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Convergent Synthesis of Polynitrile and/or Polyamine Dendrimers through Hydroaminomethylation and Michael Addition

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A general concept for a versatile convergent synthesis of polynitrile and/or polyamine dendrimers has been developed by applying Vögtle's procedure in combination with the tandem hydroformylation/reductive amination sequence, known as hydroaminomethylation. In this approach, first Vögtle's procedure is used to generate the desired dendron, which can then be attached to different types of polyfunctionalized cores (e.g., polyamine, polyhalide, or polyolefin cores) to provide the desired globular architecture. This method can be used as a general procedure for the synthesis of dendrimers with designed shell and core properties as shown by the examples presented.

Introduction

Hydroaminomethylation[1] is an environmentally benign and atom-efficient rhodium-catalyzed one-pot reaction that combines hydroformylation of olefins[2] with reductive amination[3] of the corresponding aldehydes in the presence of an amine (Figure 1).

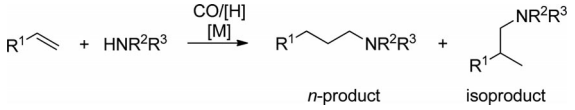

Figure 1. Hydroaminomethylation reaction.

This method has already been used in the synthesis of linear and cyclic polyfunctionalized amines including polyamines and azamacroheterocycles.[4] Moreover, application of this method has been proven in the synthesis of dendritic structures as well as in their modification, offering versatile access to new features of dendrimers.[5]

The interest in dendrimers,[6] which are – ideally – perfect monodisperse macromolecules with a regular three-dimensional architecture, has grown exponentially over the last two decades. Due to the highly branched globular structure of dendrimers, they are attractive scaffolds for a wide variety of high-end applications, such as liquid crystals,[7] diagnostics,[8] solar cells,[9] sensors,[10] gene-transfection agents,[11] drug-delivery systems,[12] coating agents,[13] additives in commodity plastics,[14] and potential drugs.[15] Moreover, they have been successfully employed in a wide variety of catalytic reactions[17] as alternatives to insoluble solid-phase supports.[16] They have also been found to be useful building blocks and carrier molecules that operate at nanoscales.[18]

Convergent[19] and divergent[20] methods are two complementary approaches that are used to synthesize highly symmetrical dendrimers with defined properties depending on their core and shell structure. Vögtle et al. developed early examples of a successful divergent synthetic procedure[21] toward the formation of well-defined, branched polyamine dendrimers. The sequence starts from a polyamine, which serves as the core of the final dendrimer. The growth of the amine core proceeds outward by repetitive application of a coupling reaction (Michael-type addition with acrylonitrile) followed by an activation step (reduction with $CoCl_2$ and $NaBH_4$) to provide primary amines in high yields.[22] According to this procedure, several commercial applications, such as the bulk production of poly(propylene imine) (PPI) type dendrimers (based on diaminobutane), have been developed.[23]

However, Vögtle's method, which is generally used in a divergent approach, has some limitations when proceeding to higher generations of dendrimers. In these cases, a decrease in the solubility of the polynitriles, incomplete reduction, and also deficient functionalization due to reverse Michael addition are observed. As an alternative, we envisioned a convergent approach by applying Vögtle's procedure for the construction of individual dendrons, with the final assembly of the polyamine/polynitrile dendrimers being achieved by other synthetic methods, including hydroaminomethylation. By using this approach, the number of functional groups on the dendron is much lower for each step and generation. Furthermore, the critical reduction step can be performed on the dendron before the complete dendrimer is assembled. In addition, this approach seems to be more flexible, because the preformed dendron could be modified at the terminal function before being attached

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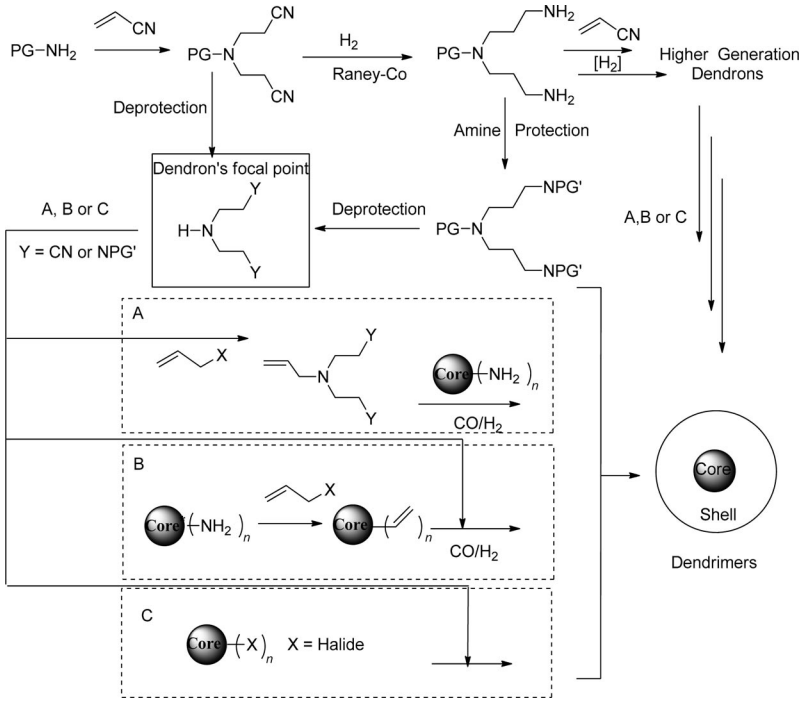


Scheme 1. Strategies for convergent syntheses of polynitrile/polyamine dendrimers.

to a suitably polyfunctionalized core to provide a globular architecture with designed core and shell properties.[18] Thus, we hoped to circumvent the disadvantages of the divergent method.

As shown in Scheme 1, the choice of the core and the reaction type used in the final step in the convergent approach is more flexible and even allows the use of small dendrimers as core molecules. When hydroaminomethylation is used as the assembly method, attachment of the dendrons to the core should be conveniently achieved by allylation of the deprotected amine function at the focal point of the dendron, followed by hydroaminomethylation in the presence of a polyamine core (Scheme 1, Method A).

In principle, this pathway can also be reversed by allylating the polyamine core to obtain a polyolefin core, which can then be converted into the desired dendrimer through hydroaminomethylation with the preformed free N–H group at the focal point of the dendron (Scheme 1, Method B). Alternatively, the allylation/hydroaminomethylation strategies (Scheme 1, Methods A and B) can be replaced by other reaction types, such as alkylation or acylation of the dendron by using a polyhalide core (Scheme 1, Method C). As shown in Scheme 1 for the first dendrimer generation, this procedure can, in principle, also be further applied to higher generation dendrons and/or higher generation cores.

We herein present the first application of this convergent approach to the preparation of polynitrile/polyamine dendrimers according to the strategy depicted in Scheme 1. The method was used to combine Vögtle's procedure either with allylation/hydroaminomethylation or alkylation/acylation to demonstrate the effectiveness of the new pathway.

Results and Discussion

Dendron Preparation

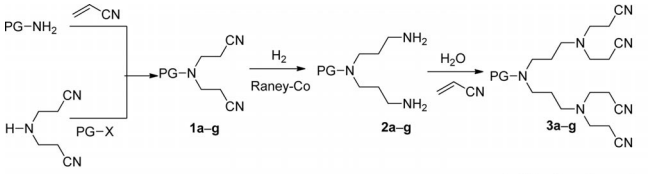
The construction of various dendrons was accomplished by repetitive Michael additions of acrylonitrile to an *N*-protected primary amine, followed by reduction of the nitrile groups (Table 1).[21] The sequence was optimized by using water as the solvent for the addition step, and Raney-Co was utilized as the catalyst for the reduction of the nitrile groups.

