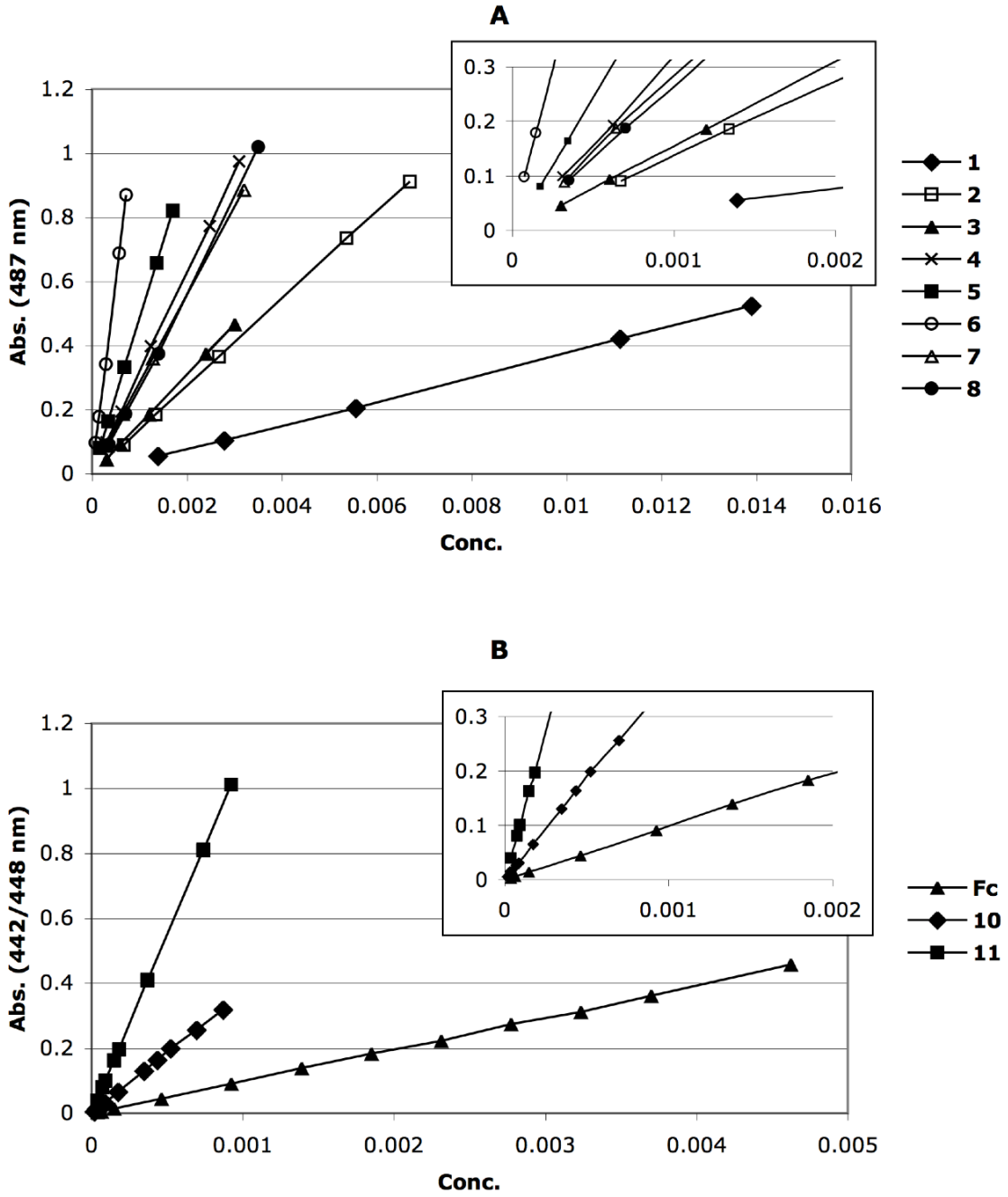



**Figure 3.** Relation between UV/Vis absorption and concentration for a) DR1-dendrimers **2-8** and TMS-DR1 (**1**), and b) Fc-dendrimers **10-11** and Fc.

The data obtained by UV/Vis spectroscopy are summarized in Table 1. For every dye compound (*i.e.* single dye molecules, model compounds and dendrimers) the measured extinction coefficient is reported, as well as the calculated extinction coefficient per dye group in the dendrimers. These data provide some extra information about the dendritic systems. For example, within the DR1-series, a certain variety in extinction coefficient per dye group is

observed. The extinction coefficient per dye grouping is similar for all first generation (**3** - **5**) dendrimers and comparable to the extinction coefficient of TMS-DR1 **1**, but when changing to the smaller G0-4-DR1 **2**, the larger G2-36-DR1 **6** or to the rigid core dendrimers G1(RC)-9-DR1 **7** and G2(RC)-9-DR1 **8**, the average extinction coefficient per dye grouping decreases.

**Table 1.** Extinction coefficients of the dye-functionalized dendrimers **2-8**, **10**, and **11**, TMS-DR1 (**1**), DR1 and Fc.

| **Compound** | **Ext. Coeff. (ε) ($cm^2$ $mmol^{-1}$)** | **Ext. Coeff. (ε) per dye group ($cm^2$ $mmol^{-1}$)** |
|---|---|---|
| DR1 | 34,000 (484 nm) | 34,120 |
| TMS-DR1 **1** | 38,000 (487 nm) | 38,000 |
| G0-4-DR1 **2** | 136,000 (487 nm) | 34,000 |
| G1-4-DR1 **3** | 156,000 (487 nm) | 39,000 |
| G1-8-DR1 **4** | 312,000 (487 nm) | 39,000 |
| G1-12-DR1 **5** | 484,000 (487 nm) | 40,330 |
| G2-36-DR1 **6** | 1,204,000 (487 nm) | 33,440 |
| G1(RC)-9-DR1 **7** | 277,000 (487 nm) | 30,780 |
| G2(RC)-9-DR1 **8** | 291,000 (487 nm) | 32,330 |
| Fc | 98 (442 nm) | 98 |
| G0-4-Fc **10** | 370 (447 nm) | 93 |
| G1-12-Fc **11** | 1,100 (448 nm) | 92 |

As expected based on the extinction coefficient of free ferrocene, the Fc-dendrimers **10** and **11** expose a much lower extinction coefficient than the DR1-dendrimers **2-8** (Table 1). Especially in case of the smaller **10**, which contains less dye molecules than the larger **11**, this can lead to a lower accuracy in the determination of the concentrations of the low-concentrated fractions collected during the diafiltration experiments (*vide infra*, section 2.3).

*4.2.2.2 Molecular Modeling*

The structures of DR1- and Fc-dendrimers **2-8** and **10-11** were modeled using SPARTAN and their energies were minimized (using SPARTAN '04 for Macintosh, with the MMFF94 force field for structure refinement; structures shown in Figures 4 and 5). The average diameter of the dendrimers was estimated by (manually) measuring the distance between two opposite outer atoms of the structures. Since the dendrimers are not perfect spherical structures but do

also adopt more disc-shaped or elliptical overall structures, both minimal and maximal distances between two outer atoms were measured and are reported in Table 2. When using the dendrimers in a diafiltration set-up, both these minimal and maximal diameters are important, since the dendrimers can approach the membranes in all possible orientations (especially under shear flow). With these diameters the average size (dynamic diameter) of the dendrimers could be estimated. These dimensions of the dendrimer might give a prediction of the retention of the dendrimers by the different membranes.

**Table 2.** Molecular weight and average diameters (measured in the molecular models) of dendrimers **2-8** and **10-11**.

| **Compound** | **Mw (g mol$^{-1}$)** | **Average cross-section (Å) (minimal-maximal)** |
|---|---|---|
| G0-4-DR1 **2** | 1680 | 22-28 |
| G1-4-DR1 **3** | 2083 | 22-34 |
| G1-8-DR1 **4** | 3677 | 27-46 |
| G1-12-DR1 **5** | 5272 | 27-46 |
| G2-36-DR1 **6** | 16039 | 37-50 |
| G1(RC)-9-DR1 **7** | 4110 | 37-49 |
| G2(RC)-9-DR1 **8** | 4338 | 37-56 |
| G0-4-Fc **10** | 1169 | 16-20 |
| G1-12-Fc **11** | 3732 | 20-30 |

In the series of the conventional, flexible DR1-dendrimers (**2**-**6**) the diameter increases with increasing generation (depicted in Figure 4). Within the G1-series (**3**-**5**) only an increase was observed when changing from dendrimer **3** (4 DR1 moieties) to **4** (8 DR1 moieties), whereas **4** and **5** (8 or 12 DR1-moieties) have comparable diameters. The increasing diameter when comparing **3** to both **4** and **5** could be due to more steric crowding (higher branching degree) and thereby less flexibility of the dendritic structures of **4** and **5**. For the rigid-core dendrimers **7** and **8** an increase in diameter with increasing rigid core size was observed.

Furthermore, when comparing the conventional, flexible, dendrimers **2** - **6** with the rigid-core dendrimers **7** and **8**, an increase in diameter is found when comparing dendrimers with similar molecular weights. The smallest rigid-core dendrimer **7** has the same dimension as the heavier, second generation dendrimer **6**, and **8** is even larger, although its molecular weight is

still lower compared to **6**. This feature will make these rigid-core dendrimers good candidates as supports for organic synthesis when (dia)filtration is used as the purification method.

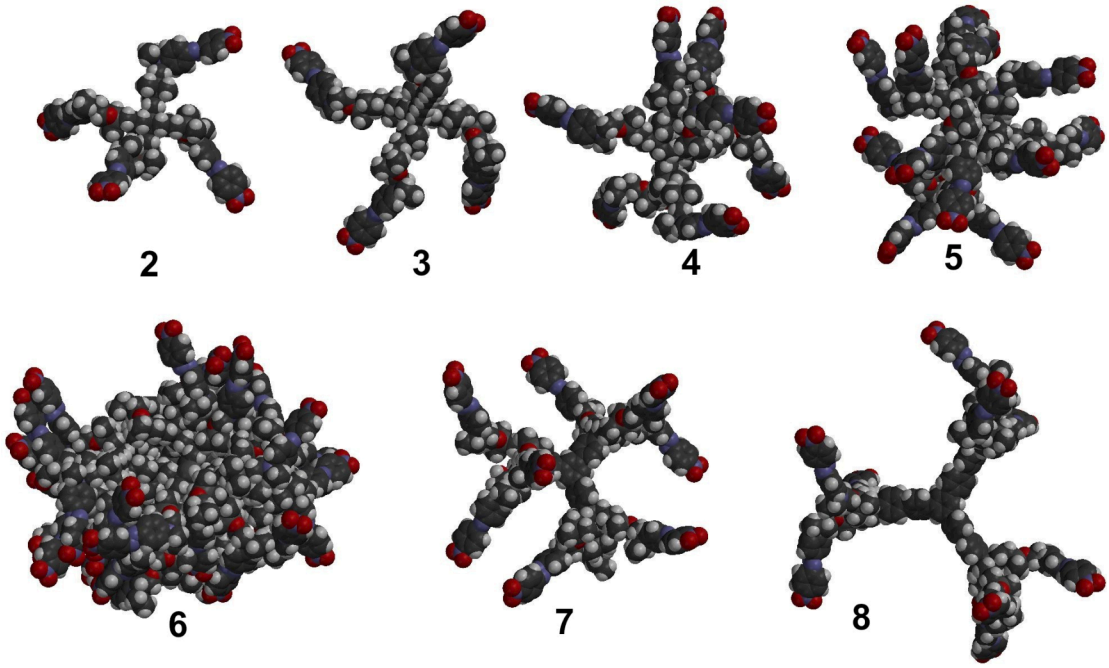



**Figure 4.** Molecular models (MMFF94) of the DR1-dendrimers **2**-**8**.

When comparing the DR1-dendrimers to the Fc-dendrimers, the diameters of the Fc-dendrimers are smaller for the same generation dendrimers (Table 2). Since the shape of the Fc-groupings is more sphere-like whereas the DR1-groupings are more rod-shaped, a difference in dendrimer diameter is indeed expected. Evaluation of the diameters of the dendritic backbones of similar DR1- and Fc-dendrimers did not reveal large differences. The difference is size between corresponding DR1- and Fc-dendrimers therefore seems to be caused mainly by the size and shape of the peripheral groups. In the models depicted in Figure 5 the effect is clearly visible, since the comparable Fc-dendrimers are more densely packed compared to the DR1-dendrimers in Figure 4.

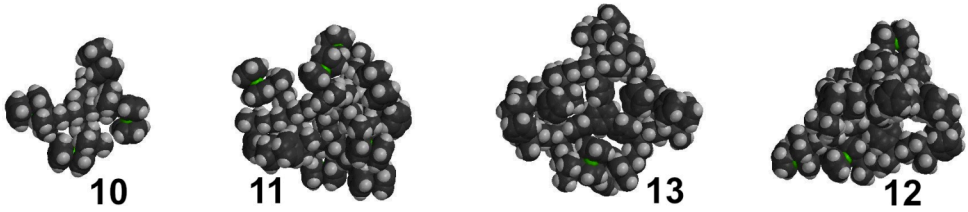



**Figure 5.** Molecular models (MMFF94) of the Fc-dendrimers **10**-**13**.

*4.2.2.3 Gel Permeation Chromatography (GPC)*

In gel permeation chromatography (GPC) the separation of molecules is based on their sizes, which can be expressed in terms of their hydrodynamic volumes, defined as $[\eta]\cdot M$ (in mL/g; $[\eta]$ = intrinsic viscosity (mL/g), M = molecular weight (u)).[36,37] GPC columns are generally calibrated using polymer samples of known molecular weight and hydrodynamic volume.[37,38] In this case, calibration was carried out using polystyrene (PS) samples in THF, resulting in a calibration line for the GPC column ($\text{Log } [\eta]M = -1.0288 * t + 10.588$ with t in min.). Using this calibration line, the (relative) hydrodynamic volumes of dendrimers **2** - **8** and **10** - **11** were determined. However, it should be taken into account that these data indicate that a dendrimer with a certain elution time on the GPC column has a comparable hydrodynamic volume as a certain PS sample. In comparison to the polymer samples, the GPC traces of the dendrimers did show lower polydispersities. In case of the DR1-dendrimers, small signals corresponding to free DR1 were observed. The data are summarized in Table 3. A graphical representation of the data is depicted in Figure 6.

**Table 3.** GPC data (retention times, molecular weight and hydrodynamic volumes) of polystyrene calibration samples and dendrimers **2-8**, **10** and **11**.

| Sample | t (min) | M (u) | [η]M (mL/g) |
|---|---|---|---|
| polystyrene | 7.50 | 687 | 861 |
| polystyrene | 6.44 | 2727 | 9289 |
| polystyrene | 5.99 | 4075 | 18572 |
| polystyrene | 5.55 | 9100 | 74257 |
| polystyrene | 4.94 | 24150 | 399875 |
| **2** (G0-4-DR1) | 6.83 | 1680 | 3642 |
| **3** (G1-4-DR1) | 6.57 | 2083 | 6742 |
| **4** (G1-8-DR1) | 6.26 | 3677 | 14051 |
| **5** (G1-12-DR1) | 6.09 | 5272 | 21019 |
| **6** (G2-36-DR1) | 5.57 | 16039 | 72042 |
| **7** (G1(RC)-9-DR1) | 6.17 | 4110 | 17390 |
| **8** (G2(RC)-9-DR1) | 6.04 | 4338 | 23662 |
| **10** (G0-4-Fc) | 7.53 | 1169 | 694 |
| **11** (G1-12-Fc) | 6.74 | 3732 | 4507 |

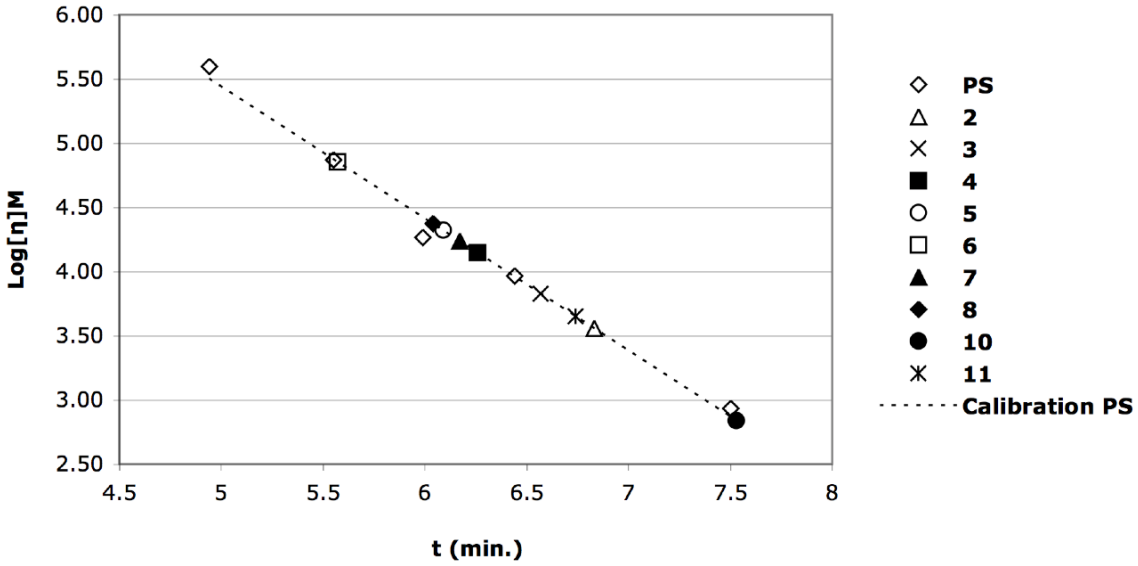



**Figure 6.** Graphical representation of the PS calibration line and the dendrimer data summarized in Table 3.

Within the flexible DR1-dendrimer (**2** - **6**) series the hydrodynamic volume increases with increasing generation, as expected based on the molecular weights of the dendrimers. However, when comparing the volumes of the two rigid-core dendrimers **7** and **8** with the volumes of **2** - **6**, apparently not only the molecular weight influences the hydrodynamic volume. Whereas the volume of the smallest rigid-core dendrimer **7** is still in line with the flexible dendrimers, the larger dendrimer **8** displays a higher hydrodynamic volume than based simply on its molecular weight (*i.e.* 4,338 g $mol^{-1}$). Its volume is even larger than the volume of flexible dendrimer **5**, which has a higher molecular weight (5,572 g $mol^{-1}$). Furthermore, when comparing the DR1-dendrimers **2**-**6** with the Fc-dendrimers **10** and **11**, the latter display significantly lower hydrodynamic volumes. This observation is in agreement with the modeling studies (*vide supra*).

In order to be able to compare the volumes of the dendrimers in more detail to the volumes of the PS samples, the relation between the molecular weight of the samples and the hydrodynamic volume is depicted in Figure 7. Based on this analysis, the hydrodynamic volumes of the flexible DR1-dendrimers **3** and **4**, as well as the smallest rigid-core dendrimer **7**, correspond very well to the hydrodynamic volumes of PS samples of comparable molecular weight. However, when changing to the smallest flexible dendrimer **2** or to the larger dendrimers **5** and **6**, the hydrodynamic volumes start to deviate from the volumes of the

PS calibration samples. Especially the second generation dendrimer **6**, which has a molecular weight of 16,039 g mol$^{-1}$, has a much smaller hydrodynamic volume than its PS equivalent and its volume is almost comparable to the volume of PS with a molecular weight of 9,100 g mol$^{-1}$. Furthermore, the volume of the second generation rigid core dendrimer **8** is larger than predicted based on the PS equivalents. From Table 3 and Figures 6 and 7 it is again clear that **8** has a slightly larger volume than the heavier, flexible **5**. The ferrocene dendrimers **10** and **11** both display smaller hydrodynamic volumes than the PS samples of comparable molecular weight. This observation is in agreement with the modeling studies described before. Of these two dendrimers, especially the volume of the first generation dendrimer **11** differs significantly from the PS calibration (Figure 7).

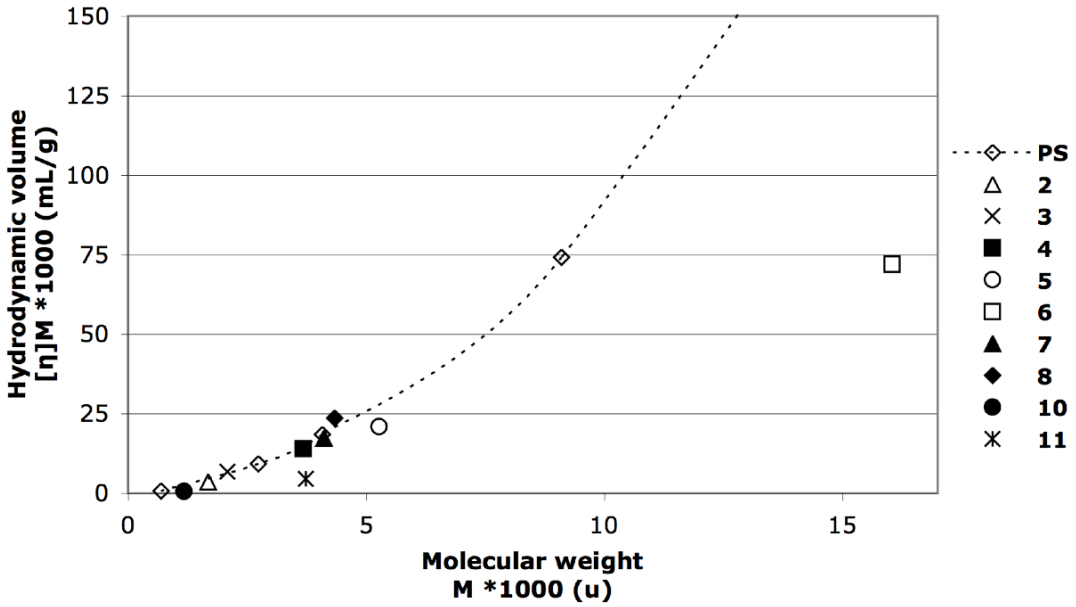



**Figure 7.** Graphical representation of the relation between the molecular weights and the hydrodynamic volumes of polystyrene standards and dendrimers **2** - **11**.

### 4.2.3 Diafiltration Experiments

Diafiltration experiments were carried out using a 50 mL solvent resistant diafiltration reactor from Millipore, equipped with regenerated-cellulose membrane discs of various molecular weight cut-off (MWCO) values, *i.e.* 1,000; 3,000; 5,000; 10,000 and 30,000 g mol$^{-1}$.[39]

A protocol in which elution fractions were collected in each experiment was developed for the diafiltration experiments in order to obtain reproducible filtration results for all dendrimers (see experimental section for details). According to the manufacturer's manual, the cellulose

membranes perfectly withstand aqueous solvents, but are to some extent delicate in many solvents used in organic synthesis, such as ethers or dichloromethane. The mixture of solvents used in our experiments (MeOH:$CH_2Cl_2$ = 1:1 or 2:3 (v/v)) was apparently just reaching the limits of solvent-tolerance. In most diafiltration experiments no problems occurred with the membranes and filtration proceeded as expected. However, in few cases, obvious leakage (much more than expected based on other experiments) of solutions through the membrane was observed. In such cases, a closer look at the leaking membranes showed the formation of a ridge in the membrane surface, which was an indication of fractures in the membrane structure. Experiments in which leakage was observed because of membranes fracturing were discarded. Besides the solvent damaging the membrane, also the presence of amine functionalities in the DR1-dendrimers could cause fracture of the membrane tissue. Indeed, the filtration experiments with the DR1-dendrimers did result in damaged membranes slightly more often than in case of the Fc-dendrimers. However, this phenomenon is neglectable compared to the solvent effect.

Measuring the UV/Vis absorption of each collected fraction (and making use of the extinction coefficients in Table 1), allowed to determine the dendrimer concentrations of the collected fractions. In general, a decrease in concentration of the fractions collected during the filtration experiments was observed. Apparently in the beginning of the filtration the membranes have a higher permeability. Since all dendrimers were purified by passive dialysis prior to the filtration experiments, it is not very likely that large amounts of free dye molecules (ferrocene or DR1) are still present in the dendrimer solution in the reactor. If present, these small molecules would indeed cause an increase of concentration of the first filtrate(s), since the smaller molecules will easily flush though the membrane when applying pressure at the start of the diafiltration. Remarkably, after refilling the reactor with fresh solvent (halfway during the filtration, see experimental section) a slight increase of concentration of the collected fractions was observed. Undoubtedly, this can not be explained as being a possible remainder of free dye molecules, since these should have been removed from the retentate by filtration of the first four fractions. Probably depressurizing followed by pressurizing the reactor, or dilution of the retentate is resulting in opening the pores of the membrane for a short time, or until blocking by dendrimer molecules occurs (again).

The retention of the dendrimers by the membranes could be determined using a slightly modified literature procedure.[40] In this reported procedure the retention is calculated based on

the concentration difference between both the permeate and the retentate. In our studies we collected the permeate in multiple fractions, which makes determination of the concentration slightly less straightforward. Instead, the concentration of each separate fraction was determined using its UV/Vis absorption (via the extinction coefficient). From these concentrations the total amount (mass) of dendritic material in the combined fractions (*i.e.* permeate) was calculated, yielding a total mass of dendritic material flushed through the membranes. Combined with the known concentration and thereby mass of dendrimer in the initial reactor loading, the retention R (in %) of dendritic material by the various membranes could be calculated using equation 1 ($m_f$ = total mass (mg) in combined filtrates; $m_0$ = initial mass (mg) loaded in reactor).

$$R(\%) = \left(1 - \frac{m_f}{m_0}\right) * 100 \qquad \text{Eq. 1}$$

In this way retentions for all dendrimers with the various membranes were obtained (Table 4). In all experiments care was taken that equal amounts of permeate were collected in order to be able to compare the retentions of the dendrimers in solution to each other.

**Table 4.** Retentions of dendrimers **2-8**, **10** and **11** by membranes with various MWCO values; solvent system used: MeOH:$CH_2Cl_2$ = 1:1 (v/v).

| **Compound** | **R (%)**[a] **(1,000)**[b] | **R (%)**[a] **(3,000)**[b] | **R (%)**[a] **(5,000)**[b] | **R (%)**[a] **(10,000)**[b] | **R (%)**[a] **(30,000)**[b] |
|---|---|---|---|---|---|
| G0-4-DR1 **2** | 67.5 | 65.5 | n.d. | n.d. | n.d. |
| G1-4-DR1 **3** | 97.4 | 95.8 | 90.3 | 82.6 | <1 |
| G1-8-DR1 **4** | 98.9 | 98.6 | 97.8 | 91.3 | <1 |
| G1-12-DR1 **5** | 95.9 | 98.3 | 95.3 | 87.3 | <1 |
| G2-36-DR1 **6** | n.d. | n.d. | 99.8 | 99.3 | 92.2 |
| G1(RC)-9-DR1 **7** | n.d. | n.d. | 95.5 | 94.0 | <1 |
| G2(RC)-9-DR1 **8** | n.d. | n.d. | 96.0 | 93.9 | <1 |
| G0-4-Fc **10**[c] | <1 | n.d. | n.d. | n.d. | n.d. |
| G1-12-Fc **11**[c] | n.d. | 99.3 | 98.9 | 95.9 | n.d. |

a) Equation 1 (*vide supra*) was used to determine the retentions.

b) Membranes from Millipore were used, with MWCO values of 1,000; 3,000; 5,000; 10,000 and 30,000 $gmol^{-1}$.

c) Solvent system: MeOH:$CH_2Cl_2$ = 2:3 (v/v).

Analysis of the data summarized in Table 4 shows several trends. For all dendrimers, a decrease in retention with increasing MWCO values of the membranes is observed. In other words, permeation through the membrane is more likely to occur with membranes with higher MWCO values. Within the results for the conventional (flexible) DR1-dendrimers **2** - **6**, in general an increase of retention with increasing dendrimer size can be observed for each membrane. Remarkably, **4** is retained better by each membrane than **5**, despite its lower molecular weight. The larger second generation dendrimer **6** is retained very well by membranes with MWCO values up to 30,000 g $mol^{-1}$ (retention >90%), although its own molecular weight is just 16,039 g $mol^{-1}$. Furthermore, the rigid-core dendrimers **7** and **8** are retained well by membranes with MWCO values of 5,000 and 10,000 g $mol^{-1}$ (retention >93%), although their molecular weights are just 4,110 and 4,338 g $mol^{-1}$, respectively. In contrast to dendrimer **6**, both **7** and **8** are not retained at all by the membrane with a MWCO value of 30,000 g $mol^{-1}$. This could be expected based on their lower molecular weights, despite their rigid structures.

For the Fc-dendrimers it was found that **10** was not retained at all by any of the membranes. This implies that **10** is smaller than its DR1-equivalent **2**, which is retained to some extent by the 1,000 and 3,000 g $mol^{-1}$ membranes. This observation is in agreement with the results obtained in both the modeling and GPC studies (*vide supra*). Remarkably, the first generation dendrimer **11** is retained slightly better than its DR1-equivalent **5**.

During every diafiltration experiment, the speed of filtration was registered as well. The average time needed for the permeation of the 10 mL fractions was recorded. Knowing the filtration rate will be helpful to determine the efficiency of the dendrimers as supporting material in organic synthesis. As expected, the filtration rate increased with increasing MWCO value of the membranes (Table 5).

**Table 5.** Average permeation times per membrane MWCO value.

| Membrane MWCO value (g mol$^{-1}$) | Filtration time for 10 mL (min.)[a] |
|---|---|
| 1,000 | 30 |
| 3,000 | 22 |
| 5,000 | 18 |
| 10,000 | 8 |
| 30,000 | 5[b] |

a) Average time required for the permeation of each 10 mL fraction.

b) Pressure of the reactor lowered to 1 bar to be able to collect separate 10 mL fractions.

## 4.3 Discussion

From previous studies it is known that the conventional carbosilane dendrimers are retained well in membrane reactors.[17,26,41,42] For example, first generation dendritic catalysts revealed retentions of more than 99% in a continuous flow membrane reactor, using a SelRO-MPF-50 membrane with a MWCO value of 700 g mol$^{-1}$.[26,42] However, changing the support structure to more rigid-core dendrimers allows for the use of more easily accessible supporting materials.[27] It was observed that rigid-core dendrimers with lower molecular weights were retained even more efficiently (>99.9%) by the same SelRO-MPF-50 membrane compared to the heavier, more flexible dendritic systems. In order to get more information about the filtration behavior of the dendrimers described here, several physical properties of these dendrimers were investigated.

### 4.3.1 UV/Vis Spectroscopy

UV/Vis spectroscopy was used for the calibration of the dendrimer solutions used in the diafiltration experiments. In analogy to previous studies,[27] the extinction coefficients for the multiple dye containing dendrimers, as well as the single dye molecules (DR1 and Fc) were determined. It appeared that all dendrimers obeyed Lambert-Beer's law, *i.e.* a linear relationship exists between concentration and absorption. This relationship allows for the application of UV/Vis spectroscopy as a tool to determine the retentions of the dendrimers during the diafiltration experiments.

Within the first generation DR1-dendrimers (**3** - **5**) the calculated average extinction coefficients per dye group are comparable to each other and to the extinction coefficient

found for TMS-DR1 **1**, which means that the ε-values correspond nicely to the number of DR1 units present in the dendrimers. However, these ε-values decrease when changing to the smaller (**2**), larger (**6**), or rigid core (**7** and **8**) dendrimers. Since all measurements were performed with fully loaded dendrimers (determined using NMR spectroscopy, elemental analysis, and MALDI-TOF MS), these differences in extinction coefficients can be explained as the presence of a "dendritic effect". The lower extinction coefficients found for the second generation flexible dendrimer **6** can be assigned to the high local concentration of the neighboring dye-groupings in the dendrimer, which could cause a deviation from the Lambert-Beer law, as was reported in literature for related Methyl Orange-functionalized PPI dendrimers.[43] Although the concentration of DR1-groups in dendrimer **2** is very low, the flexibility of the relatively short dendritic arms could still bring the DR1-groups closely together, resulting in a comparable effect. The presence of the aromatic core in the rigid dendrimers **7** and **8** can influence the UV/Vis absorption of the dendrimer as a whole, making it no longer directly related to the number of peripheral dye molecules.[27,44]

### 4.3.2 Dimensions of the dendrimers

In order to get more information about the solution-dimensions and shapes of the dendrimers, both modeling studies and GPC measurements were performed. The results of these studies can be used to predict or explain the diafiltration performance of the dendrimers (*vide infra*, section 3.3), and could eventually even lead to a calibration of the membranes in organic solvents.[45]

Within the series of flexible DR1-dendrimers **2**-**6**, the dimensions of the molecules increase with increasing generation in both the modeling and GPC studies. When including the dimensions of the rigid-core DR1-dendrimers **7** and **8** and the Fc-dendrimers **10** and **11** in the studies, the correlation between molecular weight and dimensions is not straightforward anymore (*vide infra*). Clearly, not only the molecular weight or the generation of a dendrimer determines its dimensions, but also the molecular structure does play an important role. Furthermore, the results obtained with the two studies do not exactly correspond with each other. An explanation could be that these studies are based on different physical forms of the dendrimers. In the modeling studies, the dendrimers are approached as static molecules of which the structures are optimized, without taking the influence of solvent molecules or other experimental conditions into account. In these static models, the flexible arms of the conventional dendrimers **2** - **6** and **10** - **11** are generally not completely stretched but often more folded back into the open dendrimer structure during the structure optimization. In GPC,

solutions of the dendrimers are analyzed, in which the (dynamic) dendrimers are surrounded by solvent molecules. Backfolding of the dendritic arms is therefore less likely to occur. This can result in a difference between the calculated diameters in the modeling studies and the measured volume of the dendrimers in solution, as determined by GPC.

In the modeling studies, the rigid core dendrimers **7** and **8** both have a (minimal) diameter that is comparable to the largest flexible dendrimer **6**, whereas their molecular weights are much lower (4,338 and 4,110 vs. 16,039 g $mol^{-1}$, respectively) and their structures are very different from that of **6**. This could be explained by the fact that the diameters are measured using the static models of the dendrimers, in which the arms of **6** are folded back into the dendritic structure, and thereby minimize its volume. The structures of **7** and **8** are more shape-persistent than of **6** and therefore more stretched out even after structure optimization, which results in larger diameters.[27] The smaller dimensions of Fc-dendrimers **10** and **11** compared to the corresponding DR1-dendrimers **2** and **5** is only partly explained by the presence of the smaller peripheral Fc-groupings (compared to DR1 end groupings), which decreases the diameter of the dendrimers as a whole. In addition, the smaller, apolar Fc units could display enhanced backfolding of the dendritic arms into the apolar dendritic interior compared to the larger and more polar DR1 units. On the other hand, a closer packing of peripheral Fc-moieties could lead to peripheral crowding, which results in a denser dendrimer structure.[46,47] In both cases, the overall diameter of the Fc-dendrimers is smaller than expected on the basis of molecular modeling.

In the GPC studies, the GPC column was calibrated using polystyrene samples of known molecular weight. Since these polymers are in principle spherical in THF solution (*i.e.* under θ-conditions),[38] the calibration can be used to determine the hydrodynamic volume of the dendritic molecules as a function of the residence time on the GPC column.[48] However, dendrimers are structurally not the same as polystyrene chains and therefore only an estimated comparison in the volumes can be made (*i.e.* a dendrimer has an estimated hydrodynamic volume that is comparable to the hydrodynamic volume of polystyrene with a certain molecular weight). Nevertheless, the hydrodynamic volumes calculated from the GPC analyses provided us with information about the relative volumes of the dendrimers. Besides the general trend of increasing volume with increasing dendrimer generation,[49-53] some remarkable observations were made as well. When comparing the rigid core DR1-dendrimers **7** and **8** to the flexible dendrimers **2** - **6**, it appeared that **7** still fits the general trend, whereas **8** (4,338 g $mol^{-1}$) is significantly larger than the heavier, but more flexible **5** (5,272 $gmol^{-1}$). In contrast to the observation in the modeling studies, the flexible second generation dendrimer

**6** (16,039 g mol$^{-1}$) seemed much larger than **8** by means of GPC. In solution, the bulky dendrimer **6** is apparently stretched out more than in the static model, probably due to the presence of solvent molecules between the dendritic arms, resulting in a larger volume. Still, **6** appears to be smaller than its corresponding PS molecular weight analogue, according to GPC. Fc-dendrimers **10** and **11** both have much smaller volumes than their DR1-equivalents **2** and **5**. Density caused by the ball-shaped Fc-units at the dendrimer's peripheries could cause inaccessibility of the open dendritic structure by solvent molecules, resulting in more densely packed dendritic structures.[46]

### 4.3.3 Diafiltration Experiments

The diafiltration experiments were performed following a general procedure, using a solvent-resistant stirred cell equipped with appropriate regenerated-cellulose membranes. A general trend that was observed is the increase of retention with increasing dendrimer generation and/or decreasing MWCO value of the membranes, which is not surprising. On the other hand, most dendrimers showed reasonable retentions (~90%) using membranes with MWCO values higher than their molecular weights. This can be explained by the fact that the membranes are calibrated using aqueous solutions, whereas in our experiments organic solvents (mixtures of dichloromethane and methanol) were used. This may cause swelling of the membrane material and, thereby, a reduction of the pore size.

Within the series of the flexible DR1-dendrimers, the largest second generation dendrimer **6** (16,039 g mol$^{-1}$) performed best for every membrane that was tested, while the smallest dendrimer **2** (1,680 g mol$^{-1}$) performed worst. Dendrimer **6** was even retained for >91% by a membrane with a MWCO value of 30,000 g mol$^{-1}$. However, in the series of first generation DR1-dendrimers **3**-**5**, the best retention was not obtained using the heaviest dendrimer amongst these three. As expected, dendrimer **3** (2,083 g mol$^{-1}$) performed worst, and the difference in retention between **3** and both **4** and **5** is relatively large. In **3** the steric crowding inside the dendritic structure is lower compared to **4** and **5**, since the dendritic arms of **3** are not branched. Probably backfolding of the long, flexible arms into the open dendritic structure is more likely to occur than stretching out of the arms (*i.e.* the elongated form), which makes **3** reasonable smaller than both **4** and **5**. Remarkably, dendrimer **4** (3,677 g mol$^{-1}$) was retained better by every membrane than the heavier dendrimer **5** (5,272 g mol$^{-1}$). Using the membrane with MWCO value of 10,000 g mol$^{-1}$ still resulted in a retention of >90% for dendrimer **4**. Dendrimers **4** and **5** both consist of branched arms, but the space between the arms in **4** is probably large enough to be occupied by solvent molecules and therefore the arms could be

more stretched out than in **5**, making **4** slightly larger than **5**. These observations can be explained by comparison with the modeling and GPC studies. The average diameters of models of dendrimers **4** and **5** (27-46 Å) are comparable, whereas dendrimer **3** (22-34 Å) is obviously smaller. The GPC analyses show that the hydrodynamic volumes of **4** and **5** are slightly closer to each other than the hydrodynamic volumes of **3** and **4**. However, no explicit confirmation for the higher retention of **4** compared to **5** was obtained from the modeling and GPC studies.

