JOURNAL OF Materials CHEMISTRY
Feature Article

Chiral dendrimers—from architecturally interesting hyperbranched macromolecules to functional materials†

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Received 8th November 2001, Accepted 21st January 2002
First published as an Advance Article on the web 5th March 2002

The development of dendrimer chemistry has seen the realisation of a diverse range of architecturally fascinating macromolecules that have received extensive attention in the literature. Perhaps the most synthetically challenging hyperbranched polymers are chiral dendrimers and this review describes notable examples in this field. However, more importantly, these structurally complex macromolecules are not just artefacts—the application of chiral dendrimer systems in catalytic processes is covered in this article and recent developments of such technologies towards novel asymmetric catalysts are described.

1. Introduction

Dendrimers represent a new class of polymers[1] that possess regular highly branched and well-defined structures. These interesting macromolecules are composed of a central core, branching units and peripheral end groups and are synthesized typically *via* stepwise repetitive reaction sequences. Although the construction of dendritic polymers was first postulated by Flory in 1952,[2] it was not until the late 1970's that the first designed syntheses of branched macromolecules of this type was reported.[3] This seminal paper described a divergent[4] approach to so-called *cascade* molecules and since this report, numerous dendrimer systems have been prepared using either convergent[5] or divergent methodologies. Consequently, poly(aromatic ether),[6] poly(acetylene),[7] poly(phenylene),[8] poly(ester)amide,[9] poly(phosphane),[10] poly(ether)amide,[11] poly(ester)[12] and poly(silane)[13] systems have been described in the academic or patent literature—furthermore, poly(amido)amine (PAMAM)[14] and poly(propyleneimine)[15] (PPI) dendrimers are now produced on multi-kilogram scales and marketed commercially. The structural and chemical diversity of these dendritic macromolecules reflect clearly the primary aim[16] of early dendrimer research, *i.e.* the preparation and characterization of new hyperbranched polymers that possessed minimal structural defects. In conjunction with the emergence of dendritic polymers, new analytical methods have developed (such as MALDI-TOF mass spectrometry[17]) that have enabled detailed structural analysis to be undertaken on these hyperbranched macromolecules. However, the intense focus upon the synthesis of novel structurally diverse dendrimer systems has moderated gradually and detailed investigations of the chemical and physical properties of existing dendrimers are now under way. The modulation of these properties *via* minimal structural modifications has ultimately led to numerous applications of these functionalised dendrimers as drug- and gene-delivery systems, artificial antennae, magnetic resonance imaging agents (MRI), sensors, biological mimics, unimolecular micelles and catalysts.[18] One property that has attracted significant attention from several research groups is the introduction of chirality within dendritic architectures.[19] As a consequence of the well-defined branched macromolecular structures,[20] the study of chiral dendrimers should enable detailed insights upon the impact of chirality in macromolecular systems and also provide valuable data on the relationship between chirality at molecular and macroscopic levels. In addition to this purely academic driven interest, potential interesting applications of chiral dendrimers have also been envisaged, for example: in molecular recognition processes,[21] in sensor technologies[22] and in the field of catalysis.[23]

Within the remit of new catalysts, the ability to define precisely the structure of dendrimers enables the incorporation of catalytic sites at either the central core, branches or at the peripheral surface. In addition, a common property of dendrimers is their improved solubility characteristics (in comparison to their linear analogues[24]) in a diverse range of solvent systems and this enhanced catalyst solubility should favour fast kinetics (as in traditional homogeneous catalysts). Furthermore, the nanosize dimensions of dendrimers endear these macromolecules to high throughput separation methods such as ultrafiltration or nanofiltration membrane techniques (*i.e.* dendritic catalysts can be 'easily' separated from the substrates and products as in traditional heterogeneous catalysts).[25] Indeed, prototype dendritic catalysts have been applied in continuous membrane reactors[26] by several groups and have afforded promising results. Additionally, the introduction of chirality within dendritic architectures enables these systems to be used in enantioselective catalysis.