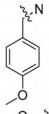
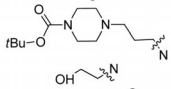
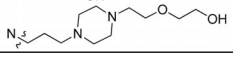
To determine the most suitable protecting group (PG) at the focal point of the dendron, different amine protecting functionalities were screened (Table 1, Entries 1–5). All the starting materials studied gave reasonable results, and the final nitrile dendrons (second generation) (**3a**–**g**) were obtained in 70–100% yield, depending on the protecting group. As shown in Table 1 (Entries 6 and 7), instead of protected amines, amino alcohols can also be attached to the dendron.[24] The corresponding functionalities offer the advantage that only the NH_2 groups act as nucleophiles in the Michael-type addition with acrylonitrile, whereas the free OH group remains available either for final couplings to the core or for further modification of the dendron.

In principle, the **e** series of dendrons, with an additional carbon atom in the chain, can also be constructed by a hydroformylation/reductive amination sequence by using the *N*-allylated dinitrile **4** followed by reduction to give **7** (Scheme 2).

According to this approach, first, 3,3′-(allylimino)dipropionitrile (**4**) was hydroformylated to form aldehyde **5** by using [Rh(acac)$(CO)_2$] as the catalyst[28] and 4,5-bis(di-

Table 1. Preparation of various *N*-protected dendrons according to Vögtle's method.



Entry	PG (Protecting Group)		Product yields (%) 1a–g	2a–g	3a–g
1		**a**	94[21,26]	100	96
2		**b**	96[27,28]	80	92
3		**c**	86	100	81
4		**d**	57	98	68
5		**e**	92[a]	98	81
6		**f**	98[29]	100	100
7		**g**	85[b]	100	89

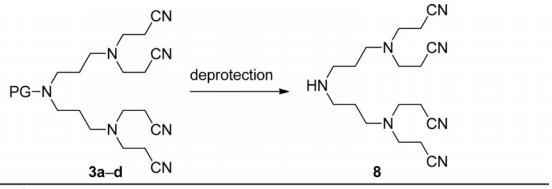
[a] Compound **1e** was prepared in four steps by starting from piperazine: (1) mono-Boc-protection of piperazine[25] (80% yield), (2) Michael addition to acrylonitrile[26] (94% yield), (3) reduction of the nitrile group[27] (100% yield), (4) Michael addition to acrylonitrile (92% yield). [b] Compound **1g** was prepared from 1-[2-(2-hydroxyethoxy)ethyl]piperazine by Michael addition and reduction, in an overall yield of 85%.

phenylphosphanyl)-9,9-dimethylxanthene (XANTPHOS)[29] as phosphane ligand, which directed the reaction toward selective formation of the linear aldehyde (linear/branched, 13:1). Subsequent reductive amination with Boc-piperazine provided the corresponding polynitrile **6**. Finally, reduction of the nitrile groups of **6** led to the formation of **7** in quantitative yield.

For final attachment of the thus obtained dendrons to an appropriate core, a suitable deprotection protocol was required. Therefore, in the next step, deprotection of the amino protecting groups of the tetranitriles (Table 1, **3a**–**e**) was tested. Debenzylation of **3a** by using various reagents, such as Pd/C/ammonium formate,[30] Pearlman's catalyst [$Pd(OH)_2$/C, H_2],[31] or Pd/C and H_2, failed. This lack of success could be attributed to the presence of the nitrile groups, which may deactivate the catalysts by complete absorption onto its surface. In this case, the palladium surface will not be accessible for the benzyl group, which is a prerequisite for deprotection. Nevertheless, reduction of the nitrile groups was not observed here.

As an alternative, debenzylation succeeded when a special Pd/C catalyst (wet, Degussa type E101 NE/W, Aldrich 33,010-8) was used to form product **8** from **3a**, but only after extended reaction time (14 d) (Table 2, Entry 1). This long reaction time and the poor yield once again indicated that strong deactivation of the palladium catalyst by the polynitrile groups was taking place.

Table 2. Deprotection of the dendrons **3a**–**d**.

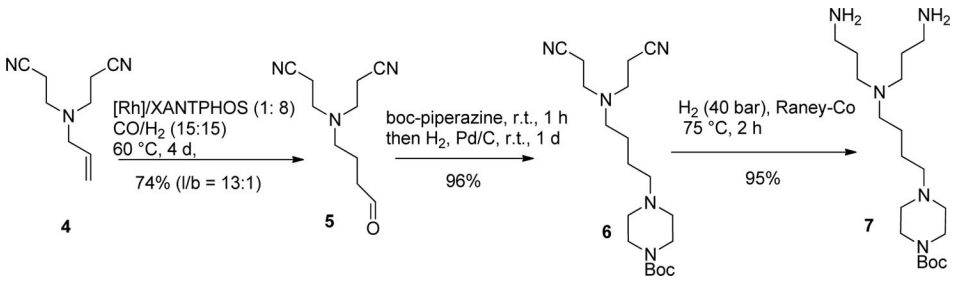


Entry	Substrate dendron	PG	Conditions	Yield (%)
1	**3a**	Bn	Pd/C, r.t, 14 d	40
2	**3b**	PMB	Pd/C, r.t.	–
3	**3b**	PMB	BBr_3, –78 to r.t., 24 h	–
4	**3c**	Boc	dioxane/HCl (3 M) (3:2), r.t., 12 h	78
5	**3d**	Moc	LiBr, MeOH	–

Deprotection and activation of the *p*-methoxybenzyl-(PMB-)amine-functionalized dendrons (**b** series), can be achieved either by debenzylation, as stated above, or by deprotection of the *p*-methoxy group, which leads to a phenol derivative. Debenzylation of **3b** is known to proceed through either reduction or oxidation; however, neither reductive debenzylation by using Pd/C as the catalyst, nor oxidative debenzylation by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or Ce^{IV} ammonium nitrate, were successful in this case. Similarly, demethylation of **3b** with BBr_3[32] did not provide the desired phenol product (Table 2, Entry 3).

For deprotection of the Moc group, harsh conditions were required, which led to decomposition of the nitrile functionalities, as well as the starting material in the case of **3d** (Table 2, Entry 5).

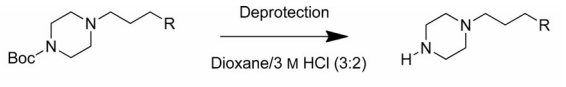
The best result was obtained for deprotection of the Boc group of **3c**, where reasonable yields were achieved when the reaction was carried out with HCl in dioxane (Table 2, Entry 4).

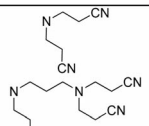
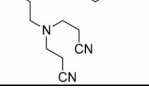


Scheme 2. Dendron synthesis by a hydroformylation/reductive amination/reduction sequence.

In case of the **e** series, with compounds starting from *tert*-butyl 4-(3-aminopropyl)piperazine-1-carboxylate, Boc deprotection was even more efficient. The corresponding deprotected dendrons **9** and **10** could be synthesized in excellent yields (Table 3) under the same conditions used above (Table 2, Entry 4). This significant improvement in yield might be attributed to the presence of an alkyl spacer in the **e** series, which makes the protected amine more accessible to the catalyst.