The retentions of rigid core dendrimers **7** and **8** by the membranes with MWCO values of 5,000 and 10,000 g $mol^{-1}$ are both above 93%, although their molecular weights are just 4,110 and 4,338 g $mol^{-1}$, respectively. This effect can be contributed to the rigid structure of these dendrimers. The rigid cores form flat, two-dimensional structures that cannot fold or deform under shear flow, which in case of the flexible dendrimers can cause migration through the membrane. This observation is in accordance with reported data[27] and the current modeling and GPC data, which also show larger dimensions than purely based on their molecular weight for **7** and **8**. Both the retention and the filtration rate will play an important role in the determination of the efficiency of the diafiltration procedures. Together with the relative high filtration rate, especially for the membrane with MWCO value of 10,000 g $mol^{-1}$ (8 min. for the filtration of 10 mL), these high retentions make dendrimers **7** and **8** good candidates for the application as support for organic syntheses.

Quite remarkably, the first generation Fc-dendrimer **11** (3,732 g $mol^{-1}$) was retained better by all tested membranes than the corresponding DR1-dendrimer **5** (5,272 g $mol^{-1}$). The densely packed peripheral ferrocene groupings probably make **11** very rigid and the inner space of the dendrimer inaccessible for solvent molecules.[46] Although could the smaller Fc-moieties reduce the dimensions of the dendrimer (in both the GPC and the modeling studies **11** displays a smaller volume/diameter than **5**), it could also make its structure more rigid and thereby its diafiltration performance could (slightly) improve. More important, besides this structural explanation, also experimental factors play a role. Small differences in the conditions used during the diafiltration experiments could influence the behavior of the dendrimers or the membranes. The main difference between the diafiltration conditions of the DR1- and Fc-dendrimers is the ratio of the solvents used. In case of the Fc-functionalized dendrimers **10** and **11** more $CH_2Cl_2$ was used in the MeOH:$CH_2Cl_2$ mixture (ratio MeOH:$CH_2Cl_2$ is 2:3 (v/v) instead of 1:1 (v/v)), which can cause further swelling of the membrane material, thereby decreasing the pore size of the membrane. In fact, this demonstrates that results obtained in the diafiltration experiments can only be compared when

using exactly the same experimental conditions. The results obtained in the diafiltration experiments can therefore not be used for the accurate determination of the influence of the shape of the peripheral groupings. As mentioned, the regenerated cellulose membranes did not resist the solvent conditions very well. Although these membranes are readily available and relatively cheap, it is therefore recommended to switch to other types of membranes when using other than aqueous solvents.[23,24]

## 4.4 Concluding Remarks

A series of flexible and rigid-core carbosilane dendrimers were functionalized with two different dye molecules, ferrocene and Disperse Red 1, in order to evaluate the filtration performance of the dendrimers in diafiltration. These dye groupings are structurally different and will therefore not only influence the size of the dendrimers, but will also influence their overall structure by changing the density of the dendrimer surface and the accessibility of its interior for small (solvent) molecules. Through a combination of UV/Vis spectroscopy, GPC and molecular modeling the dimensions and solution behavior of the dendrimers were investigated. In general, an increase of the dimensions of the dendrimers with increasing molecular weight was observed. Both in the modeling and GPC studies, the rigid core dendrimer **8** did, however, display larger dimensions than purely based on its molecular weight. In the GPC analysis, the largest flexible dendrimer **6** appeared much larger than **8**, which was contrasted by their similar sizes in the modeling studies. This indicates that besides the structural parameters of the dendrimers also other effects such as the presence of solvent molecules play a decisive role in determining the dimensions of the dendrimers.

In the diafiltration experiments a general correlation between the molecular weight of the dendrimers and their retentions was found, which can be related to the data from the GPC and modeling studies. A remarkable observation was that within the first generation DR1-dendrimer series **3** - **5**, dendrimer **4** was retained better by every membrane than its heavier congener **5**. In this case, the presence of solvent molecules in the relative open dendritic structure of **4** seems to result in a stretching of the dendritic arms and, accordingly, an increase in dendrimer dimensions.

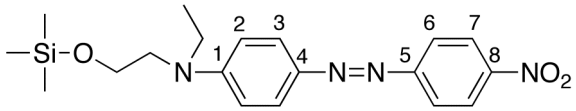
The largest DR1-dendrimer **6** and the rigid-core dendrimers **7** and **8** showed the best performance in diafiltration. This clearly demonstrates the influence of the size and rigidity of the dendrimer on the diafiltration performance. The elaborate synthesis of higher generation dendrimers can actually be compensated for by the design of rigid dendritic supports with an

increased shape-persistency. On the other hand, the facile synthesis and robustness of the first generation dendrimer **4** make it a good candidate for the application as support in organic syntheses. The sacrifice in the use of **4** would be a decreased filtration rate because it requires membranes with lower MWCO values, while it might have an enhanced chemical resistivity against certain harsh reagents compared to the poly-aryl core in rigid supports like **7** and **8**.

## 4.5 Experimental Section

All air- and moisture sensitive reactions were carried out under an oxygen-free, dry nitrogen atmosphere using standard Schlenk techniques. THF and benzene were dried over sodium/benzophenone and distilled prior to use. Triethylamine was dried on potassium hydroxide and distilled prior to use. 1-Bromo-4-iodobenzene was purified prior to use by flash column chromatography (eluent: pentane). 1-Bromo-4-lithiobenzene, triallylsilane, triallylbromosilane and the dendrimer cores G0(Ph)-4-Br, G1(Ph)-12-allyl, G0(Bz)-3-Br and G1(Bz)-9-allyl were prepared according to previously developed procedures.[28] Allylmagnesiumbromide and the dendrimers G0(C3)-4-allyl and G1(C3)-12-allyl were prepared according to optimized literature procedures.[20,21] $^{1}$H NMR, $^{13}$C{$^{1}$H} NMR and $^{29}$Si{$^{1}$H} NMR spectra were recorded on Varian Inova 300 and Varian AS400 spectrometers at 25 °C unless stated otherwise. Chemical shifts are reported in ppm relative to residual solvent signals. UV/Vis-spectra were recorded on a Varian Cary 50 Scan UV-Visible spectrometer. Microanalyses were performed by Microanalytisches Laboratorium Dornis&Kolbe, Mulheim a.d. Ruhr, Germany. GC-MS chromatograms and spectra were recorded on a Perkin-Elmer AutoSystem XL (GC) coupled to a TurboMass (MS). MALDI-TOF mass spectra were recorded using an Applied Biosystems Voyager System 6347 spectrometer. Passive dialysis was performed using benzoylated cellulose dialysis tubing (molecular weight cut off 1200 g mol$^{-1}$) purchased from Sigma-Aldrich and rinsed with a dichloromethane/methanol mixture (1:1 (v/v)) prior to use.

**$Me_3SiOCH_2CH_2N(CH_2CH_3)C_6H_4N{=}NC_6H_4NO_2$, TMS-DR1 (1)**



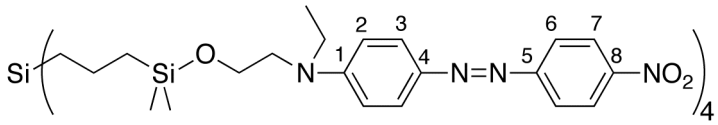

To a solution of Disperse Red 1 (0.3 g, 0.95 mmol) in diethyl ether (20 mL) was added chlorotrimethylsilane (0.2 g, 1.8 mmol) and triethylamine (1 mL). After 1.5 h stirring the reaction mixture was poured into water and extracted with a mixture of diethyl ether and pentane (70/30 (v/v)). The solvents were removed *in vacuo*. Yield after purification by column chromatography over silica, using diethyl ether as eluent: 0.35 g (0.91 mmol, 95%). $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.30 (d, $^{3}J_{H\text{-}H}$ = 9.1 Hz, 2 H, Ar-H$_7$), 7.89 (d, $^{3}J_{H\text{-}H}$ = 8.9 Hz, 2 H, Ar-H$_3$), 7.87 (d, $^{3}J_{H\text{-}H}$ = 8.9 Hz, 2 H, Ar-H$_6$), 6.72 (d, $^{3}J_{H\text{-}H}$ = 9.1 Hz, 2 H, Ar-H$_2$), 3.75 (t, $^{3}J_{H\text{-}H}$ = 6.2 Hz, 2 H, $OCH_2$), 3.56-3.46 (m, 4 H, $NCH_2$), 1.23 (t,

$^{3}J_{H\text{-}H}$ = 6.2 Hz, 3 H, $CH_3$), 0.06 (s, 9 H, $SiCH_3$). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 157.0 (Ar-$C_5$), 151.8 (Ar-$C_1$), 147.4 (Ar-$C_8$), 143.7 (Ar-$C_4$), 126.5 (Ar-$C_3$), 124.8 (Ar-$C_7$), 122.7 (Ar-$C_6$), 111.4 (Ar-$C_2$), 59.8 ($OCH_2$), 52.8 ($NCH_2$), 46.3 ($NCH_2$), 12.4 ($CH_3$), –0.4($SiCH_3$). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 487 (37770). ESI MS: *m/z* 387.1722 [$(C_{19}H_{26}N_4O_3Si + H)^+$] (calcd 387.1847).

**General procedure for the syntheses of carbosilane - Disperse Red 1 (DR1) dendrimers:**

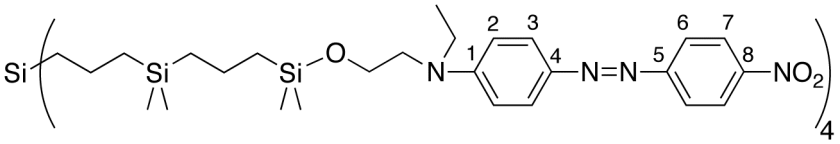
To a solution of the appropriate chlorosilane-terminated carbosilane dendrimer (0.2 mmol) in a mixture of benzene (5 mL) and THF (10 mL) was added Disperse Red 1 (0.22 mmol (1.1 eq.) for each Si-Cl grouping). After the addition of triethylamine (1 mL), the reaction mixture was stirred for 1.5 h at room temperature and subsequently treated with methanol (1 mL) in order to quench SiCl groups that might not have reacted. The organic solvents were removed *in vacuo*. The product was separated from the excess of Disperse Red 1 and triethylamine-hydrochloride by passive dialysis (for dendrimer **2** column chromatography was used instead). To this end, a dialysis bag was filled with a concentrated solution of the reaction mixture and the bag was submerged in a solution of dichloromethane and methanol (1:1 (v/v), 400 mL). After stirring overnight the contents of the tubing were collected and the pure compound was obtained as a sticky red solid after removal of the solvents *in vacuo*.

**$Si((CH_2)_3Si(Me)_2(OCH_2CH_2N(CH_2CH_3)C_6H_4N{=}NC_6H_4NO_2))_4$, G0-4-DR1 (2)**



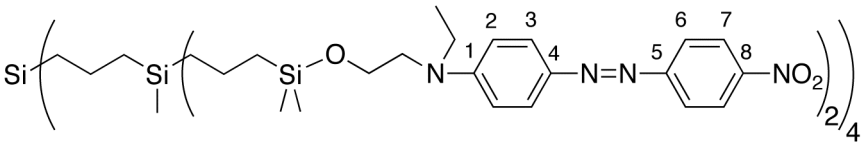

G0-4-Cl (0.114 g, 0.2 mmol) was reacted with Disperse Red 1 (0.27 g, 0.86 mmol). Yield after purification by column chromatography over silica, using diethyl ether as eluent: 0.18 g (0.11 mmol, 55 %). $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.30 (d, $^{3}J_{H\text{-}H}$ = 9.1 Hz, 8 H, Ar-$H_7$), 7.89 (d, $^{3}J_{H\text{-}H}$ = 8.9 Hz, 8 H, Ar-$H_3$), 7.87 (d, $^{3}J_{H\text{-}H}$ = 8.9 Hz, 8 H, Ar-$H_6$), 6.73 (d, $^{3}J_{H\text{-}H}$ = 9.1 Hz, 8 H, Ar-$H_2$), 3.75 (t, $^{3}J_{H\text{-}H}$ = 6.2 Hz, 8 H, $OCH_2$), 3.56-3.46 (m, 16 H, $NCH_2$), 1.40-1.27 (m, 8 H, $SiCCH_2$), 1.23 (t, $^{3}J_{H\text{-}H}$ = 6.2 Hz, 12 H, $CH_3$), 0.64 (t, $^{3}J_{H\text{-}H}$ = 8.0 Hz, 8 H, $CH_2SiO$), 0.55 (t, $^{3}J_{H\text{-}H}$ = 8.4 Hz, 8 H, $SiCH_2$), 0.06 (s, 24H, $SiCH_3$). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 157.0 (Ar-$C_5$), 151.7 (Ar-$C_1$), 147.5 (Ar-$C_8$), 143.7 (Ar-$C_4$), 126.5 (Ar-$C_3$), 124.9 (Ar-$C_7$), 122.7 (Ar-$C_6$), 111.5 (Ar-$C_2$), 60.0 ($OCH_2$), 52.8 ($NCH_2$), 46.3 ($NCH_2$), 21.3, 18.1, 17.4 ($CH_2$), 12.5 ($CH_3$), –1.8 ($SiCH_3$). $^{29}Si\{^{1}H\}$ NMR (60 MHz, $CDCl_3$): $\delta$ 18.69 (SiO), 0.56 (SiC). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 487 (135970). MALDI-TOF MS (9-Nitroanthracene): *m/z* 1681.41 [$(C_{84}H_{116}N_{16}O_{12}Si_5)^+$] (calcd 1681.78). Anal. Calcd. for $C_{84}H_{116}N_{16}O_{12}Si_5$ (1682.37): C, 59.97; H, 6.95; N, 13.32; Si, 8.35. Found: C, 59.96; H, 7.08; N, 13.26; Si, 8.41.

**$Si((CH_2)_3Si(Me)_2(CH_2)_3Si(Me)_2(OCH_2CH_2N(CH_2CH_3)C_6H_4N{=}NC_6H_4NO_2))_4$, G1-4-DR1 (3)**



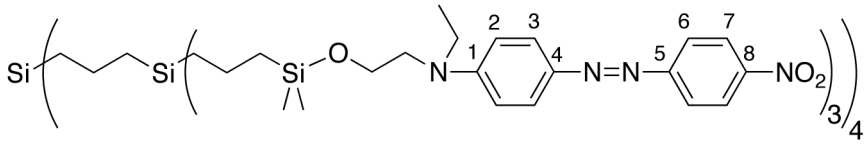
G1-4-Cl (0.206 g, 0.2 mmol) was reacted with Disperse Red 1 (0.27 g, 0.86 mmol). Yield after purification by passive dialysis: 0.25g (0.12 mmol, 59 %). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.30 (d, $^3J_{H\text{-}H}$ = 9.1 Hz, 8 H, Ar-$H_7$), 7.89 (d, $^3J_{H\text{-}H}$ = 8.9 Hz, 8 H, Ar-$H_3$), 7.88 (d, $^3J_{H\text{-}H}$ = 8.9 Hz, 8 H, Ar-$H_6$), 6.73 (d, $^3J_{H\text{-}H}$ = 9.1 Hz, 8 H, Ar-$H_2$), 3.76 (t, $^3J_{H\text{-}H}$ = 6.2 Hz, 8 H, $OCH_2$), 3.57-3.46 (m, 16 H, $NCH_2$), 1.40-1.27 (m, 16 H, $SiCCH_2$), 1.23 (t, $^3J_{H\text{-}H}$ = 6.2 Hz, 12 H, $CH_3$), 0.64 (t, $^3J_{H\text{-}H}$ = 8.0 Hz, 8 H, $CH_2SiO$), 0.53 (t, $^3J_{H\text{-}H}$ = 8.4 Hz, 16 H, $SiCH_2$), 0.01 (s, 24 H, $SiCH_3$), –0.06 (s, 24 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 156.6 (Ar-$C_5$), 151.6 (Ar-$C_1$), 147.2 (Ar-$C_8$), 143.4 (Ar-$C_4$), 126.4 (Ar-$C_3$), 124.6 (Ar-$C_7$), 122.5 (Ar-$C_6$), 111.3 (Ar-$C_2$), 59.7 ($OCH_2$), 52.5 ($NCH_2$), 46.1 ($NCH_2$), 20.8, 20.3, 19.9, 18.6, 17.7, 17.5 ($CH_2$), 12.2 ($CH_3$), –2.1 $(SiCH_3)_2$, –3.2 $(SiCH_3)_2$. $^{29}Si\{^1H\}$ NMR (60 MHz, acetone-$d_6$): $\delta$ 17.55 (SiO), 0.81 ($SiCH_3$), 0.64 (SiC). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 487 (155700). MALDI-TOF MS (9-Nitroanthracene): *m/z* 2083.28 [$(C_{104}H_{164}N_{16}O_{12}Si_9+2H)^+$] (calcd 2083.07). Anal. Calcd. for $C_{104}H_{164}N_{16}O_{12}Si_9$ (2083.32): C, 59.96; H, 7.93; N, 10.76; Si, 12.13. Found: C, 59.84; H, 8.02; N, 10.62; Si, 12.06.

**$Si((CH_2)_3Si(Me)((CH_2)_3Si(Me)_2(OCH_2CH_2N(CH_2CH_3)C_6H_4N{=}NC_6H_4NO_2))_2)_4$, G1-8-DR1 (4)**



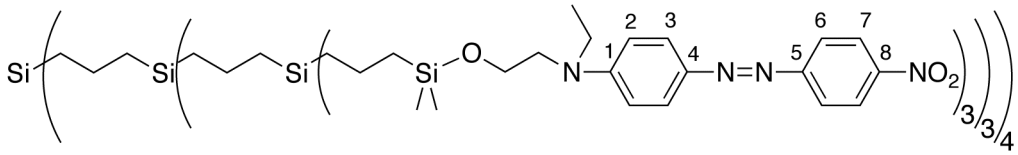
G1-8-Cl (0.18 g, 0.12 mmol) was reacted with Disperse Red 1 (0.32 g, 1.02 mmol). Yield after purification by passive dialysis: 0.37 g (0.10 mmol, 85 %). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.30 (d, $^3J_{H\text{-}H}$ = 9.1 Hz, 16 H, Ar-$H_7$), 7.89 –7.85 (m, 32 H, Ar-$H_{3,6}$), 6.73 (d, $^3J_{H\text{-}H}$ = 9.1 Hz, 16 H, Ar-$H_2$), 3.76 (m, 16 H, $OCH_2$), 3.57-3.46 (m, 32 H, $NCH_2$), 1.40-1.27 (m, 24 H, $SiCCH_2$), 1.23 (m, 24 H, $CH_3$), 0.64 (t, $^3J_{H\text{-}H}$ = 8.0 Hz, 24 H, $SiCH_2CCSiCH_2$), 0.53 (m, 24 H, $SiCCCH_2SiCCCH_2Si$), 0.01 (s, 48 H, $SiCH_3$), –0.06 (s, 12 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 156.6 (Ar-$C_5$), 151.6 (Ar-$C_1$), 147.3 (Ar-$C_8$), 143.5 (Ar-$C_4$), 126.5 (Ar-$C_3$), 124.7 (Ar-$C_7$), 122.5 (Ar-$C_6$), 111.4 (Ar-$C_2$), 59.8 ($OCH_2$), 52.6 ($NCH_2$), 46.2 ($NCH_2$), 21.0, 19.2, 18.6, 17.8, 17.5 ($CH_2$), 12.3 ($CH_3$), –2.0 ($SiCH_3$), –5.0 ($SiCH_3$). $^{29}Si\{^1H\}$ NMR (60 MHz, $CD_2Cl_2$): $\delta$ 18.40 (SiO), 1.04 ($SiCH_3$), 0.57 (SiC). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 487 (311850). MALDI-TOF MS (9-Nitroanthracene): *m/z* 3680.60 $[(C_{184}H_{268}N_{32}O_{24}Si_{13}+Li)^+]$ (calcd 3680.79). Anal. Calcd. for $C_{184}H_{268}N_{32}O_{24}Si_{13}$ (3677.46): C, 60.10; H, 7.34; N, 12.20; Si, 9.93. Found: C, 59.93; H, 7.43; N, 12.08; Si, 10.04.

**$Si((CH_2)_3Si((CH_2)_3Si(Me)_2(OCH_2CH_2N(CH_2CH_3)C_6H_4N{=}NC_6H_4NO_2))_3)_4$, G1-12-DR1 (5)**



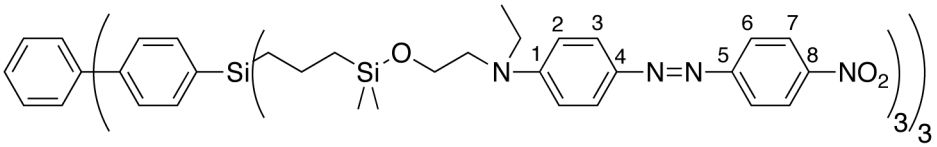
G1-12-Cl (0.18 g, 0.093 mmol) was reacted with Disperse Red 1 (0.40 g, 1.27 mmol). Yield after purification by passive dialysis: 0.31 g (0.059 mmol, 63 %). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.30 (d, $^3J_{H\text{-}H}$ = 9.1 Hz, 24 H, Ar-$H_7$), 7.89 –7.85 (m, 48 H, Ar-$H_{3,6}$), 6.73 (d, $^3J_{H\text{-}H}$ = 9.1 Hz, 24 H, Ar-$H_2$), 3.76 (m, 24 H, $OCH_2$), 3.57-3.46 (m, 48 H, $NCH_2$), 1.40-1.27 (m, 32 H, $SiCCH_2$), 1.23 (m, 36 H, $CH_3$), 0.64 (t, $^3J_{H\text{-}H}$ = 8.0 Hz, 24 H, $CH_2SiO$), 0.53 (m, 32 H, $SiCH_2$), 0.01 (s, 72 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 156.6 (Ar-$C_5$), 151.6 (Ar-$C_1$), 147.4 (Ar-$C_8$), 143.6 (Ar-$C_4$), 126.5 (Ar-$C_3$), 124.8 (Ar-$C_7$), 122.6 (Ar-$C_6$), 111.4 (Ar-$C_2$), 59.9 ($OCH_2$), 52.6 ($NCH_2$), 46.2 ($NCH_2$), 21.3, 18.0, 17.3 ($CH_2$), 12.4 ($CH_3$), –1.9 ($SiCH_3$). $^{29}Si\{^1H\}$ NMR (60 MHz, $CD_2Cl_2$): $\delta$ 18.25 (SiO), 0.55 ($SiCH_3$ and SiC). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 487 (484120). MALDI-TOF MS (9-Nitroanthracene): *m/z*: 5273.56 [$(C_{264}H_{372}N_{48}O_{36}Si_{17}+Li)^+$] (calcd 5273.50). Anal. Calcd. for $C_{264}H_{372}N_{48}O_{36}Si_{17}$ (5271.61): C, 60.15; H, 7.11; N, 12.75; Si, 9.06. Found: C, 60.04; H, 6.99; N, 12.82; Si, 9.15.

**$Si((CH_2)_3Si((CH_2)_3Si((CH_2)_3Si(Me)_2(OCH_2CH_2N(CH_2CH_3)C_6H_4N{=}NC_6H_4NO_2))_3)_3)_4$, G2-36-DR1 (6)**



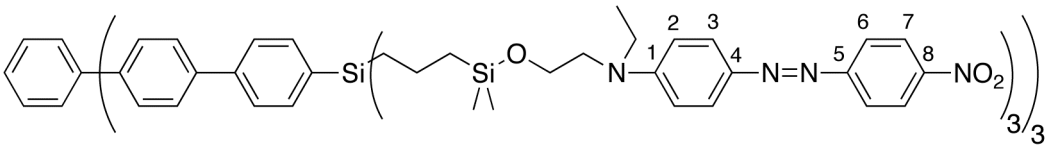
G2-36-Cl (0.20 g, 0.0327 mmol) was reacted with Disperse Red 1 (0.40 g, 1.27 mmol). Yield after purification by passive dialysis: 0.35 g (0.022 mmol, 67 %). $^1$H NMR (300 MHz, $CD_2Cl_2$): $\delta$ 8.30 (m, 72 H, Ar-$H_7$), 7.89-7.85 (m, 144 H, Ar-$H_{3,6}$), 6.73 (m, 72 H, Ar-$H_2$), 3.68 (m, 72 H, $OCH_2$), 3.40 (m, 144 H, $NCH_2$), 1.36 (m, 104 H, $SiCCH_2$), 1.12 (m, 108 H, $CH_3$), 0.63-0.58 (m, 208 H, $SiCH_2$), 0.04 (s, 216 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CD_2Cl_2$): $\delta$ 156.8 (Ar-$C_5$), 151.7 (Ar-$C_1$), 147.5 (Ar-$C_8$), 143.6 (Ar-$C_4$), 126.4 (Ar-$C_3$), 124.8 (Ar-$C_7$), 122.6 (Ar-$C_6$), 111.4 (Ar-$C_2$), 60.0 ($OCH_2$), 52.7 ($NCH_2$), 46.2 ($NCH_2$), 21.5, 18.2, 17.4 ($CH_2$), 12.3 ($CH_3$), –1.8 ($SiCH_3$). $^{29}Si\{^1H\}$ NMR (60 MHz, $CD_2Cl_2$): $\delta$ 18.06 (SiO), 0.84 ($SiCH_2$), 0.57 ($SiCH_3$ and SiC). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 487 (1204370). Anal. Calcd. for $C_{804}H_{1140}N_{144}O_{108}Si_{53}$ (16039.33): C, 60.21; H, 7.16. Found: C, 59.94; H, 7.22.

**$C_6H_3(C_6H_4Si(CH_2CH_2CH_2Si(Me)_2(OCH_2CH_2N(CH_2CH_3)C_6H_4N{=}NC_6H_4NO_2))_3)_3$, G1(RC)-9-DR1 (7)**

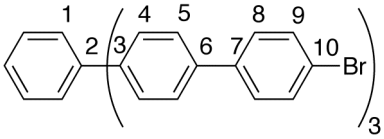


G1(RC)-9-Cl (0.26 g, 0.16 mmol) was reacted with Disperse Red 1 (0.68 g, 2.2 mmol). Yield after purification by passive dialysis: 0.5 g (0.12 mmol, 76 %). $^1$H NMR (300 MHz, $CD_2Cl_2$): $\delta$ 8.30 (d, $^3J_{H\text{-}H}$ = 9.1 Hz, 18 H, Ar-$H_7$), 7.89 (m, 39 H, Ar-$H_{3,6,core}$), 7.77 (m, 12 H, Ar-$H_{core}$), 6.74 (d, $^3J_{H\text{-}H}$ = 9.2 Hz, 18 H, Ar-$H_2$), 3.78 (t, $^3J_{H\text{-}H}$ = 6.2 Hz, 18 H, $OCH_2$), 3.56-3.46 (m, 36 H, $NCH_2$), 1.47-1.45 (m, 18 H, $SiCCH_2$), 0.94 (t, $^3J_{H\text{-}H}$ = 8.3 Hz, 18 H, $CH_2SiO$), 0.72 (t, $^3J_{H\text{-}H}$ = 8.2 Hz, 18 H, $SiCH_2$), 1.23 (t, $^3J_{H\text{-}H}$ = 6.2 Hz, 18 H, $CH_3$), 0.08 (s, 54 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CD_2Cl_2$, partial overlapping signals): $\delta$ 157.0 (Ar-$C_5$), 151.9 (Ar-$C_1$), 147.5 (Ar-$C_8$), 143.6 (Ar-$C_4$), 134.9 ($Ar_{core}$Ar-C), 126.6 ($Ar_{core}$Ar-C), 126.4 (Ar-$C_3$), 124.8 (Ar-$C_7$), 122.6 (Ar-$C_6$), 111.5 (Ar-$C_2$), 60.0 ($OCH_2$), 52.7 ($NCH_2$), 46.2 ($NCH_2$), 21.2, 18.0, 17.2 ($CH_2$), 12.2 ($CH_3$), –2.2 ($SiCH_3$). $^{29}Si\{^1H\}$ NMR (60 MHz, $CD_2Cl_2$): $\delta$ 18.35 (SiO), –3.75 ($SiC_6H_4$). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 487 (276870). MALDI-TOF MS (9-nitroanthracene/$AgBF_4$): *m/z*: 4112.10 [$(C_{213}H_{276}N_{36}O_{27}Si_{12}+Li)^+$] (calcd 4112.87). Anal. Calcd. for $C_{213}H_{276}N_{36}O_{27}Si_{12}$ (4109.79): C, 62.25; H, 6.77. Found: C, 62.90; H, 6.72.

**$C_6H_3((C_6H_4)_2Si(CH_2CH_2CH_2Si(Me)_2(OCH_2CH_2N(CH_2CH_3)C_6H_4N{=}NC_6H_4NO_2))_3)_3$, G2(RC)-9-DR1 (8)**



Precursor core molecule **$C_6H_3((C_6H_4)_2Br)_3$** was synthesized according to a literature procedure,[54] starting from 4'-(4-bromophenyl)acetophenone (4.4 g, 16 mmol) and trifluoromethane sulfonic acid (0.8 mL, 3.1 mmol) in refluxing toluene (35 mL). After cooling down to room temperature, the red solids were filtered and washed with methanol (100 ml). The salmon red solids were dissolved in boiling chloroform (600 ml). The crystals were filtered and dried and obtained in 21 % yield (0.86 g, 1.11 mmol).



$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.83 (d, $^3J_{H\text{-}H}$ = 7.6 Hz, 6 H, Ar-$H_9$), 7.73 (d, $^3J_{H\text{-}H}$ = 7.6 Hz, 6 H, Ar-$H_8$), 7.6 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 6 H, Ar-$H_5$), 7.56 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 6 H, Ar-$H_4$), 7.30 (s, 3 H, Ar-$H_1$), $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 142.14, 140.58, 139.78, 139.57, 132.19, 128.82, 128.04, 127.61, 125.27 and 121.97 (Ar-C).

The triallyl wedge was attached to the core in analogy to the synthesis of G1(RC)-9-allyl as reported earlier by our group.[28] $C_6H_3((C_6H_4)_2Br)_3$ (0.77 g, 1 mmol) was dissolved in diethyl ether (75 mL). Subsequently *n*-BuLi (1.6 M in hexanes, 3.75 mL, 6 mmol) was added and the mixture was stirred for 2 h at room temperature. The resulting suspension was centrifuged, the supernatant was decanted and the white solid was washed twice with pentane (25 mL). Diethyl ether was added to the solid followed by the addition of triallylbromosilane (1 g, 4.3 mmol). The reaction mixture was stirred at room temperature for 1 week, quenched with methanol (1 mL) and poured into water. The water layer was separated and extracted with a mixture of diethyl ether and pentane (1:1 (v/v)). The solution was dried over sodium sulfate, filtered and the solvents were removed *in vacuo*, yielding product **G2(RC)-9-allyl** ($C_6H_3((C_6H_4)_2Si(CH_2CH{=}CH_2)_3)_3$) in 91% (0.9 g, 0.91 mmol). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.91-7.68 (m, 27 H, Ar-H), 5.90 (m, $^3J_{H\text{-}H}$ = 7.60 Hz, 9 H, =CH), 5.01 (m, 18 H, $=CH_2$), 1.98 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 18 H, $=CCH_2$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 142.19 (Ar-C), 141.69 (Ar-C), 140.44 (Ar-C), 140.39 (Ar-C), 135.13 (Ar-C), 134.10 (=CH), 133.67 (Ar-C), 133.43 (Ar-C), 128.03 (Ar-C), 127.83 (Ar-C), 126.64 (Ar-C), 114.84 ($=CH_2$), 19.93 ($=CCH_2$).

In analogy to the conventional dendrimer synthesis,[20] the conversion of G2(RC)-9-allyl to the final product was achieved by hydrosilylation reaction with $HSiMe_2Cl$ in the presence of Lukevics catalyst, yielding product **G2(RC)-9-Cl** ($C_6H_3((C_6H_4)_2Si(CH_2CH_2CH_2Si(Me)_2Cl)_3)_3$) in quantitative yield.

$^1$H NMR (300 MHz, $CD_2Cl_2$): $\delta$ 7.90 (s, 3 H, Ar-H), 7.82 (d, $^3J_{H\text{-}H}$ = 8.20 Hz, 6 H, Ar-H), 7.76 (d, $^3J_{H\text{-}H}$ = 8.20 Hz, 6 H, Ar-H), 7.68 (d, $^3J_{H\text{-}H}$ = 8.20 Hz, 6 H, Ar-H), 7.58 (d, $^3J_{H\text{-}H}$ = 8.20 Hz, 6 H, Ar-H), 1.58-1.46 (m, 18 H, $CCH_2C$), 0.4 (m, 36 H, $CH_2CC$), 0.40 (s, 54 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CD_2Cl_2$): $\delta$ 142.21 (Ar-C), 141.30 (Ar-C), 140.52 (Ar-C), 140.36 (Ar-C), 136.37 (Ar-C), 134.83 (Ar-C), 127.98 (Ar-C), 127.81 (Ar-C), 126.68 (Ar-C), 125.25 (Ar-C), 23.75, 23.63, 20.08, 17.96, 17.35, 16.83 ($CH_2$), 2.09 ($SiCH_3$).

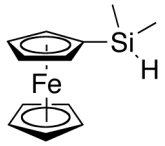
**G2(RC)-9-DR1 (8)**

G2(RC)-9-Cl (0.47 g, 0.256 mmol) was reacted with Disperse Red 1 (0.75 g, 2.39 mmol).

Yield after purification by passive dialysis: 0.75 g (0.173 mmol, 69%).

$^1$H NMR (300 MHz, $CD_2Cl_2$): $\delta$ 8.30 (m, 18 H, Ar-$H_7$), 7.89 (m, 39 H, Ar-$H_{core,3,6}$), 7.77 (m, 24 H, Ar-$H_{core}$), 6.74 (d, $^3J_{H\text{-}H}$ = 9.2 Hz, 18 H, Ar-$H_2$), 3.78 (t, $^3J_{H\text{-}H}$ = 6.2 Hz, 18 H, $OCH_2$), 3.56-3.46 (m, 36 H, $NCH_2$), 1.47-1.45 (m, 18 H, $SiCCH_2$), 0.94 (t, $^3J_{H\text{-}H}$ = 8.3 Hz, 18 H, $CH_2SiO$), 0.72 (t, $^3J_{H\text{-}H}$ = 8.2 Hz, 18 H, $SiCH_2$); 1.23 (t, $^3J_{H\text{-}H}$ = 6.2 Hz, 18 H, $CH_3$), 0.08 (s, 54 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CD_2Cl_2$): $\delta$ 157.0 (Ar-$C_5$), 151.9 (Ar-$C_1$), 147.5 (Ar-$C_8$), 143.6 (Ar-$C_4$), 142.4 (Ar-$C_{core}$), 135.0 (Ar-$C_{core}$), 133.5 (Ar-$C_{core}$), 131.7 (Ar-$C_{core}$), 130.5 (Ar-$C_{core}$), 127.9 (Ar-$C_{core}$), 127.6 (Ar-$C_{core}$), 126.4 (Ar-$C_3$), 124.8 (Ar-$C_7$), 122.6 (Ar-$C_6$), 111. 6 (Ar-$C_2$), 60.9 ($OCH_2$), 52.8 ($NCH_2$), 46.2 ($NCH_2$), 21.2, 18.0, 17.2 ($CH_2$), 12.2 ($CH_3$), –2.2 ($SiCH_3$). $^{29}Si\{^1H\}$ NMR (60 MHz, $CD_2Cl_2$): $\delta$ 18.34 (SiO), –3.74 ($SiC_6H_4$). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 487 (291270). MALDI-TOF MS (trans-3-indole acrylic acid): *m/z*: 4340.91 [$(C_{231}H_{288}N_{36}O_{27}Si_{12}+Li)^+$] (calcd 4340.97).

**Ferrocenyldimethylsilane (9)**



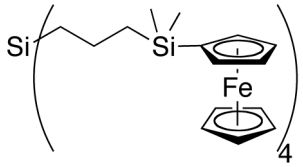

Ferrocenyldimethylsilane was prepared making use of two literature procedures (optimized to meet our conditions), one for the lithiation of ferrocene,[33] and one for the reaction with chlorodimethylsilane.[34]

To a solution of ferrocene (1.40 g, 7.5 mmol) and *t*-BuOK (0.10 g, 0.92 mmol) in THF (40 mL) was added *t*-BuLi (10.0 mL, 1.5 M in pentane, 15.0 mmol) over 20 min. at –78 °C. The mixture was stirred for 1 h at –78 °C and subsequently warmed to –40 °C. The red solution of lithioferrocene was added to a solution of chlorodimethylsilane (0.84 mL, 7.5 mmol) in THF (20 mL) via cannula. The resulting mixture was stirred for 1 h after which the solvent was removed *in vacuo*. The residue was extracted with hexane (3 x 25 mL), filtered over celite and dried on $MgSO_4$. Purification by column chromatography with hexane yielded **9** as a red oil. GC-MS analysis showed a purity of 86%, with ferrocene being the impurity. Overall yield: 2.05 g (86% purity: ~7.22 mmol, ~96 %).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.41 (sept, $^3J_{H\text{-}H}$ = 3.60 Hz, 1 H, SiH), 4.53 (t, $^3J_{H\text{-}H}$ = 1.50 Hz, 2 H, Cp-H), 4.14 (s, 2 + 5 H, Cp-H), 0.31 (d, $^3J_{H\text{-}H}$ = 3.60 Hz, 6 H, $SiCH_3$).

GC-MS: *m/z* (rel. intensity) 244.3 (86%, $M^+$), 186 (14%, Fc).