Several excellent reviews on chiral dendrimers have already been published that describe progress in this field, clearly reflecting the impact of this subclass of dendrimers in polymer science.[18,27] In this review, we wish to present a discussion of important examples of chiral dendrimers, and also offer an overview of the application and potential of these chiral hyperbranched macromolecules as catalysts in enantioselective reactions.

2. Dendrimers and chirality

Macroscopic and nanoscopic chirality are interesting properties of many polymers. However, it is essential to understand the fundamental relationships between molecular and

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†Abbreviations used: BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; BINOL: binaphthol; Boc: *tert*-butyloxycarbonyl; CD: circular dichroism; CE: Cotton effect; DDB: (*S*,*S*)-1,4-bis(dimethylamine)-2,3-dimethoxybutane; [G-*x*] represents a dendrimer of the *x*th generation; ICD: induced circular dichroism; MALDI-TOF MS: matrix assisted laser desorption ionization time-of-flight mass spectrometry; MRI: magnetic resonance imaging; ORD: optical rotatory dispersion; PAMAM: poly(amido)amine; PPI: poly(propyleneimine); STM: scanning tunnel microscopy; TADDOL: $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol.

DOI: 10.1039/b110218b

macroscopic chirality in order to access new materials whose properties and functions depend on the expression of chirality at a macromolecular level.[28] Major difficulties encountered in such structural and physical studies are generally related to the complexity of the materials under investigation. Despite these limitations, the effect of chiral units on the global conformation of linear polymers has been extensively studied.[29] However, in order to attain a comprehensive understanding of these chiroptical features, well-defined polymers (*i.e.* molecular weights, polydispersity) are required. In this respect, dendrimers represent excellent candidates for use in such studies as a consequence of their well-defined structure, topology and molecular weight.[4]

Several key questions have arisen upon consideration of the expression of chirality in hyperbranched systems and include:

(1) How are the chirality of dendritic building blocks and the resultant three-dimensional structure related?

(2) More specifically, can chiral building blocks induce a chiral conformational order within dendritic macromolecules?

(3) As evident in atactic linear polymer systems,[30] can chiral dendrimers manifest *cryptochirality* (*i.e.* lack of detectable optical activity of a structurally chiral molecule)?[31]

(4) In addition, by comparison with linear polymers (both isotactic and syndiotactic polymers, even if achiral, can generate optical activity by adopting a favoured helical conformation),[32] can structurally achiral dendrimers generate chiral conformations?

The importance of determining the general elements that govern macromolecular chirality in dendrimers as well as developing analytical methods for the determination of dendritic conformational order are related to the potential application of these hyperbranched materials in fields such as catalysis.[23]

Several types of chiral dendrimers have been described.[19,27] Since naturally occurring asymmetric building blocks such as amino acids,[33] carbohydrates[34] and oligonucleotides[35] are available readily from the natural chiral pool, these substrates have been targeted for use in the construction of chiral dendrimers. However, apart from a few exceptions, the chiroptical properties of these chiral macromolecules have not been described as the attention focused mainly on their roles in biological systems.[36] Chiral dendrimers have also been prepared by employing synthetic monomers, and this alternative approach enabled extensive investigations upon the effect of the chiral units on the dendrimer conformation to be carried out.

To date, all of the chiral dendrimer systems reported in literature can be categorised into one of the following classes (see Fig. 1): (A) dendrimers possessing a chiral core and achiral branches; (B) dendrimers possessing chiral peripheral surface groups; (C) dendrimers constructed from an achiral core and constitutionally different branches; (D) dendrimers featuring chiral branched units; (E) chiral dendrimers incorporating a chiral core, asymmetric branching units and optically active peripheral surface groups.

Important cases of each of the above sub-classes of chiral dendrimers will be highlighted in the following sections.

2.1 Dendrimers possessing a chiral core and achiral branches

Within the different studies describing the synthesis and analysis of chiroptical properties of dendrimers possessing a chiral core, several key common questions have been posed:

(1) Is the chirality of the chiral core maintained when incorporated into a large chiral environment?

(2) Can the chirality of a single sub-unit be transmitted to a distal portion of the macromolecule inducing a chiral conformational order?