Table 3. Boc deprotection of **e**-series dendrons.



Entry	Substrate dendron	R	Product dendron	Yield (%)
1	**1e**		**9**	92
2	**3e**		**10**	99

In conclusion, the Boc functionality was chosen as the most appropriate protecting group for further experiments.

Attachment of the Dendrons to a Core

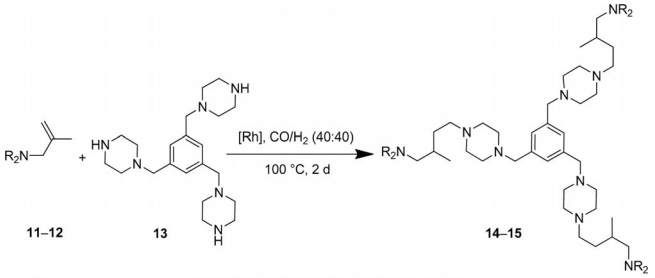
As discussed above (Scheme 1), the idea of the new strategy was to apply Vögtle's procedure in combination with hydroaminomethylation to construct the desired polyamine/polynitrile dendrimers through a convergent approach. Therefore, having prepared the model dendrons through Vögtle's procedure, the dendrons needed to be attached to a suitably polyfunctionalized core to provide the desired globular architecture (Scheme 1).

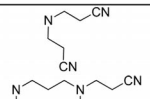
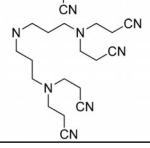
To emphasize the generality of this method, different kinds of star-shaped cores [e.g., polyamine (Method A), polyolefin (Method B), and polyhalide (Method C) (Scheme 1)] were considered for attachment to the corresponding dendron. Detailed results are discussed in the following sections.

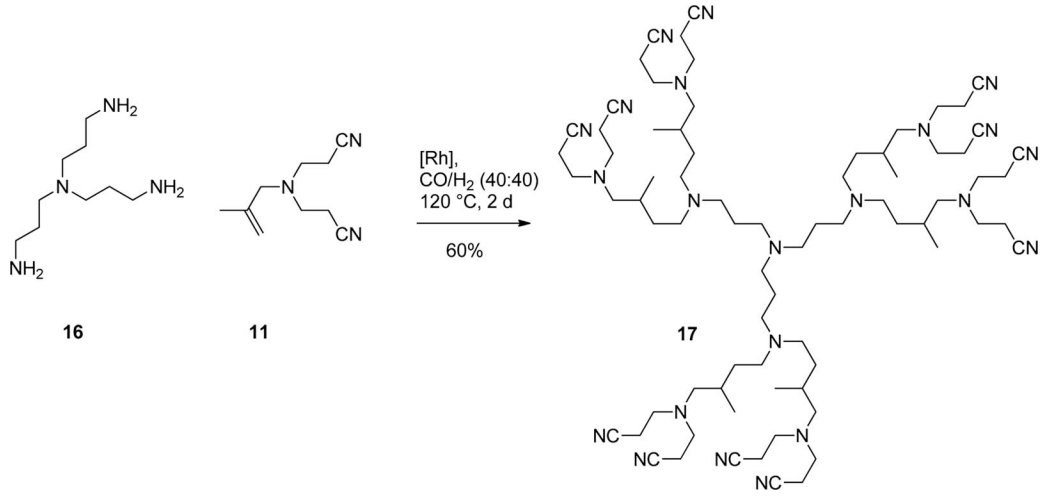
Attachment of Dendrons to a Polyamine Core (Method A)

To attach an amine-functionalized dendron to a polyamine core, an olefinic chain was introduced at the focal point of the dendron by *N*-allylation. The allylated dendron could be attached to the amine core through hydroaminomethylation. To circumvent the selectivity problem in hydroformylation of allyl groups, first the methallyl group was introduced by using methallyl chloride as the *N*-alkylating agent. The results of hydroaminomethylation of methallyl-modified dendrons **11** and **12** with 1,3,5-tris(piperazino-

Table 4. Hydroaminomethylation of modified olefinic dendrons with polyamine core **13**.



Entry	Allylated dendron	R	Dendrimer	Yield (%)
1	**11**		**14**	60
2	**12**		**15**	43



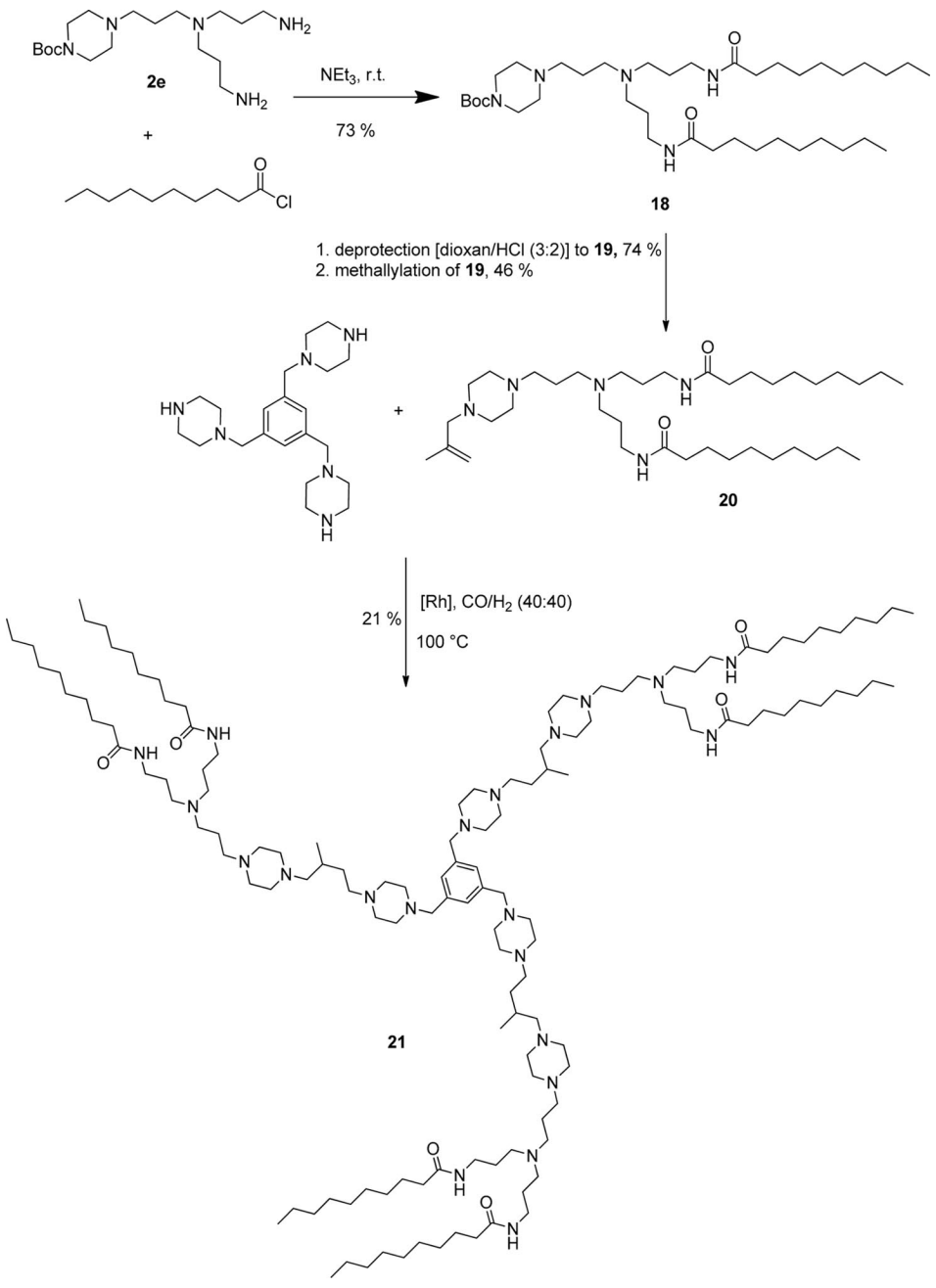
Scheme 3. Hydroaminomethylation of **11** with the tris(primary amine) core **16**.

methyl)benzene (**13**) as a triamine core with secondary amino groups, are shown in Table 4.