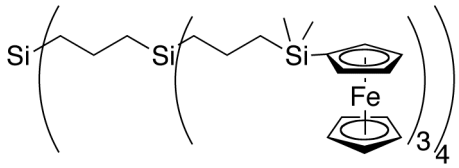
**$Si(CH_2CH_2CH_2Si(Me)_2Fc)_4$, G0-4-Fc (10)**




To a solution of tetra-allylsilane (0.19 g, 1.0 mmol) in THF (30 mL) was added **9** (1.42 g, 5.0 mmol) and Lukevics catalyst (4 x 1.0 mol%). The resulting mixture was refluxed for 2 h, and allowed to cool to room temperature. The solvent was removed *in vacuo* and the product was purified by column chromatography using hexane as eluent, yielding **10** as red viscous oil. Yield: 0.53 g (0.45 mmol, 45 %).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.33 (t, $^3J_{H\text{-}H}$ = 1.50 Hz, 8 H, Cp-H), 4.14 (s, 20 H, Cp-H), 4.08 (t, $^3J_{H\text{-}H}$ = 1.50 Hz, 8 H, Cp-H), 1.38 (m, 8 H, $SiCCH_2$), 0.75 (t, $^3J_{H\text{-}H}$ = 8.10 Hz, 8 H, $CH_2SiFc$), 0.57 (t, $^3J_{H\text{-}H}$ = 8.40 Hz, 8 H, $SiCH_2$), 0.23 (s, 24 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 73.13 (Cp-C), 71.60 (Cp-C), 70.79 (Cp-C), 68.28 (Cp-C), 21.84, 18.94, 17.72 ($CH_2$), –1.82 ($SiCH_3$). $^{29}Si\{^1H\}$ NMR (60 MHz, $CDCl_3$): $\delta$ 0.70 (Si-$CH_2$), –3.16 (Si-Cp). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 447 (370). MALDI-TOF MS: (2,5-dihydroxybenzoic acid): *m/z* 1169.80 [$(C_{60}H_{84}Si_5Fe_4)^+$] (calcd 1169.12).

**$Si(CH_2CH_2CH_2Si(CH_2CH_2CH_2Si(Me)_2Fc)_3)_4$, G1-12-Fc (11)**




To a solution of G1-12-allyl ($Si(CH_2CH_2CH_2Si(CH_2CH=CH_2)_3)_4$) (0.56 g, 0.70 mmol) in THF (30 mL) was added **9** (2.57 g, 10.5 mmol) and Karstedt catalyst (12 x 1.0 mol%). The resulting mixture was refluxed for 5 days, and allowed to cool to room temperature. The solvent was removed *in vacuo* and the product was purified by passive dialysis using a solution of dichloromethane and methanol (1:1 (v/v), 3 x 400 mL), yielding **11** as a red viscous oil. Yield: 1.82 g (0.49 mmol, 70 %).
$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 4.34 (s, 24 H, Cp-H), 4.14 (s, 60 H, Cp-H), 4.09 (s, 24 H, Cp-H), 1.38 (m, 32 H, $SiCCH_2$), 0.75 (t, $^3J_{H\text{-}H}$ = 8.1 Hz, 24 H, $CH_2SiFc$), 0.58 (t, $^3J_{H\text{-}H}$ = 8.1 Hz, 40 H, $SiCH_2$) 0.24 (s, 72 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 73.03 (Cp-C), 71.40 (Cp-C), 70.71 (Cp-C), 68.18 (Cp-C), 21.84, 18.92, 18.28, 17.93, 17.61 ($CH_2$), –1.76 ($SiCH_3$). UV/Vis ($CH_2Cl_2$) [$\lambda_{max}$, nm ($\varepsilon$, $M^{-1}cm^{-1}$)]: 448 (1100).

**Diafiltration experiments**

All diafiltration experiments were carried out under the same conditions unless stated otherwise. The diafiltration experiments were performed using an Amicon Ultrafiltration solvent-resistant stirred cell, with a diameter of 47 mm, purchased from Millipore.[39] The membranes used were Amicon Ultracel PL Ultrafiltration Discs, having molecular weight cut off values (MWCO) of 1,000; 3,000; 5,000; 10,000 and 30,000 g $mol^{-1}$. The membranes were wetted prior to use by submerging them in pure methanol for 2 x 10 min (turning upside down after 10 min), followed by submerging in a 1:1 (v/v) mixture of MeOH and $CH_2Cl_2$ (2 x 10 min), according to the manufacturer's manual. During assemblage of the diafiltration reactor, the membranes were still submerged and afterwards flushed with a mixture of MeOH and $CH_2Cl_2$ (10 mL, 1:1 (v/v)). The remainder of solvent was replaced by a solution of the functionalized dendrimer in a mixture of $CH_2Cl_2$ and MeOH of a total volume of 55 mL. In case of the ferrocene-functionalized dendrimers, a mixture of MeOH and $CH_2Cl_2$ in a ratio of 2:3 (v/v) was needed to keep the dendrimers in solution; for the Disperse Red 1 functionalized dendrimers a 1:1 (v/v) solution was appropriate. During the experiments the reactor was pressurized up tot 3 bars air pressure; only for the diafiltration of **6** using the membrane with MWCO value 30,000 g $mol^{-1}$ a pressure of 1 bar was used to decrease the filtration rate to be able to collect the separate 10 mL fractions. The solution was internally, magnetically stirred at ~75 rpm. Five fractions of 10 mL each were collected, leaving 5 mL inside the reactor to prevent drying of the membranes. Subsequently another volume of 50 mL was added to the reactor and again 5 fractions of 10 mL each (or in case of the ferrocene dendrimers 2 fractions of 25 mL each) were collected. The amounts of compound in the separate fractions were calculated from the UV/Vis absorptions of the fractions and

the extinction coefficient obtained from the calibration lines. The retention of a dendrimer by each membrane was calculated using the, modified (see section 2.3), literature formula:[40]

$$R(\%) = \left(1 - \frac{m_f}{m_0}\right) * 100 \qquad \text{Eq. 1}$$

in which $m_f$ is the total mass (mg) in the combined filtrates and $m_0$ is the initial mass (mg) loaded in reactor.

## 4.6 References and Notes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(30) General formula to indicate the dendrimers: Gx-y-R, in which n = generation number, y = amount of peripheral groups, R is type of peripheral group, (RC) = Rigid Core dendrimer
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# Chapter 5

## Carbosilane Dendrimers functionalized with SPOS-type Linkers and Their Application as Support in Organic Synthesis

*SPOS (Solid Phase Organic Synthesis) is a widely used method for the synthesis of libraries of (pharmaceutically interesting) small molecules. To make use of the advantages of SPOS, e.g. ease of purification, and at the same time overcome some of its disadvantages, e.g. its heterogeneous nature, soluble carbosilane dendrimers have been developed as support material for organic synthesis. In order to be able to compare the performance of these dendritic supports to the well-established SPOS supports, the functionalization of carbosilane dendrimers with various SPOS-type linker groupings, i.e. benzylbromide, diethanol amine (DEAM) and REM-type linkers, has been investigated. The synthesis of the dendritic supports **1** (benzylbromide linker), **2** (DEAM linker) and **3** (REM linker) as well as their application as support for the stepwise synthesis of a small library of pharmaceutically interesting compounds based on piperazine and piperidine building blocks is reported. Compared to SPOS, an advantage of these dendritic supports is the ease of characterization of the functionalized dendritic species after each modification step during the stepwise synthesis, without the need for release of (intermediate) products from the support. The yields and purities of the products after release from the dendritic supports are rather comparable to SPOS for the dendritic DEAM support **2**, but still low for dendritic benzylbromide **1** and REM **3** supports.*

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## 5.1 Introduction

Solid phase organic synthesis (SPOS) is a widely applied method in both academia and industry for the (combinatorial) synthesis of (pharmaceutically interesting) small molecules. Compared to classical solution-phase organic synthesis, SPOS has several advantages, like the ease of purification of intermediate supported products by filtration techniques, high yields by using excess of reagents, and facile separation of released products from the reaction mixture. One of the most well-known synthesis supports is the Merrifield resin, initially developed in the 1960's for the synthesis of peptides.[1] The Merrifield resin is a polystyrene (PS) based resin with methylene chloride end groupings, which can be substituted by a variety of substrates (*e.g.* amines). These supported substrates can then undergo several modification steps, resulting in the step-wise synthesis of larger molecules, *e.g.* peptides (Fig. 1). Other well-known and widely used PS resins are the Rink resin,[2] the Wang resin,[3] the REM resin,[4,5] the Wang REM resin,[6] the Amide REM resin,[7] and the vinyl sulfone resin.[8,9] The advantages of many of these resins compared to the Merrifield resin result from their confirmed robustness in the application as supports for various types of organic reactions due to the increased stability of the end groupings. Some of these supports even show compatibility with Grignard or metal hydride chemistry, making supported synthesis applicable for a wider scope of organic transformation reactions.

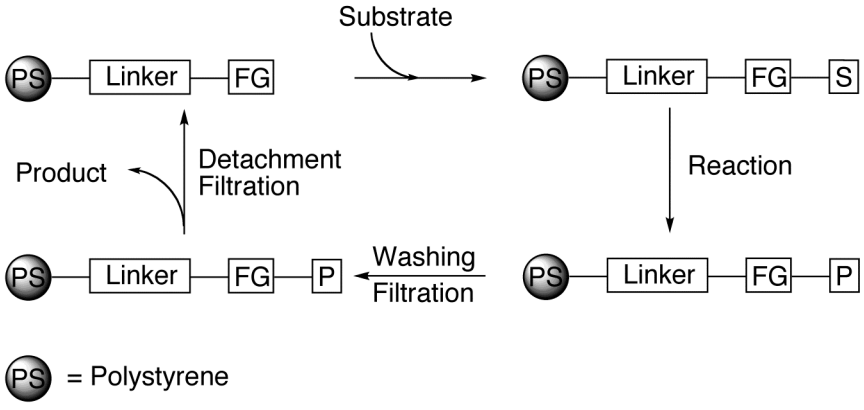



**Figure 1.** Schematic representation of SPOS (PS = polystyrene resin; FG = Functional Group; S = Substrate; P = Product).[10]

Although SPOS offers many possibilities for the stepwise synthesis of more complex molecules, it also has several shortcomings.[10] The major disadvantages originate from the structural irregularity of the resins and their insolubility in most common organic solvents. One problem arising from the insolubility is the inaccessibility to standard spectroscopic analysis techniques, like NMR spectroscopy (although techniques like gel-phase NMR are

available for the analysis of PS resins[11]). In SPOS generally part of the supported product or intermediate has to be cleaved from the support in order to examine the progress of the reaction. The irregular structure of the support can lead to inhomogeneous reaction kinetics, resulting in less uniform product formation. Changing to soluble polymeric supports (liquid phase organic synthesis, LPOS) partly solves these problems.[12-17] Soluble supports like (modified) polyethylene glycol, polyvinyl alcohol and crosslinked polystyrene (*e.g.* *J*anda*J*el™) are successfully used, but their loading capacity is rather low and the irregularity of these supports makes application of spectroscopic analysis still not straightforward.

In the last decades, dendritic structures were developed and tested as supporting material, both as catalyst support[18-25] and as synthesis support.[10,26-31] Dendrimers, and specifically carbosilane dendrimers,[32] were found to be highly regular, well-defined and robust structures, which can easily be functionalized at their periphery. The star-shaped nature of dendrimers originates from the relatively facile, divergent synthesis of the dendrimers, and allows for the formation of dendrimers of increasing generation. The unique dendritic structure and solubility properties make them suitable for analysis during the reaction by, *e.g.*, NMR spectroscopy.

In previous reports, the application of carbosilane dendrimers as soluble support for organic synthesis has been demonstrated.[30,33] The dendrimer-supported synthesis of β-lactams was described, which makes use of a dendritic support bearing 4-(hydroxymethyl)phenyl end groupings as a starting material for further synthesis. In fact, this type of end group can be seen as a linker grouping as well, providing a synthesis scaffold for chemical transformations. This first example of the application of a carbosilane dendrimer as synthesis support does not describe preparative separation techniques to purify the supported products from the reaction media.

The initial application of the carbosilane dendrimers as catalyst support already provided more information about separation techniques to separate the dendrimers from smaller molecules. For example, the use of a zeroth generation carbosilane dendritic catalyst in a membrane reactor was successful, but resulted in moderate retention of the dendrimer.[34] The first generation carbosilane dendrimer (G1-dendrimer, containing 12 end groupings, see Fig. 2) was found to be large enough to be efficiently separated from solutions and reaction mixtures by dialysis or diafiltration techniques, in analogy to several polymeric supports.[35-37] Several types of membranes have been used; first to separate the dendrimer-supported catalysts from the product solutions, later also in dendrimer-supported synthesis to separate the supported products from excess of reagents.

In SPOS most often PS-based supports are used. In order to connect any starting material covalently to the support, the introduction of linker groups to the PS is required. The choice of linker system is crucial for the planning of the synthetic approach, since stability during synthesis and ease of release of the final products is essential.[38,39] Linker groups usually consist of halide, alcohol or ether-like moieties, which are used to connect the phenyl groupings of the PS to the functionalizable end groupings.

Here we present the synthesis and application of three dendritic supports for organic synthesis. In order to be able to compare the performance of the dendritic supports to the well-known solid supports, the carbosilane dendrimers were peripherally functionalized with SPOS-type linker groupings, making their periphery comparable to the SPOS resins. For this purpose three common SPOS-linkers were selected, *i.e.* the benzylbromide linker (comparable to the Merrifield resin),[1] the diethanolamine (DEAM) linker,[40] and the REM (*Re*generated after cleavage of the product and functionalized via *M*ichael reaction) linker[4,5] (Fig. 2).

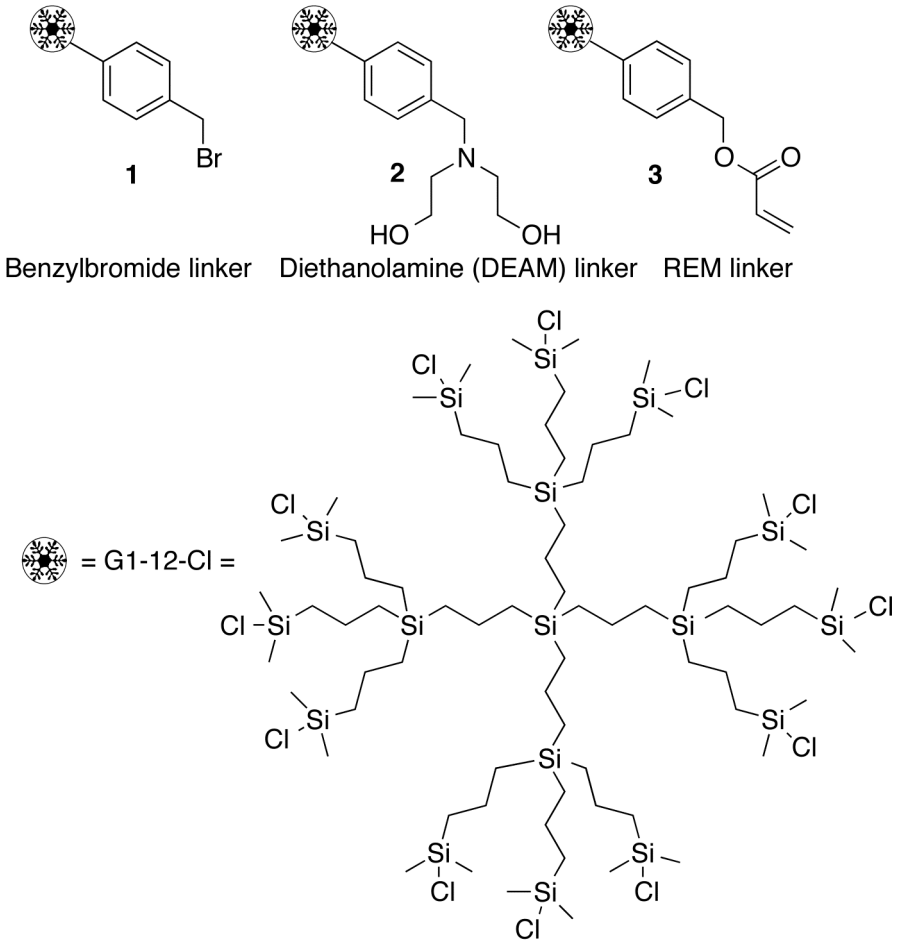



**Figure 2.** Carbosilane dendritic supports **1**, **2** and **3** for LPOS.

Using these prototypical linker-modified dendrimers, the stepwise synthesis of pharmaceutically interesting small molecules based on piperazine and 4-aminopiperidine, using the obtained dendritic supports will be described. In analogy to the procedures used in SPOS, every intermediate supported product is purified using filtration techniques to remove the excess of reagents from the reaction mixture. For this purpose passive dialysis is chosen, which makes use of the concentration differences (osmosis) in a solution on either side of a membrane to separate large and smaller molecules (Fig. 3). With the dendritic supports the same type of reaction sequences to synthesize the piperidine and piperazine derivatives will be applied as described for SPOS, resulting in a proof of principle for the dendrimer-supported synthesis of secondary and tertiary amines. The major goal is to investigate and compare the overall reaction sequences in order to evaluate the application of the dendritic synthesis supports, including their size-dependent separation (passive dialysis), for the synthesis of active pharmaceutical ingredients (API's).

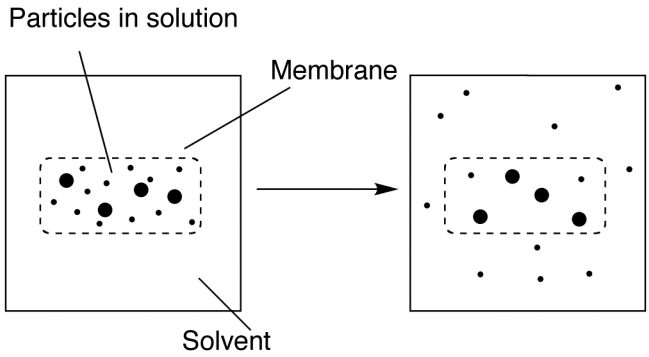



**Figure 3.** Schematic representation of passive dialysis.

## 5.2 Results

### 5.2.1. Attachment of Functional Linker Groupings at the Dendrimer Periphery

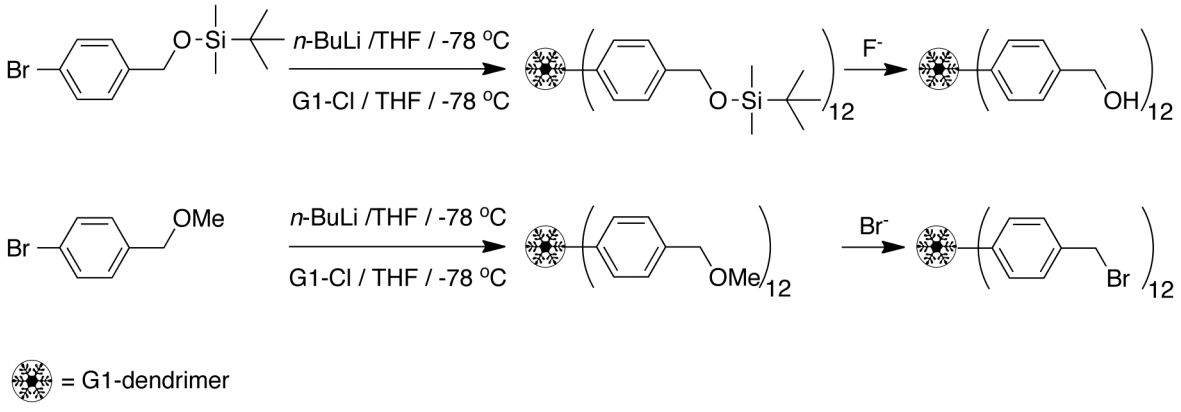
*5.2.1.1 Synthetic Strategy*

The three dendritic supports **1**, **2**, and **3** all possess benzylic end groupings connected directly to their periphery, to which the actual functional groups (bromide, diethanolamine, and acrylate) used for the attachment of substrates are connected. Synthetic access to a G1-carbosilane dendrimer carrying benzylic end groupings at its periphery is therefore desirable. The attachment of a benzylic alcohol on the dendrimer surface was investigated since this is an excellent starting point for the synthesis of the three anticipated dendritic supports (Fig. 2, *vide supra*).

A procedure for the peripheral functionalization of carbosilane dendrimers with benzyl alcohol moieties was developed earlier.[30,33] In this procedure, the dendrimer surface was

functionalized with *t*-butyldimethylsilyl(TBDMS)-protected benzyl alcohol groups, which were connected to the chlorosilane end groupings of the dendrimers via lithiation chemistry, *i.e.* lithiation of the protected *p*-bromobenzyl alcohol using *n*-BuLi followed by reaction of the aryllithium reagent with the dendritic Si-Cl end groups, followed by deprotection of the alcohol (Scheme 1). We have now found that the deprotection of the TBDMS-protected alcohols on carbosilane dendrimers is not always straightforward. Most likely does the introduction of a second type of (dimethyl)silyl grouping in the dendritic structure result in difficulties with the selective cleavage of the protective group. Since the Si-O cleavage is performed using $F^-$-sources like $Bu_4NF$ or $Et_3N{\bullet}3HF$, the possible cleavage of Si-C bonds is not unlikely to occur as well. Varying both the type of $F^-$-source and the cleavage conditions did not lead to a reliable cleavage procedure of carbosilane-supported TBDMS groups.

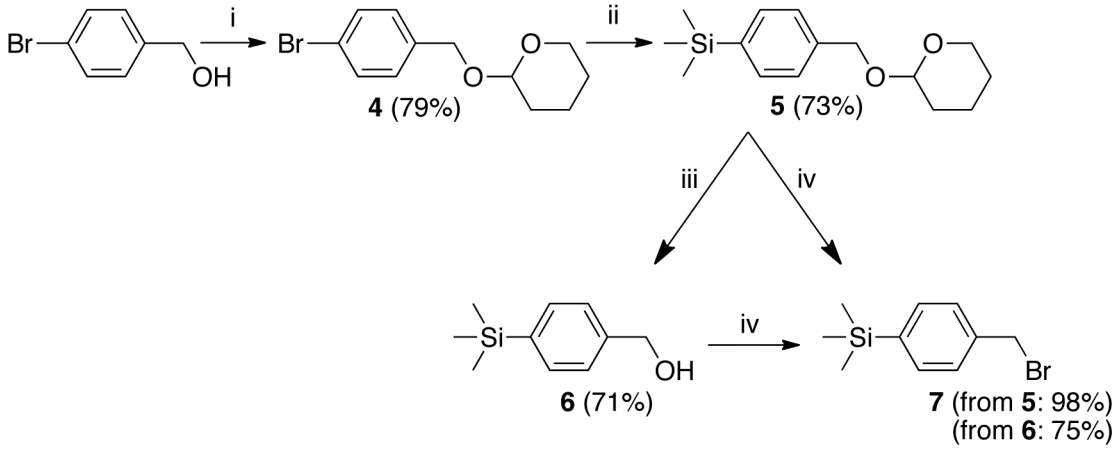
In order to prevent the presence of competing dimethylsilyl groupings in the dendritic structure, the type of protecting group was changed. Accordingly, we turned our attention to an alternative alcohol-protecting group, *i.e.* the methylether moiety. For this purpose, bromobenzyl bromide was converted into *p*-bromo-methoxybenzyl by reaction with NaOMe,[41] which was subsequently connected to the dendrimer periphery via lithiation chemistry as used in the previous procedure (Scheme 1). Unfortunately, the (direct) conversion of these benzylmethoxy dendrimers into the corresponding benzylbromide dendrimer using a variety of brominating agents (*e.g.* $BBr_3$, $Me_3SiBr/PhCl$, $BF_3{\bullet}Et_2O$/acetylbromide, HBr/AcOH) under different conditions did not yield the desired dendrimer in appreciable yield and purity.




**Scheme 1.** Functionalization of carbosilane dendrimers with benzylic groupings.

Next, we changed the nature of the protecting group and found that the tetrahydropyranyl (THP) works for our purpose. The protection of 4-bromobenzyl alcohol with a THP group in the presence of *p*-tolyl sulfonic acid monohydrate (*p*-TsOH) is described in literature[42] and

yields the desired protected 4-bromobenzyl alcohol **4** (*O*-tetrahydropyranyl-4-bromobenzyl ether) in high yield (79% in our hands). The attachment of a trimethylsilyl (TMS) group, used as a dendrimer mimic, to **4** was achieved via lithiation of **4** using 1.0 equivalent of *n*-BuLi in THF at –78 °C, followed by the addition of 1.0 equivalent of chlorotrimethylsilane (TMS-Cl) (Scheme 2). The crude product was obtained after aqueous workup and purified by filtration over a short plug of silica, to yield the protected 4-(TMS)benzyl alcohol **5** in a yield of 73%. Removal of the THP-protecting group was achieved by reacting **5** with *p*-TsOH in methanol, which yielded 4-(TMS)benzyl alcohol **6** in 71% yield. The subsequent transformation of the alcohol moiety **6** into bromide moiety **7**, which is required for the synthesis of both the benzylbromide and DEAM linker, was carried out by reaction of **6** with $PBr_3$ in diethyl ether. This procedure gave 4-(TMS)benzyl bromide **7** in 75% yield.[43] Remarkably, from GC-MS data it was observed that all starting material was converted into **7**, even in cases where **6** was contaminated with small amounts of THP-ether **5**. This encouraged us to test the direct bromination of the **5** under the same reaction conditions. Indeed, upon treatment of **5** with $PBr_3$, **7** was obtained in quantitative yield. The analytical data of both **6** and **7** were compared to literature data of these compounds, which were obtained by other reaction pathways,[44,45] and which confirmed their formation.




**Scheme 2.** Test reactions toward the dendrimer loading of protected benzyl alcohols and bromides. *Reagents and conditions*: (i) 1.1 eq. 3,4-dihydro-2*H*-pyran, 20 mol% *p*-TsOH, $CH_2Cl_2$, rt, 3 h; (ii) (a) 1.0 eq. *n*-BuLi, THF, –78 °C; (b) 1.0 eq. TMS-Cl, THF, –78 °C to rt, 2 h; (iii) 7.5 mol% *p*-TsOH, MeOH, 65 °C, 6 h; (iv) excess $PBr_3$, $Et_2O$, rt, 16 h.

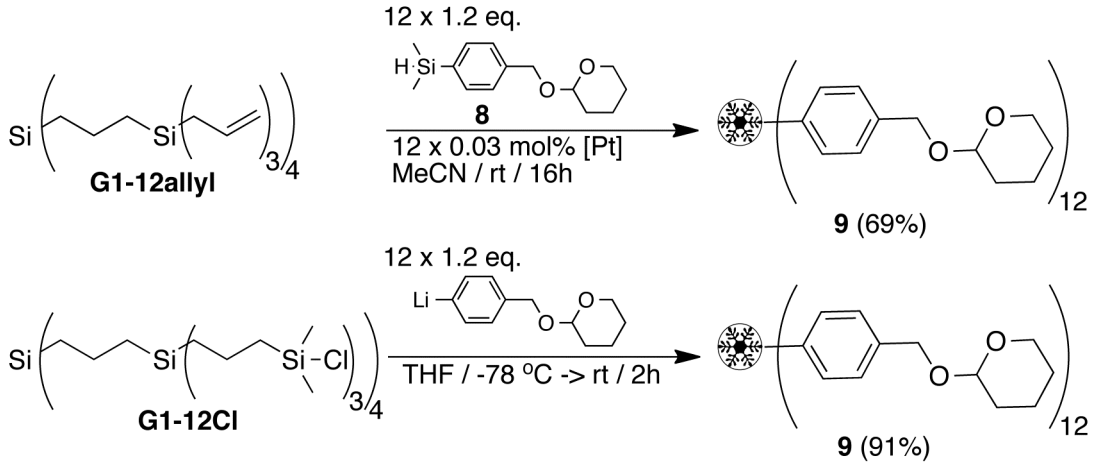
*5.2.1.2 Synthesis of the G1-dendritic supports*

The above described protection-deprotection protocol was applied for the functionalization of the G1-carbosilane dendrimers with benzylalcohol and benzylbromide moieties. The

attachment of **4** to the dendrimers was pursued via two different approaches (Scheme 3), starting from dendrimers containing either chlorosilane (**G1-12Cl**) or allyl (**G1-12allyl**) peripheral groupings. In the first approach, a dimethylsilyl group was introduced to **4** via lithiation using *n*-BuLi, followed by reaction with $HSiMe_2Cl$, to result in the aryldimethyl silane **8** in 92% yield. Next, **G1-12allyl** was hydrosilylated with 12 x 1.14 eq. of **8** in the presence of Karstedt's catalyst, yielding the fully substituted, *i.e.* containing 12 THP-ether end groupings, first generation dendrimer **9** in 69% isolated yield (based on **G1-12allyl**) after purification by passive dialysis.

The second approach makes use of a direct reaction between lithiated **4** and **G1-12Cl**, like described above for the introduction of the TMS group. In this way again the fully substituted G1-dendrimer **9** was obtained in 91% isolated yield, relative to the initial amount of **G1-12Cl**, after purification by passive dialysis.

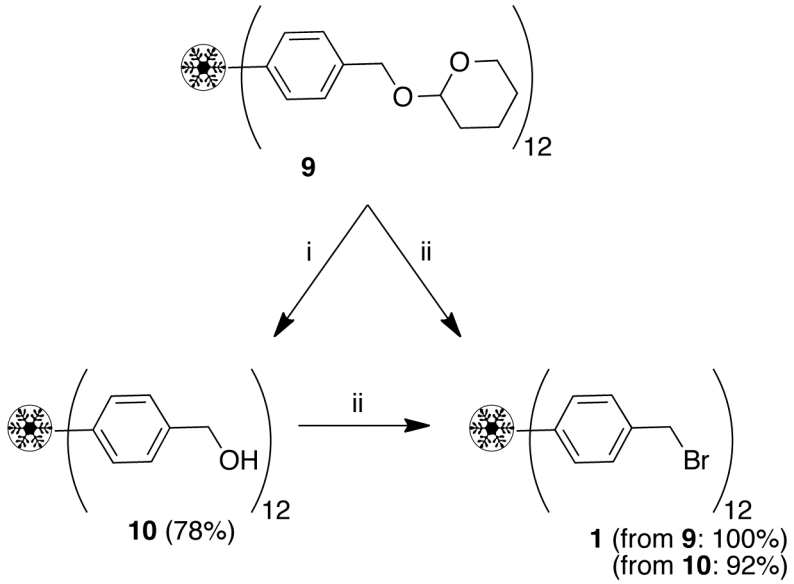
In summary, both methods yielded the desired dendrimer **9** as a fully loaded dendrimer, and in both cases full conversion into the THP-protected alcohols was reached, as could be observed from the NMR data. However, the second method which started from **G1-12Cl**, resulted in a higher yield of the dendrimer after purification by passive dialysis and is therefore the preferred method to synthesize **9**.




**Scheme 3.** Synthesis of G1-dendrimer **9** with peripheral THP-protected alcohol groupings.

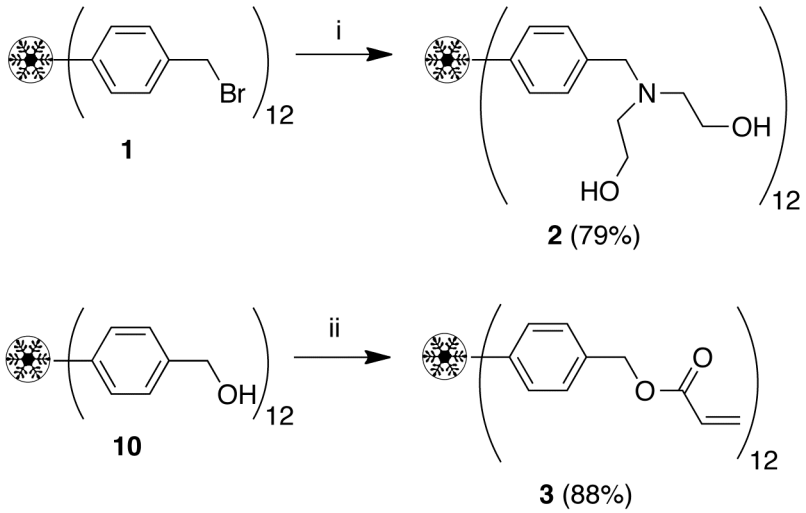
With the THP-protected benzylic alcohol groupings on the G1-dendrimer surface, the next steps to synthesize the linker groupings were performed (Scheme 4). The deprotection step under the same conditions (*p*-TsOH, MeOH) as described for the TMS-substituted test compounds yielded the dendrimer containing the peripheral deprotected benzylic alcohol **10** in 78% yield after passive dialysis. NMR data confirmed the formation of a fully loaded dendrimer and full conversion of all peripheral groupings. The subsequent bromination step

was again performed in two different ways, starting either from **9** or **10** in reaction with 2 equivalents $PBr_3$ per end grouping in diethyl ether. Both methods yielded the fully substituted dendrimer **1** (*i.e.* containing 12 benzylbromide end groupings) in high yields (resp. 92 and 100%). The degree of loading and conversion of the peripheral groupings is 100% for both obtained products. Although the direct bromination from **9** is generally higher yielding, in some experiments full conversion was not reached. Therefore we selected the synthetic pathway via the alcohol intermediate **10** to be the preferred method to synthesize **1**. Dendrimer **1** is one of the three proposed dendritic supports and was used as such in further reaction steps.




**Scheme 4.** Synthesis of dendritic support **1**. *Reagents and conditions*: (i) (a) 12 x 0.1 eq. *p*-TsOH, MeOH:$CH_2Cl_2$ (1:1 v/v), 60 °C, 5 h, (b) passive dialysis; (ii) (a) 12 x 2 eq. $PBr_3$, $Et_2O$, rt, 16 h, (b) passive dialysis.

Next, the DEAM and REM dendritic supported **2** and **3** were prepared from **1** and **10**, respectively (Scheme 5). The attachment of DEAM linker groupings to methylene chloride terminated PS resins can be achieved by reaction with diethanolamine in NMP in the presence of NaI, as described in literature.[40] Using a slightly adapted procedure, the reaction of **1** with diethanolamine in DMF in the presence of $K_2CO_3$ at room temperature yielded the dendritic DEAM support **2** in a yield of 79% after purification by passive dialysis. The dendritic support was obtained containing 12 DEAM end groupings per dendrimer (*i.e.* full loading and complete conversion).




**Scheme 5.** Synthesis of dendritic supports **2** and **3**. *Reagents and conditions*: (i) 12 x 1.1 eq. diethanolamine, 12 x 1.1 eq. $K_2CO_3$, DMF, rt, 16h; (ii) 12 x 10 eq. acryloyl chloride, 12 x 10 eq. DIEA, $CH_2Cl_2$, 0 °C to rt, 20 h.

The attachment of the REM linker to the dendrimer surface also followed a SPOS procedure described in literature,[4] in which the benzylic alcohol undergoes a reaction with a large excess (10 eq.) of acryloyl chloride in the presence of *N,N*-diisopropylethylamine (Hünig's base, DIEA; Scheme 5). Product **3** was purified by passive dialysis, which removed smaller side products but at the same time did not separate the additional polymeric material (polyacrylic acid, formed during the synthesis in the presence of DIEA) from the product. The amount of polyacrylic material present was estimated based on the $^1$H NMR spectrum and found to be ~35.5wt% of the total weight of the product, which corresponds to a yield of 88% for dendrimer **3**. No attempts were made to purify **3** any further and it was used as such in following reaction steps.

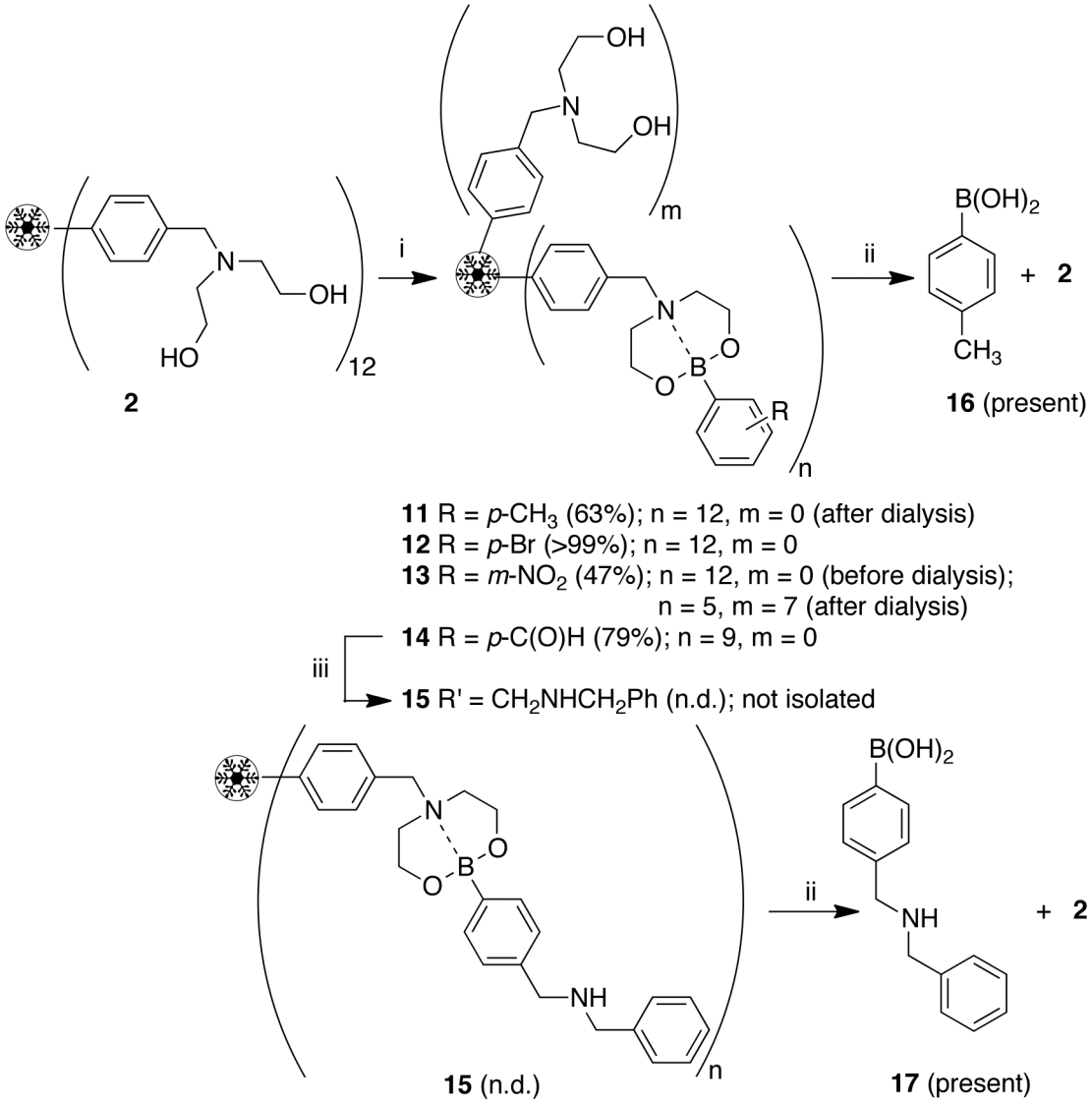
### 5.2.2 Application of the dendritic DEAM Support

*5.2.2.1 Investigation of the principle*

Diol anchors like (solid) DEAM supports are known to immobilize and thereby stabilize or scavenge boronic acids.[40,46-53] To make use of the advantages of these (solid) supports and at the same time be able to work in homogeneous reaction conditions, the application of dendritic DEAM support **2** for the immobilization of boronic acids was explored. The immobilization of boronic acids using the PS-supported DEAM anchors[40] was carried out by simple mixing the PS-DEAM support and the boronic acid in dry THF at room temperature for 1.5 h. Application of this method to the dendritic DEAM support **2** allowed us to

immobilize a small series of boronic acids (*p*-tolyl boronic acid, *p*-bromophenyl boronic acid, *m*-nitrophenyl boronic acid, and *p*-formylphenyl boronic acid) to the dendrimer surface (Scheme 6). Since the DEAM-boronic acid connection is somewhat water-labile, purification by passive dialysis using technical grade solvents can be troublesome and result in the release of boronic acid. Nevertheless, dendrimer supported *p*-tolyl boronic acid **11** and 3-nitrophenyl boronic acid **13** were subjected to purification via passive dialysis. In case of **11**, this procedure was found to be successful, yielding pure **11**, still containing all 12 boronic acid groupings, in 63% yield. However, 3-nitrophenyl boronic acid was partly released from dendrimer **13**, most probably due to the electronic effect induced by the electron-withdrawing *m*-$NO_2$ group, which makes the boron group more susceptible for nucleophilic attack by water. After dialysis, only 5 boronic acid groupings appeared to be left at the dendritic support, as was observed by comparing the $^1$H NMR spectra of dendrimer **13** before and after dialysis.