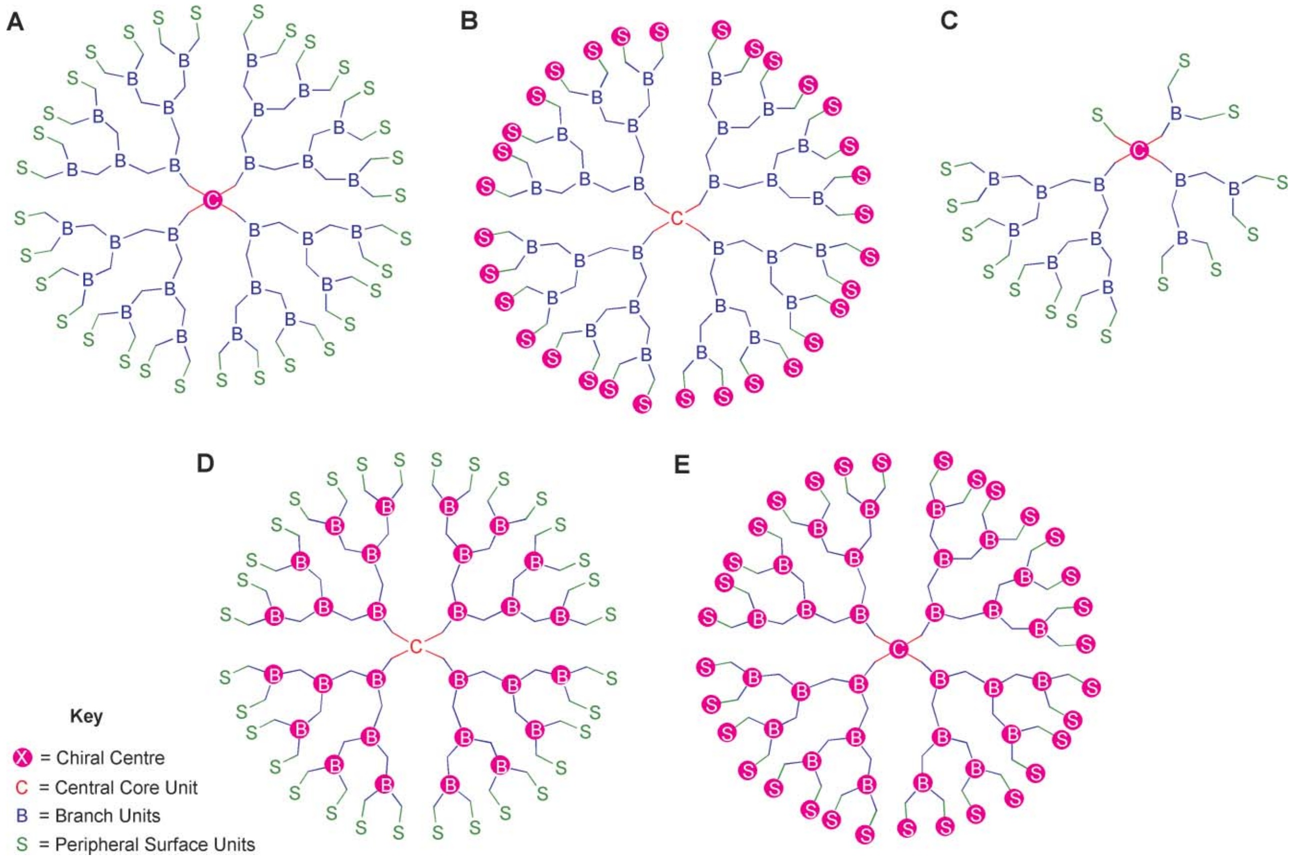

Fig. 1 A cartoon representation of the variety of possible formats for chiral dendrimers that feature: (A) a chiral central core, (B) chiral units at the peripheral surface, (C) achiral core coupled to constitutionally different branches, (D) chiral branching units and (E) chiral units at the core, branches and peripheral surface.

(3) Can a chiral core develop cavities for enantioselective molecular recognition within the macromolecular system?