The corresponding dendrimers **14** and **15** with molecular weights higher than 1000 g mol^{-1} were purified by dialysis and could be isolated in 60 and 43% yields, respectively (Table 4).[33]

The triamine core **16**, with primary amino groups, was then tested for rapid assembly of dendrimers. This core was prepared in two steps from ammonium acetate and acrylonitrile followed by reduction with Raney cobalt.[34] Polyamine **16** underwent a six-fold hydroaminomethylation with dendron **11** to generate in one step dendrimer **17** in 60% yield with a molecular weight above 1300 g mol^{-1} (Scheme 3).

Instead of using polynitrile-terminated dendrons, as an alternative the nitrile groups can be reduced and further modified at the amine functions prior to assembling the dendrimer. Thus, the terminal amine groups in dendron **2e** were modified with decanoyl chloride to form **18** followed by deprotection to provide **19**. Allylation of **19** with methallyl chloride delivered **20** as the desired dendron. Hydroaminomethylation of **20** with the triamine core **13** was successfully accomplished to give the hexadecanoate dendrimer **21** in 21% yield (Scheme 4). Dendrimers with structural prop-



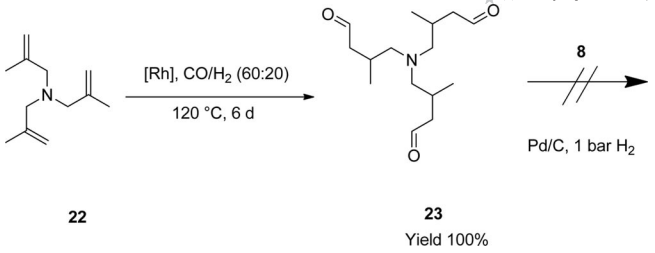
Scheme 4. Modification of dendron **2e** with decanoyl chloride, olefinic functionalization, and hydroaminomethylation to the hexadecanoate dendrimer **21**.

erties typified by compound **21**, bearing a basic polar core and a hydrophobic shell, have potential applications as supramolecular hosts for encapsulating polar guest molecules.[35]

Attachment of Dendrons to a Polyolefin Core (Method B)

As an alternative to Method A, hydroaminomethylation can also be applied to polyolefin cores by using dendrons with free N–H groups at the focal point. As a first example of this version, hydroaminomethylation of the commercially available triolefinic core, tris(2-methylallyl)amine (**22**), with amine-functionalized dendron **8** was investigated under different conditions (temperature, pressure, and time). This approach, however, was unsuccessful.

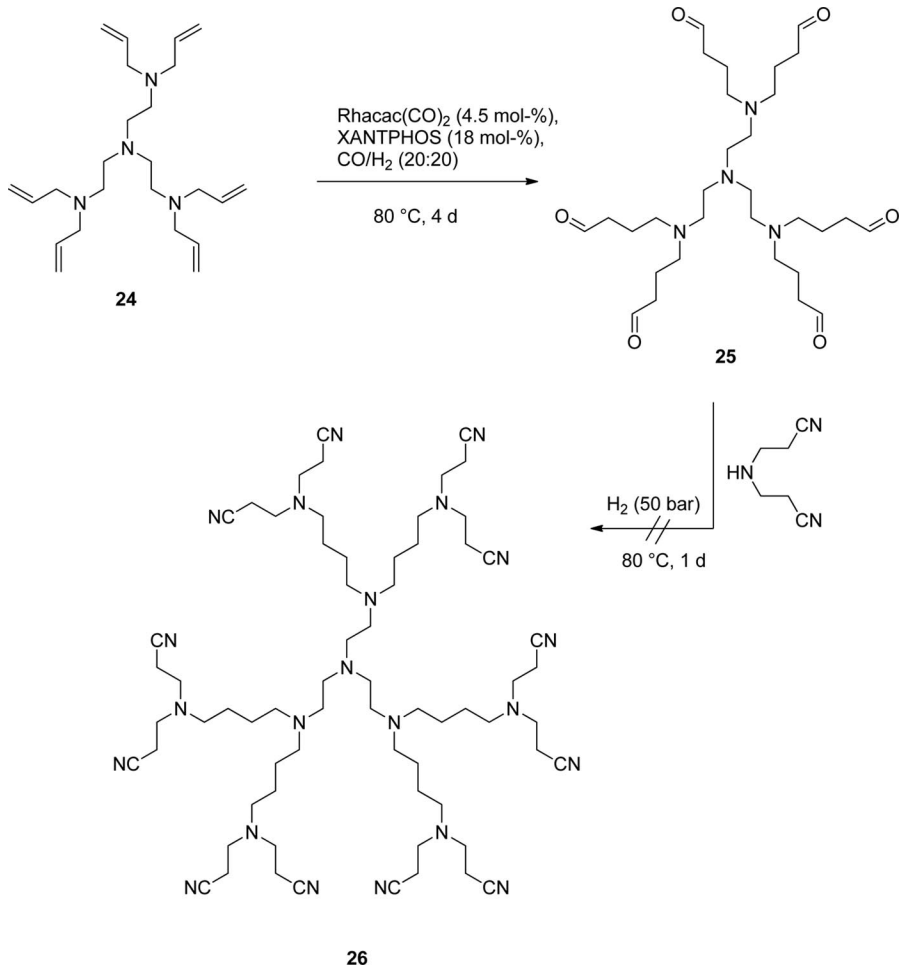
When the reaction was performed in a stepwise manner by hydroformylation and subsequent reductive amination, tris(aldehyde) **23** was obtained in quantitative yield; however, reductive amination in the second step failed, due to polycondensation of the polyaldehyde after addition of the polyamine/polynitrile dendron **8** (Scheme 5).