As a test reaction, *p*-tolyl boronic acid **16** was released from the dendritic support before performing any modification reaction. Release of the boronic acid from the DEAM support was achieved by mixing **11** with a 95:5 (v/v) THF/water mixture. After passive dialysis, **16** was recovered from the beaker solution (together with some undefined impurities) as could be confirmed by NMR analysis and the typical smell of the compound, but the yield (theoretical maximum of 32.3 mg) was too low to determine (Scheme 6). NMR analysis of the contents of the dialysis bag, however, revealed the presence of completely unloaded **2**, proving that the boronic acid was indeed fully released from the dendritic support.




**Scheme 6.** Attachment and modification of substituted aryl boronic acids using DEAM dendrimer **2**. *Reagents and conditions*: (i) 12 x 1.5 eq. boronic acid, $CH_2Cl_2$, rt, 1.5 h; (ii) **11**, THF/$H_2O$ (95:5 v/v), rt, 1.5 h, passive dialysis; (iii) (a) 12 x 2 eq. benzylamine, THF, rt, 2 h, (b) 12 x 2 eq. $NaBH_4$, rt, 16 h.

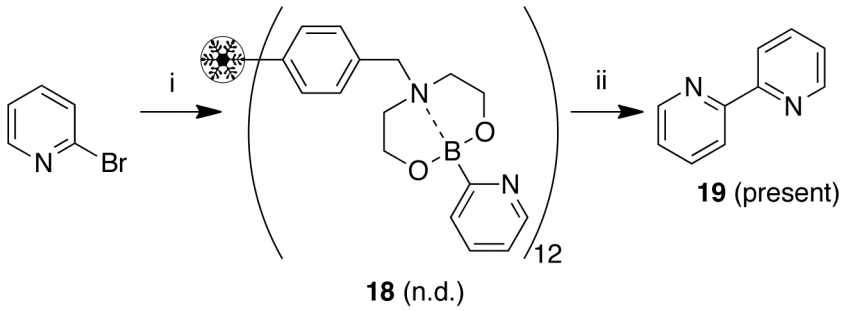
In order to investigate the possibility of a modification reaction using a supported boronic acid, *p*-formylphenyl boronic acid was immobilized, yielding dendrimer **14**. According to the $^1$H NMR spectrum, **14** contained 9 immobilized boronic acid groupings, and 3 end groupings that do not seem to contain the diethanolamine or the boronic acids groups. The reductive amination reaction of supported *p*-formylphenyl boronic acid **14** with benzylamine, immediately followed by product release resulted in the formation of the desired (4-((benzylamino)methyl)phenyl)boronic acid **17** (Scheme 6). Work up of the reaction included a passive dialysis purification step. The formation of **17** was demonstrated by $^1$H NMR

analysis of the residue from the beaker solution, which did not show the presence of **15** or dendrimer **2**. At the same time, $^{13}C$ NMR showed additional, non-assignable peaks next to those corresponding to **17**. Furthermore, $^{1}H$ NMR analysis of the dialysis bag content confirmed the complete cleavage of the product from the dendrimer by displaying the presence of recovered, unloaded **2**.

*5.2.2.2 Stabilization and application of in-situ formed boronic acids*

Besides the anchoring of stable boronic acids, diol anchors can also be used to stabilize or scavenge *in situ* formed, unstable 2-pyridyl boronic acids.[54,55] These pyridyl boronic acids, which have a strong tendency to undergo protodeborylation, are very useful building blocks in the synthesis of, *e.g.*, oligopyridines. Therefore, stabilized forms of these boronic acids are preferred. 2-Pyridyl boronic acid was obtained via the lithiation of 2-bromopyridine with 1.2 eq. *n*-BuLi in the presence of 1.2 eq. triisopropyl borate in THF at –78 °C (Scheme 7).[54] After allowing the mixture to warm to room temperature, dendritic support **2** was added to the reaction mixture. The mixture was refluxed for 3 h, resulting in the formation of the immobilized DEAM-2-pyridyl boronate **18**, which was obtained as a fully loaded dendrimer containing 12 pyridiyl end groupings. NMR analysis showed that **18** was obtained in the presence of *i*-PrOLi, which formed during the synthesis (1 equivalent per pyridyl end grouping) and acts as a stabilizing salt. Therefore, the exact yield could not be determined.

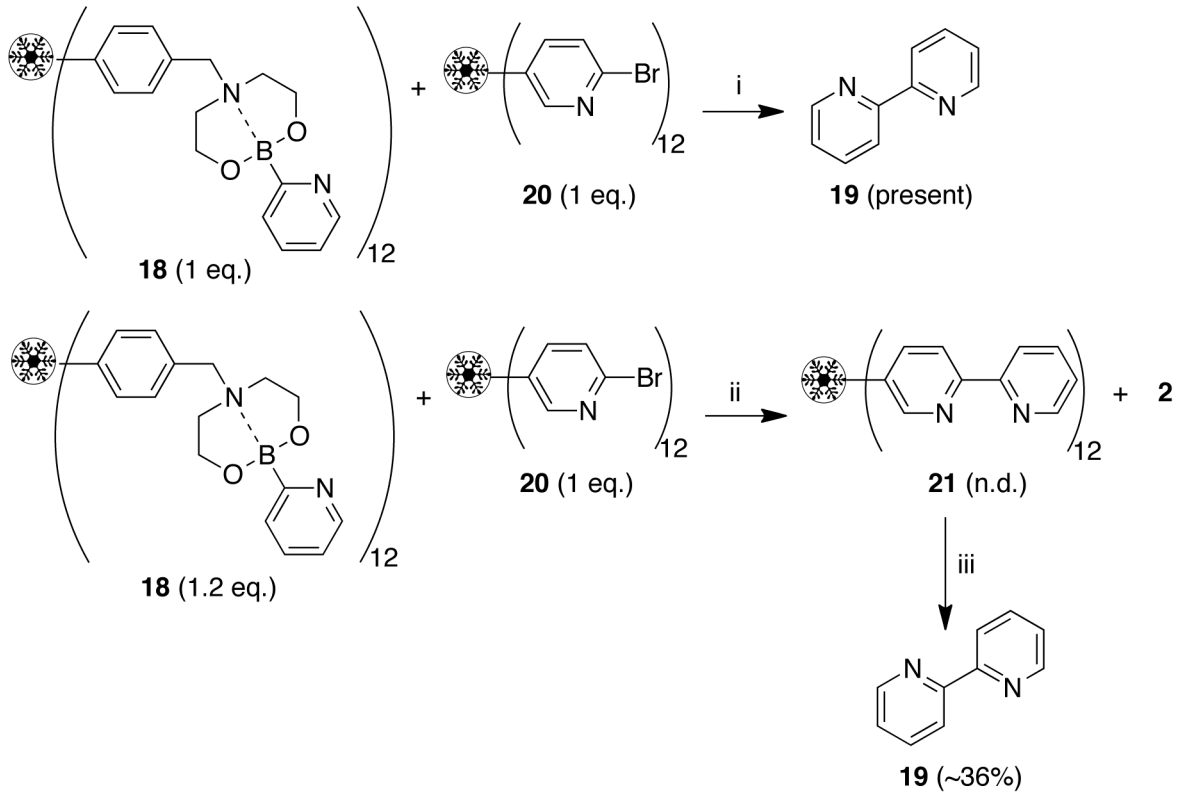
Dendrimer **18** was applied in a Suzuki coupling reaction with a small excess of 2-bromopyridine in the presence of a base (CsF) using literature conditions (Scheme 7).[55] After passive dialysis to remove the recovered dendritic DEAM support **2**, 2,2'-bipyridine **19** was recovered from the beaker solution in a mixture with other pyridyl compounds (due to the slight excess of 2-bromopyridine used). The presence of **19** in the reaction mixture was established by a test reaction using $FeSO_4$[56] and by $^{1}H$ NMR.




**Scheme 7.** Stabilization and coupling of 2-pyridylboronic acid using DEAM dendrimer **2**. *Reagents and conditions*: (i) (a) 1.2 eq. B(O*i*-Pr)$_3$, 1.2 eq. *n*-BuLi, THF, –78 °C to rt, 60 h, (b) 1/12 x 0.5 eq. **2**, THF, reflux, 3 h; (ii) (a) 12 x 1.25 eq. 2-bromopyridine, DMF, 12 x 5 mol% $PdCl_2(PPh_3)_2$, 12 x 1 eq. $PPh_3$, 12 x 1 eq. CuI, 80 °C, 0.5 h, (b) 12 x 3 eq. CsF, DMF, 80 °C, 16 h, (c) passive dialysis.

*5.2.2.3 Dendrimer-to-dendrimer coupling*

Finally, a 'resin-to-resin' type Suzuki coupling reaction was performed as described for PS-DEAM in literature, as a proof of principle of the application of the dendritic DEAM support **2**.[40] The reaction between **18** and dendritic 2-bromopyridine **20**[57] was performed in the presence of a base, using comparable conditions as for the Suzuki coupling described above (Scheme 8).[55] Like in the literature procedure, initially CsF was used as base. After purification of the product by passive dialysis, **19** was recovered from the beaker solution[56] and not from the dialysis bag as expected. All bipyridine moieties were expected to stay inside the dialysis bag, since these should be covalently bound to the dendrimer and therefore be large enough to be retained by the membrane. Most probably the CsF present in the reaction mixture caused the release of the (bi)pyridine moieties from the dendrimer via Si-C bond cleavage.




**Scheme 8.** Dendrimer-to-dendrimer coupling of pyridines. *Reagents and conditions*: (i) (a) 12 x 5 mol% $PdCl_2(PPh_3)_2$, 12 x 0.1 eq. $PPh_3$, 12 x 0.1 eq. CuI, 12 x 3 eq. CsF, DMF, 60 °C, 50 h, (b) passive dialysis; (ii) (a) 12 x 5 mol% $PdCl_2(PPh_3)_2$, 12 x 0.1 eq. $PPh_3$, 12 x 0.1 eq. CuI, 12 x 0.25 eq. $K_2CO_3$, DMF, 80 °C, 16 h, (b) passive dialysis; (iii) 12 x 1.4 eq. *n*-$Bu_4NF$, THF, rt, 60 h.

The use of $K_2CO_3$ as base instead of CsF resulted in the recovery (after passive dialysis) of a mixture of the covalently dendrimer-bound 2,2'-bipyridine **21** and recovered **2** (Scheme 8). From this observation it is clear that the 'resin-to-resin' Suzuki coupling, making use of **18**, indeed resulted in the formation of the coupled product covalently bound to the dendrimer surface. The presence of the dendrimer-bound 2,2'-bipyridine **21** in the mixture was revealed by a test reaction with $FeSO_4$[56] and by $^1$H NMR (overlapping signals of **21** and **2**).
In the next reaction step, **19** was released from dendrimer **21** by reaction with *n*-$Bu_4NF$ in THF, yielding **19** in an estimated yield of 36% yield, together with minor amounts of pyridine-like side-products, after purification by filtration over a short plug of silica.

### 5.2.3 Application of the REM and Benzylbromide Supports: Proof of Principle

The polystyrene bound benzylbromide and REM linkers are widely used for the supported, stepwise synthesis of tertiary amines. To explore the applicability of the dendritic

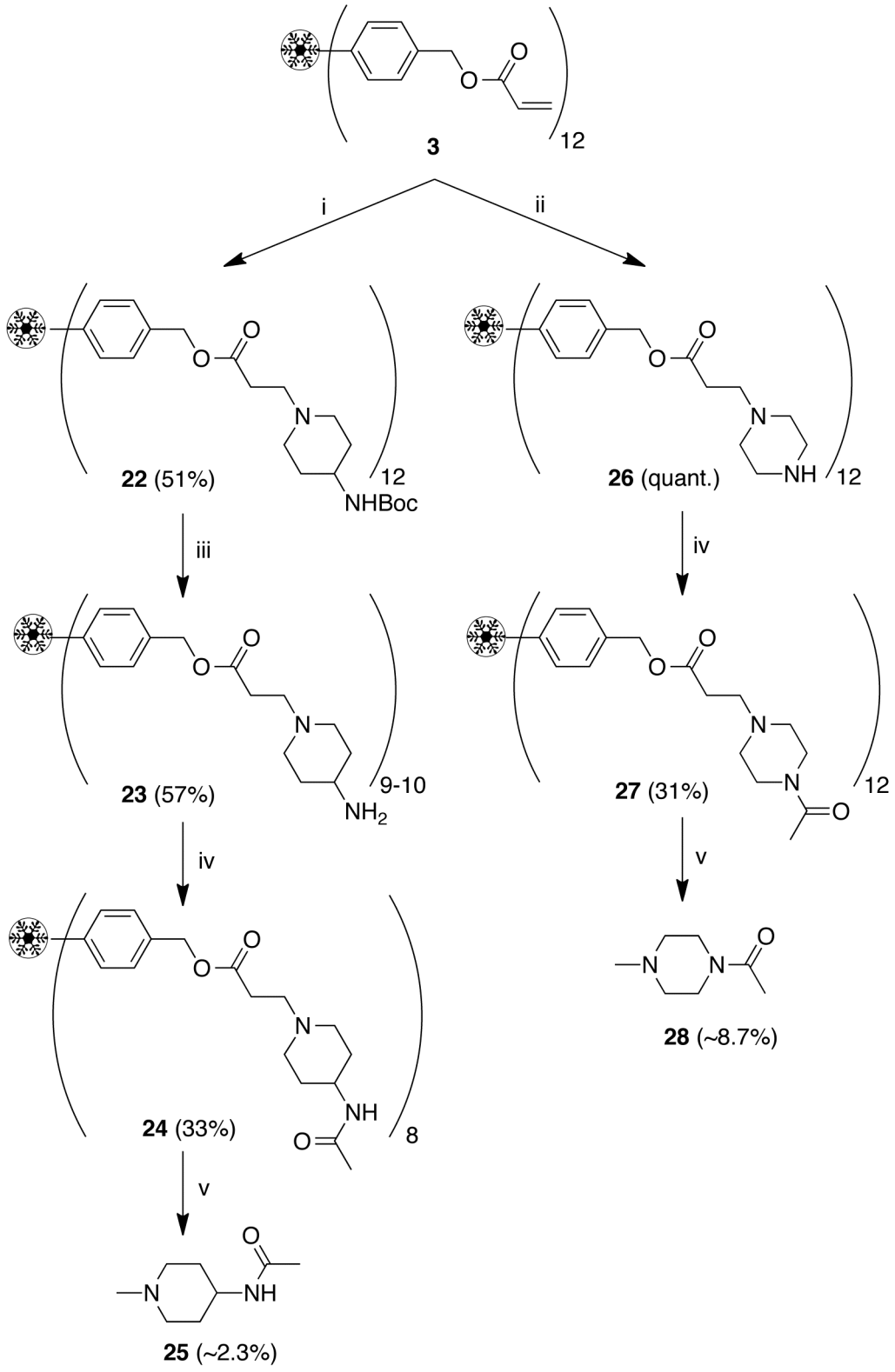
benzylbromide and REM supports **1** and **3**, attachment, modification and release steps were performed on these supports. Initially, two pharmaceutically interesting substrates were chosen for this purpose, *i.e.* piperazine and 4-aminopiperidine, in order to show a proof of principle for the dendrimer-supported synthesis of secondary and tertiary amines.

*5.2.3.1 Dendritic REM Support*

The attachment of primary or secondary amines to a REM linker generally occurs via a Michael addition reaction at room temperature.[4,5] Application of these conditions in the reaction of dendritic REM support **3** with 4-*N*-Boc-aminopiperidine resulted in the attachment of up to 12 amines, *i.e.* full functionalization, to the dendrimer periphery (Scheme 9). The resulting functionalized dendritic support **22** was purified by passive dialysis in 51% isolated yield, based on the initial amount of **3**. The low yield of this reaction can be explained by the high solubility of the reaction product in water over a large pH-range and the use of aqueous washings during work up. Boc-protected dendrimer **22** was deprotected by reaction with large amounts of TFA (30 equivalents per dendrimer end grouping), to yield **23** in 57% yield (based on **22**), and high purity, *i.e.* a narrow molecular weight distribution, containing on average 9-10 substituted REM groupings per dendrimer (according to $^1$H NMR). This high purity of dendrimer **23**, after basic aqueous workup only, made further purification by passive dialysis unnecessary. Dendrimer **23** was modified by an acylation reaction with 20 equivalents acetic anhydride per dendritic end grouping in the presence of pyridine. After basic aqueous work up, **24** was obtained as a sticky orange oil in 33% yield (based on **23**). This dendrimer is highly soluble in water, which makes isolation of the compound by standard aqueous work up procedures somewhat complicated. According to the $^1$H NMR spectrum, **24** contained only about 8 substituted REM groupings per dendrimer after the reaction. The other four dendritic end groupings did not consist of the REM linker grouping, since typical signals corresponding to the protons of the double bond were not present in the $^1$H NMR spectrum. Probably cleavage of the (substituted) REM linker groupings from the dendrimer took place, leaving the peripheral benzyl groupings intact (both the aryl and $CH_2$ signals were present in the $^1$H NMR spectrum), which could have been transformed into, *e.g.*, benzyl alcohol groupings.

In the last step, the modified piperidine was released from the dendrimer via a quaternization reaction using methyl iodide, followed by Hofmann elimination using DIEA. However, analysis of the solution from the dialysis bag after passive dialysis revealed the presence of partly unloaded, recovered **3**, containing on average 5 unloaded REM linker groupings per

dendrimer. The typical signals corresponding to the REM linker groupings were clearly visible in the $^{1}$H NMR spectra. This observation confirmed the occurrence of the cleavage step, although no complete cleavage took place. Analysis of the beaker solution after passive dialysis revealed the presence of 1-methyl-*N*-acetylaminopiperidine **25**, as detected by GC-MS, but only together with substantial amounts of DIEA (approximately 6 equivalents, according to $^{1}$H NMR) and some indefinable side-products, at an estimated yield of 2.3% relative to **24**. The major problem in isolating the desired product lays in the fact that it is obtained together with DIEA, and that **25** and DIEA are hardly separable.




**Scheme 9.** Supported piperidine and piperazine functionalization using REM dendrimer **3**. *Reagents and conditions*: (i) (a) 12 x 2 eq. 4-*N*-Boc-aminopiperidine, $CH_2Cl_2$, rt, 6 h, (b) passive dialysis; (ii) (a) addition of **3** to 12 x 19 eq. piperazine, $CH_2Cl_2$, rt, 16 h, (b) passive dialysis; (iii) 12 x 30 eq. TFA, $CH_2Cl_2$, rt, 1.5 h, $NaHCO_3$ (aq.); (iv) (a) 12 x 20 eq. acetic anhydride, 12 x 20 eq. pyridine, $CH_2Cl_2$, rt, 2-4 h, (b) $NaHCO_3$ (aq.), (c) passive dialysis

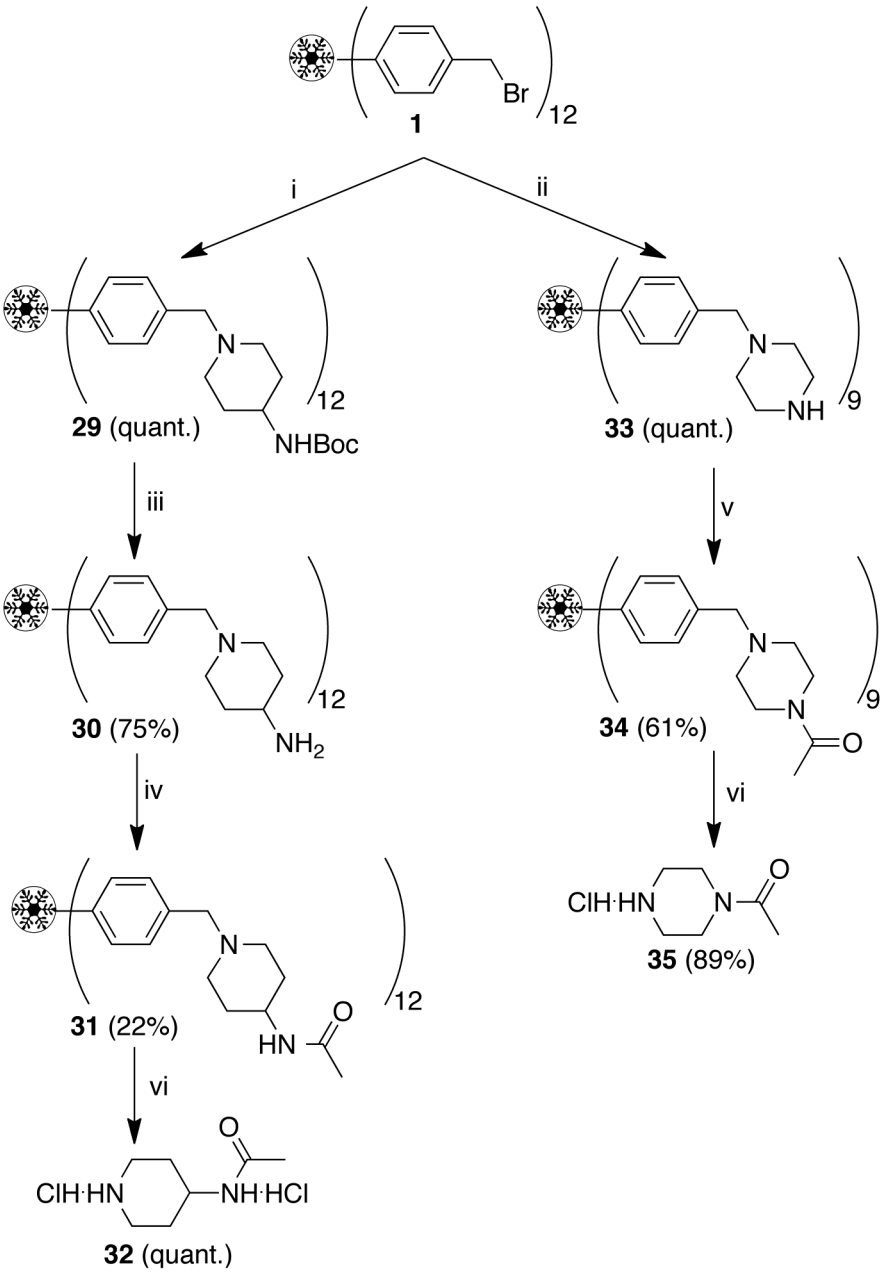
(only in case of piperazine-product); (v) (a) excess MeI, $CH_2Cl_2$, rt, 24 h, (b) 12 x 5-10 eq. DIEA, $CH_2Cl_2$, rt, 16 h, (c) passive dialysis.

Functionalization of **3** with equimolar amounts or a slight excess of piperazine (2-10 equivalents per dendrimer end grouping) initially did not result in full loading of the dendrimer. Signals corresponding to the protons of the remaining, unloaded REM linker groupings, *i.e.* the C-C double bonds, were still clearly visible in the $^1$H NMR spectrum of the reaction product. Apparently, the Michael addition reaction of **3** with piperazine requires a large excess of reagent (20 eq. per dendrimer end grouping) and a reverse addition procedure, due to the possible multiple substitution at the piperazine moieties, *e.g.* attachment at both nitrogens. This procedure yielded fully functionalized **26** in quantitative yield (based on the amount of **3**) after purification by passive dialysis. Modification of the immobilized piperazine was performed by reaction with acetic anhydride (20 equivalents per end dendrimer grouping) in the presence of pyridine. Aqueous work-up followed by passive dialysis resulted in the isolation of **27** as a sticky orange oil in a yield of 31%, based on the initial amount of **26**. Much like **24**, **27** is highly soluble in water, which results in low isolated yields. In contrast to the reaction yielding dendrimer **24**, the reaction to form **27**, which was carried out under comparable reaction conditions, did not lead to cleavage of the product or REM linker groupings from the dendrimer. Release of the modified piperazine was performed by quaternization with methyl iodide followed by Hofmann elimination using DIEA. In analogy to the isolation of **25**, isolating **28** from the beaker solution after passive dialysis was somewhat problematic, and **28** was obtained in a yield of 8.7% relative to **27** together with some remaining DIEA (one equiv. according to $^1$H NMR). Analysis of the dialysis bag contents after dialysis revealed the presence of (partly) unloaded **3**, containing on average 9 unloaded REM linker groups per dendrimer (according to $^1$H NMR).

*5.2.3.2 Dendritic Benzylbromide Support*

Loading of the benzylbromide support **1** was performed by a somewhat different method (Scheme 10). In fact, one example for the attachment of an amine functionality to **1** was already given by the attachment of the DEAM linker (see paragraph 2.1.2). In case of attachment of 4-*N*-Boc-aminopiperidine, simple mixing of **1** and the amine (2 eq. per dendritic end group) in $CH_2Cl_2$ overnight yielded the fully loaded product **29** in quantitative yield (based on the initial amount of **1**) after purification by passive dialysis. Like for dendrimer **22**, compound **29** was deprotected by reaction with large amounts of TFA (30

equivalents per dendrimer end grouping), yielding fully loaded **30** in 75% yield (relative to **29**) after basic aqueous work up. The modification of **30** was achieved by the acylation reaction with acetic anhydride (20 equivalents per dendritic end grouping) in the presence of pyridine. Dendrimer-bound product **31** (fully loaded) was isolated as a colorless sticky oil by basic aqueous work up, in 22% yield based on **30**. The yield of **31** is very low, due to the high solubility in water (as described above for **24** and **27**). Both dendrimers **30** and **31** were not further purified by passive dialysis because of the purities of both dendrimers after basic aqueous work up procedures, *i.e.* small molecules were not observed in the NMR spectra. The cleavage of amine products from benzyl linker groupings is described in literature for SPOS procedures.[58] The release step was performed accordingly via quaternization using α-chloroethyl chloroformate (ACE-Cl) in $CH_2Cl_2$, followed by refluxing in methanol, yielding the secondary amine **32** as its HCl-salt after passive dialysis.[59] In this particular case, *N*-acetylaminopiperidine•2HCl (**32**) was obtained together with some inseparable and undefined side products in quantitative yield relative to **31** (estimated from $^1$H NMR, based on relative integrals).

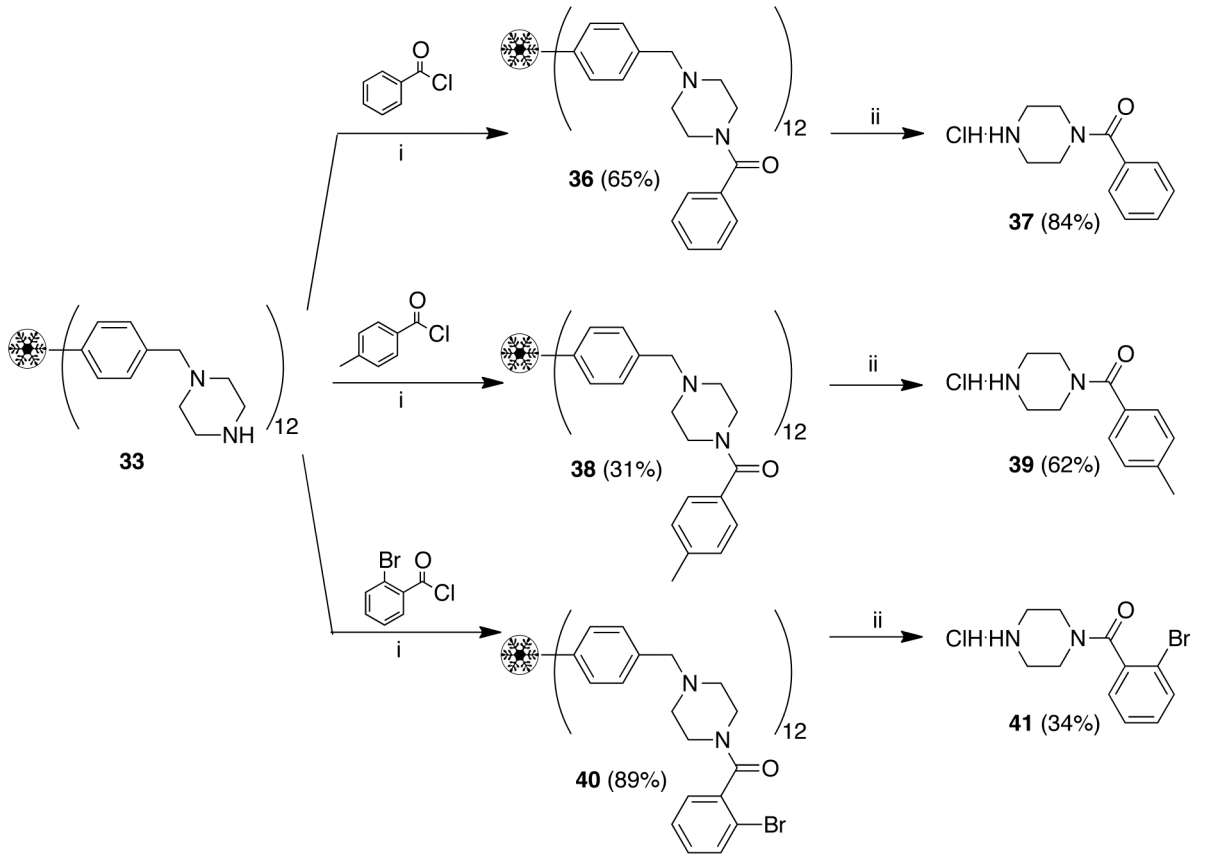



**Scheme 10.** Functionalization of 4-aminopiperidine and piperazine using benzyl bromide dendrimer **1**. *Reagents and conditions*: (i) (a) 12 x 2 eq. 4-*N*-Boc-aminopiperidine, $CH_2Cl_2$, rt, 6 h, (b) passive dialysis; (ii) (a) addition of **1** to 12 x 20 eq. piperazine, $CH_2Cl_2$, rt, 5 h, (b) passive dialysis; (iii) (a) 12 x 30 eq. TFA, $CH_2Cl_2$, rt, 1.5 h, (b) $NaHCO_3$ (aq.); (iv) (a) 12 x 20 eq. acetic anhydride, 12 x 20 eq. pyridine, $CH_2Cl_2$, rt, 2-4 h, (b) $NaHCO_3$ (aq.); (v) (a) 12 x 20 eq. acetic anhydride, $CH_2Cl_2$, rt, 2-4 h, (b) $NaHCO_3$ (aq.); (vi) (a) excess ACE-Cl, $CH_2Cl_2$, rt, 3 h, (b) MeOH, reflux, 16 h, (c) passive dialysis.

In analogy to the synthesis of **26**, reversed addition of **1** to a large excess of piperazine (20 eq. per dendritic end group) in $CH_2Cl_2$ significantly increased the yield and purity of **33**

compared to the 'normal' addition sequence. Although over-alkylation at the piperazine nitrogen(s) can occur in reactions with benzylbromide moieties, this was not observed and **33** was obtained in a quantitative yield (based on **1**), although just containing 9-10 piperazine moieties per dendrimer, after passive dialysis in order to remove the excess of free amine. With the immobilized piperazine **33**, an acylation reaction with acetic anhydride (20 equivalents per dendrimer end grouping) was performed, yielding dendrimer **34** as a colorless sticky oil after basic aqueous work up, in 61% yield (based on **33)**. Release of the modified piperazine product from **34** was achieved by quaternization with ACE-Cl, followed by refluxing in methanol, yielding pure 1-acetylpiperazine•HCl (**35**), as recovered from the beaker solution after passive dialysis, in 89% yield.

Dendrimer-supported piperazine **33** was furthermore reacted with three different aromatic acid chloride compounds in the presence of pyridine, yielding products **36**, **38**, and **40** (Scheme 11). In order to remove the excess of reagents used, the reaction products were purified by passive dialysis, yielding pure and fully loaded **36**, **38**, and **40** in yields varying from 31 to 89%, based on the initial amount of **33** used. The release of the products from the dendrimers was carried out by the quaternization reaction with ACE-chloride, followed by refluxing in methanol, yielding the desired products **37**, **39**, and **41** as their HCl-salts in varying yields (27-84%, based on the amounts of **36**, **38** and **40**, respectively) after purification by passive dialysis (Scheme 11).
In general, the reactions proceeded smoothly and as expected (although sometimes low yielding), based on the proof of principle. However, during the release of the acylated 2-bromobenzoyl-piperazine **41**, the formation of 2-bromobenzoyl methylester was observed. Apparently this compound was formed during the reaction of the ACE-Cl intermediate in methanol under reflux conditions, since it was not present in the dendritic, acylated compound **40**. So, in the case of this type of activated piperazines the quaternization reaction using ACE-Cl may be reconsidered.




**Scheme 11.** Dendrimer-supported mono-functionalization of piperazine. *Reagents and conditions*: (i) (a) 12 x 30 eq. pyridine, $CH_2Cl_2$, 3 h, (b) $NaHCO_3$ (1 M in water), (c) passive dialysis, 18 h; (ii) (a) 12 x 10 eq. ACE-Cl, $CH_2Cl_2$, 3 h, rt, (b) MeOH, reflux, 3 h, (c) passive dialysis, 16 h.

## 5.3 Discussion

### 5.3.1 Proof of Principle with Dendritic Supports 1-3

*5.3.1.1 Dendritic DEAM Support*

With the synthesis of dendritic DEAM support **2** and its application in the immobilization and scavenging of several pyridyl-compounds, a proof of principle for its use as synthesis support has been demonstrated (*vide supra*, section 5.2.2). With these results in hand, a comparison can be made to the PS-DEAM system described in literature.[40,55] The synthesis of **2** is performed in analogy to the synthesis of the PS-DEAM resin, yielding **2** in rather comparable yields.[40] Also the immobilization of various boronic acids to **2** was performed according to the literature procedure for PS-DEAM.[40] Although these reactions did yield the various immobilized boronic acids **11-15** and **18**, several problems occurred during work up. In contrary to loaded PS-DEAM, compounds **11-15** and **18** were more difficult to purify, due to the water-labile nature of the DEAM-boronic acid connection. The PS-DEAM-immobilized

boronic acids are simply purified by washing and filtration steps using dry THF. However, the (relatively large amounts of) solvents used for passive dialysis to purify the boronic acids **11-15** and **18** were not completely water-free and therefore release of boronic acid from the linker occurred to a certain extent. Changing to diafiltration, which requires much smaller amount of solvents and which can therefore be performed with dry solvents, will probably prevent this leaching of boronic acid from the dendritic supports and thereby improve the loading degrees ('purities') of dendrimers **11-15** and **18**.

As an additional proof of principle, the modification of supported *p*-formyl-phenylboronic acid **14** by a reductive amination reaction with benzylamine was performed as described for PS-DEAM.[40] This reaction resulted in formation of the desired, dendrimer-bound product **15**, from which (4-((benzylamino)methyl)phenyl)boronic acid **17** was subsequently released (resulting in recovery of support **2**). Released product **17**, obtained after passive dialysis in order to separate the large support **2** from much smaller **17**, appeared to be not as pure as the same product released from PS-DEAM,[40] as was observed by comparing the $^{1}$H NMR spectra. In contrary to the PS-DEAM procedure, both intermediate dendrimers **14** and **15** were not purified (by passive dialysis) due to their water-labile nature, before continuing with the next synthetic step. This could have resulted in the built up of impurities during the reaction sequence, which only became visible after release of **17** from the support, since intermediate dendrimer **15** was not analyzed. Unfortunately, the overall yield of the dendrimer-supported synthesis of **17** could not be determined and, therefore, not be compared to the PS-DEAM supported synthesis.