Dendrimers that incorporated a chiral core were first reported[37] by Seebach *et al.* The synthesis and studies of a series of chiral dendrimers (up to the 3rd generation) based on a tris(hydroxymethyl)methane core unit (see **1** (R = H) in Fig. 2) and coupled to aromatic polyether (Fréchet type) dendrons were described. Studies of the chiroptical properties revealed that in the case of the branched systems featuring an aliphatic spacer between the achiral dendrons and the chiral tris(hydroxymethyl)methane core unit (**2a–c**), both optical and molar rotations were minimal for each generation. The rationale presented to explain the 'loss' of chiral information was a *dilution effect* (that is predicted when achiral branches are anchored to a chiral core[31]) and increased flexibility of the dendrons induced by the aliphatic spacer linker. This hypothesis was supported by studies upon dendrimers containing the same chiral core unit that was coupled to the aromatic polyether dendrons directly (**1a–c**) or *via* a rigid aromatic spacer moiety (**3a–c**). These structural modifications led to different chiroptical properties, and in the case of (**3a–c**) the molar rotation values were virtually constant as the generation number increased ($[\Phi]_{D}^{rt}$ = **3a**: +98, **3b**: +101, **3c**: +103). This trend indicates that the chirality of the core unit is 'maintained' but does not induce chiral substructures within the hyperbranched macromolecule. More remarkably, in the case of (**1a–c**) the molar rotation decreased slightly from the 1st to 2nd generation dendrimer ($[\Phi]_{D}^{rt}$ = **1a**: +48, **1b**: +46), but almost doubled upon progression to the 3th generation ($[\Phi]_{D}^{rt}$ = **1b**: +46 , **1c**: +87). This result could indicate the presence of an induced conformational chiral order within the larger dendrimer system as a consequence of the enhanced rigidity of the overall structure.