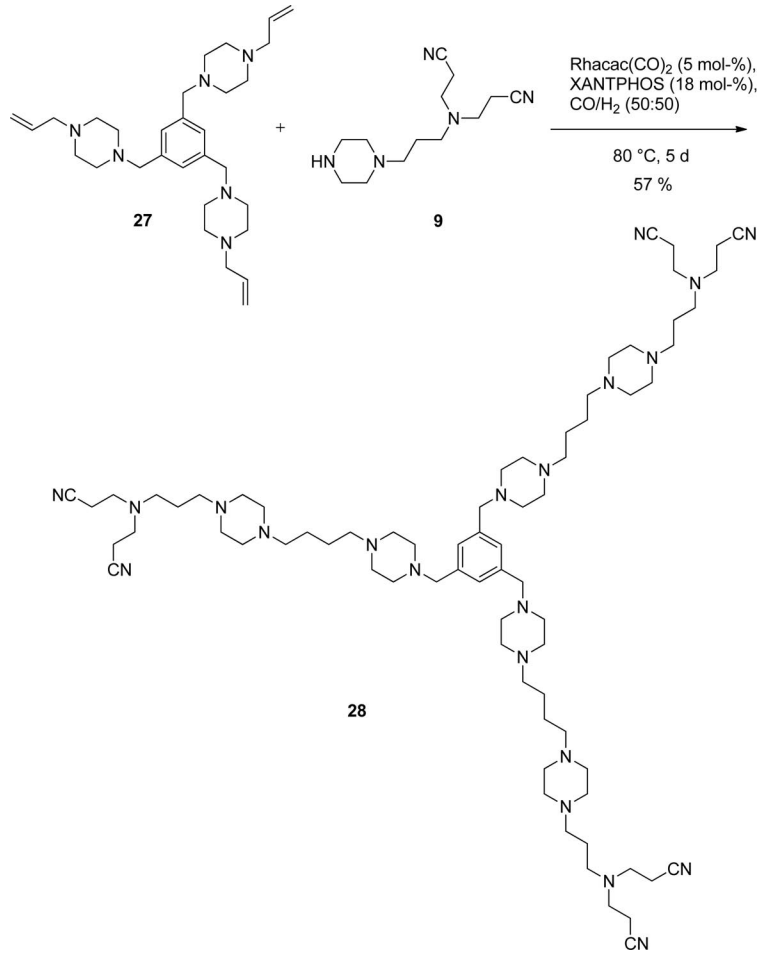
Scheme 5. Stepwise hydroformylation and reductive amination of tris(2-methylallyl)amine (**22**).

As discussed above, polyolefin cores can also be obtained by perallylation of polyamine cores. Thus, allylation of tris(2-aminoethyl)amine with triethylamine in toluene provided *N*,*N*-diallyl-*N*′,*N*′-bis[2-(diallylamino)ethyl]ethane-1,2-diamine (**24**) in 60% yield. Here again, direct hydroaminomethylation of **24** failed, and in the stepwise version, although polyaldehyde **25** could be detected in the reaction mixture, due to its instability it could neither be isolated in pure form nor converted into the desired product **26** through reductive amination (Scheme 6).

As shown by these results, Method B is clearly less favorable than Method A due to the local concentration of aldehyde groups in close vicinity and, consequently, side reactions that cannot be avoided by higher dilution. Therefore, polyolefin cores needed to be designed with larger spacers



Scheme 6. Stepwise hydroaminomethylation of *N*,*N*-diallyl-*N*′,*N*′-bis[2-(diallylamino)ethyl]ethane-1,2-diamine (**24**).



Scheme 7. Hydroaminomethylation of **27**.

that separate the olefin and aldehyde functions further. To test this hypothesis, the olefinic core **27** was prepared by allylation of 1,3,5-tris-(piperazinomethyl)benzene (**13**) in 65% yield. As expected, hydroaminomethylation of **27** with 3-{(2-cyanoethyl)[3-(piperazin-1-yl)propyl]amino}propionitrile (**9**) as the dendron succeeded, and **28** was generated in 57% yield (Scheme 7).

Attachment of Dendrons to Halogenated Cores (Method C)

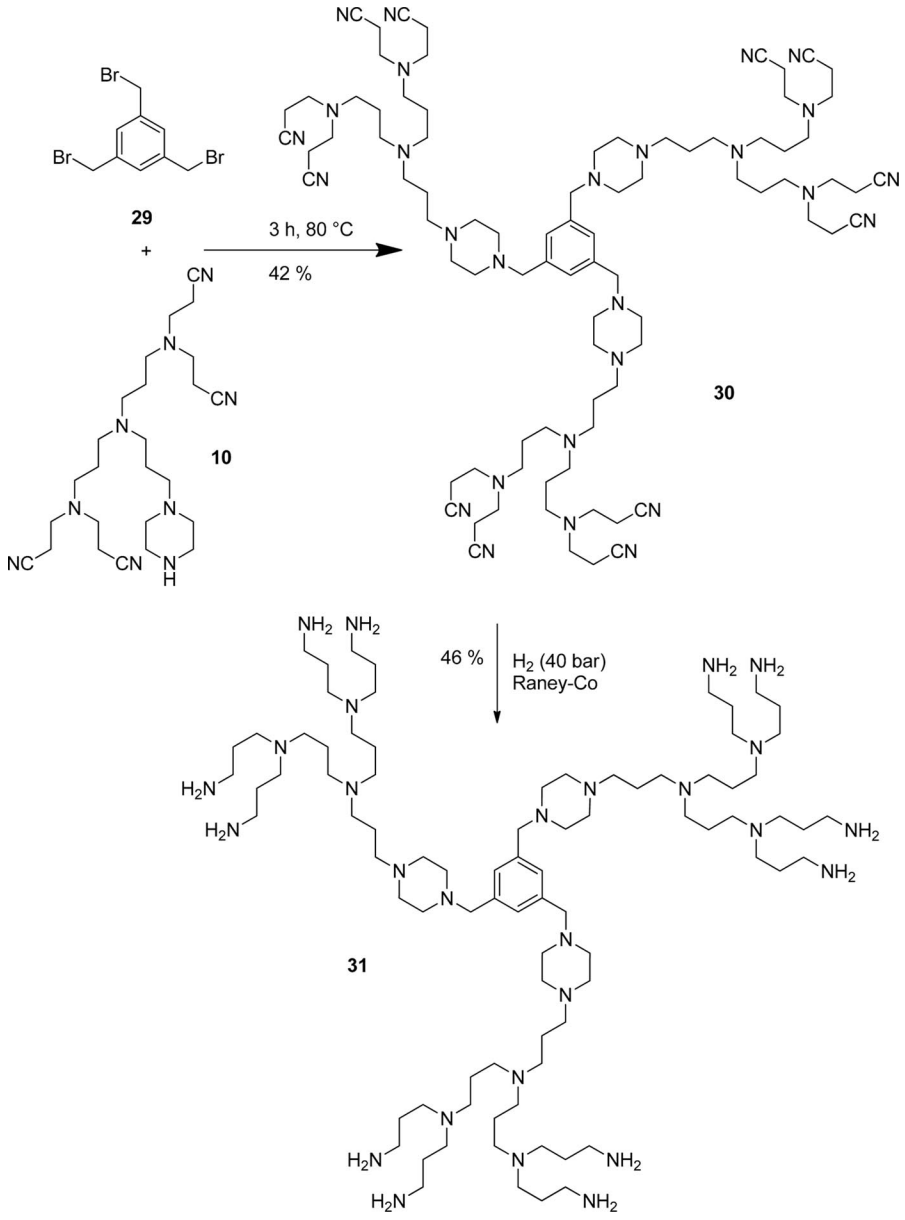
As discussed above, another alternative for the construction of polynitrile/polyamine dendrimers is offered by alkylation or acylation of dendrons such as **8**, **9**, or **10** with free N–H groups at the focal point with appropriately functionalized cores. As an example, nucleophilic substitution reaction of 1,3,5-tris(bromomethyl)benzene (**29**) with the amine-functionalized dendron **10** provided dodecanitrile **30** in one step with 42% yield. This polynitrile could be subsequently reduced to form dodecaamine **31** in 46% yield (Scheme 8).

Another strategy was to apply dendrons with the free OH groups at the focal point, which can be attached to tricarboxylic chloride core **32** as reported by Tschierske et al.[36] Appropriate amino alcohol dendrons, such as **1f** or **3f**, are conveniently constructed without requiring any protection step. Conversion with the tris(carbonyl chloride) core **32** furnished the respective polyamine dendrimers **33** and **34** in excellent yields (Scheme 9). Similarly, amine-functionalized dendron **10** reacted with the tris(carbonyl chloride) core **32** to provide **35** in high yield.