The stabilization of 2-pyridyl boronic acids, performed in analogy to literature procedures,[54,55] was very successful using dendritic DEAM support **2**. Supported 2-pyridylboronic acid **18**, which was obtained in high yield, was directly used in several Suzuki coupling reactions under various conditions (including 'simple' and 'resin-to-resin' coupling). The yield for the 'simple' Suzuki reaction of **18** with 2-bromopyridine was comparable to reported values for PS-DEAM,[55] although the purity of bipyridine **19** was not as high as for the reported products. Due to the water-labile nature of the DEAM-boronic acid connection, **18** was not purified by passive dialysis before use, which could have resulted in build up of impurities. In the literature procedure, CsF appeared to be the best base, probably due to the formation of a pyridine-$BF_3^-$ ate complex, which enhances efficiently the *trans*-metallation step.[55] Indeed, the 'simple' Suzuki coupling between **18** and 2-bromopyridine proceeded smoothly. However, in the dendrimer-to-dendrimer Suzuki coupling between **18** and carbosilane

dendrimer bound 2-bromopyridine **20**, the presence of CsF as a source of fluoride ions in the reaction mixture, resulted in release of the substrate or the coupled product from the dendrimer. In order to verify that the coupling reaction took place at the dendrimer surface, another base ($K_2CO_3$) was used instead, which indeed resulted in the formation of bipyridine product at the dendrimer surface (compound **21**). The dendrimer-to-dendrimer coupling reaction (using $K_2CO_3$ as base) yielded only 36% of bipyridine **19** after cleavage from the dendrimer. However, this yield is rather comparable to the reported literature values.[40]

*5.3.1.2 Dendritic Benzylbromide Support and REM support*

The proof of principle for the benzylbromide and REM supports (**1** and **3**) with piperidine and piperazine demonstrated the application of SPOS-linker literature procedures to the dendritic supports. The attachment of piperazine and (protected) piperidine to **1** and **3** followed literature procedures describing the attachment of these compounds to similar PS-based supports.[4,5,60,61] These reactions were in general high yielding and resulted, after passive dialysis, in products pure enough to be used in further modification steps. The acylation reactions of these products (**23**, **30**, **26** and **33**) with acetic anhydride and with three different acid chlorides did result in full conversion of the peripheral amine functionalities but the isolated yields were rather low, even when using a large excess of reagents. Recovery of the acylated products **24**, **27**, **31** and **34** from the aqueous layer during work up appeared to be problematic due to the high solubility of the compounds in water. Yet, aqueous work up was required in order to remove the acetic acid formed during reaction. Not all dendrimers were purified by passive dialysis, since NMR spectroscopy demonstrated high purity (dendrimers **24**, **31**, and **34**) after aqueous work up.

The overall yields of the reaction sequences were rather low compared to the results reported for comparable SPOS procedures. Since the very same reactions were not described for SPOS chemistry, only rough comparisons could be made for the proof of principle. However, in general yields up to 80% were reported for SPOS linkers (REM[4,5] and benzylhalide[58,59,62]), whereas for the dendritic supports yields up to 10% (REM) and 30-60% (benzylbromide) were obtained. Furthermore, the products released from the dendritic supports appeared to contain more impurities than the products obtained by SPOS (up to 99% pure). In case of REM support **3**, all products were obtained together with DIEA, which was used for the Hofmann elimination reaction. Due to the similar character of the amines (products and DIEA), separation was not successful on the small scale used for the proof of principle studies.

In the reaction sequence starting from dendritic REM support **3** to synthesize 1-methyl-*N*-acetylaminopiperidine **25**, a significant observation was made. In every modification step, full conversion of the existing peripheral groups was observed. However, the loading degree of the dendrimer decreased after every modification step. NMR analysis of the products showed that the 'missing' groupings do not contain any piperidine moieties or 'empty' REM linker groupings, *i.e.* no $CH_2$–$CH_2$ or CH=$CH_2$ signals were observed. Apparently the ester bond of the REM linker grouping is sensitive towards hydrolysis, which can occur during the aqueous work up procedures, leaving a benzylic end group behind. Indeed, signals corresponding to these benzyl groupings have been observed in the NMR spectra of the products. Remarkably, this phenomenon was only observed in this specific reaction sequence. In the synthesis of 1-methyl-4-acetylpiperazine **28**, also starting from **3**, similar procedures were followed, but hydrolysis of the REM linker was not observed. Possibly minor changes in, *e.g.*, reaction times during work up may have resulted in these inconsistent observations.

### 5.3.2 General evaluation of dendritic supports

The application of carbosilane dendrimers both as catalyst-support and as support in organic synthesis is demonstrated in literature to some extent.[21,24,25,27,28,30,33] It has, however, not reached the level of the application of PS-based supports for organic synthesis by far. In order to be able to make a fair comparison of the two types of supports, the peripheral functionalization of carbosilane dendrimers with some well-known SPOS linker groupings was carried out (*vide supra*). In this way, the exact same reactions can be performed at the dendrimer's periphery as are described in literature for certain standard SPOS procedures.
In this section, the application of carbosilane dendrimers as synthesis support, both functionalized with and without peripheral linker groupings, will be evaluated and a comparison to existing SPOS and LPOS systems will be made.

#### *5.3.2.1 Structural considerations*

Carbosilane dendrimers are readily available, since their synthesis is relative easy and straightforward.[32,63] The highly regular dendritic structure is robust and thereby resistant towards many reagents like main group organometallics.[64] This is an advantage of the carbosilane dendrimers when compared to well-known PS resins and many LPOS supports, which in general do not show this compatibility. However, a proper modification of the linker groupings, which are necessary when using PS-based supports, can lead to a better compatibility towards, *e.g.*, Grignards and metal hydrides.[7] Carbosilane dendrimers can be

used as support either with or without linker groupings at their periphery, as has been described in literature.[27,28,30,33] However, most of the linkers used so far will not result in traceless cleavage of the supported products from the dendrimers, which can in fact be achieved by using carbosilane dendritic supports without any linker. In principle, the Si-Cl end groupings of the dendrimers can function as (traceless) anchoring positions for various substrates, making extra synthetic steps to introduce linker groups avoidable.[65] On the other hand, the combination of these very reactive Si-Cl end groupings with other reactive species, *e.g.* lithio-pyridine moieties, can sometimes also be problematic, as was observed in recent studies by our group.[57] By changing the method to functionalize the dendrimers, the use of these very reactive Si-Cl end groupings could be circumvented, without the introduction of linker moeities.[57] In other cases, the use of the SPOS-type linker groupings on dendrimer peripheries, as described in this chapter (*vide supra*), can be advantageous as well, since the functionalized dendrimers **1** – **3** appeared to be stable and thereby easy to handle. However, reactions with reactive species like the lithio-pyridine compounds used earlier in combination with the carbosilane dendrimers, can not be performed with linker-functionalized dendrimers or PS-based supports. The fact that carbosilane dendrimers can be compatible with this type of compounds directly shows the advantage of these supports over the more classical SPOS or LPOS supports.[28,57,66]

*5.3.2.2 Purification methods*

Working in homogeneous reaction media is still one of the advantages of the dendritic supports compared to SPOS. The advantages resulting from the inhomogeneous nature of solid PS-supports, *i.e.* higher conversions and yields by using large excess of reagents and easy separation of the supported products form the reactants by filtration techniques, still hold when using the dendritic supports. Application of carbosilane dendrimers as synthesis support requires particular conditions related to the media and procedures used, as was observed during the application of functionalized dendrimers **1**–**3**. For example, the solubility in or the sensitivity towards water of the dendrimer-supported substrates and products can be a problem during workup of the reactions mixtures. Whereas the comparable PS-based supports are simply washed on a filter with small amounts of dry solvents to remove impurities and excess of reagents,[4,5,40] the carbosilane dendrimers need to be purified by more delicate filtration techniques. Passive dialysis used to purify most of the dendritic supports is very slow compared to the (nano)filtration techniques used in SPOS and it takes several cycles and thereby relatively large amounts of solvents to fully separate the excess of reagents from the

product. This is particularly the case when using very large excesses of reagents (more than 20 equivalents per dendritic arm, *vide supra*), in analogy to SPOS. Long residence in aqueous media can result in hydrolysis of the REM linker or the DEAM-boronic acid connection (*vide supra*). Changing to diafiltration using a pressurized reactor will increase the filtration speed, although suitable membranes that resist the required solvents are not readily available or still relative expensive.[37,67] Furthermore, diafiltration would be more favorable in the scale up of these kind of processes, since it will be possible to incorporate it in larger scale or parallel synthesis set ups. Due to their star-shaped structure instead of the more linear LPOS supports, dendritic supports can easier be purified by dialysis or filtration techniques, since they will be retained better by most membranes. The more bulky the dendrimers are, the better their retention is.[66]

*5.3.2.3 Spectroscopy and reaction monitoring*

In SPOS procedures, the standard method to monitor separate reaction steps involves (partial) cleavage of products from the support, followed by standard spectroscopic analysis.[38] Such standard, solution phase spectroscopic techniques, *e.g.* NMR spectroscopy, cannot be applied for analysis of the solid-supported products. Changing to LPOS can partly improve this situation. For example, the synthesis of arylpiperazines (and piperidines) using a soluble PEG-based support allows for routine analytical methods (UV, IR, NMR, TLC) to monitor reaction progress without prior cleavage steps.[68] Dendrimer-supported synthesis has the same advantages as LPOS procedures, *i.e.* application of standard solution-phase analytical methods. However, in the case of dendrimers more detailed information about the supported product including the support itself will be obtained due to the regular structure of the dendrimer backbone compared to polymer-based supports. Exact loading degrees can be calculated using, *e.g.*, NMR spectroscopy, but also using mass analysis techniques like MALDI-TOF MS (*vide infra*). In this way more information can be obtained about separate reaction steps in a synthesis sequence, resulting in a detailed monitoring of the progress of the reactions. Furthermore, the purity of the starting materials can be confirmed. For example, one of the observed advantages of **2** compared to PS-DEAM is the possibility to control the degree of functionalization and the purity of dendritic DEAM **2** (Figure 4).[40] For SPOS generally only overall yields are reported, so no judgment can be given on the yield of the separate reaction steps, in contrary to dendrimer-supported synthesis. This was demonstrated by the dendrimer-supported synthesis of piperidine and piperazine derivatives described here,

but also in an earlier report on the linkerless use of carbosilane dendrimers as soluble supports.[28,57]

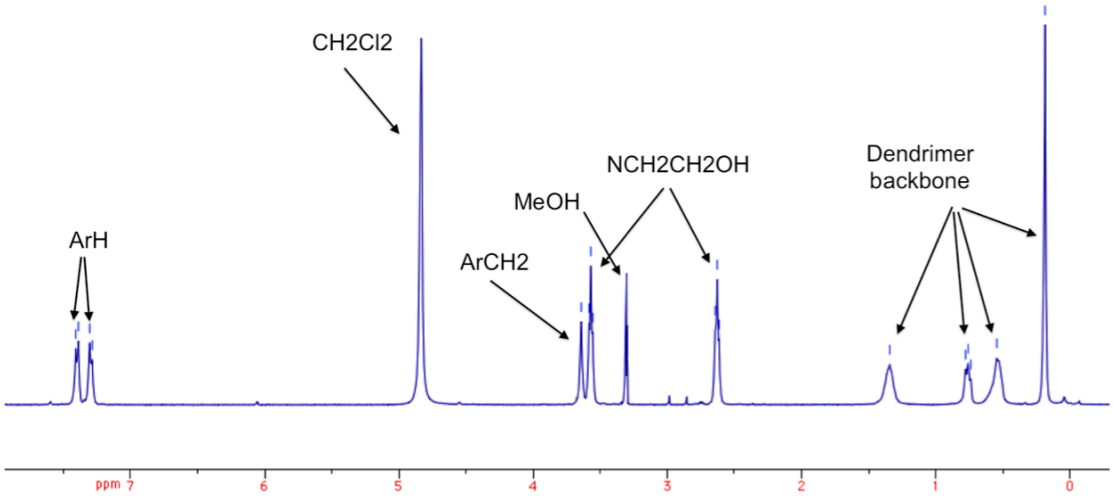



**Figure 4.** NMR spectrum of dendritic DEAM support **2** (before application as support).

Mass spectrometry techniques like MALDI-TOF MS can be used to determine the molecular weight distribution of the dendrimers, which is another indication of the purity of the dendrimers, both of the dendritic starting material and the intermediate reaction products.[69,70] A small molecular weight distribution can be interpreted as the presence of a high purity dendrimer-supported product. In all mass spectrometric data obtained during the research described in this report, small molecular weight distributions were observed. Another method to determine molecular weight distributions is Gel Permeation Chromatography (GPC). In a previous report, we have used GPC to determine the size of various loaded dendrimers.[67] However, the dendrimers analyzed in that project, which are comparable to the dendrimers described in this report, gave only one single peak in the chromatograms, indicating low polydispersities as well.

In SPOS recycling of the support after cleavage of the products is usually not preferred, since complete cleavage is never guaranteed, which will lead to impurities in next reaction sequences. As described above, application of spectroscopic techniques is not routinely available during SPOS processes, and thereby analysis of the support during a synthesis sequence and after product cleavage (recycled support) is often not possible. During the application of the dendritic supports on the other hand, NMR spectroscopy appeared to be a very useful technique to follow the progress of all reaction steps, including the release of

products from the supports. After cleavage of the products, the dendritic supports could be recovered from the dialysis bag after passive dialysis. Especially in case of dendrimers **2** and **3**, the typical resonances for the linker groups could clearly be observed in the $^{1}$H NMR spectra. In this way an estimation of the amount of cleaved product could be made. For example, from the spectra it was clear that by applying the chosen reaction conditions to release 1-methyl-4-acetylpiperazine **28** from REM dendrimer **3**, no full unloading took place. Approximately 5 to 9 REM linker groupings (based on olefinic resonances in $^{1}$H NMR; for illustration see Figure 5) were present after cleavage, whereas the other dendritic arms contained either the REM-substrate-unit or the 'empty' benzyl moiety (*i.e.* hydrolysis of the REM-grouping occurred, *vide supra*).

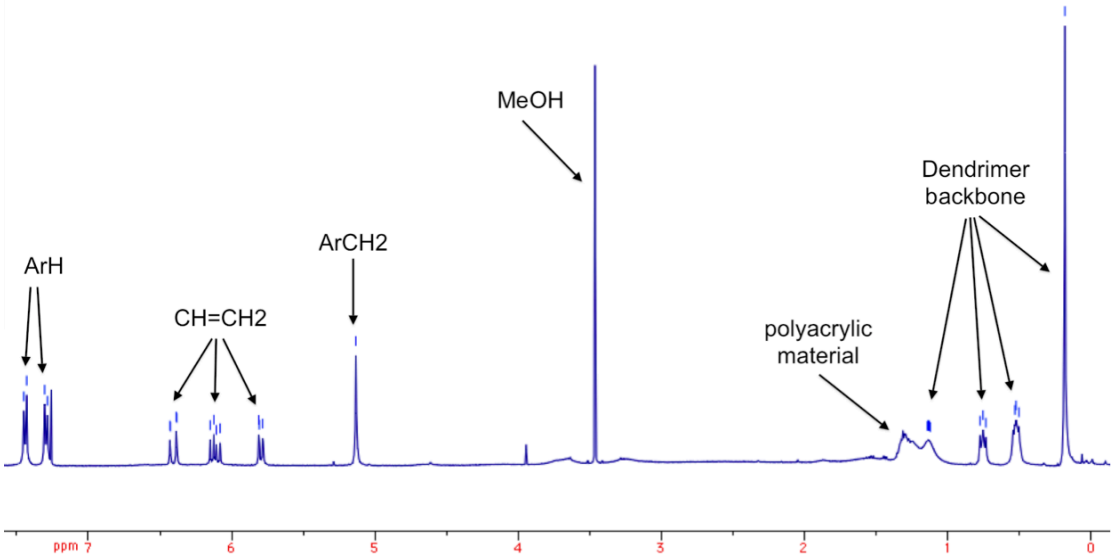



**Figure 5.** NMR spectrum of dendritic REM support **3** (before application as support).

## 5.4 Concluding Remarks

Three different novel dendritic supports were synthesized: benzylbromide **1**, DEAM **2** and REM **3**. These dendrimers were successfully applied in a proof of principle study as soluble supports in the step-wise synthesis of (pharmaceutically interesting) small molecules. When comparing the results obtained with the dendritic supports to similar SPOS chemistry, the major advantage, *i.e.* the solubility of the supports in the reaction media, does not stand out as a doubtless benefit. The yields and purities of the released products were not as high as for similar the SPOS results, due to difficulties with work up of the functionalized dendritic supports. The purification technique used with these dendrimers, passive dialysis, appeared to be successful, but only in combination with water-stable products. Therefore, amongst others,

passive dialysis is not the preferred technique for further scale-up or parallel synthesis methods. Changing to diafiltration techniques, which require less solvents and shorter filtration times, will definitely improve the applicability of carbosilane dendritic supports in organic synthesis.

On the other hand, clear advantages of carbosilane dendrimers as synthesis supports were demonstrated in this study. The structural regularity of the dendritic backbone and the solubility in the reaction media did result in better monitoring of the separate reaction steps, which also allows for a better understanding of the reaction sequences in supported synthesis. Although more research is required to fully demonstrate the application of carbosilane dendrimers as soluble synthesis supports, this study has shown their promise in the (small scale) synthesis of delicate pharmaceutically interesting molecules.

## 5.5 Experimental Section

Solvents were dried and distilled over sodium/benzophenone prior to use. The carbosilane dendrimers (G0-Cl and G1-Cl),[32] *p*-bromo-methoxybenzyl[41] and *O*-tetrahydropyranyl-4-bromobenzyl ether[42] were prepared according to literature procedures. All other chemicals were used as purchased. $^{1}$H, $^{13}$C{$^{1}$H} and $^{29}$Si{$^{1}$H} NMR spectra were recorded on a Varian AS400 or Varian Inova 300 instrument at room temperature unless stated otherwise. Chemical shifts are reported in ppm relative to residual solvent signals. IR-spectra were measured on a Perkin-Elmer Spectrum One FT-IR. Microanalyses were performed by Microanalytisches Laboratorium Dornis & Kolbe, Mülheim a.d. Ruhr, Germany. MALDI-TOF MS spectra were recorded using 2,5-dihydroxybenzoic acid as matrix on a Voyager-DE BioSpectrometry Workstation. GC-MS chromatograms and spectra were recorded on a Perkin-Elmer AutoSystem XL (GC) coupled to a TurboMass (MS).

**Synthesis of *O*-tetrahydropyranyl-4-bromobenzyl ether (4)**

Synthesized according to a literature procedure.[42] To a solution of 4-bromobenzyl alcohol (9.7 g, 51.8 mmol) and 3,4-dihydro-2*H*-pyran (5.2 mL, 4.79 g, 57.0 mmol) in dichloromethane (120 mL) was added *p*-toluene sulfonic acid monohydrate (200 mg, 1.05 mmol). The mixture was stirred at room temperature for 3 h. The solvent was removed *in vacuo* and the residue was filtered over silica using EtOAc:hexane (1:6), to give a slight yellow liquid. Yield: 11.14 g (41.08 mmol, 79%). $^{1}$H NMR: (400 MHz, $CDCl_3$): δ = 7.46 (d, $^{3}J_{H\text{-}H}$ = 8.40 Hz, 2 H, Ar*H*), 7.23 (d, $^{3}J_{H\text{-}H}$ = 8.00 Hz, 2 H, Ar*H*), 4.72 (d, $^{3}J_{H\text{-}H}$ = 12.40 Hz, 1 H, C$H_2$), 4.68 (t, $^{3}J_{H\text{-}H}$ = 3.60 Hz, 1 H, O-C*H*), 4.45 (d, $^{3}J_{H\text{-}H}$ = 12.40 Hz, 1 H, C$H_2$), 3.89 (m, 1 H, O-C$H_2$-$CH_2$), 3.54 (m, 1 H, O-C$H_2$-$CH_2$), 1.89-1.49 (m, 6 H, CH-(C$H_2$)$_3$C$H_2$). $^{13}$C{$^{1}$H} NMR: (100 MHz, $CDCl_3$): δ = 137.41 (Ar*C*), 131.50 (Ar*C*), 129.47 (Ar*C*), 121.39 (Ar*C*),

97.83 (O-*C*H), 68.09 (Ph-*C*$H_2$O), 62.20 (O-*C*$H_2$-$CH_2$), 30.58 (CH-*C*$H_2$-$CH_2$), 25.50 ($OCH_2$-*C*$H_2$-$CH_2$), 19.38 ($OCH_2CH_2$-*C*$H_2$-$CH_2CH$). GC-MS: *m/z* 271 ($M^+$).

**Synthesis of *O*-tetrahydropyranyl-4-trimethylsilylbenzyl ether (5)**

To a solution of **4** (2.0 g, 7.38 mmol) in THF (40 mL) was added *n*-butyllithium (4.6 mL, 1.6M solution in hexanes, 7.38 mmol) at –78 °C. After the addition was complete, the solution was stirred for 2 h at –78 °C. A solution of trimethylsilyl chloride (0.9 mL, 7.38 mmol) in THF (5 mL) was added dropwise at –78 °C, after which the solution was allowed to warm to room temperature in 2 h. Water (50 mL) was added, the organic layer separated and the water layer extracted with $Et_2O$ (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by filtration over a short plug of silica using EtOAc:hexane (1:10), yielding intermediate product **5** as a colorless liquid. Yield: 1.43 g (5.41 mmol, 73%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, $^3J_{H\text{-}H}$ = 7.80 Hz, 2 H, Ar*H*), 7.41 (d, $^3J_{H\text{-}H}$ = 7.80 Hz, 2 H, Ar*H*), 4.83 (d, $^3J_{H\text{-}H}$ = 12.00 Hz, 1 H, C*H*$_2$), 4.76 (t, $^3J_{H\text{-}H}$ = 3.40 Hz, 1 H, O-C*H*), 4.54 (d, $^3J_{H\text{-}H}$ = 12.00 Hz, 1 H, C*H*$_2$), 3.97 (m, 1 H, O-C*H*$_2$-$CH_2$), 3.59 (m, 1 H, O-C*H*$_2$-$CH_2$), 1.96-1.53 (m, 6 H, CH-(C*H*$_2$)$_3$$CH_2$), 0.31 (s, 9 H, SiC*H*$_3$). GC-MS: *m/z* 264 ($M^+$). Microanalysis Calc. for $C_{15}H_{24}O_2Si$ (264.44): C, 68.13; H, 9.15; Si, 10.62. Found: C, 68.20; H, 9.18; Si, 10.45.

**Synthesis of 4-trimethylsilylbenzyl alcohol (6)**

To a solution of **5** (7.34 g, 27.76 mmol) in methanol (70 mL) was added *p*-toluene sulfonic acid monohydrate (400 mg, 2.10 mmol). The mixture was heated at 65 °C for 6 h and cooled to room temperature. The solvent was removed *in vacuo*. The residue was purified by filtration over a short plug of silica using methanol, yielding **6** as a colorless liquid. Yield: 3.55 g (19.69 mmol, 71%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 2 H, Ar*H*), 7.35 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 2 H, Ar*H*), 4.67 (s, 2 H, C*H*$_2$), 0.29 (s, 9 H, SiC*H*$_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 141.37 (Ar*C*), 139.98 (Ar*C*), 133.71 (Ar*C*), 126.49 (Ar*C*), 65.32 (*C*$H_2$), –1.01 (Si*C*$H_3$). GC-MS: *m/z* 180 ($M^+$).

**Synthesis of 4-trimethylsilylbenzyl bromide (7)**

Method 1:

To a solution of **5** (0.31 g, 1.17 mmol) in diethyl ether (20 mL) was added phosphorus tribromide (0.22 mL, 2.34 mmol) and the mixture was stirred at room temperature overnight. Water (5 mL) was added and the water layer was extracted with diethyl EtOAc (3 x 20 mL). The combined organic layers were dried on $MgSO_4$, filtered and the solvent was removed *in vacuo*. Product **7** was obtained as a colorless liquid, in a mixture with both **6** and **5**, according to GC-MS. Yield: 0.28 g (1.15 mmol, 98%).

Method 2:

To a solution of **6** (0.77 g, 4.27 mmol) in diethyl ether (20 mL) was added phosphorus tribromide (0.8 mL, 8.54 mmol) and the mixture was stirred at room temperature overnight. Water (5 mL) was added and the water layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried on $MgSO_4$, filtered and the solvent was removed *in vacuo*. Product **7** was obtained as a colorless liquid, in a mixture with **6** and 4-butylbenzyl bromide as side products, according to GC-MS. Yield: 0.78 g (2.21 mmol, 75%).

Analytical data:

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, $^3J_{H\text{-}H}$ = 8.00 Hz, 2 H, Ar*H*), 7.38 (d, $^3J_{H\text{-}H}$ = 8.00 Hz, 2 H, Ar*H*), 5.09 (d, $^4J_{H\text{-}H}$ = 8.80 Hz, 1 H, C$H_2$), 0.28 (s, 9 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 141.26 (Ar*C*), 138.29 (Ar*C*), 133.97 (Ar*C*), 128.40 (Ar*C*), 33.74 (*C*$H_2$), –1.05 (Si*C*$H_3$). GC-MS: *m/z* 243 ($M^+$, 80%).

**Synthesis of *O*-tetrahydropyranyl-4-dimethylsilylbenzyl ether (8)**

To a solution of **4** (2.0 g, 7.38 mmol) in THF (25 mL) was added *n*-butyllithium (4.6 mL, 1.6M solution in hexanes, 7.38 mmol) at –78 °C. After the addition was complete, the solution was stirred for 1.5 h at –78 °C. A solution of chlorodimethylsilane (0.8 mL, 7.38 mmol) in THF was added dropwise at –78 °C, after which the solution was allowed to warm to room temperature in 3 h. Extra chlorodimethylsilane (1.2 mL, 10.82 mmol) was added and the mixture was stirred for 1 h. Water (20 mL) was added, the organic layer separated and the water layer extracted with $Et_2O$ (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by filtration over a short plug of silica using EtOAc:hexane (1:10), yielding the protected intermediate product **8** as a slight yellow liquid. Yield: 1.70 g (6.80 mmol, 92%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, $^3J_{H\text{-}H}$ = 7.00 Hz, 2 H, Ar*H*), 7.40 (d, $^3J_{H\text{-}H}$ = 7.00 Hz, 2 H, Ar*H*), 4.82 (d, $^3J_{H\text{-}H}$ = 12.40 Hz, 1 H, C$H_2$), 4.75 (t, $^3J_{H\text{-}H}$ = 3.40 Hz, 1 H, O-C*H*), 4.53 (d, $^3J_{H\text{-}H}$ = 12.40 Hz, 1 H, C$H_2$), 4.48 (m, 1 H, Si-*H*), 3.95 (m, 1 H, O-C$H_2$-$CH_2$), 3.58 (m, 1 H, O-C$H_2$-$CH_2$), 1.96-1.53 (m, 6 H, CH-(C$H_2$)$_3$$CH_2$), 0.37 (dd, $^4J_{H\text{-}H}$ = 1.00 Hz, $^3J_{H\text{-}H}$ = 3.40 Hz, 6 H, SiC$H_3$). GC-MS: *m/z* 249 ($M^+$).

**Synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$$SiMe_2$($C_6H_4$-4)$CH_2$OTHP)$_3$}$_4$ (G1-$CH_2$OTHP, 9)**

Method 1:

To a solution of **8** (0.79 g, 3.15 mmol) and Si($CH_2CH_2CH_2$Si($CH_2CH$=$CH_2$)$_3$)$_4$ (0.18 g, 0.23 mmol) in dry MeCN (5 mL) was added Karstedt catalyst (0.16 g, 3 wt% solution in xylenes, 0.0124 mmol) and the mixture was stirred at room temperature overnight. All volatiles were removed *in vacuo* and the residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 400 mL) over the weekend. Product **9** was obtained as a brown colored viscous oil. Yield 0.59 g (0.16 mmol, 69%).

Method 2:

To a solution of **4** (13.42 g, 49.50 mmol) in THF (100 mL) was added *n*-butyllithium (30.9 mL, 1.6M solution in hexanes, 49.50 mmol) at –78 °C. After the addition was complete, the solution was stirred for 2.5 h at –78 °C. A solution of $Si(CH_2CH_2CH_2Si(CH_2CH_2CH_2SiMe_2Cl)_3)_4$ (6.85 g, 3.54 mmol) in THF (20 mL) was added dropwise at –78 °C, after which the solution was allowed to warm to room temperature overnight. A few mL of MeOH were added and the mixture was stirred for an additional 0.5 h. Water (50 mL) was added, the organic layer separated and the water layer extracted with $Et_2O$ (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 500 mL) overnight, yielding **9** as a viscous light brownish liquid. Yield: 12.31 g (3.23 mmol, 91%).

Analytical data:

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, $^3J_{H-H}$ = 7.20 Hz, 24 H, Ar*H*), 7.34 (d, $^3J_{H-H}$ = 7.20 Hz, 24 H, Ar*H*), 4.78 (d, $^3J_{H-H}$ = 12.00 Hz, 12 H, ArC$H_2$), 4.72 (t, $^3J_{H-H}$ = 3.40 Hz, 12 H, O-C*H*), 4.48 (d, $^3J_{H-H}$ = 12.00 Hz, 12 H, ArC$H_2$), 3.93 (m, 12 H, O-C$H_2$-$CH_2$), 3.55 (m, 12 H, O-C$H_2$-$CH_2$), 1.89-1.52 (m, 72 H, CH-(C$H_2$)$_3$$CH_2$), 1.36 (m, 32 H, $CH_2$C$H_2$$CH_2$), 0.80 (t, $^3J_{H-H}$ = 8.20 Hz, 24 H, C$H_2$SiAr), 0.56 (t, $^3J_{H-H}$ = 8.20 Hz, 40 H, SiC$H_2$), 0.22 (s, 72 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 139.08 (Ar*C*), 139.05 (Ar*C*), 133.82 (Ar*C*), 127.34 (Ar*C*), 97.98 (O-*C*H), 69.01 (Ar-*C*$H_2$O), 62.24 (O-*C*$H_2$-$CH_2$), 30.80 (CH-*C*$H_2$-$CH_2$), 25.73 (OC$H_2$-*C*$H_2$-$CH_2$), 20.85 (*C*$H_2$SiAr), 19.55 (OC$H_2$C$H_2$-*C*$H_2$-$CH_2$CH), 18.87 ($CH_2$*C*$H_2$$CH_2$SiAr), 18.41 ($CH_2$*C*$H_2$$CH_2$), 18.07 (Si*C*$H_2$), 17.71 (Si*C*$H_2$$CH_2$), –2.52 (Si*C*$H_3$). $^{29}$Si{$^1$H} NMR (60 MHz, $CDCl_3$): δ = 0.69 ($Si_{core}$+$Si_{inner}$), –3.94 (*Si*-Ar). Microanalysis Calc. for $C_{216}H_{348}O_{24}Si_{17}$ (3806.51): C, 68.15; H, 9.21; Si, 12.54. Found: C, 67.65; H, 9.18; Si, 12.54.

**Synthesis of $Si\{(CH_2)_3Si((CH_2)_3SiMe_2(C_6H_4\text{-}4)CH_2OH)_3\}_4$ (G1-$CH_2$OH, 10)**

To a solution of **9** (1.02 g, 0.27 mmol) in MeOH:$CH_2Cl_2$ (1:1, 5 mL) was added *p*-toluene sulfonic acid monohydrate (60 mg, 0.32 mmol). The mixture was heated at 60 °C for 5 h and cooled to room temperature. The solvent was removed *in vacuo*. The residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 600 mL) overnight, yielding **10** as a pale yellow viscous liquid. Yield: 0.59 g (0.21 mmol, 78%). $^1$H NMR (400 MHz, $CD_3OD$): δ = 7.39 (d, $^3J_{H-H}$ = 6.40 Hz, 24 H, Ar*H*), 7.24 (d, $^3J_{H-H}$ = 7.60 Hz, 24 H, Ar*H*), 4.50 (s, 24 H, ArC$H_2$), 1.29 (m, 32 H, $CH_2$C$H_2$$CH_2$), 0.72 (t, $^3J_{H-H}$ = 7.80 Hz, 24 H, C$H_2$SiAr), 0.49 (t, $^3J_{H-H}$ = 8.10 Hz, 40 H, SiC$H_2$), 0.16 (s, 72 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CD_3OD$): δ = 143.20 (Ar*C*), 139.13 (Ar*C*), 134.60 (Ar*C*), 127.43 (Ar*C*), 65.15 (Ar*C*$H_2$OH), 21.71, 20.09, 19.88, 19.04, 18.57 (5 x *C*$H_2$), –2.18 (Si*C*$H_3$). $^{29}$Si{$^1$H} NMR (60 MHz, $CD_3OD$): δ = 0.24 ($Si_{core}$+$Si_{inner}$), –4.72 (*Si*-Ar). IR: 3312 cm$^{-1}$ (OH). MALDI-TOF-MS: *m/z*: 2904.94 [G1-$CH_2$OH + Ag]$^+$ (Calcd 2904.98). Microanalysis Calc. for $C_{156}H_{252}O_{12}Si_{17}$ (2797.12): C, 66.99; H, 9.08; Si, 17.07. Found: C, 66.80; H, 9.12; Si, 17.26.

**Synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$Si$Me_2(C_6H_4$-4)$CH_2Br)_3$}$_4$ (G1-$CH_2$Br, 1)**

Method 1:

To a solution of **9** (1.07 g, 0.28 mmol) in diethyl ether (20 mL) was added phosphorus tribromide (0.63 mL, 6.75 mmol) and the mixture was stirred at room temperature overnight and evaporated *in vacuo*. The residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 500 mL) overnight, yielding **1** as a pale yellow viscous liquid. Yield: 0.99 g (0.28 mmol, 100%).

Method 2:

To a solution of **10** (0.90 g, 0.32 mmol) in $Et_2O$:benzene (1:1, 20 mL) was added phosphorus tribromide (0.8 mL, 8.54 mmol) at 0 °C and the mixture was stirred at 0 °C for 5 h. Water (5 mL) was added and the mixture was allowed to warm to room temperature. The water layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried on $MgSO_4$, filtered and the solvent was removed *in vacuo*. Product **1** was obtained as a colorless viscous liquid. Yield: 1.05 g (0.30 mmol, 92%).

Analytical data:

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 7.33 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 4.45 (s, 24 H, ArC$H_2$), 1.33 (m, 32 H, $CH_2CH_2CH_2$), 0.80 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 24 H, C$H_2$SiAr), 0.54 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 40 H, SiC$H_2$), 0.22 (s, 72 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 140.40 (Ar*C*), 138.29 (Ar*C*), 134.11 (Ar*C*), 128.40 (Ar*C*), 33.66 (Ar*C*$H_2$Br), 20.65, 18.73, 18.28, 17.97, 17.54 (5 x *C*$H_2$), –2.66 (Si*C*$H_3$). $^{29}$Si{$^1$H} NMR (60 MHz, $CDCl_3$): δ = 0.61 ($Si_{core}$+$Si_{inner}$), –3.69 (*Si*-Ar). Microanalysis Calc. for $C_{156}H_{240}Br_{12}Si_{17}$ (3551.88): C, 52.75; H, 6.81; Br, 27.00; Si, 13.44. Found: C, 52.24; H, 6.86; Br, 26.45; Si, 13.87.

**Synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$Si$Me_2(C_6H_4$-4)$CH_2N(CH_2CH_2OH)_2)_3$}$_4$ (G1-$CH_2N(CH_2CH_2OH)_2$, 2)**

To a solution of **1** (0.96 g, 0.27 mmol) in DMF (10 mL) were added $K_2CO_3$ (0.52 g, 3.78 mmol) and diethanol amine (0.36 mL, 3.78 mmol). The mixture was stirred at room temperature overnight and subsequently cooled to 0 °C and water (5 mL) was added. The reaction mixture was purified by repeated passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 3 x 600 mL) overnight, yielding **2** as a pale yellow viscous liquid. Yield: 0.82 g (0.21 mmol, 79%). $^1$H NMR (400 MHz, $CD_3OD$): δ = 7.39 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 7.26 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 3.65 (s, 24 H, ArC$H_2$), 3.58 (t, $^3J_{H\text{-}H}$ = 5.60 Hz, 48 H, $NCH_2CH_2OH$), 2.64 (t, $^3J_{H\text{-}H}$ = 5.60 Hz, 48 H, $NCH_2CH_2OH$), 1.35 (m, $^3J_{H\text{-}H}$ = 4.80 Hz, 32 H, $CH_2CH_2CH_2$), 0.77 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 24 H, C$H_2$SiAr), 0.55 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CD_3OD$): δ = 139.71 (Ar*C*), 138.87 (Ar*C*), 134.07 (Ar*C*), 129.06 (Ar*C*), 59.96 ($NCH_2CH_2OH$), 59.74 (Ar$CH_2$N), 56.37 ($NCH_2CH_2OH$), 21.13, 19.23, 18.63, 18.42, 18.03 (5 x *C*$H_2$), –2.37 (Si*C*$H_3$). $^{29}$Si{$^1$H} NMR (60 MHz, $CD_3OD$): δ = 0.73

($Si_{core}$+$Si_{inner}$), –4.17 (*Si*-Ar). MALDI-TOF-MS: *m/z*: 3842.23 [G1-$CH_2N(CH_2CH_2OH)_2$] (Calcd. 3842.56).

**Synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$OC(O)CH=$CH_2$)$_3$}$_4$ (G1-$CH_2$OC(O)CH=$CH_2$, 3)**

To a solution of **10** (0.91 g, 0.33 mmol) in $CH_2Cl_2$ (20 mL) were added DIEA (6.5 mL, 39.33 mmol) and 2-propenoyl chloride (3.2 mL, 39.39 mmol) and the mixture was shortly cooled to 0 °C and subsequently stirred at room temperature for 20 h. The solvents were removed *in vacuo* and the residue was purified by repeated passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 3 x 600 mL) overnight, yielding **3** as an orange solid. Combined yield: 1.55 g, including polyacrylic material. $^1$H NMR indicated a dendrimer/polymer weight-ratio of ~64.45/35.55, which corresponds to a yield of ~0.999 g (0.29 mmol, 88%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, $^3J_{H\text{-}H}$ = 8.00 Hz, 24 H, Ar*H*), 7.30 (d, $^3J_{H\text{-}H}$ = 8.00 Hz, 24 H, Ar*H*), 6.41 (dd, $^3J_{H\text{-}H}$ = 17.60 Hz, $^2J_{H\text{-}H}$ = 1.40 Hz, 12 H, CH=C$H_2$), 6.12 (m, $^3J_{H\text{-}H}$ = 10.40 Hz, $^3J_{H\text{-}H}$ = 6.80 Hz, 12 H, C*H*=$CH_2$), 5.80 (dd, $^3J_{H\text{-}H}$ = 10.40 Hz, $^2J_{H\text{-}H}$ = 1.20 Hz, 12 H, CH=C$H_2$), 5.13 (s, 24 H, ArC$H_2$), 1.31 (m, 63 H, polyacrylic material), 1.14 (m, 32 H, $CH_2CH_2CH_2$), 0.75 (t, $^3J_{H\text{-}H}$ = 8.20 Hz, 24 H, C$H_2$SiAr), 0.52 (t, $^3J_{H\text{-}H}$ = 8.20 Hz, 40 H, SiC$H_2$), 0.18 (s, 72 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 166.08 (*C*(O)), 139.97 (Ar*C*), 136.42 (Ar*C*), 133.85 (Ar*C*), 131.22 (*C*H=$CH_2$), 128.37 (CH=*C*$H_2$), 127.60 (Ar*C*), 66.35 (Ar*C*$H_2$), 20.64, 18.72, 18.28, 17.93, 17.55 (5 x *C*$H_2$), –2.71 (Si*C*$H_3$). $^{29}$Si{$^1$H} NMR (60 MHz, $CDCl_3$): δ = 0.19 ($Si_{core}$+$Si_{inner}$), –4.61 (*Si*-Ar).