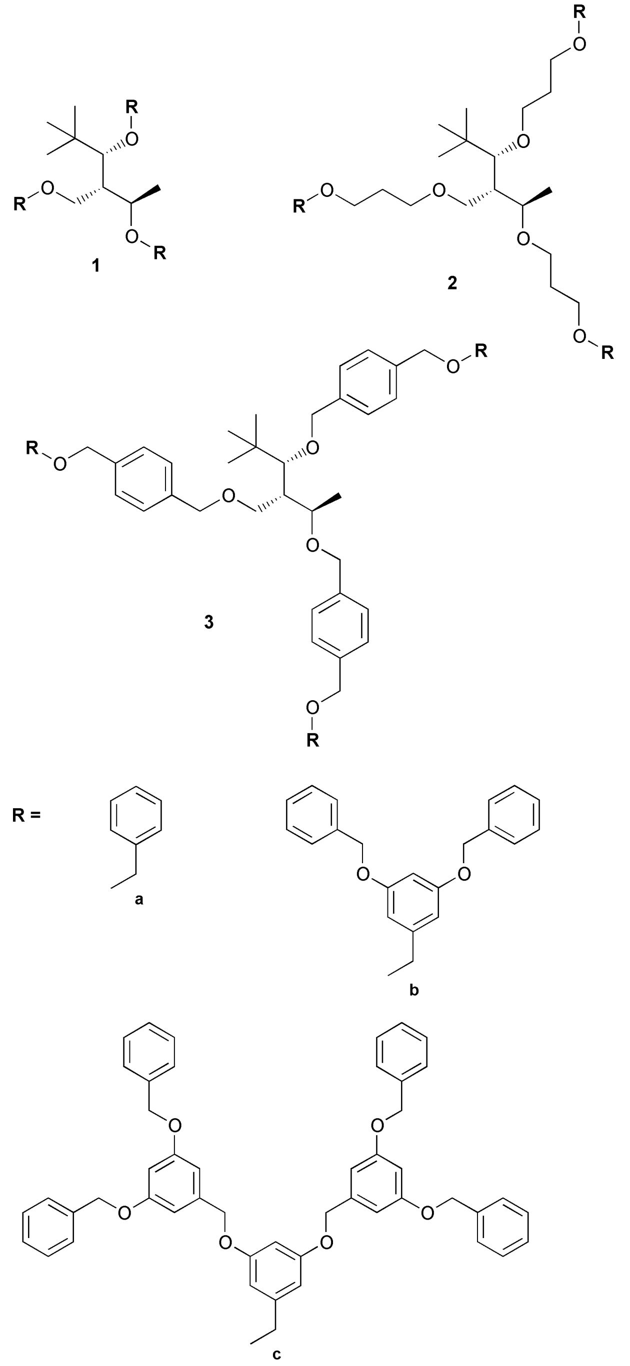

Fig. 2 Chiral dendrimers based on the tris(hydroxymethyl)methane core unit coupled to aromatic polyether (Fréchet type) dendrons (**a**, **b**, **c**) either directly **1**, through an alkyl spacer **2** or *via* an aromatic spacer **3**.[37]

Seebach also described, as part of the same study, the chiroptical properties of related dendrimers that possessed the same chiral core but that were coupled to rigid polyamide aromatic dendrons (see **4a–b** in Fig. 3). In this series, increasing the generation number of the polyamide aromatic dendrons (from the 1st to 2nd) resulted in the molar rotation not only changing value *but* more significantly sign (from −124 to +155). This remarkable behaviour was attributed to the contribution to the optical activity from chiral substructures induced at the periphery of the dendrimer.

However, several studies have demonstrated that these observed anomalies in the optical activity behaviour of dendrimers that possess a chiral core cannot always be attributed to induced conformational order within the dendritic architecture. Many structural and conformational factors have to be considered when interpreting the chiroptical properties as illustrated by Parquette and co-workers.[38] In this investigation, it was observed that both the optical and molar rotations of ester terminated dendrimers based on

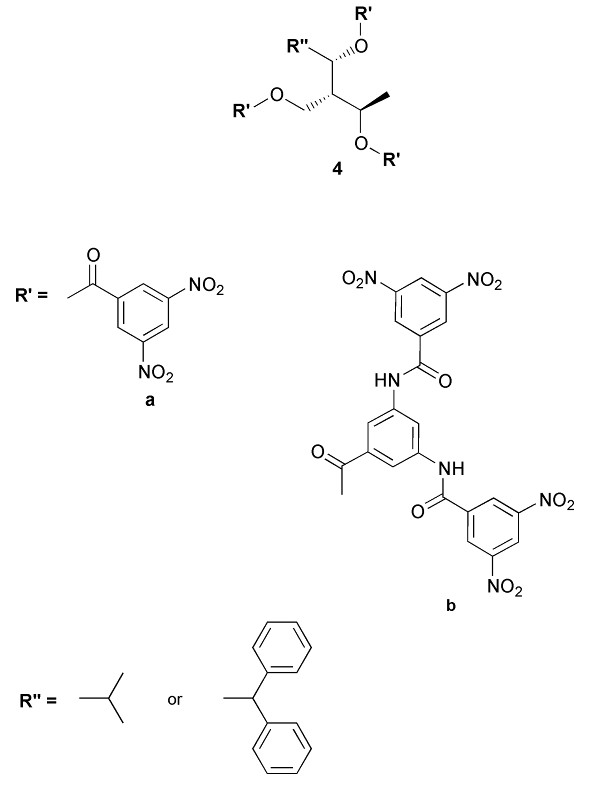

Fig. 3 Rigid polyamide aromatic dendrimers (**4a** and **b**) featuring a tris(hydroxymethyl)methane chiral core unit.[37]