Conclusions

We have expanded a general concept for the flexible synthesis of polyamine dendrimers starting with highly versatile dendrons obtained by Vögtle's method. These dendrons can be combined with suitable cores in various ways, thus providing a powerful and versatile toolbox for the rapid assembly of dendrimers with any desired molecular weight in only a very few steps by coupling individually designed cores, dendrons, and shells. According to our results, Method B was found to be less favorable than Methods A and C, due to the high local concentration of aldehyde groups, which leads to side reactions that cannot be overcome by higher dilution.

To the best of our knowledge, this is the first time that dendrons of this type (prepared according to Vögtle's procedure) have been used in a convergent manner.



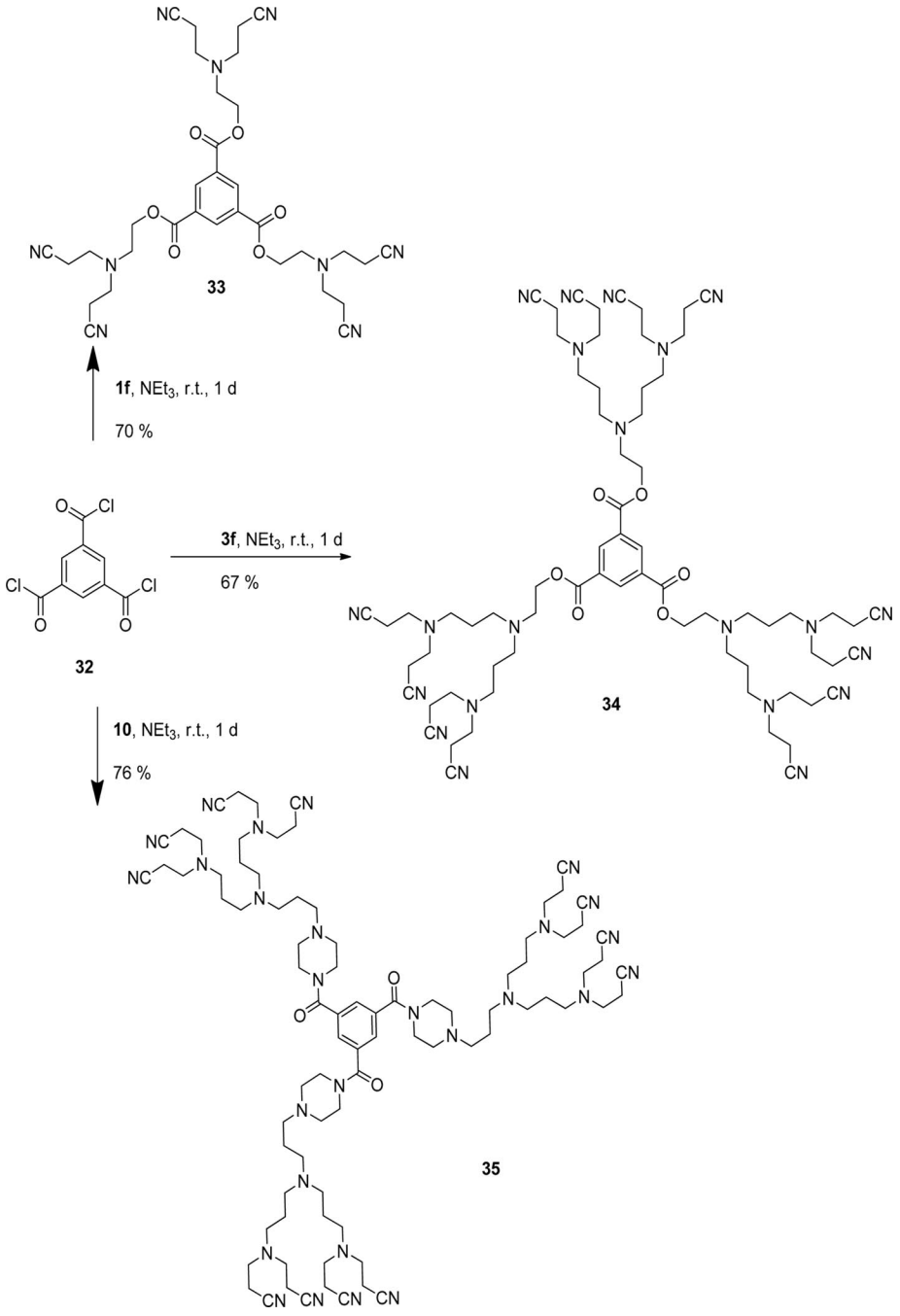
Scheme 8. Synthesis of polyamine dendrimer **31** by nucleophilic substitution/reduction.

Experimental Section

General Experimental Details: All reagents and solvents were purified or dried before use by the usual procedures. $[Rh(cod)Cl]_2$ was prepared according to a literature procedure.[36] Column chromatography was carried out on 70–230 mesh silica gel (Macherey-Nagel; silica gel 60). Dialysis was performed by using benzoylated cellulose tubing (Sigma–Aldrich, MWCO 1000) with chloroform, dichloromethane, or methanol as the solvent. High-pressure reactions were carried out in a magnetically stirred Berghof type A (250 mL, four glass vials, each 20 mL) pressure vessel, a similar in-house made autoclave (100 mL), or in a PARR autoclave. ^{1}H NMR spectra were recorded with a Bruker Avance DRX 400 or Bruker Avance DRX 500 spectrometer. Chemical shifts (δ) are reported in ppm relative to TMS, with $CDCl_3$ (δ_H= 7.24 ppm, δ_C = 77.0 ppm) or CD_3OD (δ_H = 3.30 ppm, δ_C = 49.0 ppm) as internal standard. Coupling constants (J) are given in Hz. IR spectra were recorded as films on NaCl or KBr plates with a Nicolet Impact 400D FTIR spectrometer. High-resolution mass analyses were performed with a Jeol JMS-SX 102A instrument operating at 70 eV.

General Procedure for the Michael Addition of Acrylonitrile to Amines (GP1): The amine (1.0 equiv.) was dissolved in water, and acrylonitrile (2.5 equiv. per amine group) was added dropwise. The mixture was heated to reflux for 2–3 h (for amino alcohols at room temperature for 3 d). The excess acrylonitrile was evaporated under vacuum, and the oily residue was mixed with chloroform and added to water. The organic layer was washed with water (×2) and dried with $MgSO_4$. Filtration and evaporation of the solvent afforded the product.

General Procedure for the Reduction of Polynitriles (GP2): The nitrile compound (100 wt.-%) was dissolved in a small amount of methanol in a PARR autoclave. Water (100 mL) was added to generate a milky suspension. Raney cobalt catalyst (200 wt.-%; wet;



Scheme 9. Synthesis of polynitrile dendrimers by reaction with an acyl chloride core.

type Grace 2724 from Grace; manufacturer's specification: 78–96 wt.-% Co, 0.5–5 wt.-% Ni, 0.5–5 wt.-% Cr, 3–12 wt.-% Al) was washed with water and introduced into the autoclave. After the autoclave had been closed, stirring of the mixture was started, and the autoclave was purged twice with Ar and once with H_2. The autoclave was heated to 65–75 °C while stirring (1500 rpm) at a H_2 pressure of 30–50 bar. The reaction was carried out under H_2 for 2 h to 1 d and stopped by cooling of the autoclave to room temperature. The H_2 was drained, and the autoclave was purged with Ar, opened, and the contents were immediately filtered. Solvent evaporation afforded the desired product.