**General procedure for the immobilization of boronic acids to the diethanolamine linker:**

To a solution of **2** in dry $CH_2Cl_2$ (20 mL) was added boronic acid (12 x 1.5 eq.). The mixture was stirred at room temperature for 1.5 h and the solvent was removed *in vacuo*. The residue was either purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v)) or used without further purification, yielding products **11-15** and **18** as colorless oils.

**Immobilization of *p*-tolyl boronic acid, synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$N($CH_2CH_2O)_2$B($C_6H_4$-4-$CH_3$))$_3$}$_4$ (G1-$CH_2$N($CH_2CH_2O)_2$B($C_6H_4$-4-Me), 11)**

Reaction between **2** (36 mg, 9.4 μmol) and *p*-tolyl boronic acid (24 mg, 0.18 mmol). The residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 400 mL) overnight and dried *in vacuo*, yielding **11**. Yield: 0.03 g (5.95 μmol, 63%). $^1$H NMR (400 MHz, $CD_3OD$): δ = 7.48-7.17 (m, 96 H, Ar*H*), 3.69 (s, 24 H, ArC$H_2$), 3.61 (m, 48H, $NCH_2CH_2O$), 2.69 (s, 36 H, C$H_3$), 2.30 (s, 48 H, $NCH_2CH_2O$), 1.30 (m, 32 H, $CH_2CH_2CH_2$), 0.75 (m, 24 H, C$H_2$SiAr), 0.52 (m, 40 H, SiC$H_2$), 0.18 (s, 72 H, SiC$H_3$).

**Immobilization of *p*-bromophenyl boronic acid, synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$N($CH_2CH_2O)_2$B($C_6H_4$-4-Br))$_3$}$_4$ (G1-$CH_2$N($CH_2CH_2O)_2$B($C_6H_4$-4-Br), 12)**

Reaction between **2** (33 mg, 8.6 μmol) and *p*-bromophenyl boronic acid (30 mg, 0.16 mmol). The residue was washed with dry THF (3 x 5 mL) and dried *in vacuo*, yielding **12**. Yield: 0.05 g (8.6 μmol, 100%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.59-7.10 (m, 96 H, Ar*H*), 4.19 (s, 24 H, ArC$H_2$), 4.06 (m, 48 H, NCH$_2$C$H_2$O), 3.20 (m, 24 H, NC$H_2$CH$_2$O), 2.76 (m, 24 H, NC$H_2$CH$_2$O), 1.25 (m, 32 H, CH$_2$C$H_2$CH$_2$), 0.70 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 24 H, C$H_2$SiAr), 0.47 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$).

**Immobilization of 3-nitrophenyl boronic acid, synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$N($CH_2CH_2O)_2$B($C_6H_4$-3-$NO_2$))$_3$}$_4$ (G1-$CH_2$N($CH_2CH_2O)_2$B($C_6H_4$-3-$NO_2$), 13)**

Reaction between **2** (45 mg, 11.7 μmol) and 3-nitrophenyl boronic acid (31 mg, 0.18 mmol). The crude product was obtained together with some aromatic side product.

Crude **13** (before dialysis): $^1$H NMR (400 MHz, $CD_3OD$): δ = 8.46 (br s, 12 H, Ar*H*), 8.20 (d, $^3J_{H\text{-}H}$ = 8.80 Hz, 12 H, Ar*H* side product), 8.06 (br s, 12 H, Ar*H*), 8.00 (d, $^3J_{H\text{-}H}$ = 6.80 Hz, 12 H, Ar*H*), 7.51 (br s, 12+12 H, Ar*H* + Ar*H* side product), 7.38 (br s, 24 H, Ar*H*), 7.18 (br s, 24 H, Ar*H*), 4.31 (s, 24 H, ArC$H_2$), 4.12 (m, 48 H, NCH$_2$C$H_2$O), 3.30 (br s, 24 H, NC$H_2$CH$_2$O), 2.90 (br s, 24 H, NC$H_2$CH$_2$O), 1.22 (m, 32 H, CH$_2$C$H_2$CH$_2$), 0.67 (m, 24 H, C$H_2$SiAr), 0.44 (m, 40 H, SiC$H_2$), 0.08 (s, 72 H, SiC$H_3$).

The residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 350 mL) overnight and dried *in vacuo*. During dialysis the boronic acid partly cleaved from the dendrimer due to presence of $H_2O$ in the solvents used, resulting in a dendrimer with 5 immobilized boronic acids and 7 'empty' diethanol amine groupings at its periphery. Yield: 0.03 g (5.54 μmol, 47%).

Product **13** (after dialysis): $^1$H NMR (400 MHz, $CD_3OD$): δ = 8.48 (br s, 5 H, Ar*H*), 8.08 (d, $^3J_{H\text{-}H}$ = 7.20 Hz, 5 H, Ar*H*), 8.01 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 5 H, Ar*H*), 7.48 (m, 5 H, Ar*H*), 7.41 (br s, 24 H, Ar*H*), 7.30 (br s, 12 H, Ar*H*), 7.20 (br s, 12 H, Ar*H*), 4.46 (s, 24 H, ArC$H_2$), 4.12 (m, 20 H, NCH$_2$C$H_2$O), 3.79 (m, 8 H, NCH$_2$C$H_2$OH), 3.63 (m, 20 H, NCH$_2$C$H_2$OH), 3.34 (m, 20 H, NCH$_2$C$H_2$O), 2.87 (m, 28 H, NC$H_2$CH$_2$OH), 1.27 (m, 32 H, CH$_2$C$H_2$CH$_2$), 0.72 (m, 24 H, C$H_2$SiAr), 0.50 (m, 40 H, SiC$H_2$), 0.14 (s, 72 H, SiC$H_3$).

**Immobilization of *p*-formylphenyl boronic acid, synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$N($CH_2CH_2O)_2$B($C_6H_4$-4-C(O)H))$_3$}$_4$ (G1-$CH_2$N($CH_2CH_2O)_2$B($C_6H_4$-4-C(O)H), 14)**

Reaction between **2** (65 mg, 17.0 μmol) and *p*-formylphenyl boronic acid (50 mg, 0.30 mmol). The residue was washed with dry THF (3 x 5 mL) and dried *in vacuo*. Product **14** contained approximately 9 immobilized boronic acids per dendrimer. Yield: 0.07 g (13.0 μmol, 79%). $^1$H NMR (400 MHz, $CD_3OD$): δ = 9.91 (s, 9 H, C(O)*H*), 7.81 (d, $^3J_{H\text{-}H}$ = 10.00 Hz, 36 H, Ar*H*), 7.39 (m, 24 H, Ar*H*), 7.16 (m, 24 H, Ar*H*), 4.14 (m, 36 H, NCH$_2$C$H_2$O), 3.31 (br s, 36 H, NC$H_2$CH$_2$O), 2.85 (br s, 24 H, ArC$H_2$),

1.22 (m, 32 H, $CH_2CH_2CH_2$), 0.68 (m, 24 H, $CH_2SiAr$), 0.46 (m, 40 H, $SiCH_2$), 0.10 (s, 72 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ = 193.35 (*C*(O)), 135.89 (Ar*C*), 133.74 (Ar*C*), 132.22 (Ar*C*), 129.99 (Ar*C*), 128.72 (Ar*C*), 62.82 ($NCH_2CH_2O$), 62.67 ($ArCH_2N$), 56.50 ($NCH_2CH_2O$), 20.26, 18.36, 17.89, 17.49, 17.18 (5 x $CH_2$), –3.24 ($SiCH_3$).

**Release of 4-tolyl boronic acid (16)**

To **11** (0.1 g, 19.8 μmol) in THF (5 mL) was added a solution of 5% $H_2O$ in THF (2 mL). The mixture was stirred at room temperature for 1.5 h. The product was separated from the dendrimer by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 400 mL) overnight, yielding cleaved, not pure, **16** in the beaker solution (characteristic odor) and the almost pure recovered **2** in the dialysis bag. In the $^1H$ NMR of the beaker solution only the signals corresponding to **16** are described. Yield was too low to determine.

Bag (**2**): $^1H$ NMR (400 MHz, $CD_3OD$): δ = 7.39 (d, $^3J_{H-H}$ = 7.40 Hz, 24 H, Ar*H*), 7.26 (d, $^3J_{H-H}$ = 7.40 Hz, 24 H, Ar*H*), 3.71 (s, 24 H, $ArCH_2$), 3.58 (t, $^3J_{H-H}$ = 5.40 Hz, 48 H, $NCH_2CH_2OH$), 2.64 (m, 48 H, $NCH_2CH_2OH$), 1.31 (m, 32 H, $CH_2CH_2CH_2$), 0.74 (t, $^3J_{H-H}$ = 8.00 Hz, 24 H, $CH_2SiAr$), 0.53 (t, $^3J_{H-H}$ = 8.00 Hz, 40 H, $SiCH_2$), 0.19 (s, 72 H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ = 139.72 (Ar*C*), 139.66 (Ar*C*), 134.29 (Ar*C*), 129.54 (Ar*C*), 59.33 ($NCH_2CH_2OH$), 58.73 ($ArCH_2N$), 55.91 ($NCH_2CH_2OH$), 21.04, 19.20, 18.58, 18.35, 18.00 (5 x $CH_2$), –2.44 ($SiCH_3$).

Beaker (**16**): $^1H$ NMR (400 MHz, $CD_3OD$): δ = 7.14 (m, 2 H, Ar*H*), 7.03 (m, 2 H, Ar*H*), 2.70 (s, 3 H, $CH_3$), 2.19 (s. 2 H, O*H*).

**Synthesis and release of *p*-((benzylamino)methyl)phenylboronic acid (17)**

To a solution of **14** (0.18 g, 35 μmol) in dry THF (20 mL) was added benzylamine (0.1 mL, 0.84 mmol). The mixture was stirred at room temperature for 2 h. $NaBH_4$ (30 mg, 0.84 mmol) was added and the mixture was stirred overnight, yielding **15** as intermediate (not isolated). The volume was reduced *in vacuo* and the remaining solids were dissolved in THF (20 mL) and $H_2O$ (2 mL). The mixture was stirred for 40 min. and evaporated. The residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 600 mL) overnight. After removal of the solvents *in vacuo*, the residue inside the dialysis bag appeared to be the recovered (not pure) **2**, according to $^1H$ NMR. The residue from the beaker (0.10 g) contained the desired **17** although it was not pure.

Beaker (**17**): $^1H$ NMR (400 MHz, $CD_3OD$): δ = 7.54 (d, $^3J_{H-H}$ = 7.60 Hz, 1 H, Ar*H*), 7.33 (d, $^3J_{H-H}$ = 4.40 Hz, 2 H, Ar*H*), 7.31 (d, $^3J_{H-H}$ = 4.40 Hz, 4 H, Ar*H*), 7.23 (m, 1 H, Ar*H*), 7.15 (d, $^3J_{H-H}$ = 7.60 Hz, 1 H, Ar*H*), 3.75 (s, 2 H, $ArCH_2$), 3.72 (d, $^3J_{H-H}$ = 5.20 Hz, 2 H, $ArCH_2$), 3.66 (s, 1 H, N*H*). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 140.04 (Ar*C*), 136.90 (Ar*C*), 132.24 (Ar*C*), 129.78 (Ar*C*), 129.54 (Ar*C*), 129.43 (Ar*C*), 129.12 (Ar*C*), 128.19 (Ar*C*), 116.47 (Ar*C*), 115.99 (Ar*C*), 65.66 ($ArCH_2$).

Bag (**2**): $^{1}$H NMR (400 MHz, $CD_3OD$): δ = 7.39 (d, $^{3}J_{H\text{-}H}$ = 6.80 Hz, 24 H, Ar*H*), 7.24 (d, $^{3}J_{H\text{-}H}$ = 6.80 Hz, 24 H, Ar*H*), 3.69 (s, 24 H, ArC$H_2$), 3.56 (m, 48 H, $NCH_2CH_2OH$), 2.62 (m, 48 H, $NCH_2CH_2OH$), 1.33 (m, 32 H, $CH_2CH_2CH_2$), 0.74 (m, 24 H, C$H_2$SiAr), 0.54 (m, 40 H, SiC$H_2$), 0.18 (s, 72 H, SiC$H_3$).

**Immobilization/scavenging of 2-pyridyl boronic acid, synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$N($CH_2CH_2O)_2$B($C_5H_4$N-2))$_3$}$_4$ (G1-$CH_2$N($CH_2CH_2O)_2$B-2-pyridyl), 18)**

To a solution of 2-bromopyridine (0.1 mL, 1.01 mmol) and triisopropyl borate (0.28 mL, 1.21 mmol) in dry THF (10 mL) was slowly added *n*-butyllithium (0.76 mL, 1.6M solution in hexanes, 1.21 mmol) at –78 °C. The mixture was stirred and allowed to warm to room temperature over the weekend, yielding an orange suspension. G1-$CH_2$N($CH_2CH_2OH)_2$ **2** (0.16 g, 42 μmol) in 5 mL dry THF was added dropwise to the suspension, which turned white upon addition. The mixture was refluxed for 3 h and cooled to room temperature. The suspension was centrifuged (5 min, 2400 rpm) and decanted twice to purify the product. Product **18** was obtained, estimated in quantitative yield, as a mixture with $^{i}$PrOLi used as stabilizing salt during the synthesis. $^{1}$H NMR (400 MHz, $CD_3OD$): δ = 8.36 (d, $^{3}J_{H\text{-}H}$ = 5.20 Hz, 12 H, Py*H*), 7.61 (t, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 12 H, Py*H*), 7.55 (d, $^{3}J_{H\text{-}H}$ = 7.20 Hz, 12 H, Py*H*), 7.39 (d, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 7.25 (d, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 7.10 (t, $^{3}J_{H\text{-}H}$ = 6.20 Hz, 12 H, Py*H*), 3.93 (sept, $^{3}J_{H\text{-}H}$ = 6.00 Hz, 12 H, LiOC*H*($CH_3)_2$), 3.64 (s, 24 H, ArC$H_2$), 3.56 (t, $^{3}J_{H\text{-}H}$ = 5.40 Hz, 48 H, C$H_2$O), 2.62 (t, $^{3}J_{H\text{-}H}$ = 4.80 Hz, 48 H, C$H_2$N), 1.34 (m, 32 H, $CH_2CH_2CH_2$), 1.14 (d, $^{3}J_{H\text{-}H}$ = 6.00 Hz, 72 H, LiOCH(C$H_3)_2$), 0.76 (t, $^{3}J_{H\text{-}H}$ = 8.20 Hz, 24 H, C$H_2$SiAr), 0.54 (t, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 40 H, SiC$H_2$), 0.18 (s, 72 H, SiC$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CD_3OD$): δ = 146.81 (Py*C*), 139.81 (Ar*C*), 138.88 (Ar*C*), 135.87 (Py*C*), 134.10 (Ar*C*), 129.13 (Ar*C*), 128.38 (Py*C*), 126.86 (Py*C*), 121.44 (Py*C*), 64.27 (LiO*C*H($CH_3)_2$), 60.00 (N*C*$H_2CH_2O$), 59.79 (Ar*C*$H_2$N), 56.41 ($NCH_2$*C*$H_2$O), 25.08 (LiOCH(*C*$H_3)_2$), 21.20, 19.30, 18.65, 18.46, 18.09 (5 x *C*$H_2$), –2.33 (Si*C*$H_3$).

**Synthesis of 2,2'-bipyridine (19, from 18)**

To a solution of **18** (94 mg, 19 μmol) in dry DMF (10 mL) were added 2-bromopyridine (0.03 mL, 0.29 mmol), $PdCl_2(PPh_3)_2$ (81 mg, 11 μmol), $PPh_3$ (61 mg, 0.23 mmol), and CuI (44 mg, 0.23 mmol). The mixture was heated at 80 °C for 30 min and cooled to room temperature again. CsF (0.11 g, 0.69 mmol) in dry DMF (5 mL) was added to the reaction mixture and the mixture was heated at 80 °C for 16 h. After cooling to room temperature, the residue was purified by repeated passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 2 x 700 mL), after which **19** was recovered from the beaker solution together with other pyridine compounds in quantitative yield (due to the slight excess of 2-bromopyridine used). The presence of **19** was confirmed by a test reaction.[56] $^{1}$H NMR (400 MHz, $CD_3OD$): δ = 8.34 (dd, $^{3}J_{H\text{-}H}$ = 4.60 Hz, $^{4}J_{H\text{-}H}$ = 1.80 Hz, 2 H, Ar*H*), 7.67 (m, $^{3}J_{H\text{-}H}$ = 7.80 Hz, $^{4}J_{H\text{-}H}$ =

2.00 Hz, 2 H, Ar*H*), 7.55 (d, $^{3}J_{H\text{-}H}$ = 8.00 Hz, 2 H, Ar*H*), 7.36 (m, $^{3}J_{H\text{-}H}$ = 5.20 Hz, $^{4}J_{H\text{-}H}$ = 1.00 Hz, 2 H Ar*H*).

**Resin-to-resin synthesis of 2,2'-bipyridine (19)**

To a solution of **20** (37.5 mg, 18.4 μmol) and **18** (90 mg, 18.4 μmol) in dry DMF (10 mL) were added $PdCl_2(PPh_3)_3$ (7.7 mg, 11 μmol), $PPh_3$ (5.8 mg, 22 μmol), CuI (4.2 mg, 22 μmol) and CsF (0.10 g, 0.66 mmol). The mixture was heated at 60 °C for 50 h and after cooling to room temperature the product was purified by passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 800 mL) for 48 h. The presence of 2,2'-bipyridine in the beaker solution, not in the bag solution, was confirmed by a test reaction.[56] Product **19** was obtained in a mixture with other pyridine-like compounds. $^{1}$H NMR (400 MHz, $CD_3OD$): δ = 8.67 (d, $^{3}J_{H\text{-}H}$ = 4.40 Hz, 2 H, Ar*H*), 8.38 (dd, $^{3}J_{H\text{-}H}$ = 8.00 Hz, $^{4}J_{H\text{-}H}$ = 0.80 Hz, 2 H, Ar*H*), 7.80 (m, 2 H, Ar*H*), 7.65 (m, 4 H, Ar*H* impurity), 7.53 (m, 2 H, Ar*H* impurity), 7.44 (m, 4 H, Ar*H* impurity), 7.29 (m, 2 H, Ar*H*).

**Resin-to-resin synthesis of $Si\{(CH_2)_3Si((CH_2)_3SiMe_2$(2,2'-bipyridine-5))$_3\}_4$ (G1-bipyridine, 21)**

To a solution of **20** (76 mg, 38 μmol) and **18** (0.22 g, 45 μmol) in dry DMF (10 mL) were added $PdCl_2(PPh_3)_3$ (16 mg, 23 μmol), $PPh_3$ (12 mg, 45 μmol), CuI (8.6 mg, 45 μmol) and $K_2CO_3$ (16 mg, 113 μmol). The mixture was heated at 80 °C overnight and after cooling to room temperature the residue was purified by passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 500 mL) overnight. The presence of (immobilized) 2,2'-bipyridine in the bag solution was confirmed by a test reaction.[56] The product was obtained as a mixture of **21** and **2**, resulting in overlapping signals in the NMR spectra. $^{1}$H NMR (400 MHz, $CD_3OD$): δ = 7.62 (m, 8 H, Ar*H*), 7.51 (m, 6 H, Ar*H*), 7.40 (d, $^{3}J_{H\text{-}H}$ = 7.20 Hz, 20 H, Ar*H*), 7.27 (d, $^{3}J_{H\text{-}H}$ = 7.20 Hz, 20 H, Ar*H*), 3.65 (s, 18 H, Ar$CH_2$), 3.57 (m, 36 H, $NCH_2CH_2OH$), 2.70 (m, 36 H, $NCH_2CH_2OH$), 1.34 (m, 78 H, $CH_2CH_2CH_2$), 0.77 (t, $^{3}J_{H\text{-}H}$ = 6.80 Hz, 42 H, $CH_2SiAr$), 0.56 (m, 111 H, $SiCH_2$), 0.19 (s, 72 H, $SiCH_3$). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 140.96 (Ar*C*), 139.03 (Ar*C*), 134.64 (Ar*C*), 130.99 (Ar*C*), 129.83 (Ar*C*), 129.34 (Ar*C*), 60.74 ($NCH_2CH_2OH$), 60.60 ($ArCH_2N$), 57.31 ($NCH_2CH_2OH$), 21.76, 19.96, 19.07, 19.69, 18.61 (5 x $CH_2$), –2.16 ($SiCH_3$).

**Release of 2,2'-bipyridine (19, from 21)**

To a solution of **21** (0.16 g, 59 μmol) in dry THF (5 mL) was added $^{n}Bu_4NF$ (1.0 M in THF, 1.0 mL, 1.0 mmol). The mixture was stirred at room temperature over the weekend. Water was added and the product was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated to dryness. After filtration over a short plug of silica **19** was obtained, together with some pyridine-like impurities (according to NMR). The formation of **19** was confirmed by a test reaction.[56] Yield: 0.04 g (0.26 mmol, 36%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.67 (br s, 2 H, Ar*H*), 8.38 (d, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 2 H, Ar*H*), 7.81 (m, $^{3}J_{H\text{-}H}$ = 7.80 Hz, $^{4}J_{H\text{-}H}$ = 1.60 Hz, 2 H, Ar*H*), 7.65

(m, 0.30 H, Ar*H* impurity), 7.52 (m, 0.15 H, Ar*H* impurity), 7.45 (m, 0.30 H, Ar*H* impurity), 7.30 (t, $^{3}J_{H\text{-}H}$ = 5.60 Hz, 2 H, Ar*H*).

**Synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$OC(O)$CH_2CH_2$(N($CH_2CH_2)_2$CH)$NH_2)_3$}$_4$ (G1-$CH_2$OC(O)$CH_2CH_2$(N($CH_2CH_2)_2$CH)$NH_2$, 23)**

To a solution of **3** (0.49 g, 0.14 mmol) in dry $CH_2Cl_2$ (10 mL) was added 4-*N*-Boc-aminopiperidine (0.68 g, 3.40 mmol). The mixture was stirred at room temperature for 6 h and the solvent was removed *in vacuo*. The residue was purified by passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 500 mL) overnight, yielding the intermediate product **22** as an orange colored oil. Yield: 0.42 g (72 μmol, 51%).

$^{1}$H NMR (400 MHz, $CD_3OD$): δ = 7.43 (d, $^{3}J_{H\text{-}H}$ = 8.00 Hz, 24 H, Ar*H*), 7.28 (d, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 5.05 (s, 24 H, ArC$H_2$), 3.53 (m, 12 H, C*H*), 3.22 (t, $^{3}J_{H\text{-}H}$ = 3.40 Hz, 24 H, C$H_2$), 3.18 (t, $^{3}J_{H\text{-}H}$ = 3.60 Hz, 24 H, C$H_2$), 2.65 (t, $^{3}J_{H\text{-}H}$ = 6.80 Hz, 24 H, C$H_2$N), 2.51 (t, $^{3}J_{H\text{-}H}$ = 7.20 Hz, 24 H, C(O)C$H_2$), 2.05 (t, $^{3}J_{H\text{-}H}$ = 10.20 Hz, 24 H, C$H_2$), 1.80 (m, 24 H, C$H_2$), 1.43 (s, 108 H, C(C$H_3$)$_3$), 1.22 (m, 32 H, $CH_2$C$H_2$$CH_2$), 0.76 (t, $^{3}J_{H\text{-}H}$ = 8.00 Hz, 24 H, C$H_2$SiAr), 0.52 (t, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$).

TFA (1.9 mL, 25.3 mmol) was added to a solution of **22** (0.42 g, 0.07 mmol) in dry $CH_2Cl_2$ (5 mL). The mixture was stirred for 1.5 h and subsequently evaporated to dryness. The residue was washed with a concentrated $NaHCO_3$ (aq.) solution (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated to dryness, **23** as an orange colored oil (0.01 g). To improve the yield the aqueous layer was diluted with methanol and extracted with $CH_2Cl_2$ (3 x 20 mL) and EtOAc (3 x 20 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated to dryness. **23** contained on average 9-10 substituted-REM end groupings and 2-3 other benzyl groupings per dendrimer, according to $^{1}$H NMR. Total yield 0.19 g (41 μmol, 57%).

$^{1}$H NMR (400 MHz, $CD_3OD$): δ = 7.40 (d, $^{3}J_{H\text{-}H}$ = 6.40 Hz, 24 H, Ar*H*), 7.27 (d, $^{3}J_{H\text{-}H}$ = 6.40 Hz, 24 H, Ar*H*), 5.05 (s, 18 H, ArC$H_2$), 4.56 (s, 6 H, ArC$H_2$), 2.91 (br s, 20 H, C$H_2$), 2.89 (br s, 10 H, C*H*), 2.68 (m, 20 H, C$H_2$N), 2.52 (m, 20 H, C(O)C$H_2$), 2.05 (m, 20 H, C$H_2$), 1.91 (m, 20 H, C$H_2$), 1.55 (m, 20 H, C$H_2$), 1.33 (m, 32 H, $CH_2$C$H_2$$CH_2$), 0.76 (m, 24 H, C$H_2$SiAr), 0.54 (m, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CD_3OD$): δ = 173.41 (*C*(O)), 143.03 (Ar*C*, benzyl), 142.11 (Ar*C*, benzyl), 140.61 (Ar*C*), 137.64 (Ar*C*), 134.69 (Ar*C*), 134.51 (Ar*C*, benzyl), 128.43 (Ar*C*), 127.31 (Ar*C*, benzyl), 119.30 (Ar*C*, benzyl), 116.41 (Ar*C*, benzyl), 67.23 (Ar*C*$H_2$), 65.06 (Ar*C*$H_2$), 54.02 (*C*$H_2$N), 52.42 (N(*C*$H_2CH_2)_2$CH), 48.36 (N($CH_2CH_2)_2$*C*H, overlapping with solvent signal), 32.88 (N($CH_2$*C*$H_2)_2$CH), 31.81 (C(O)*C*$H_2$), 21.51, 19.93, 19.73, 18.86, 18.45 (5 x *C*$H_2$), –2.25 (Si*C*$H_3$).

**Synthesis of $Si\{(CH_2)_3Si((CH_2)_3SiMe_2(C_6H_4$-4)$CH_2OC(O)CH_2CH_2(N(CH_2CH_2)_2CH)NHC(O)CH_3)_3\}_4$ (G1-$CH_2OC(O)CH_2CH_2(N(CH_2CH_2)_2CH)NHC(O)Me$, 24)**

Pyridine (0.40 mL, 4.65 mmol) and acetic anhydride (0.44 mL, 4.65 mmol) were added to a solution of **23** (0.09 g, 19.3 μmol) in dry $CH_2Cl_2$ (10 mL). The mixture was stirred at room temperature for 2 h. Water (10 mL) and $NaHCO_3$ (aq.) (10 mL) were added and the $CH_2Cl_2$ layer was separated. The product was extracted from the aqeous layer with EtOAc (2 x 20 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated to dryness, yielding **24** as a pale orange colored oil, containing on average 8 substituted-REM and 4 other benzyl end groupings per dendrimer, according to $^1$H NMR. Yield: 33 mg (6.4 μmol, 33%). $^1$H NMR (400 MHz, $CD_3OD$): δ = 7.43 (d, $^3J_{H\text{-}H}$ = 7.20 Hz, 24 H, Ar*H*), 7.28 (d, $^3J_{H\text{-}H}$ = 6.80 Hz, 24 H, Ar*H*), 5.06 (s, 16 H, ArC$H_2$), 4.56 (s, 8 H, ArC$H_2$), 3.63 (m, 8 H, C*H*), 2.86 (m, 16 H, C$H_2$), 2.70 (t, $^3J_{H\text{-}H}$ = 6.40 Hz, 16 H, C$H_2$N), 2.54 (t, $^3J_{H\text{-}H}$ = 6.20 Hz, 16 H, C(O)C$H_2$), 2.14 (t, $^3J_{H\text{-}H}$ = 10.60 Hz, 16 H, C$H_2$), 1.91 (s, 24 H, C$H_3$), 1.82 (d, $^3J_{H\text{-}H}$ = 11.60 Hz, 16 H, C$H_2$), 1.46 (m, 16 H, C$H_2$), 1.33 (m, 32 H, $CH_2CH_2CH_2$), 0.76 (m, 24 H, C$H_2$SiAr), 0.52 (m, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ = 173.34 (*C*(O)), 172.54 (*C*(O)), 140.64 (Ar*C*), 138.05 (Ar*C*), 134.85 (Ar*C*), 134.67 (Ar*C*, benzyl), 128.69 (Ar*C*), 127.48 (Ar*C*, benzyl), 67.32 (Ar*C*$H_2$), 65.18 (Ar*C*$H_2$), 54.46 (*C*$H_2$N), 53.22 (N(*C*$H_2CH_2)_2$CH), 47.61 (N$(CH_2CH_2)_2$*C*H), 32.72 (N$(CH_2$*C*$H_2)_2$CH), 32.21 (C(O)*C*$H_2$), 22.70 (*C*(O)$CH_3$), 21.65, 20.15, 19.94, 19.07, 18.61 (5 x *C*$H_2$), –2.23 (Si*C*$H_3$).

**Release of 1-methyl-*N*-acetylaminopiperidine (25)**

Iodomethane (0.50 mL, 8.03 mmol) was added to a solution of **24** (33 mg, 6.4 μmol) in dry $CH_2Cl_2$ (10 mL). The mixture was stirred at room temperature for 24 h and the volatiles were removed *in vacuo*. Fresh dry $CH_2Cl_2$ (10 mL) was added to the residue together with diisopropyl ethylamine (DIEA, 0.13 mL, 0.79 mmol) and the mixture was stirred overnight at room temperature. The crude product was purified by passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 500 mL) overnight, yielding **25** as a mixture together with DIEA (~1:6 according to $^1$H NMR) and some indefinable impurities in the beaker solution, which was evaporated to dryness. Combined yield: 10 mg (**25** and 6 eq. DIEA, 0.011 mmol, ~2.3%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 3.97 (m, $^3J_{H\text{-}H}$ = 6.60 Hz, 1 H, C*H*), 3.54 (d, $^3J_{H\text{-}H}$ = 13.00 Hz, 2 H, C$H_2$), 3.41 (m, 2 H, C$H_2$), 2.86 (s, 3 H, C$H_3$), 2.13 (d, $^3J_{H\text{-}H}$ = 13.00 Hz, 2 H C$H_2$), 1.94 (s, 3 H, C$H_3$), 1.78 (d, $^3J_{H\text{-}H}$ = 13.00 Hz, 2 H, C$H_2$), signals corresponding to DIEA are not reported. $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ = 129.34 (*C*(O)), 54.72 (N(*C*$H_2CH_2)_2$CH), 45.35 (N$(CH_2CH_2)_2$*C*H), 43.84 (N*C*$H_3$), 30.30 (N$(CH_2$*C*$H_2)_2$CH), 22.61 (C(O)*C*$H_3$), signals corresponding to DIEA are not reported. GC-MS: *m/z* 156 ($M^+$).

The bag-solution, which was evaporated to dryness after dialysis, contained recovered **3**, although not completely unloaded. On average 5 unloaded REM end groupings were present per dendrimer,

according to the $^{1}$H NMR spectrum. $^{1}$H NMR (400 MHz, $CD_3OD$): δ = $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, $^{3}J_{H\text{-}H}$ = 7.20 Hz, 24 H, Ar*H*), 7.27 (d, $^{3}J_{H\text{-}H}$ = 6.80 Hz, 24 H, Ar*H*), 6.38 (d, $^{3}J_{H\text{-}H}$ = 17.20 Hz, 5 H, CH=C$H_2$), 6.10 (m, $^{3}J_{H\text{-}H}$ = 10.40 Hz, $^{3}J_{H\text{-}H}$ = 6.80 Hz, 5 H, C*H*=$CH_2$), 5.79 (d, $^{3}J_{H\text{-}H}$ = 10.40 Hz, 5 H, CH=C$H_2$), 5.11 (s, 10 H, C$H_2$), 5.07 (s, 2 H, C$H_2$), 5.01 (s, 2 H, C$H_2$), 5.07 (s, 10 H, C$H_2$), 3.90-1.94 (multiple undesigned signals), 1.31 (m, 32 H, $CH_2CH_2CH_2$), 0.75 (m, 24 H, C$H_2$SiAr), 0.52 (m, 40 H, SiC$H_2$), 0.17 (s, 72 H, SiC$H_3$).

**Synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$OC(O)$CH_2CH_2$(N($CH_2CH_2)_2$NH))$_3$}$_4$ (G1-$CH_2$OC(O)$CH_2CH_2$(N($CH_2CH_2)_2$NH), 26)**

A solution of **3** (0.47 g, 0.14 mmol) in dry $CH_2Cl_2$ (5 mL) was added to a solution of piperazine (2.8 g, 32.4 mmol) in dry $CH_2Cl_2$ (20 mL). The mixture was stirred at room temperature overnight and the solvent was removed *in vacuo*. The residue was purified by repeated passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 2 x 500 mL) for 3 h and for 2.5 h, yielding **26** together with traces of free piperazine as an orange oil. Yield: 0.72 g (0.16 mmol, 100%). $^{1}$H NMR (400 MHz, $CD_3OD$): δ = 7.43 (d, $^{3}J_{H\text{-}H}$ = 7.20 Hz, 24 H, Ar*H*), 7.28 (d, $^{3}J_{H\text{-}H}$ = 7.20 Hz, 24 H, Ar*H*), 5.06 (s, 24 H, ArC$H_2$), 2.88 (m, 48 H, N($CH_2$C$H_2)_2$NH), 2.78 (m, 48 H, N(C$H_2CH_2)_2$NH), 2.55 (m, 24 H, C$H_2$N), 2.48 (m, 24 H, C(O)C$H_2$), 1.18 (m, 32 H, $CH_2$C$H_2CH_2$), 0.76 (m, 24 H, C$H_2$SiAr), 0.51 (m, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CD_3OD$): δ = 174.25 (*C*(O)), 143.29 (Ar*C*), 139.17 (Ar*C*), 134.64 (Ar*C*), 127.46 (Ar*C*), 65.15 (Ar*C*$H_2$), 54.35, 54.28, 53.42, 52.19, 50.99, 47.64, 45.04, 44.90, 44.34 (*C*$H_2$N, 4 x N(*C*$H_2)_2$N and 4 x free HN(*C*$H_2)_2$NH) , 32.67 (C(O)*C*$H_2$), 21.72, 20.12, 19.91, 18.97, 18.57 (5 x *C*$H_2$), –2.26 (Si*C*$H_3$).

**Synthesis of Si{$(CH_2)_3$Si($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$OC(O)$CH_2CH_2$(N($CH_2CH_2)_2$NC(O)$CH_3$))$_3$}$_4$ (G1-$CH_2$OC(O)$CH_2CH_2$(N($CH_2CH_2)_2$NC(O)Me), 27)**

Pyridine (3.1 mL, 38.58 mmol) and acetic anhydride (3.6 mL, 38.58 mmol) were added to a solution of **26** (0.72 g, 0.16 mmol) in dry $CH_2Cl_2$ (20 mL). The mixture was stirred at room temperature for 4 h, water (10 mL) and $NaHCO_3$ (aq.) (10 mL) were added and the $CH_2Cl_2$ layer was separated. The organic layer was evaporated to dryness. The residue was purified by passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 600 mL) overnight, yielding **27** as an orange oil. Yield: 0.25 g (0.05 mmol, 31%). $^{1}$H NMR (400 MHz, $CD_3OD$): δ = 7.43 (d, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 7.29 (d, $^{3}J_{H\text{-}H}$ = 8.00 Hz, 24 H, Ar*H*), 5.07 (s, 24 H, ArC$H_2$), 3.48 (t, $^{3}J_{H\text{-}H}$ = 5.00 Hz, 24 H, N($CH_2$C$H_2)_2$NC(O)Me), 3.43 (t, $^{3}J_{H\text{-}H}$ = 5.00 Hz, 24 H, N($CH_2$C$H_2)_2$NC(O)Me), 2.67 (t, $^{3}J_{H\text{-}H}$ = 6.00 Hz, 24 H, C$H_2$N), 2.53 (t, $^{3}J_{H\text{-}H}$ = 6.80 Hz, 24 H, C(O)C$H_2$), 2.43 (t, $^{3}J_{H\text{-}H}$ = 4.60 Hz, 24 H, N(C$H_2CH_2)_2$NC(O)Me), 2.36 (t, $^{3}J_{H\text{-}H}$ = 5.00 Hz, 24 H, N(C$H_2CH_2)_2$NC(O)Me), 2.05 (s, 36 H, C$H_3$), 1.17 (m, 32 H, $CH_2$C$H_2CH_2$), 0.76 (t, $^{3}J_{H\text{-}H}$ = 7.80 Hz, 24 H, C$H_2$SiAr), 0.51 (t, $^{3}J_{H\text{-}H}$ = 7.60 Hz, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CD_3OD$): δ = 173.48 (*C*(O), 2 x overlapping), 140.64 (Ar*C*), 138.22 (Ar*C*), 134.85 (Ar*C*),

128.76 (Ar*C*), 67.20 (Ar*C*$H_2$), 54.45, 54.00, 53.53, 47.18, 42.42 (*C*$H_2$N and 4 x N(*C*$H_2$)$_2$N), 33.03 (C(O)*C*$H_2$), 21.65, 21.19, 19.94, 19.19, 18.60 (5 x *C*$H_2$), –2.21 (Si*C*$H_3$).