aromatic polyether dendrons and (1*R*,2*S*)-2-amino-1-phenylpropane-1,3-diol as the chiral core decreased as the dendrimer generation number increased ($[\Phi]_D^{rt}$ = [G-1]: +2352, [G-2]: +1418, [G-3]: +1209). This behaviour was rationalised by significant back-folding of the terminal groups and dendritic arms, leading to a higher density located near the central core rather than at the periphery of the dendrimer.[39] This steric effect induces a perturbation of the conformational equilibrium at the core and consequently changes its optical activity. In support of this hypothesis, Parquette and co-workers demonstrated that model compounds that were constructed from the same core yet featuring small, hindered substituents exhibited completely different optical activity—*not only* in the scale of the optical rotation but also in the sign. Circular dichroism (CD) analysis of these model systems provided even more conclusive evidence to support this back-folding behaviour of dendrimers of this type. The CD spectra obtained for the single chiral core and the dendrimers were very similar, exhibiting comparable shapes and amplitudes of the Cotton effect (CE). Exciton coupling that is related to interactions between chromophores in the branches or in the peripheral units was not detected in any of the CD spectra of the chiral aromatic polyether dendrimers. In addition, the study of the solvent dependence[40] of the chiroptical properties revealed that an increase in the polarity of the solvent used (from $CHCl_3$ to THF–CH_3CN (1 : 4)) had a profound effect with both optical rotation and ellipticity diminishing significantly. This solvent effect indicates that an increase in solvent polarity causes the branched dendritic arms to collapse upon the core in order to reduce unfavourable interactions between the polar solvent and the apolar interior, resulting in a drastic change of the conformation at the chiral core. The same research group obtained similar results when the chiroptical properties of a dendrimer system based on 2,5-anhydromannitol coupled to aromatic polyether (Fréchet type) dendrons were studied.[41] This investigation found that an increase in the size of the dendrimer (from 1st to 3rd generation) led to a gradual decrease in the negative molar rotation values ($[\Phi]_D^{rt}$ = [G-1]: −1644, [G-2]: −1307, [G-3]: −1041). The only deviation from this trend was observed upon increasing the generation number of the polyether dendrimer from the 0th to the 1st generation, in which case the molar rotation increased ($[\Phi]_D^{rt}$ = [G-0]: −1055, [G-1]: −1644). It has been proposed that this result could indicate the presence of chiral conformational order within the dendritic structure, but further studies are required since optical activity may vary with changes in constitution[42] or solvent systems used.[43]

In the previous examples reported, chirality has been introduced by using stereocentres. However, several reports have described the synthesis of asymmetric dendrimers possessing axial chirality originating at the central core component of the dendrimer. For example, Chen *et al.*[44] coupled (*R*)-1,1′-bi-2-naphthol either to the same or different generation Fréchet-type dendrons up to the 2nd generation. The study of the chiroptical properties revealed a molar rotation enhancement as the dendron size increased, especially in the case of dendrimers bearing aromatic polyether dendrons of the same generation. This result was not attributed to the presence of chiral substructure induced by the chiral core but to changes of the dihedral angle between the molecular planes of the aromatic moieties. The similarity of the CD spectra that exhibit two significant CE characteristics of the naphthalene ring (negative at 240 and positive at 228 nm) for the independent binaphthol core and the corresponding dendrimers support this interpretation. The only anomalies within this trend were intensity changes of the CE and a decrease of the curve amplitude observed as the generation number of the dendron increased. This behaviour was ascribed to an increased dihedral angle in the binaphthol unit,[45] caused by an enhanced repulsion of the bulky dendritic substituents that are located closely together in the 2,2′-positions of the binaphthol rings. The dependence of the optical activity of dendrimers that possess a binaphthol unit at the core upon its characteristic torsional angle has also been demonstrated by Meijer *et al.*[46] in an independent study. (*S*)-1,1′-Bi-2-naphthol was coupled to aromatic polyether dendrons up to the 5th generation and the molar rotations (Φ) observed for the 0th and 1st generation dendrimers remained almost constant ($[\Phi]_D^{rt} \approx -200$). However, as the generation number of the dendritic component increased, the molar rotation value increased in a negative fashion ($[\Phi]_D^{rt}$ = −203, −271, −424, −678 for the 2nd, 3rd, 4th and 5th generation dendrimers, respectively). In previous studies of modified bridged (*S*)-1,1′-bi-2-naphthol systems,[47] positive molar rotation values were observed suggesting that the high degree of conformational rigidity that is present in these structures leads to a small torsional angle between the two aromatic rings. The sign inversion of the molar rotation for the related dendritic substrates indicates that the dihedral angle of the binaphthol core exceeds 90° as a consequence of the steric hindrance. Therefore, the increasing size of the dendritic wedges at higher generation leads to larger negative molar optical rotation values. In a related study, a quantitative correlation between the CD spectral data and the dihedral angle between the aromatic rings of a binaphthol system has been reported[48] by Rosini and co-workers. Yamago, Yoshida and co-workers have also described[49] the incorporation of binaphthol units within a dendritic structure, in order to create metal ligands for use in asymmetric catalysis (*vide infra*). When aromatic polyether dendrons (up to the 4th generation) were coupled to the binaphthol core *via* the 6,6′-positions, the dihedral angle between the naphthyl ring systems changed, but not, however, to the same extent reported in the case of the 2,2′-substituted binaphthyl dendrimers—in this study the molar rotation values observed remained almost constant irrespective of the generation number of dendrons used. These data sets suggest that the relationship between the molar rotation values observed and the torsional angle of the binaphthyl unit are not only dependent upon the bulkiness of the dendritic substituents but also on their position on the binaphthyl backbone. An attempt to reduce the conformational flexibility of dendrimers containing a binaphthol core in order to induce chiral amplification was reported[22,50] by Pu and co-workers. Rigid poly(phenylacetylene) dendrons were coupled to (*S*)- or (*R*)-1,1′-bi-2-naphthol units at either the 4,4′- or 6,6′-positions. The molar rotation values observed remained constant for each of the dendrimers synthesized and both the intensities and wavelength of the CE did not change significantly. It was evident that even the introduction of structurally rigid poly(phenylacetylene) dendrons did not lead to the induction of chiral conformational order in these chiral dendrimers. However, as a consequence of extended conjugation within these dendritic systems, very strong fluorescent emissions were observed and thereby offering potential applications as enantioselective fluorescence sensors.