General Procedure for the Boc Deprotection (GP3): The Boc-protected amine was dissolved in dioxane/HCl (3 M; 3:2) and stirred at room temperature overnight. The solvent was removed, and sodium hydroxide was added until a strongly basic solution was obtained; then the solution was extracted immediately with dichloromethane (× 3). The organic layer was dried with $MgSO_4$, and the solvent was removed under reduced pressure.

General Procedure for the Hydroaminomethylation Reaction (GP4): The olefinic compound (1 equiv. for every secondary amine group, 2 equiv. for every primary amine group), $[Rh(acac)(CO)_2]$ (1 mol-%), and the amine (core) were dissolved in a solvent mixture (usually dioxane/methanol/triethylamine), placed in an autoclave, and pressurized with 40 bar H_2 and 40 bar CO. After stirring at 80–120 °C for 2–3 d, the solvent was removed, and the crude product was purified by dialysis and analyzed by NMR spectroscopy.

Supporting Information (see footnote on the first page of this article): Synthetic procedures and full characterization data of all new compounds.

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[1] a) P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev.* **1999**, *99*, 3329–3366; b) P. Eilbracht, A. Schmidt, *Top. Organomet. Chem.* **2006**, *18*, 65–95; c) R. Kubiak, I. Prochnow, S. Doye, *Angew. Chem.* **2010**, *122*, 2683–2686; *Angew. Chem. Int. Ed.* **2010**, *49*, 2626–2629; d) B. Hamers, E. Kosciusko-Morizet, C. Muller, D. Vogt, *ChemCatChem* **2009**, *1*, 103–106; e) M. A. Subhani, K. S. Mueller, P. Eilbracht, *Adv. Synth. Catal.* **2009**, *351*, 2113–2123; f) T. O. Vieira, H. Alper, *Org. Lett.* **2008**, *10*, 485–487; g) M. Ahmed, C. Buch, L. Routaboul, R. Jackstell, H. Klein, A. Spannenberg, M. Beller, *Chem. Eur. J.* **2007**, *13*, 1594–1601; h) M. Ahmed, R. P. J. Bronger, R. Jackstell, P. C. L. Kamer, P. W. N. M. van Leeuwen, M. Beller, *Chem. Eur. J.* **2006**, *12*, 8979–8988.

[2] a) C. Claver, P. W. N. M. van Leeuwen, in *Rhodium Catalyzed Hydroformylation*; Kluwer Academic Publishers, Dordrecht, The Netherlands, **2000**; b) C. Claver, M. Dieguez, O. Pamies, S. Castillon, *Top. Organomet. Chem.* **2006**, *18*, 35–64; c) M. Vasylyev, H. Alper, *Synthesis* **2010**, 2893–2900; d) S. Chercheja, S. K. Nadakudity, P. Eilbracht, *Adv. Synth. Catal.* **2010**, *352*, 637–643; e) B. P. Bondzic, A. Farwick, J. Liebich, P. Eilbracht, *Org. Biomol. Chem.* **2008**, *6*, 3723–3731.

[3] a) E. W. Baxter, A. B. Reitz, *Org. React.* **2002**, *59*, 1–714; b) S. Gomez, J. A. Peters, T. Maschmeyer, *Adv. Synth. Catal.* **2002**, *344*, 1037–1055; c) T. E. Mueller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795–3892.

[4] a) T. Rische, P. Eilbracht, *Synthesis* **1997**, 1331–1337; b) C. L. Kranemann, P. Eilbracht, *Synthesis* **1998**, 71–72; c) T. Rische, P. Eilbracht, *Tetrahedron* **1999**, *55*, 7841–7846; d) C. L. Kranemann, B. Costisella, P. Eilbracht, *Tetrahedron Lett.* **1999**, *40*, 7773–7776; e) C. L. Kranemann, P. Eilbracht, *Eur. J. Org. Chem.* **2000**, 2367–2377; f) G. Angelovski, P. Eilbracht, *Tetrahedron* **2003**, *59*, 8265–8274; g) A. Schmidt, M. Marchetti, P. Eilbracht, *Tetrahedron* **2004**, *60*, 11487–11492.

[5] a) F. Koç, P. Eilbracht, *Tetrahedron* **2004**, *60*, 8465–8476; b) F. Koç, M. Wyszogrodzka, P. Eilbracht, R. Haag, *J. Org. Chem.* **2005**, *70*, 2021–2025.

[6] a) D. A. Tomalia, A. M. Taylor, W. A. Goddard, *Angew. Chem.* **1990**, *102*, 119–157; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138–175; b) A. W. Bosman, H. M. Jamsem, E. W. Meijer, *Chem. Rev.* **1999**, *99*, 1665–1688; c) G. R. Newkome, C. N. Moorefield, F. Vögtle, in *Dendrimers and Dendrons*, Wiley-VCH, Weinheim, **2001**.

[7] a) T. Chuard, M. T. Béguin, R. Deschenaux, *C. R. Chim.* **2003**, *6*, 959–962; b) M. Marcos, R. Martin-Rapun, A. Omenat, J. L. Serrano, *Chem. Soc. Rev.* **2007**, *36*, 1889–1901.

[8] a) C. Heeschen, B. U. Goldmann, L. Langenbrink, G. Matschuck, C. W. Hamm, *Clin. Chem.* **1999**, *45*, 1789–1796; b) S. E. Stiriba, H. Frey, R. Haag, *Angew. Chem.* **2002**, *114*, 1385–1390; *Angew. Chem. Int. Ed.* **2002**, *41*, 1329–1334; c) S. Bai, C. Thomas, A. Rawat, F. Ahsan, *Crit. Rev. Ther. Drug Carrier Syst.* **2006**, *23*, 437–495.

[9] S. C. Lo, P. L. Burn, *Chem. Rev.* **2007**, *107*, 1097–1116.

[10] a) R. P. Briñas, T. Troxler, R. M. Hochstrasser, S. Vinogradov, *J. Am. Chem. Soc.* **2005**, *127*, 11851–11862; b) V. Balzani, P. Ceroni, S. Gestermann, C. Kauffmann, M. Gorka, F. Vögtle, *Chem. Commun.* **2000**, 853–854; c) N. Jayarman, in *Nanomaterials Chemistry* (Eds: C. N. R. Rao, A. Müller, A. K. Cheetham), Wiley-VCH, Weinheim, **2007**, pp. 249–298.

[11] a) Y. Gao, G. Gao, Y. He, T. Liu, R. Qi, *Mini-Rev. Med. Chem.* **2008**, *8*, 889–900; b) C. Dufes, I. F. Uchegbu, A. G. Schaetzlein, *Adv. Drug Delivery Rev.* **2005**, *57*, 2177–2202.

[12] a) U. Boas, P. M. H. Heegaard, *Chem. Soc. Rev.* **2004**, *33*, 43–63; b) M. Liu, J. M. J. Fréchet, *Pharm. Sci. Technol. Today* **1999**, *2*, 393–401; c) G. R. Newkome, C. N. Moorefield, R. Güther, G. R. Baker, *Polym. Prepr.* **1995**, *36*, 609–610; d) A. Agarwal, A. Asthana, U. Gupta, N. K. Jain, *J. Pharm. Pharmacol.* **2008**, *60*, 671–688.