**Release of 1-methyl-4-acetylpiperazine (28)**

Iodomethane (0.35 mL, 5.62 mmol) was added to a solution of **27** (92 mg, 18.5 μmol) in dry $CH_2Cl_2$ (10 mL). The mixture was stirred at room temperature for 24 h and the volatiles were removed *in vacuo*. Fresh dry $CH_2Cl_2$ (10 mL) was added to the residue together with diisopropyl ethylamine (DIEA, 0.2 mL, 1.11 mmol) and the mixture was stirred overnight at room temperature. The crude product was purified by repeated passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 2 x 600 mL) overnight, yielding **28** as a mixture together with DIEA (~1:1 according to $^1$H NMR) and some minor impurities in the beaker solution, which was evaporated to dryness. Combined yield: 10 mg (**28** and DIEA, 0.037 mmol, ~8.7%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 4.02 (m, 2 H, N(C*H*$_2$)$_2$NH), 3.92 (br s, 2 H, N(C*H*$_2$)$_2$NH), 3.72 (br s, 2 H, N(C*H*$_2$)$_2$NH), 3.27 (br s, 2 H, N(C*H*$_2$)$_2$NH), 3.16 (m, 4 H, C*H* and C*H*$_2$, DIEA), 2.83 (s, 3 H, C*H*$_3$N), 2.13 (s, 3 H, C(O)C*H*$_3$), 1.54 (m, 15 H, C*H*$_3$, DIEA). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 169.27 (*C*(O)), 54.71 (*C*H, DIEA), 53.90 (N(*C*H$_2$)$_2$N), 53.66 (N(*C*H$_2$)$_2$N), 44.19 (N(*C*H$_2$)$_2$N), 43.62 (N(*C*H$_2$)$_2$N), 42.96 (*C*H$_3$N), 38.77 (*C*H$_2$, DIEA), 21.59 (C(O)*C*H$_3$), 18.41 (*C*H$_3$, DIEA), 12.48 (*C*H$_3$, DIEA). GC-MS: *m/z* 141 ($M^+$).

The bag-solution, which was evaporated to dryness after dialysis, contained recovered **3**, although not completely unloaded. On average 9 unloaded REM end groupings were present per dendrimer, according to the $^1$H NMR spectrum. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, $^3J_{H\text{-}H}$ = 8.00 Hz, 24 H, Ar*H*), 7.29 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 6.41 (dd, $^3J_{H\text{-}H}$ = 17.20 Hz, $^2J_{H\text{-}H}$ = 1.20 Hz, 9 H, CH=C*H*$_2$), 6.11 (m, $^3J_{H\text{-}H}$ = 10.40 Hz, $^3J_{H\text{-}H}$ = 6.80 Hz, 9 H, C*H*=CH$_2$), 5.79 (dd, $^3J_{H\text{-}H}$ = 10.40 Hz, $^2J_{H\text{-}H}$ = 1.20 Hz, 9 H, CH=C*H*$_2$), 5.13 (s, 18 H, C*H*$_2$), 5.05 (m, 6 H, C*H*$_2$), 3.55 (t, $^3J_{H\text{-}H}$ = 4.80 Hz, 6 H, N(CH$_2$C*H*$_2$)$_2$NC(O)Me), 3.38 (t, $^3J_{H\text{-}H}$ = 4.80 Hz, 6 H, N(CH$_2$C*H*$_2$)$_2$NC(O)Me), 2.69 (t, $^3J_{H\text{-}H}$ = 7.20 Hz, 6 H, C*H*$_2$N), 2.51 (t, $^3J_{H\text{-}H}$ = 7.20 Hz, 6 H, C(O)C*H*$_2$), 2.40 (m, 12 H, N(C*H*$_2$CH$_2$)$_2$NC(O)Me), 2.04 (s, 9 H, C*H*$_3$), 1.13 (m, 32 H, CH$_2$C*H*$_2$CH$_2$), 0.75 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 24 H, C*H*$_2$SiAr), 0.52 (t, $^3J_{H\text{-}H}$ = 8.00 Hz, 40 H, SiC*H*$_2$), 0.18 (s, 72 H, SiC*H*$_3$).

**Synthesis of Si{(CH$_2$)$_3$Si((CH$_2$)$_3$SiMe$_2$(C$_6$H$_4$-4)CH$_2$(N(CH$_2$CH$_2$)$_2$CH)NH$_2$)$_3$}$_4$ (G1-CH$_2$(N(CH$_2$CH$_2$)$_2$CH)NH$_2$, 30)**

To a solution of **1** (0.42 g, 0.12 mmol) in dry $CH_2Cl_2$ (10 mL) was added 4-*N*-Boc-aminopiperidine (0.57 g, 2.84 mmol). The mixture was stirred for 6 h at room temperature and the solvent was removed *in vacuo*. The residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 600 mL) overnight, yielding the intermediate product **29** as a colorless oil. Yield: 0.60 g (0.12 mmol, 100%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 7.29 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar*H*), 4.63 (br s, 12 H, C*H*), 3.54 (br s, 24 H, ArC*H*$_2$), 2.89 (br s, 24 H, C*H*$_2$), 2.15 (br s, 24 H, C*H*$_2$),

1.89 (br s, 24 H, C$H_2$), 1.54 (br s, 24 H, C$H_2$), 1.43 (s, 108 H, C(C$H_3$)$_3$), 1.32 (m, $^3J_{H\text{-}H}$ = 5.20 Hz, 32 H, $CH_2CH_2CH_2$), 0.75 (t, $^3J_{H\text{-}H}$ = 7.80 Hz, 24 H, C$H_2$SiAr), 0.53 (m, 40 H, SiC$H_2$), 0.18 (s, 72 H, SiC$H_3$).

TFA (1.9 mL, 25.3 mmol) was added to a solution of **29** (0.35 g, 0.07 mmol) in dry $CH_2Cl_2$ (5 mL). The mixture was stirred for 1.5 h at room temperature and subsequently evaporated to dryness. The residue was washed with a concentrated $NaHCO_3$ (aq.) solution (20 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated to dryness, yielding **30** as a colorless oil (0.01 g). To improve the yield the aqueous layer was diluted with methanol and extracted with $CH_2Cl_2$ (3 x 20 mL) and EtOAc (3 x 20 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated to dryness. Total yield: 0.20 g (0.05 mmol, 75%). $^1$H NMR (400 MHz, $CD_3OD$): δ = 7.40 (d, $^3J_{H\text{-}H}$ = 7.20 Hz, 24 H, Ar$H$), 7.25 (d, $^3J_{H\text{-}H}$ = 7.20 Hz, 24 H, Ar$H$), 3.45 (br s, 24 H, ArC$H_2$), 3.00 (br s, 12 H, C$H$), 2.88 (d, $^3J_{H\text{-}H}$ = 10.60 Hz, 24 H, C$H_2$), 2.07 (t, $^3J_{H\text{-}H}$ = 11.60 Hz, 24 H, C$H_2$), 1.91 (d, $^3J_{H\text{-}H}$ = 10.80 Hz, 24 H, C$H_2$), 1.58 (q, $^3J_{H\text{-}H}$ = 11.20 Hz, 24 H, C$H_2$), 1.33 (m, 32 H, $CH_2CH_2CH_2$), 0.76 (t, $^3J_{H\text{-}H}$ = 7.80 Hz, 24 H, C$H_2$SiAr), 0.52 (m, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CD_3OD$): δ = 139.48 (Ar$C$), 139.24 (Ar$C$), 134.66 (Ar$C$), 130.01 (Ar$C$), 63.65 (Ar$C$H$_2$), 52.66 (N($C$H$_2$CH$_2$)$_2$CH), 48.37 (N(CH$_2$CH$_2$)$_2$$C$H), 31.90 (N(CH$_2$$C$H$_2$)$_2$CH), 21.67, 20.14, 19.92, 19.02, 18.56 (5 x $C$H$_2$), –2.21 (Si$C$H$_3$).

**Synthesis of Si{(CH$_2$)$_3$Si((CH$_2$)$_3$SiMe$_2$(C$_6$H$_4$-4)CH$_2$(N(CH$_2$CH$_2$)$_2$CH)NHC(O)CH$_3$)$_3$}$_4$ (G1-CH$_2$(N(CH$_2$CH$_2$)$_2$CH)NHC(O)Me, 31)**

Pyridine (0.53 mL, 6.53 mmol) and acetic anhydride (0.6 mL, 6.53 mmol) were added to a solution of **30** (0.10 g, 27.0 μmol) in dry $CH_2Cl_2$ (10 mL). The mixture was stirred at room temperature for 2 h. Water (10 mL) and $NaHCO_3$ (aq.) (10 mL) were added and the $CH_2Cl_2$ layer was separated. The product was extracted from the aqueous layer with EtOAc (2 x 20 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated to dryness, yielding **31** as a colorless oil. Yield: 26 mg (6.06 μmol, 22%). $^1$H NMR (400 MHz, $CD_3OD$): δ = 7.43 (d, $^3J_{H\text{-}H}$ = 7.60 Hz, 24 H, Ar$H$), 7.30 (d, $^3J_{H\text{-}H}$ = 7.20 Hz, 24 H, Ar$H$), 3.65 (m, $^3J_{H\text{-}H}$ = 10.60 Hz, 12 H, C$H$), 3.56 (br s, 24 H, ArC$H_2$), 2.90 (d, $^3J_{H\text{-}H}$ = 10.80 Hz, 24 H, C$H_2$), 2.20 (t, $^3J_{H\text{-}H}$ = 10.20 Hz, 24 H, C$H_2$), 1.91 (s, 36 H, C$H_3$), 1.82 (d, $^3J_{H\text{-}H}$ = 11.60 Hz, 24 H, C$H_2$), 1.53 (q, $^3J_{H\text{-}H}$ = 11.60 Hz, 24 H, C$H_2$), 1.33 (m, 32 H, $CH_2CH_2CH_2$), 0.76 (t, $^3J_{H\text{-}H}$ = 7.80 Hz, 24 H, C$H_2$SiAr), 0.51 (t, $^3$J$_{H\text{-}H}$ = 7.80 Hz, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CD_3OD$): δ = 172.56 (($C$(O)), 139.98 (Ar$C$), 138.12 (Ar$C$), 134.78 (Ar$C$), 130.41 (Ar$C$), 63.71 (Ar$C$H$_2$), 53.29 (N($C$H$_2$CH$_2$)$_2$CH), 47.60 (N(CH$_2$CH$_2$)$_2$$C$H), 32.05 (N(CH$_2$$C$H$_2$)$_2$CH), 22.70 (C(O)$C$H$_3$), 21.70, 19.95, 19.07, 18.59 (5 x $C$H$_2$ overlapping), –2.20 (Si$C$H$_3$).

**Release of *N*-acetylaminopiperidine·HCl (32)**

ACE-Cl (0.20 mL, 1.85 mmol) was added to a solution of **31** (11 mg, 2.57 μmol) in dry $CH_2Cl_2$ (10 mL) and the mixture was stirred for 3 h at room temperature. The solvent was removed *in vacuo*. Methanol (10 mL) was added to the residue and the mixture was refluxed overnight. After cooling to room temperature and removal of the solvent *in vacuo*, the residue was purified by passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 500 mL) for 5 h, yielding **32** as its HCl-salt and some undefined side-products (according to $^{13}C$ NMR) in the beaker solution, which was evaporated to dryness. Combined yield: 0.04 g (from $^1H$ NMR estimated to be quantitative). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 4.27 (br s, 4 H, N*H*.*H*Cl) 3.37 (t, $^3J_{H-H}$ = 7.00 Hz, 2 H, C$H_2$), 3.31 (br s, 1 H, C*H*), 2.78 (s, 3 H, C$H_3$), 2.49 (br s, 1 H, N*H*), 2.35 (t, $^3J_{H-H}$ = 8.00 Hz, 1 H, C$H_2$), 2.00 (t, $^3J_{H-H}$ = 7.40 Hz, 2 H, C$H_2$), 1.66 (br s, 1 H, C$H_2$), 1.58 (br s, 1 H, N*H*), 1.33 (br s, 1 H, C$H_2$), 1.18 (br s, 1 H, C$H_2$). $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ = 128.50 (*C*(O)), 50.28 (N($CH_2CH_2$)$_2$*C*H), 40.35 (N(*C*$H_2CH_2$)$_2$CH), 34.01 (N($CH_2$*C*$H_2$)$_2$CH), 30.95, 29.95, 29.86, 28.03, 27.09, 26.71, 25.13 (7 x side product), 17.72 (C(O)*C*$H_3$). GC-MS: *m/z* 100 ($M^+$–C(O)Me – 2x HCl).

**Synthesis of Si{$(CH_2)_3$Si(($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$(N($CH_2CH_2$)$_2$NH))$_3$}$_4$ (G1-$CH_2$(N($CH_2CH_2$)$_2$NH), 33)**

A solution of **1** (0.29 g, 0.08 mmol) in dry $CH_2Cl_2$ (7 mL) was slowly added to a solution of piperazine (1.69 g, 19.60 mmol) in dry $CH_2Cl_2$ (5 mL). The resulting mixture was stirred for 5 h at room temperature. The solvent was removed *in vacuo* and the residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 500 mL) overnight, yielding **33** as a colorless oil, containing 9-10 piperazine end groupings per dendrimer. Yield: 0.35 g (0.09 mmol, 100%). $^1H$ NMR (400 MHz, $CD_3OD$): δ = 7.40 (d, $^3J_{H-H}$ = 7.20 Hz, 20 H, Ar*H*), 7.25 (d, $^3J_{H-H}$ = 7.60 Hz, 20 H, Ar*H*), 3.48 (br s, 20 H, ArC$H_2$), 2.83 (br s, 40 H, N($CH_2$C$H_2$)$_2$NH), 2.43 (br s, 40 H, N(C$H_2CH_2$)$_2$NH), 1.33 (m, $^3J_{H-H}$ = 5.20 Hz, 32 H, $CH_2$C$H_2$C$H_2$), 0.77 (t, $^3J_{H-H}$ = 7.80 Hz, 24 H, C$H_2$SiAr), 0.54 (t, $^3J_{H-H}$ = 7.60 Hz, 40 H, SiC$H_2$), 0.19 (s, 72 H, SiC$H_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ = 139.69 (Ar*C*), 134.45 (Ar*C*), 129.37 (Ar*C*), 128.94 (Ar*C*), 63.16 (Ar*C*$H_2$), 53.41 (N(*C*$H_2$)$_2$N), 50.40 (N(*C*$H_2$)$_2$N), 47.07 (N(*C*$H_2$)$_2$N), 44.47 (N(*C*$H_2$)$_2$N), 21.32, 19.48, 18.67, 18.60, 18.24 (5 x *C*$H_2$), –2.25 (Si*C*$H_3$). MALDI-TOF-MS: *m/z*: 3611.25 [G1-$CH_2$(N($CH_2CH_2$)$_2$NH)]$^+$ (Calcd. 3611.41).

**Synthesis of Si{$(CH_2)_3$Si(($(CH_2)_3$SiMe$_2$($C_6H_4$-4)$CH_2$(N($CH_2CH_2$)$_2$N)C(O)$CH_3$)$_3$}$_4$ (G1-$CH_2$(N($CH_2CH_2$)$_2$N)C(O)Me, 34)**

Acetic anhydride (0.6 mL, 6.64 mmol) was added to a solution of **33** (0.10 g, 27.7 μmol) in dry $CH_2Cl_2$ (10 mL). The mixture was stirred at room temperature for 4 h and the solvent was removed *in vacuo*. Water and $NaHCO_3$ (aq.) were added to the residue and the product was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated to dryness,

yielding **34** as a colorless oil, containing 9 modified piperazine groups per dendrimer. Yield: 0.07 g (17.0 μmol, 61%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, $^{3}J_{H\text{-}H}$ = 6.80 Hz, 18 H, Ar*H*), 7.26 (d, $^{3}J_{H\text{-}H}$ = 6.80 Hz, 18 H, Ar*H*), 3.58 (br s, 18 H, ArC$H_2$), 3.46 (br s, 18 H, N($CH_2CH_2$)$_2$NH), 3.41 (br s, 18 H, N($CH_2CH_2$)$_2$NH), 2.39 (br s, 36 H, N($CH_2CH_2$)$_2$NH), 2.05 (s, 27 H, C$H_3$), 1.33 (m, 32 H, $CH_2CH_2CH_2$), 0.77 (t, $^{3}J_{H\text{-}H}$ = 8.00 Hz, 24 H, C$H_2$SiAr), 0.54 (t, $^{3}J_{H\text{-}H}$ = 8.00 Hz, 40 H, SiC$H_2$), 0.20 (s, 72 H, SiC$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$): δ =168.94 (*C*(O)), 138.57 (Ar*C*), 138.33 (Ar*C*), 133.61 (Ar*C*), 128.55 (Ar*C*), 62.91 (Ar$CH_2$), 53.28 (N($CH_2$)$_2$N), 52.75 (N($CH_2$)$_2$N), 46.36 (N($CH_2$)$_2$N), 41.48 (N($CH_2$)$_2$N), 22.25 (1 x $CH_2$), 21.41 (C(O)$CH_3$), 20.71, 18.72, 17.53 (4 x $CH_2$, overlapping), –2.63 (Si$CH_3$). MALDI-TOF-MS: *m/z*: 4142.58 [G1-$CH_2$(N($CH_2CH_2$)$_2$NH) + Na]$^{+}$ (Calcd. 4141.99).

**Release of 1-acetylpiperazine·HCl (35)**

ACE-Cl (α-chloroethyl chloroformate, 0.22 mL, 2.04 mmol) was added to a solution of **34** (70 mg, 17.0 μmol) in dry $CH_2Cl_2$ (10 mL). The mixture was stirred at room temperature for 3 h and all volatiles were removed *in vacuo*. Methanol (10 mL) was added to the residue and the resulting solution was refluxed overnight. The product was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 500 mL) for 5 h, yielding **35** as its HCl-salt in the beaker solution, which was evaporated to dryness. Yield: 0.03 g (0.182 mmol, 89%). $^{1}$H NMR (400 MHz, $CD_3OD$): δ = 4.53 (br s, 2 H, N*H*.*H*Cl) 3.84 (br s, 2 H, N(C$H_2$)$_2$NH), 3.81 (br s, 2 H, N(C$H_2$)$_2$NH), 3.23 (br s, 2 H, N(C$H_2$)$_2$NH), 3.16 (br s, 2 H, N(C$H_2$)$_2$NH), 2.13 (s, C$H_3$). $^{13}$C{$^{1}$H} NMR (100 MHz, $CD_3OD$): δ = 171.16 (*C*(O)), 43.91 (N($CH_2$)$_2$NH), 43.72 (N($CH_2$)$_2$NH), 43.49 (N($CH_2$)$_2$NH), 38.56 (N($CH_2$)$_2$NH), 21.08 (C(O)$CH_3$). GC-MS: *m/z* 128 ($M^{+}$–HCl).

**Library synthesis**

**General procedure**

To a solution of **33** (0.30 g, 83 μmol) in dry $CH_2Cl_2$ (20 mL) were added pyridine (2.4 mL, 29.67 mmol) and the appropriate acylating agent (16 mmol). The mixture was stirred at room temperature for 3 h and subsequently poured into an aqueous solution of $NaHCO_3$ (1 M in water). The product was extracted with $CH_2Cl_2$ (2 x 20 mL). The combined organic layers were dried on $Na_2SO_4$, filtered and evaporated to dryness. The residue was further purified by passive dialysis using $CH_2Cl_2$:MeOH (1:1 (v/v), 400 mL) for 18 h.

ACE-Cl (0.68 mL, 6.3 mmol) was added to a solution of the dendritic acylated piperazine (**36**, **38** and **40**) in dry $CH_2Cl_2$ (20 mL). The mixture was stirred at room temperature for 3 h and all volatiles were removed *in vacuo*. Methanol (30 mL) was added to the residue and the resulting solution was refluxed for 3 h and subsequently evaporated to dryness. The residue was purified by passive dialysis using MeOH:$CH_2Cl_2$ (1:1 (v/v), 400 mL) for 16 h, yielding the product (**37**, **39** and **41**) in the beaker

solution, which was evaporated to dryness.

**Synthesis of $Si\{(CH_2)_3Si((CH_2)_3SiMe_2(C_6H_4\text{-}4)CH_2(N(CH_2CH_2)_2N)C(O)(C_6H_5)_3\}_4$ (G1-$CH_2(N(CH_2CH_2)_2N)C(O)(C_6H_5)$, 36)**

Reaction of dendrimer **33** (0.30 g, 83 μmol) with benzoyl chloride (2.7 mL, 16 mmol), in the presence of pyridine (2.4 mL, 29.67 mmol). Yield: 0.26 g (21.6 μmol, 65%). Characteristics: $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ = 177.9 (C(O)N. MALDI-TOF-MS: *m/z*: 4862.94 [G1-$CH_2(N(CH_2CH_2)_2N)C(O)(C_6H_5)]^+$ (Calcd. 4863.92). IR: ν ($cm^{-1}$) = 1631 (C(O)N stretch).

**Release of phenylbenzoyl piperazine·HCl (37)**

Reaction of **36** (0.16 g, 32.8 μmol) with ACE-Cl (0.43 mL, 3.93 mmol) in dry $CH_2Cl_2$ (20 mL). Yield: 0.096 g (0.276 μmol, 84%). $^1H$ NMR (400 MHz, $CD_3OD$): δ = 7.49 (m, 5 H, Ar*H*), 4.84 (br s, 2 H, N*H*.*H*Cl), 3.86 (m, 4 H, C(O)NC$H_2$), 3.31 (m, 4 H, C(O)NCH$_2$C$H_2$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 171.5 (*C*(O)), 134.4, 130.6, 129.8 and 127.1 (Ar*C*), 48.7 (C(O)N*C*H$_2$), 43.3 and 40.6 (HN*C*H$_2$). GC-MS: *m/z* 190 ($M^+$–HCl). IR: ν ($cm^{-1}$) = 1610 (C(O) stretch).

**Synthesis of $Si\{(CH_2)_3Si((CH_2)_3SiMe_2(C_6H_4\text{-}4)CH_2(N(CH_2CH_2)_2N)C(O)(C_6H_4\text{-}4)Me_3\}_4$ (G1-$CH_2(N(CH_2CH_2)_2N)C(O)(C_6H_4\text{-}4)Me$, 38)**

Reaction of dendrimer **33** (0.44 g, 0.12 mmol) with 4-methylbenzoyl chloride (4 mL, 0.7 mmol), in the presence of pyridine (2.4 mL, 29.67 mmol). Yield: 0.19 g (0.038 mmol, 31%). Characteristics: $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ = 170.7 (C(O)N. MALDI-TOF-MS: *m/z*: 5031.64 [G1-$CH_2(N(CH_2CH_2)_2N)C(O)(C_6H_4\text{-}4)Me]^+$ (Calcd. 5032.24). IR: ν ($cm^{-1}$) = 1631 (C(O)N stretch).

**Release of 4-methylbenzoyl piperazine·HCl (39)**

Reaction of **38** (0.137 g, 27 μmol) and ACE-Cl (0.4 mL, 3.9 mmol) in $CH_2Cl_2$ (20 mL). Yield: 0.034 g (0.17 mmol, 62%). $^1H$ NMR (400 MHz, $CD_3OD$): δ = 7.37 (d, $^3J_{H\text{-}H}$ = 7.8 Hz, 2 H, Ar*H*), 7.29 (d, $^3J_{H\text{-}H}$ = 7.8 Hz, 2 H, Ar*H*), 4.88 (s, 2 H, N*H*.*H*Cl), 3.86 (m, 4 H, C(O)NC$H_2$), 3.30 (m, 4 H, C(O)NCH$_2$C$H_2$), 2.38 (s, 3 H, C$H_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 171.8 (*C*(O)), 141.2, 131.3, 129.3 and 127.3 (Ar*C*), 48.7 (C(O)N*C*H$_2$), 43.4 and 40.6 (HN*C*H$_2$), 20.3 (*C*H$_3$). GC-MS: *m/z* 204 ($M^+$–HCl). IR: ν ($cm^{-1}$) = 1612 (C(O) stretch).

**Synthesis of $Si\{(CH_2)_3Si((CH_2)_3SiMe_2(C_6H_4\text{-}4)CH_2(N(CH_2CH_2)_2N)C(O)(C_6H_4\text{-}2)Br)_3\}_4$ (G1-$CH_2(N(CH_2CH_2)_2N)C(O)(C_6H_4\text{-}2)Br$, 40)**

Reaction of dendrimer **33** (0.35 g, 96.8 μmol) with 2-bromobenzoyl chloride (3 mL, 22.8 mmol), in the presence of pyridine (2.4 mL, 29.67 mmol). Yield: 0.5 g (86.2 μmol, 89%). Characteristics: $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ = 167.8 (C(O)N. MALDI-TOF-MS: *m/z*: 5810.90 [G1-$CH_2(N(CH_2CH_2)_2N)C(O)(C_6H_4\text{-}2)Br]^+$ (Calcd. 5810.67). IR: ν ($cm^{-1}$) = 1634 (C(O)N stretch).

**Release of 2-bromobenzoyl piperazine·HCl (41)**

Reaction of **40** (0.30 g, 51.6 μmol) and ACE-Cl (0.45 mL, 3.95 mmol) in $CH_2Cl_2$ (20 mL). Yield: 0.080 g (71% in GC-MS, 0.21 mmol, 34%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.90 (s, 1 H, N*H*), 7.75 (m, 1 H, Ar*H*), 7.16 (m, 1 H, Ar*H*), 7.30 (m, 2 H, Ar*H*), 3.60 (s, 2 H, N*H*.HCl), 3.30 (m, 4 H, C(O)NC$H_2$), 2.80 (m, 4 H, C(O)NCH$_2$C$H_2$). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): δ = 167.9 (*C*(O), 136.5, 133.3, 131.4,128.4, 128.1 and 119.2 (Ar*C*), 44.0 and 43.8 (C(O)N*C*H$_2$), 38.6 and 29.9 (HN*C*H$_2$). GC-MS: *m/z* 269 ($M^+$–HCl, 71%), 214 (2-bromobenzoyl methylester, 29%). IR: ν ($cm^{-1}$) = 1639 (C(O) stretch).

## 5.6 References and Notes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# Summary

## 'Dialyzable' Carbosilane Dendrimers as Soluble supports for Organic Synthesis

Since the development of polystyrene as support for the syntheses of peptides by Merrifield in the 1960s, the application of supported synthesis (SPOS, Solid Phase Organic Synthesis) in both industrial and academic research has increased. In SPOS, the supports consist of solid, insoluble polystyrene beads that can be loaded peripherally with a substrate, which can be transformed into the desired product by means of a sequence of various reactions. Since these (loaded) beads are large enough to be separated from solution by filtration techniques, the excess of reagents, used to achieve complete conversions, can be easily separated from the supported product. In this way the substrate can simply be modified on the support, while in every step the excess reagents can be washed away and a clean supported product will be obtained (Figure 1). Finally, the product will be released from the support and a pure end product will be obtained, which can be used in, *e.g.*, the pharmaceutical industry (Active Pharmaceutical Ingredients, API's).

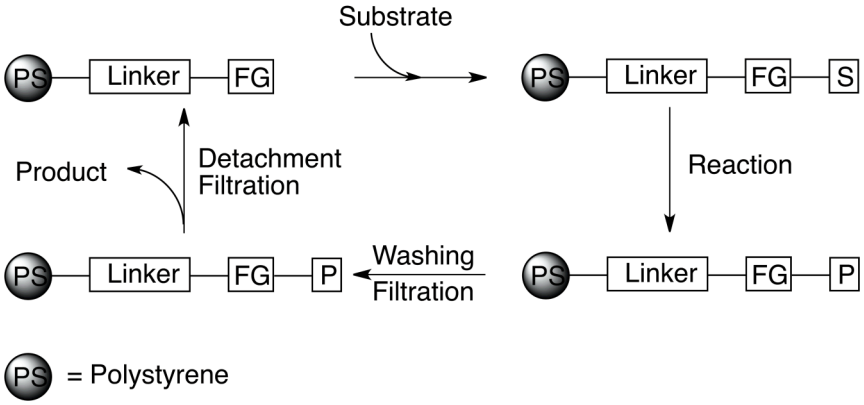



**Figure 1.** Schematic representation of the SPOS methodology (FG = functional group, S = substrate, P = product).

Besides these advantages of SPOS, also several disadvantages of this method are known. Since the supports are insoluble, reactions are carried out in inhomogeneous media, which causes reactions to proceed slow and less 'perfect'. In many cases it is also impossible or very difficult to perform spectroscopic analyses during the reaction sequences. The introduction of soluble supports (LPOS, Liquid Phase Organic Synthesis) overcame some of these

disadvantages, like working in inhomogeneous reaction media. Other disadvantages, like the difficult analysis and the loading capacity, are still present due to the irregular structure of the polymers. A possible solution for these problems is the use of dendrimers as supporting materials. These large, regularly branched macromolecules are highly soluble in various reaction media and standard spectroscopic analysis in solution phase is well applicable. Within the class of dendrimers the carbosilane dendrimers take a special position due to their chemical robustness and stability, also in more harsh reaction conditions (Figure 2).

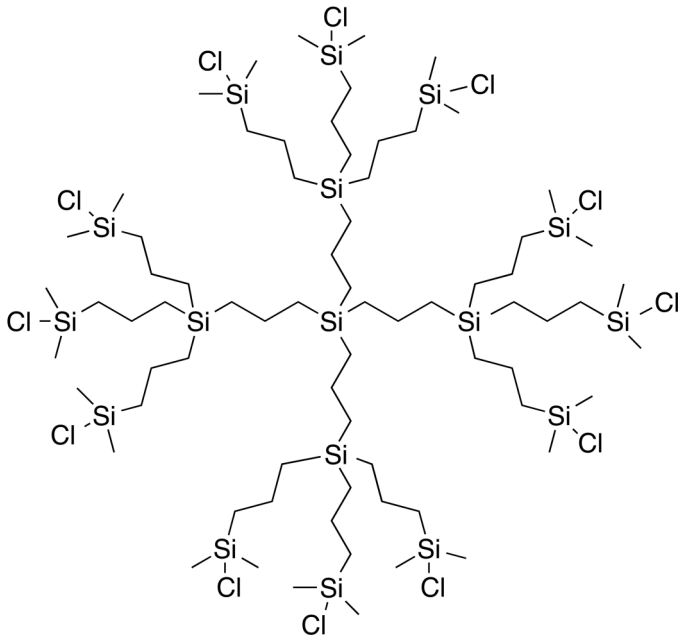



**Figure 2.** A first generation carbosilane dendrimers with reactive end groupings.

Initially, these (carbosilane) dendrimers were used as support for homogeneous catalysts. In this way the homogeneous catalyst can easily be removed from the reaction mixture by nano- or diafiltration after the reaction. It also appeared that the structure of the dendritic catalysts (the catalyst molecules are located closely together on the dendritic surface) can influence various reactions in a positive way (a positive dendritic effect). In *Chapter 1* of this thesis an overview of the use of carbosilane dendrimers as support for homogeneous catalysts is presented. Various dendrimer-supported catalysts, their applications and activities are described. The experience gained in this field has been applied later for the use of carbosilane dendrimers as support for organic synthesis, especially in the synthesis of the supported catalysts and the filtration techniques. The development of the procedures for the application

of carbosilane dendrimers as support in organic synthesis and optimization of the filtration steps in this procedure are subject of the experimental chapters in this thesis.

Carbosilane dendrimers can be functionalized at their periphery with various substrates, among which the so-called N-heterocyclic compounds. In *Chapter 2*, a study towards the supported modification of this type of compounds is described. These N-heterocyclic compounds, in this case 2-bromopyridines, can be attached to the dendrimers via lithiation reactions, while the bromofunctionality remains available for further coupling reactions. In order to optimize this reaction, first several test reactions were performed with substrates that contain a trimethylsilyl group as mimic for the dendrimers. The complete attach-modify-release sequence was optimized using this model. The optimized loading reaction was used to load the dendrimers with the bromopyridine moieties. It appeared that the conditions used for the model reactions (lithiation chemistry) could not always be directly translated to the dendrimer-supported syntheses. The presence of the very reactive lithiopyridines, together with the chlorosilane end groupings of the dendrimer resulted in unwanted side reactions. Two of the examined methods to load the dendrimers with bromopyridine moieties did not result in full loading of the dendrimers. In order to overcome the use of these reactive materials, a new method for the loading of the dendrimers with bromopyridines was developed, which makes use of a hydrosilylation reaction between the allyl end groupings of the dendrimer and dimethylsilane-modified bromopyridine **1** (Figure 3). In the following steps, the supported bromopyridines were converted into a series compounds using metal-catalyzed coupling reactions (*e.g.* the Suzuki-type coupling reaction) and finally the formed products were released from the dendrimers. From this study it appeared that the synthetic sequences performed using carbosilane dendrimers loaded via a hydrosilylation step resulted in higher yields and purities of the products compared to sequences in which the dendrimers were loaded via a lithiation step.

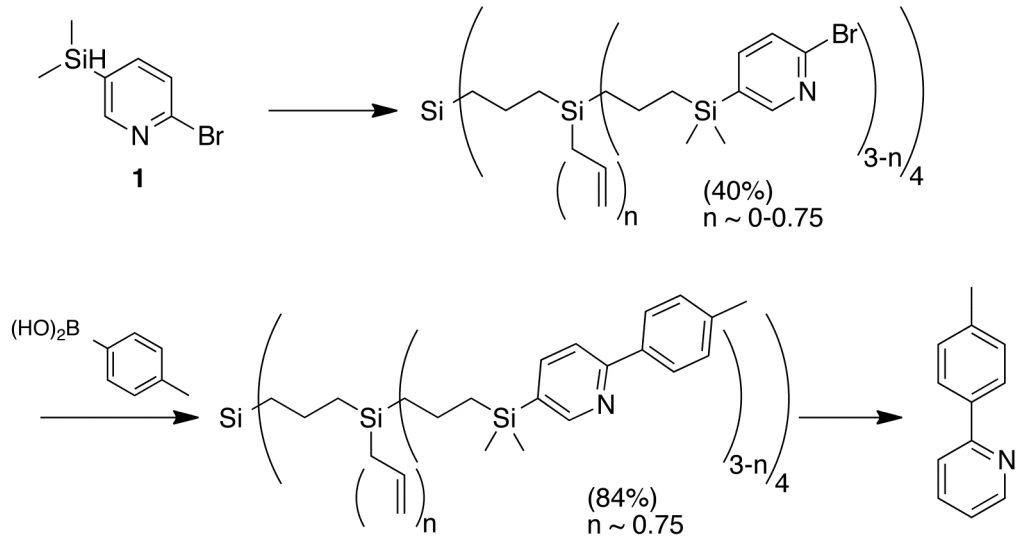



**Figure 3.** Attach-modify-release sequence of 2-bromo-pyridine on a carbosilane dendrimer.

During the filtration experiments with membranes of various pore sizes, it appeared that the dendrimers are also retained by membranes that have a theoretical pore size larger than the dimensions of the dendrimer. However, the applied filters are calibrated for aqueous solutions, whereas organic solvents (dichloromethane, methanol) are used for the dendrimers. This causes swelling of the membranes, which decreases the pore size. Furthermore, it was found that the speed of filtration increases with increasing pore size. Since the applied dendrimers are flexible, especially under the 'shear flow' conditions of the filtration, it is expected that more rigid dendrimers will be retained better by membranes with an even larger theoretical pore size, and that even higher filtration speeds will be achieved. In *Chapter 3*, the synthesis of various new, rigid dendrimers is described. For this purpose two core molecules, *i.e.* 1,3,5-tris(4-bromophenyl)benzene en tetrakis(4-bromophenyl)silane, and two wedges, tris(4-bromophenyl)chlorosilane and bromotriallylsilane were synthesized using lithiation chemistry. The synthesis of tetrakis(4-bromophenyl)silane was optimized starting from literature procedures, using rather unconventional methods in order to minimize formation of side products due to the self-reactivity of the 1-bromo-4-lithiobenzene intermediate. From this it appeared that for the nucleophilic substitution of chlorosilanes by aryllithiums at room temperature, no extra solvent activation is required. Polylithiation and substitution of the various core molecules with the various wedges resulted in formation of several new dendrimers. Both dendrimers with a complete rigid structure as well as dendrimers with a rigid core and flexible peripheries were synthesized in this way (Figure 4).

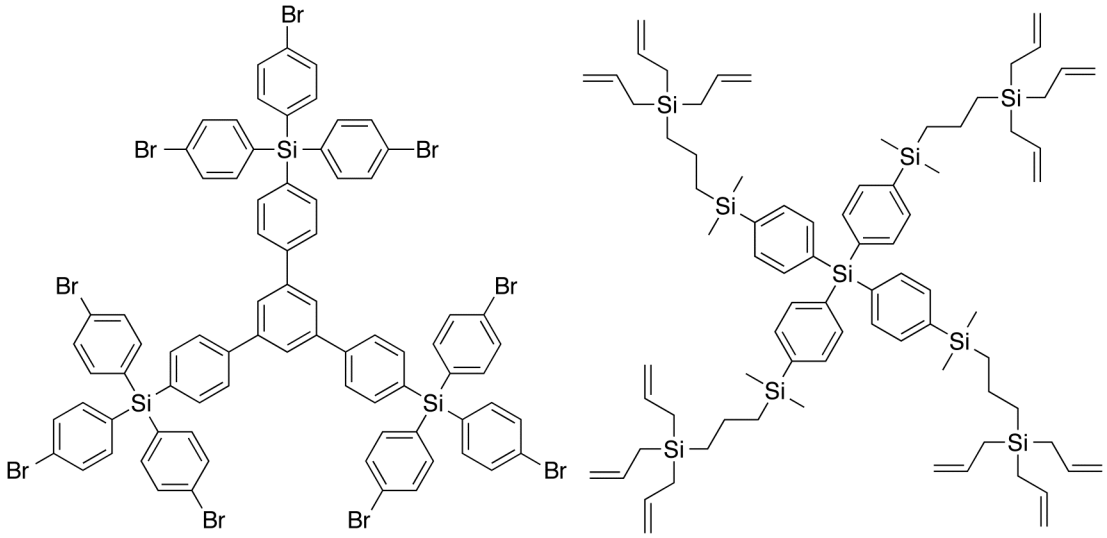



**Figure 4.** Examples of two new dendrimers.

In order to be able to detect the dendrimers during the filtration experiments, both the normal, flexible dendrimers as well as the new, rigid dendrimers were loaded with the dye molecules Disperse Red 1 and ferrocene (Figure 5, **2** and **3**). With the dye-functionalized dendrimers filtration experiments were performed using a series of membranes varying in pore size, as described in *Chapter 4*.