Chiral dendrimers based on planar chirality at the central core have also been described[51] by Vögtle *et al.* Three different supramolecular chiral core units were employed in these studies, a [2]rotaxane, a [2]catenane and a [2,2]paracyclophane.[52,53] These macromolecular cores were coupled to Fréchet type dendrons (up to the 3rd generation). Only slight variations in the CE intensities were observed upon increasing the generation number of the aromatic polyether dendrons for both of the mechanically interlocked systems—this effect was attributed to subtle conformational changes in the structure of the core. As the size of the dendron increased, the cyclic component of the rotaxane system modified its position on its axle and in a similar fashion, the catenated cyclophane rings adopted different conformations relative to each other as a direct consequence of the bulky branched substituents. In contrast, significant changes of the CE intensities were observed for the series of cyclophanes that bore dendritic components, the so-called *dendrophanes*. By simple consideration of the dendrophanes' structure, rationalization of these experimental findings was difficult by consideration of conformational changes at the central macrocyclic core unit alone. It has been proposed that the chiral unit at the core imparts significant conformational changes and order upon all of the macromolecule—however, this macroscopic effect is difficult to envisage taking into account the findings of other investigations that have employed relatively flexible polyether dendrons of this type (*vide supra*).

The first example of the application of core functionalised chiral dendrimers as enantioselective receptors in molecular recognition processes was described[54] by Diederich *et al.* The so-called *dendroclefts* feature a central 9,9′-spirobi[9*H*-fluorene] core moiety bearing 2,6-bis(carbonylamino)pyridine groups at the 2,2′-position that in turn are coupled to triethyleneglycol monomethyl ether dendrons (up to the 2nd generation) (see **5** in Fig. 4). The molar rotation values for this series of chiral dendrimers were found to remain almost constant indicating that the axial chirality of the core is the principal contributor to the molar rotation, with no influence from the dendritic branches. However, the CD spectra of the dendroclefts revealed interesting features that were not evident from the optical rotation studies. A shift of the peak maximum of the positive CE band to shorter wavelengths and a decrease of the relative intensities of the major positive (I_{Max}) and the major negative (I_{Min}) bands were observed as the size of the dendron increased. The hypothesis proposed to account for these results detailed either changes in the torsional angle between the fluorene and the pyridine rings or to hydrogen bonding interactions[55] between the oxygen atoms in the dendritic wedges and the amide protons of the core unit. Remarkably, these dendroclefts can complex monosaccharides in a stereoselective fashion. Both ^{1}H NMR and CD spectroscopic studies revealed that the enantioselective recognition of monosaccharide systems by the dendroclefts decreased progressively upon an increase in the size of the dendritic component of the receptor. In the case of the dendroclefts possessing smaller dendrons, significant changes in the CD spectra were observed when the solution of the dendrocleft was titrated with solutions of the monosaccharide octyl α-D-glucoside. These spectroscopic changes included the appearance of a negative band at 280 nm, a bathochromic shift with increasing intensity of the positive band at 296 nm and a decrease in the intensity of the negative band at 332 nm. However, when the enantiomer octyl α-L-glucoside was added at the same concentration, the responses were markedly different especially for the negative band at 332 nm—no changes were observed at this wavelength. These results indicate that stereospecific sugar recognition occurs at the chiral core as the sugars are able to migrate through the branched periphery. Although the dendroclefts that incorporate higher generation dendrons also exhibit chiroptical monosaccharide sensing, the responses were significantly smaller. It has been suggested that as a result of the increased dimensions of the peripheral branches, the monosaccharide guests are not bound within close proximity to the spirobifluorene cleft leading to smaller changes in its chiroptical properties and to a 'less specific' complex formation with the dendritic branches.[56]