[13] a) B. J. Hong, J. Y. Shim, S. J. Oh, J. W. Park, *Langmuir* **2003**, *19*, 2357–2365; b) E. Kontturi, P. C. Thüne, J. W. Niemantsverdriet, *Polymer* **2003**, *44*, 3621–3625.

[14] a) A. K. Andreopoulou, B. Carbonnier, J. K. Kallitsis, T. Pakula, *Macromolecules* **2004**, *37*, 3576–3587; b) G. R. Newkome, C. D. Weis, C. N. Moorefield, G. R. Baker, B. J. Childs, J. D. Epperson, *Angew. Chem.* **1998**, *110*, 318–321; *Angew. Chem. Int. Ed.* **1998**, *37*, 307–310.

[15] I. Singh, A. K. Rehni, R. Kalra, G. Joshi, M. Kumar, *Pharmazie* **2008**, *63*, 491–496.

[16] a) D. Astruc, F. Chardac, *Chem. Rev.* **2001**, *101*, 2991–3024; b) A. Datta, K. Ebert, H. Plenio, *Organometallics* **2003**, *22*, 4685–4691; c) H. U. Blaser, A. Indolese, A. Schnyder, H. Steiner, M. Studer, *J. Mol. Catal. A* **2001**, *173*, 3–18.

[17] a) R. Haag, S. Roller, in *Polymeric Materials in Organic Synthesis and Catalysis* (Ed.: M. R. Buchmeiser), Wiley-VCH, Weinheim, **2003**, pp. 305–344; b) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3430; c) R. Haag, S. Roller, *Top. Curr. Chem.* **2004**, *242*, 1–42; d) J. P. K. Reynhardt, Y. Yang, A. Sayari, H. Alper, *Adv. Synth. Catal.* **2005**, *347*, 1379–1388; e) R. Kreiter, A. W. Kleij, R. J. M. K. Gebbink, G. van Koten, *Top. Curr. Chem.* **2001**, *217*, 163–199.

[18] a) R. Haag, *Chem. Eur. J.* **2001**, *7*, 327–335; b) C. A. Schalley, F. Vögtle, *Dendrimers V: Functional and Hyperbranched Building Blocks, Photophysical Properties, Applications in Materials and Life Sciences*, Springer, Berlin, **2003**; c) F. Vögtle, *Dendrimers II: Architecture, Nanostructure and Supramolecular Chemistry*, Springer, Berlin, **2000**.

[19] a) M. Scott, S. M. Grayson, J. M. J. Frechet, *Chem. Rev.* **2001**, *101*, 3819–3868; b) C. J. Hawker, J. M. J. Frèchet, *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647; c) C. Hawker, J. M. J. Frèchet, *J. Chem. Soc., Chem. Commun.* **1990**, 1010–1013.

[20] a) D. A. Tomalia, H. Baker, J. Dewald, M. Hall, G. Kallos, S. Martin, J. Roek, J. Ryder, P. Smith, *Polym. J.* **1985**, 117–132; b) G. R. Newkome, Z. Yao, V. K. Gupta, *J. Org. Chem.* **1985**, *50*, 2004–2006; c) G. R. Newkome, Z. Yao, G. R. Baker, V. K. Gupta, P. S. Russo, M. J. Saunders, *J. Am. Chem. Soc.* **1986**, *108*, 849–850.

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

[22] a) R. Moors, F. Vögtle, *Chem. Ber.* **1993**, *126*, 2133–2135; b) C. Wörner, R. Mülhaupt, *Angew. Chem.* **1993**, *105*, 1367–1370; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1306–1308; c) R. J. Bergeron, J. R. Garlich, *Synthesis* **1984**, 782; d) E. M. M. Brabander-van den Berg, E. W. Meijer, *Angew. Chem.* **1993**, *105*, 1370–1372; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1308–1311; e) J. C. Hummelen, J. L. J. Van Dongen, E. W. Meijer, *Chem. Eur. J.* **1997**, *9*, 1489–1493.

[23] a) K. N. Ganesh, D. Nagamani, *Org. Lett.* **2001**, *3*, 103; b) G. R. Newkome, A. Mishra, C. N. Moorefield, *J. Org. Chem.* **2002**, *67*, 3957–3960.

[24] E. De Brabander-van Den Berg, E. W. Meijer, F. H. Vandenbooren, H. J. M. Bosman, *Int. Pat. Appl.* **1993**, WO9314147.

[25] D. Boschi, A. Di Stilo, R. Fruttero, C. Medana, G. Sorba, A. Gasco, *Arch. Pharm. (Weinheim, Ger.)* **1994**, *327*, 661–667.

[26] C. J. Ohnmacht, J. B. Melick, *U. S. Pat. Appl.* **1981**, US4247549.

[27] a) C. D. Jones, R. W. A. Luke, W. McCoull, *Int. Pat. Appl.* **2005**, WO2005060970; b) H. G. Lerchen, H. U. Siegmund, D. Immler, A. Schumacher, D. Auriel, *Int. Pat. Appl.* **2003**, WO2003040288; c) G. S. Poindexter, M. Bruce, S. Y. Sit, S. W. Martin, *Int. Pat. Appl.* **2001**, WO2001085173.

[28] a) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675–703; b) C. R. Landis, J. Uddin, *J. Chem. Soc., Dalton Trans.* **2002**, 729–742; c) P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *Acc. Chem. Res.* **2001**, *34*, 895–907; d) J. J. Carbó, F. Maseras, C. Bo, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2001**, *123*, 7630–7637.
[29] a) L. A. van der Veen, P. H. Keeven, G. C. Schoemaker, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, M. Lutz, A. L. Spek, *Organometallics* **2000**, *19*, 872–883; b) M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Franje, *Organometallics* **1995**, *14*, 3081–3089.
[30] S. Ram, L. D. Spicer, *Synth. Commun.* **1987**, *17*, 415–418.
[31] R. C. Bernotas, R. V. Cube, *Synth. Commun.* **1990**, *20*, 1209–1212.
[32] J. Apelt, X. Ligneau, H. H. Pertz, J. M. Arrang, C. R. Ganellin, J. C. Schwartz, W. Schunack, H. Stark, *J. Med. Chem.* **2002**, *45*, 1128–1141.
[33] a) H. P. Dijkstra, G. P. M. van Klink, G. van Koten, *Acc. Chem. Res.* **2002**, *35*, 798–810; b) J. T. Scarpello, D. Nair, L. M. Freitas dos Santos, L. S. White, A. G. Livingston, *J. Membr. Sci.* **2002**, *203*, 71–85; c) J. Wöltinger, K. Drauz, A. S. Bommarius, *Appl. Catal. A* **2001**, *221*, 171–185.
[34] Monsanto Chem. Co., *U. S. Pat. Appl.* **1957**, US2816129.
[35] a) C. B. Gorman, J. C. Smith, *Acc. Chem. Res.* **2001**, *34*, 60–71; b) J. F. G. A. Jansen, E. M. M. de Brabander van den Berg, E. W. Meijer, *Science* **1994**, *266*, 1226–1229; c) S. Xu, Y. Luo, R. Haag, *Macromol. Biosci.* **2007**, *7*, 968–974.
[36] a) B. Neumann, C. Sauer, S. Diele, C. Tschierske, *J. Mater. Chem.* **1996**, *6*, 1087–1903; b) J. Andersch, S. Diele, P. Goering, J. A. Schroeter, C. J. Tschierske, *J. Chem. Soc., Chem. Commun.* **1995**, 107–108.

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