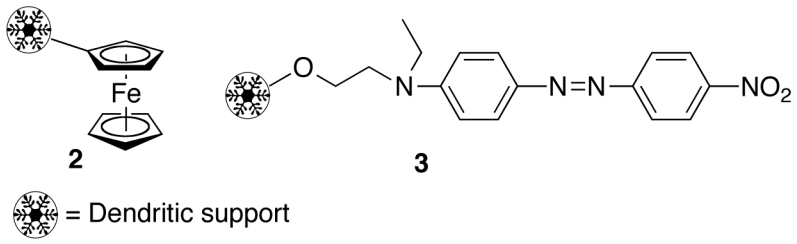
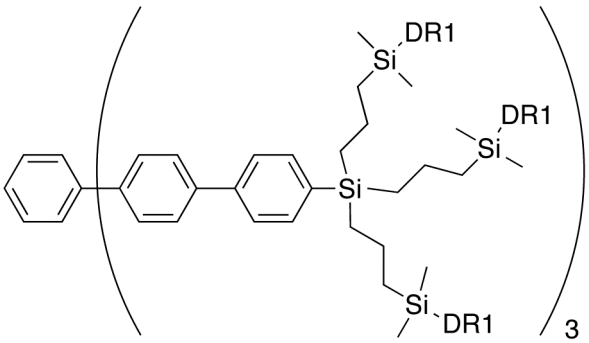



**Figure 5.** Dendrimers loaded with dye molecules.

The new, rigid dendrimers are retained somewhat better by membranes with larger pore sizes, but generally the difference with the normal, 'flexible' dendrimers is not big, when comparing (loaded) dendrimers with a comparable mass. Dendrimer **4**, on the other hand, which was synthesized from 1,3,5-tris(*p*-biphenyl)benzene and loaded with 'rigid' dye Disperse Red 1 (see Figure 6), clearly shows a much better filtration performance compared to the flexible dendrimers. Besides the diafiltration experiments, also UV/Vis spectroscopy, GPC, and molecular modeling were used in order to obtain more information about the dimensions of the dendrimers (in solution). The results obtained from these studies generally correspond to the results of the diafiltration experiments, showing a correlation between the dimensions and the molecular weights of the dendrimers. Again, dendrimer **4** appeared to be larger than based

solely on its molecular weight. However, from the GPC studies it seemed that the largest flexible dendrimer has larger dimensions than **4**, which is not in line with the molecular weights. This suggests that besides structural parameters of the dendrimers also other effects, like the presence of solvent molecules, play a role in determining the dimensions of the dendrimers in solution.




**4**

**Figure 6.** Dendrimer **4** shows best retention during filtration (DR1 = Disperse Red 1).

In SPOS the substrates are not directly coupled to the polystyrene beads, but instead beads are first functionalized with so-called linker groupings that make loading and release easier. In order to compare the results obtained with the dendrimers directly to the results of SPOS, the first generation dendrimer G1-12-Cl (Figure 2) is loaded with three typical SPOS linker groupings. In *Chapter 5* the application of this carbosilane dendrimer equipped with benzylbromide-linkers **5**, DEAM-linkers **6** and REM-linkers **7** (Figure 7) in LPOS is described.

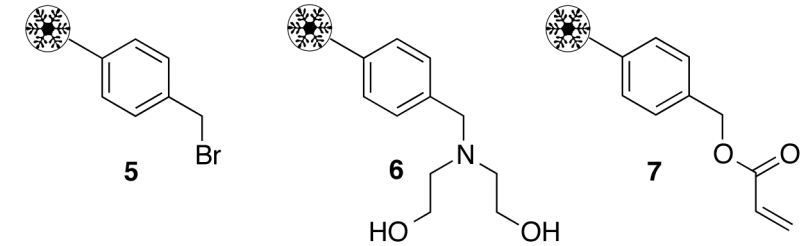



**Figure 7.** Dendritic supports loaded with linker groupings.

DEAM linkers are used for the immobilization and stabilization of boronic acids. In order to investigate the application of dendritic support **5**, various boronic acids were immobilized on this support. One of these supported boronic acids, *p*-formylphenyl boronic acid, was converted using a reductive amination reaction, after which the formed product was

immediately released from the dendritic support. As additional proof, the 'dendrimer-to-dendrimer' synthesis of 2,2'-bipyridine was performed. The supported bromopyridine from chapter 2 was coupled to a DEAM-immobilized pyridyl boronic acid by means of a Suzuki-type coupling reaction, after which the target product was released from the dendrimer (Figure 8).

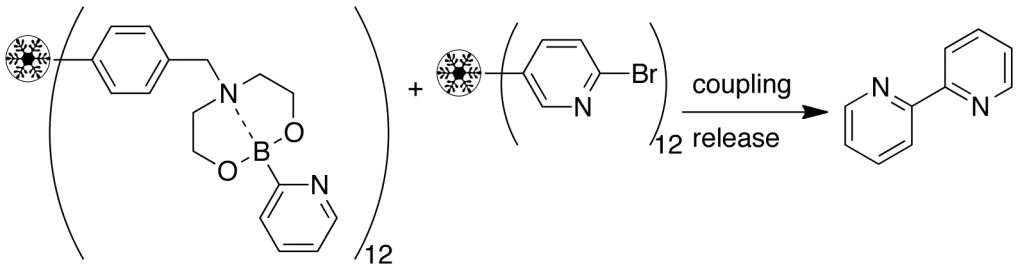



**Figure 8.** 'Dendrimer-to-dendrimer' synthesis of 2,2'-bipyridine

To the dendritic linkers **6** and **7** two different substrates were coupled, *i.e.* piperidine and piperazine. These substrates were converted by SPOS methodologies into various small molecules, API's (Figure 9). For all three linkers the yields and purities of the products appeared not to be as high as for comparable SPOS results. This was partly due to the incompatibility of the used purification method (passive dialysis) with water-labile and water-soluble products.

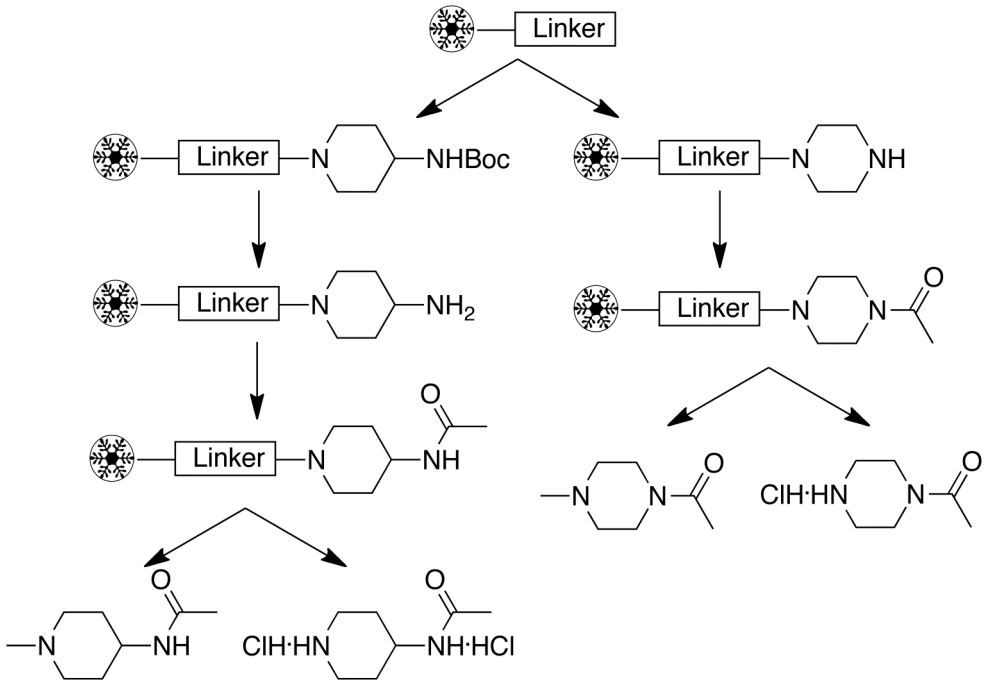



**Figure 9.** SPOS method on dendritic supports **6** and **7**.

**General conclusions and perspective**

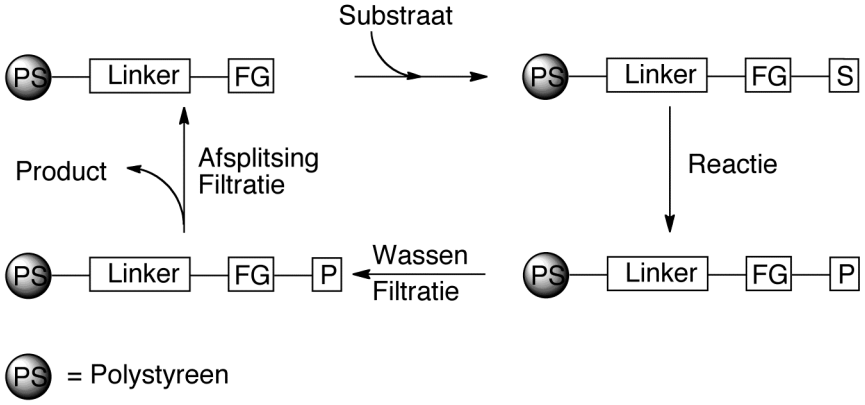
In general the advantages and shortcomings of the application of carbosilane dendrimers as synthesis supports have been shown in this research. The regular structure and solubility in the reaction media resulted in better monitoring of the various reaction steps, resulting in more insight in the reaction sequences. The applied purification methods, passive dialysis and diafiltration, can be optimized even further, *e.g.* by using improved membrane materials. Combined with more rigid dendrimers, the filtration speed can be increased even further and the supported synthesis of water-labile can be made possible as well (less contact time with the solvents during filtration). However, the synthesis of these supports is time consuming, possibly resulting in minimal economic benefit. In that case the more simple flexible dendrimers will offer good alternatives although lower filtration speeds need to be taken for granted.

The carbosilane dendrimers appear to be robust supports; step-wise dendrimer-supported synthesis of small molecules like API's appear to be well possible, even in harsh reaction conditions. The carbosilane dendrimers also appear to have clear advantages as support in organic synthesis compared to SPOS and LPOS methods. Further optimization of the dendrimer-supported synthetic procedures can, therefore, lead to the development of parallel synthesis protocols that make use of carbosilane dendrimers as support.

# Samenvatting

## ‘Dialyseerbare’ Carbosilaandendrimeren als oplosbare drager voor organische synthese

Sinds de ontwikkeling van polystyreen als dragermateriaal voor de synthese van peptiden door Merrifield in de jaren 1960, is de toepassing van gedragen synthese (SPOS, Solid Phase Organic Synthesis) in zowel het industriële als het academische onderzoek toegenomen. In SPOS bestaan de dragers uit vaste, onoplosbare polystyreenbolletjes, die aan het oppervlak beladen kunnen worden met een substraat, dat m.b.v. een sequentie van verschillende reacties omgezet kan worden in het gewenste product. Aangezien deze (beladen) bolletjes groot genoeg zijn om uit een reactiemengsel te filteren, kan de overmaat aan reagentia, die gebruikt wordt om volledige omzettingen te bereiken, op simpele wijze van het gedragen product gescheiden. Op deze manier kan het substraat eenvoudig op de drager gemodificeerd worden, waarbij in elke stap de overmaat reagentia weggewassen wordt en een schoon product op de drager verkregen wordt (Figuur 1). Uiteindelijk wordt het product van de drager afgesplitst en wordt een zuiver eindproduct verkregen, dat bijvoorbeeld gebruikt kan worden in de farmaceutische industrie (Actieve Farmaceutische Ingrediënten, API’s).

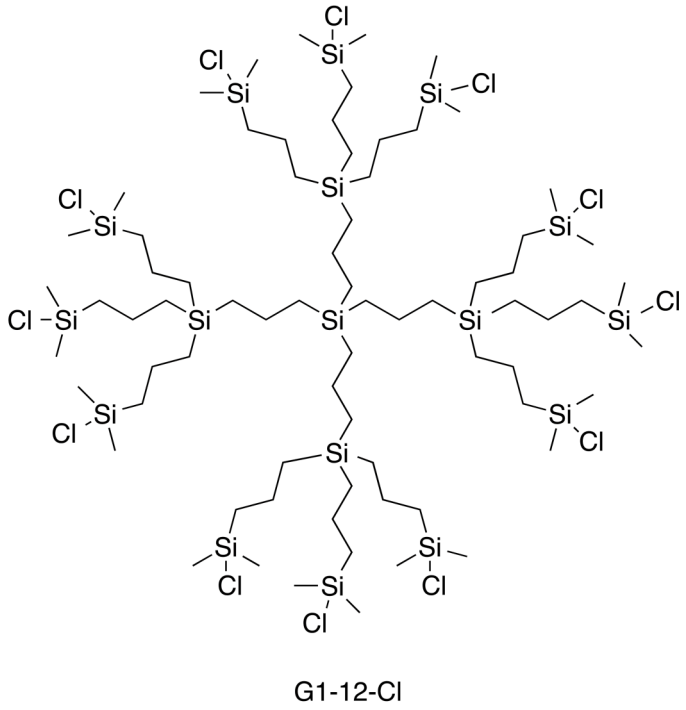



**Figuur 1.** Schematische weergave van de SPOS methode (FG = functionele groep, S = substraat, P = product).

Naast deze voordelen van SPOS kleven er ook nadelen aan deze methode. Aangezien de dragers niet oplosbaar zijn, wordt er gewerkt in niet-homogene media, waardoor reacties langzaam en minder ‘perfect’ verlopen. Ook is het hierdoor in vele gevallen niet mogelijk of zeer moeilijk om tussentijds spectroscopische analyses uit te voeren. De introductie van

oplosbare polymere dragers (LPOS, Liquid Phase Organic Synthesis) heeft enkele van deze nadelen, zoals het werken in niet-homogene media, overkomen. Andere nadelen, waaronder de moeilijke analyse en de ladingscapaciteit, blijven echter aanwezig door de onregelmatige structuur van de polymere dragers.

Een mogelijke oplossing voor deze problemen is het gebruik van dendrimeren als dragermateriaal. Deze grote, regelmatig vertakte macromoleculen zijn goed oplosbaar in verschillende reactiemedia en standaard spectroscopische analyse in oplossing is goed mogelijk. Binnen de klasse van de dendrimeren nemen de carbosilaandendrimeren een speciale plaats in door hun chemische robuustheid en stabiliteit, ook onder meer reactieve reactie-omstandigheden (Figuur 2).

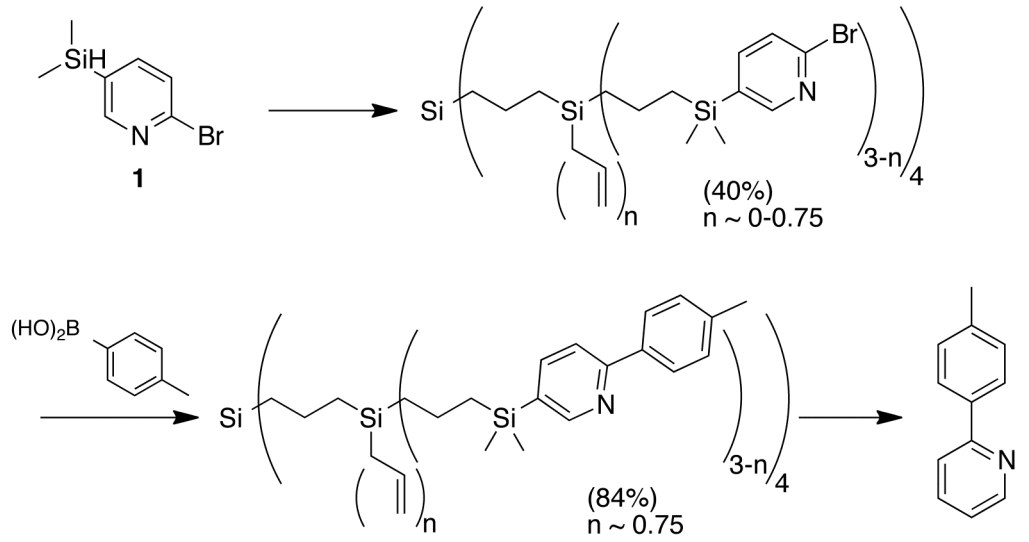



**Figuur 2.** Een eerste generatie carbosilaandendrimeer met reactieve eindgroepen

In eerste instantie werden deze (carbosilaan)dendrimeren vooral gebruikt als drager voor homogene katalysatoren. Op deze manier kan de homogene katalysator na afloop van een reactie eenvoudig uit een reactiemengsel gefiltreerd worden m.b.v. nano- of diafiltratie. Ook is gebleken dat de structuur van de dendritische katalysatoren (de katalysator moleculen zitten op het oppervlak van de dendrimeren dicht op elkaar) verschillende reacties op een positieve manier kan beïnvloeden (een positief dendritisch effect). In *hoofdstuk 1* van dit proefschrift wordt een overzicht gegeven van het gebruik van carbosilaandendrimeren als drager voor homogene katalysatoren. Verschillende dendrimeer-gedragen katalysatoren, hun

toepassingen en activiteit worden beschreven. De ervaring die opgedaan is binnen dit werkveld is later toegepast op het gebruik van carbosilaandendrimeren als dragermateriaal voor organische synthese, met name wat betreft de synthese van de gedragen katalysatoren en de filtratietechnieken. De ontwikkeling van de procedures voor het gebruik van carbosilaandendrimeren als dragermateriaal in de organsiche synthese en de optimalisatie van de filtratiestappen in deze procedure zijn het onderwerp van de experimentele hoofdstukken in dit proefschrift.

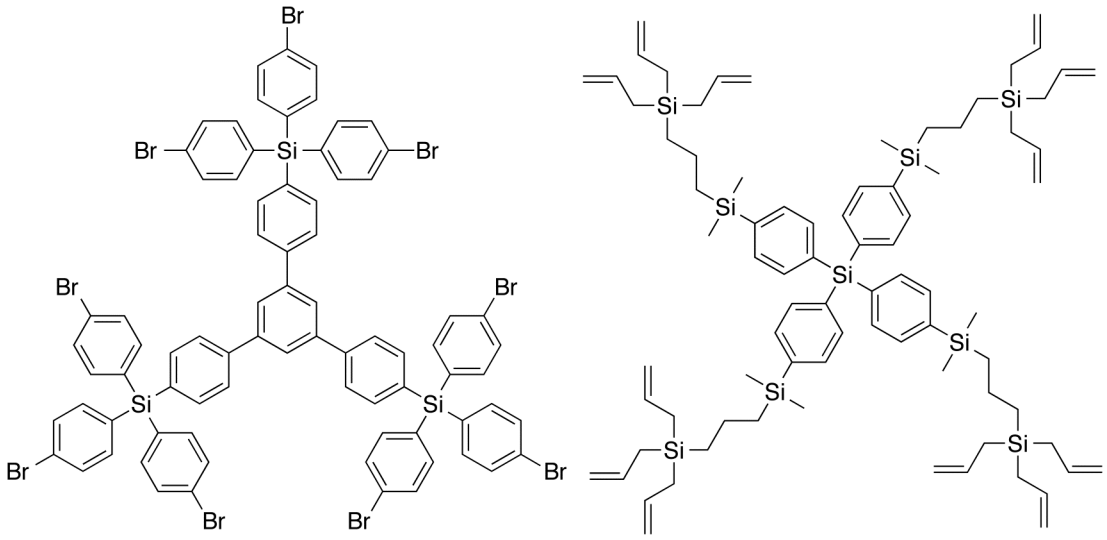
Carbosilaandendrimeren kunnen aan hun oppervlak beladen worden met verschillende substraten, waaronder zogenaamde N-heterocyclische verbindingen. In *hoofdstuk 2* wordt een studie beschreven naar de gedragen modificatie van dit type verbindingen. Deze N-heterocyclische verbindingen, in dit geval 2-bromopyridines, kunnen via lithieringsreacties aan de dendrimeren worden bevestigd, waarbij de broom-functionaliteit behouden blijft voor verdere koppelingsreacties. Om deze reactie te optimaliseren, zijn eerst verschillende testreacties uitgevoerd met substraten die een trimethylsilyl groep als model voor de dendrimeren bevatten. De gehele belading-modificatie-afsplitsing sequentie is met behulp van dit model geoptimaliseerd. De geoptimaliseerde beladingsreactie is gebruikt om de dendrimeren te beladen met bromopyridines. Het is gebleken dat de condities van de modelreacties (lithieringschemie) niet altijd direct vertaald konden worden in de dendrimeergedragen syntheses. De aanwezigheid van de zeer reactieve lithiopyridines en de chloorsilaan-eindgroepen van het dendrimeer zorgden voor ongewenste nevenreacties. Twee onderzochte methodes om de dendrimeren te beladen met bromopyridines resulteerden dan ook niet in volledige belading. Om dit te omzeilen is een nieuwe methode voor de belading van de carbosilaandendrimeren met bromopyridines ontwikkeld, die gebruikt maakt van een hydrosilyleringsreactie tussen de allylgroepen van het dendrimeer en het dimethylsilaan-gemodificeerde bromopyridine **1** (Figuur 3). In de volgende stappen werden de gedragen bromopyridines omgezet in een serie van verschillende verbindingen met behulp van metaal-gekatalyseerde koppelingsreacties (bv. de Suzuki-koppelingsreactie) en tenslotte zijn de gevormde producten van de dendrimeren afgesplitst. Uit deze studie is gebleken dat de synthese-sequenties uitgevoerd aan carbosilaandendrimeren beladen via een hydrosilyleringstap tot hogere opbrengsten en zuiverheden van de producten leiden dan sequenties waarin het dendrimeren beladen worden via een lithieringstap.




**Figuur 3.** Belading-modificatie-afsplitsing sequentie aan een carbosilaandendrimeer.

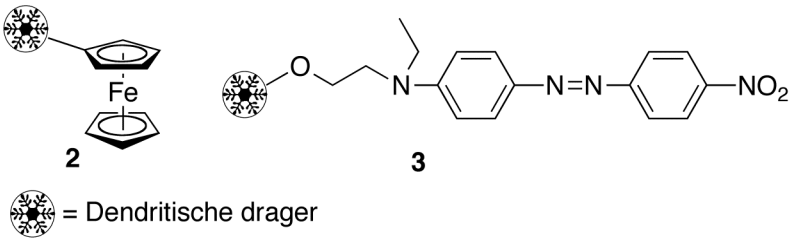
Gedurende de filtratie-experimenten met membranen met verschillende poriegroottes is gebleken dat de dendrimeren ook worden tegengehouden door membranen met een theoretische poriegrootte die groter is dan de afmeting van het dendrimeer. Echter, de gebruikte filters zijn geijkt voor waterige oplossingen, terwijl organische oplosmiddelen (dichloormethaan, methanol) gebruikt worden voor de dendrimeren. Hierdoor zwelt het membraanmateriaal meer op, waardoor de poriën kleiner worden. Ook is gebleken dat bij toenemende poriegrootte de filtratiesnelheid toeneemt. Omdat de gebruikte dendrimeren flexibel zijn, met name onder de 'shear flow' condities van de filtratie, is het de verwachting dat meer starre dendrimeren beter tegengehouden zullen worden door membranen die een nog grotere theoretische poriegrootte hebben en dat daarbij een hoge filtratiesnelheid verkregen kan worden. In *hoofdstuk 3* is de synthese van verschillende nieuwe, starre dendrimeren beschreven. Hiervoor werden twee verschillende kernmoleculen, te weten (1,3,5-tris(4-bromophenyl)benzeen en tetrakis(4-bromophenyl)silaan, en twee 'wedges', tris(4-bromophenyl)chlorosilaan en bromotriallylsilaan gesynthetiseerd met behulp van van lithieringschemie. De synthese van tetrakis(4-bromophenyl)silaan werd geoptimaliseerd uitgaande van literatuurprocedures, waarbij enigszins onconventionele methodes werden gebruikt om de vorming van bijproducten door de zelfreactiviteit van het intermediair 1-bromo-4-lithiobenzeen te minimaliseren. Hierbij is gebleken dat in de nucleofiele substitutie van chloorsilanen door aryllithiums bij kamertemperatuur geen extra oplosmiddelactivering nodig is. Polylithiering en substitutie van de verschillende kernmoleculen met de verschillende wedges resulteerde in de vorming van verschillende nieuwe dendrimeren.

Zowel dendrimeren met een geheel starre structuur, als dendrimeren met een starre kern en flexibele periferieën zijn zodoende gesynthetiseerd (Figuur 4).




**Figuur 4.** Voorbeelden van twee nieuwe dendrimeren.

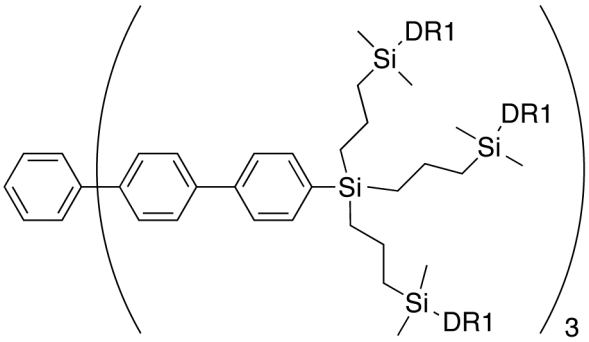
Om de dendrimeren goed te kunnen volgen tijdens de filtratie-experimenten, zijn zowel de gewone, flexibele dendrimeren als de nieuwe, starre dendrimeren beladen met de kleurstoffen Dispers Rood 1 en ferroceen (Figuur 5, **2** en **3**). Met deze 'gekleurde' dendrimeren zijn filtratie-experimenten met een serie in poriegrootte verschillende membranen uitgevoerd, zoals beschreven in *hoofdstuk 4*.




**Figuur 5.** Dendrimeren geladen met kleurstoffen.

Hierbij is gebleken dat de nieuwe, starre dendrimeren wel wat beter worden tegengehouden door membranen met grotere poriën, maar dat in het algemeen het verschil met de gewone, 'flexibele' dendrimeren niet heel groot is, wanneer (beladen) dendrimeren met een soortgelijke massa met elkaar vergeleken worden. Wel vertoont het dendrimeer **4**, afgeleidt van 1,3,5-tris(*p*-biphenyl)benzeen en beladen met de 'starre' kleurstof Disperse Rood 1 (zie figuur 6) een duidelijk beter filtratiegedrag in vergelijking met de flexibele dendrimeren. Behalve de diafiltratie-experimenten zijn ook UV/Vis spectroscopie, GPC en moleculaire modelering gebruikt om meer informatie over de afmetingen van de dendrimeren (in

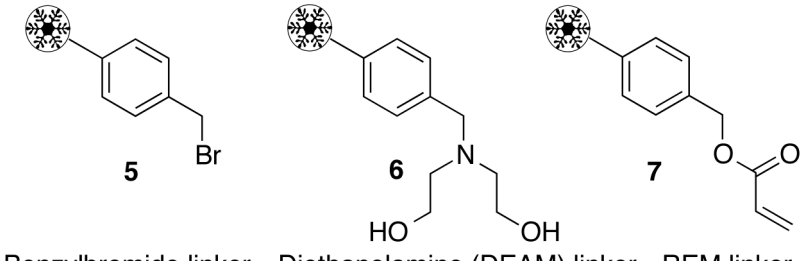
oplossing) te verkrijgen. De resultaten van deze studies komen grotendeels overeen met de resultaten van de filtratie-experimenten. In het algemeen is er een correlatie tussen de afmeting en het molecuulgewicht van de dendrimeren. Ook in deze studies blijkt dendrimeer **4** groter te zijn dan dat op basis van het molecuulgewicht verwacht kan worden. Echter, uit GPC-metingen blijkt het grootste flexibele dendrimeer groter te zijn dan **4**, hetgeen niet in lijn is met de molecuulgewichten. Dit duidt er op dat er behalve de structurele parameters van de dendrimeren ook andere effecten, zoals de aanwezigheid van oplosmiddelmoleculen, een rol spelen voor de dynamische afmeting van de dendrimeren in oplossing.




**4**

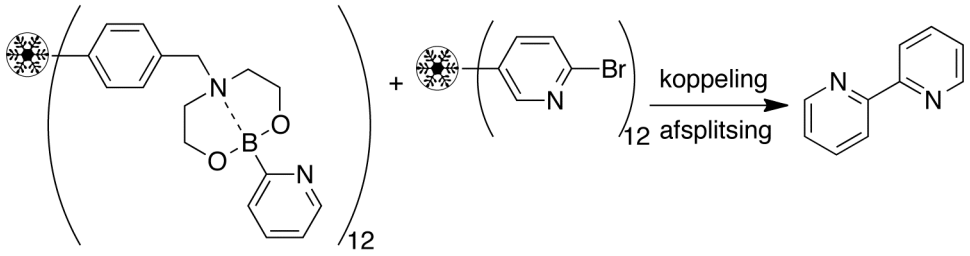
**Figuur 6.** Dendrimeer **4** geeft beste retentie bij filtratie (DR1 = Dispers Rood 1).

In SPOS worden de substraten niet direct aan het polystyreen gekoppeld, maar worden de polystyreenbolletjes eerst gefunctionaliseerd met zogenaamde linker-groepen die de belading en het afsplitsen vereenvoudigen. Om de resultaten die worden verkregen met de dendrimeren direct te kunnen vergelijken met de resultaten verkregen met SPOS is het eerste generatie dendrimeer G1-12-Cl (zie figuur 2) beladen met een drietal typische SPOS-linker-groepen. In *hoofdstuk 5* wordt het gebruik van dit carbosilaandendrimeer uitgerust met benzylbromide-linkers **5**, DEAM-linkers **6** en REM-linkers **7** (Figuur 7) in LPOS beschreven.



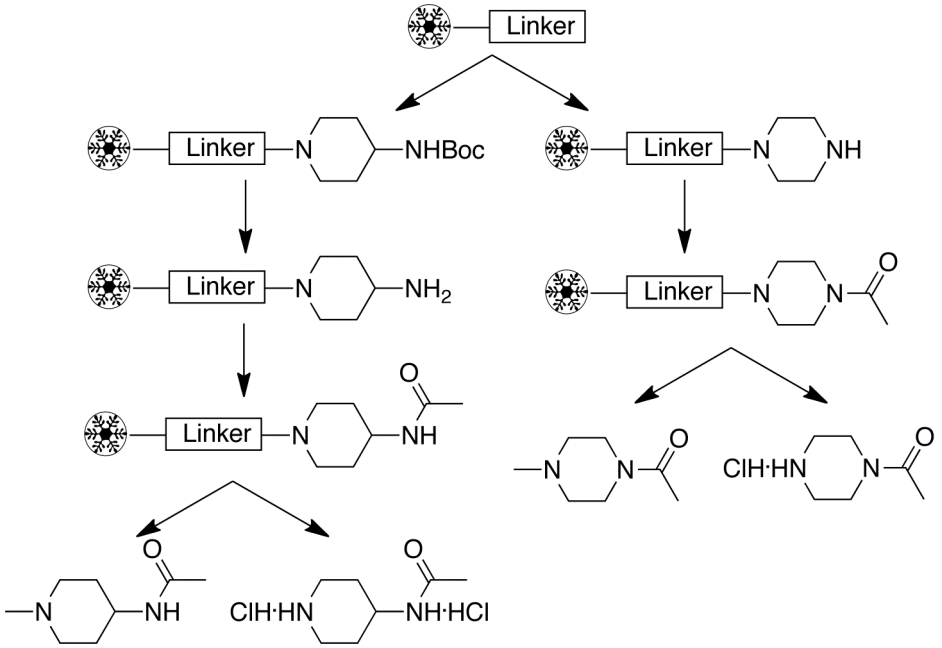

**Figuur 7.** Dendritische supports beladen met linker groepen.

DEAM linkers worden gebruikt voor de immobilisatie en stabilisatie van boorzuren. Om de toepasbaarheid van dendritische drager **5** te onderzoeken zijn verschillende boorzuren op deze drager geïmmobiliseerd. Een van de gedragen boorzuren, *p*-formylphenylboorzuur, is omgezet m.b.v. een reductieve amineringsreactie waarna het gevormde product direct van de dendritische drager gescheiden is. Als extra test is de 'dendrimer-to-dendrimer' synthese van 2,2'-bipyiridine uitgevoerd. Het gedragen bromopyridine uit hoofdstuk 2 is m.b.v. een Suzuki-koppelingsreactie gekoppeld aan een DEAM-geïmmobiliseerd pyridylboorzuur, waarna het gewenste product van het dendrimeer is afgesplitst (Figuur 8).




**Figuur 8.** 'Dendrimer-to-dendrimer' synthese van 2,2'-bipyridine.

Aan de dendritische linkers **6** en **7** zijn twee verschillende substraten gekoppeld, piperidine en piperazine. Deze zijn volgens SPOS methodes omgezet in verschillende kleine moleculen, API's (Figuur 9). Voor alle drie de linkers bleken de opbrengsten en zuiverheden van de producten minder hoog te zijn als voor vergelijkbare SPOS resultaten. Dit werd mede veroorzaakt doordat de gebruikte zuiveringsmethode (passieve dialyse) alleen goed bruikbaar bleek te zijn in combinatie met water-stabiele en niet-wateroplosbare producten.




**Figuur 9.** SPOS methode op dendritische dragers **6** en **7**.

**Algemene conclusies en perspectief**

In het algemeen zijn de voordelen en de beperkingen van het gebruik van carbosilaandendrimeren als synthese-supports aangetoond in dit onderzoek. De regelmatige structuur en de oplosbaarheid in de reactiemedia heeft geleid tot betere monitoring van de verschillende reactiestappen, waardoor meer inzicht in de reactiesequenties is verkregen. De hierbij gebruikte zuiveringsmethoden, passieve dialyse en diafiltratie, kunnen verder geoptimaliseerd worden, bijvoorbeeld door het gebruik van betere membraanmaterialen. Door de ontwikkeling van meer starre dendrimeren kan de filtratiesnelheid in dergelijke gevallen verder omhoog en de gedragen synthese van water-labiele producten ook mogelijk worden (minder contacttijd met het oplosmiddel tijdens filtratie). De synthese van dergelijke dragers is echter tijdrovend, waardoor het economische voordeel mogelijk klein zal zijn. De eenvoudigere flexibele dendrimeren bieden in dat geval een goed alternatief waarbij lagere filtratiesnelheden voor lief genomen moeten worden.

De carbosilaandendrimeren blijken robuuste dragers te zijn; stapsgewijze dendrimeergedragen synthese van kleine moleculen zoals API's blijkt namelijk goed mogelijk, ook onder veeleisende reactie-omstandigheden. De carbosilaandendrimeren blijken dus duidelijk voordelen te hebben als dragermateriaal in de organische synthese ten opzichte van SPOS en LPOS methoden. Een verdere optimalisatie van de dendrimeer-gedragen syntheseprocedures kan leiden tot de ontwikkeling van parallelle syntheseprotocollen die gebruik maken van carbosilaandendrimeren als dragermateriaal.

# Curriculum Vitae

Maaike Wander was born on January 20, 1979, in Breda, The Netherlands. In 1997 she started her chemistry studies at the University of Groningen. During her studies she performed an MSc research project in the Molecular Inorganic Chemistry Group of prof. dr. J. H. Teuben. In 2002, she stayed for 6 months at the University of Edinburgh in the research group of Dr. P. J. Bailey for an internship. Both research projects involved the synthesis and application of either early or late transition metal catalysts. In August 2003, she received her MSc degree. In 2004, she started her PhD research project in the Organic Chemistry & Catalysis Group of prof. dr. G. van Koten and prof. dr. R.J.M. Klein Gebbink at Utrecht University. Parts of the work have been presented at several national conferences as well as at the International Dendrimer Symposium (IDS5) in Toulouse. In January 2009, she started her industrial career at AkzoNobel Functional Chemicals B.V. Initially, she worked as researcher at the Organometallics Specialties department. From April 2011, she continued her career as Technical Development Manager Organometallic Specialties at AkzoNobel.

Maaike Wander is geboren op 20 januari 1979 in Breda, Nederland. In 1997 begon ze haar scheikundeopleiding aan de Rijksuniversiteit Groningen. Tijdens haar studie heeft ze een MSc onderzoeksproject uitgevoerd in de Molecular Inorganic Chemistry groep van prof. dr. J. H. Teuben. In 2002 verbleef ze 6 maanden aan de Universiteit van Edinburgh in de onderzoeksgroep van Dr. P. J. Bailey voor een stageperiode. Beide onderzoeksprojecten hadden betrekking op de synthese en toepassing van zowel vroege als late overgangsmetaal katalysatoren. In augustus 2003 behaalde ze haar masterdiploma. In 2004 begon ze haar promotieonderzoek in de Organische Chemie & Katalyse groep van prof. dr. G. Van Koten en prof. dr. R. J. M. Klein Gebbink aan de Universiteit van Utrecht. Delen van het werk zijn gepresenteerd op verschillende nationale conferenties en op het International Dendrimer Symposium (IDS5) in Toulouse. In januari 2009 begon ze haar industriële carrière bij AkzoNobel Functional Chemicals B.V. In eerste instantie werkte ze als onderzoeker op de afdeling Organometallic Specialties. Vanaf april 2011 heeft ze haar carrière voortgezet als Technical Development Manager Organometallic Specialties bij AkzoNobel.

# List of Publications

*Polycarbosilane Dendrimers - Molecular Supports and Containers for Homogeneous Catalysis and Organic Synthesis*

Wander, M.; van Koten, G.; Klein Gebbink, R. J. M. In *Silicon-Containing Dendritic Polymers*; Dvornic, P. R., Owen, M. J., Eds.; Springer Netherlands, 2009; Vol. 2.

*Synthesis of polyaryl rigid core carbosilane dendrimers for supported organic synthesis*

Wander, M.; Hausoul, P. J. C.; Sliedregt, L. A. J. M.; van Steen, B. J.; van Koten, G.; Klein Gebbink, R. J. M. *Organometallics* **2009**, *28*, 4406-4415.

*The Application of Carbosilane Dendrimers as Soluble Supports for the Stepwise Modification of 2-Bromopyridine Moieties*

Wander, M.; Sliedregt, L. A. J. M.; van Steen, B. J.; van Koten, G.; Klein Gebbink, R. J. M. *To be submitted* **2012**.

*Dye-functionalized Carbosilane Dendrimers: Synthesis, Physical Properties and Application in a Diafiltration Set-up*

Wander, M.; Zugwitz, M.; Kleijn, H.; Sliedregt, L. A. J. M.; van Steen, B. J.; Klein Gebbink, R. J. M. *To be submitted* **2012**.

*Carbosilane Dendrimers functionalized with SPOS-type Linkers and Their Application as Support in Organic Synthesis*

Wander, M.; Kleijn, H.; Sliedregt, L. A. J. M.; van Steen, B. J.; Klein Gebbink, R. J. M. *To be submitted* **2012**.

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Maaike