These studies indicate clearly that many structural factors are influential in the relationship between the chirality located at the central core unit and the nanoscopic conformation of the whole dendritic structure. It is also clear that further studies are necessary on chiral hyperbranched systems of this type in order to gain more detailed information upon the way in which a chiral central core can induce a chiral global effect on the dendrimer architecture.

2.2 Dendrimers possessing chiral peripheral surface groups

As described in the introduction, dendrimers are highly defined branched macromolecules that possess a large number of peripheral functional groups. These surface groups have been shown, in both theoretical and practical studies, to be exposed primarily at the surface of the dendrimer.[39b] However, studies have also demonstrated that dendritic branches are susceptible to 'folding' processes and in several systems back-folding of the dendritic arms towards the central core unit has been observed.[39a] Consequently, these branched macromolecules do not always present the maximum degree of functionality to their surrounding environment as was first thought. However, in contrast to linear polymers that can experience considerable chain entanglement (that in turn masks significant proportions of the macromolecules' chemical functionalities), dendritic structures do, in general, permit higher percentages of their peripheral surface groups to be available for direct interaction with reagents and other substrates. As a direct consequence of this macroscopic conformational characteristic, chemical modifications on the peripheral groups of the dendritic arms can be performed relatively easily in order to anchor different residues (such as peptides, antibodies, saccharides or metal ligands) at the dendrimer surface and thus impart different properties to the resultant dendrimers. The introduction of chiral moieties at the periphery of these branched macromolecules represents an important route to the production of new hyperbranched materials with potential applications in enantioselective catalysis or molecular recognition processes.

The first reported study upon dendrimers possessing a chiral peripheral surface was presented[57] by Newkome *et al.* in 1991. The synthesis of polyether amide dendrimers[58] (so-called *arborols*) up to the 2nd generation with enantiomerically pure tryptophan moieties at the surface were described. CD studies revealed that the molecular ellipticity increased in a proportional manner with respect to the number of tryptophan moieties at the peripheral surface. This study indicated that the chiral amino acid residues are independent from each other and do not induce any additional chiral substructure upon the dendritic framework. Similar results were obtained[59] by Chow and Mak who described the synthesis and studies of chiral dendritic fragments up to 3rd generation that featured L-tartrate derivatives between 4-*tert*-butylphenyl peripheral units and the branching monomers. The molar rotation values of these tartrate-based dendrimers were directly proportional to the number of chiral units at the dendritic surface, indicating that the chiral units were independent of each other.

In a subsequent study, Meijer *et al.* reported[60] very interesting chiroptical properties of PPI dendrimers that were terminated with a range of *tert*-butyloxycarbonyl (Boc) protected amino acids (see **6** in Fig. 5). The optical rotation values observed for this series of chiral macromolecules decreased as the generation number of the dendrimer increased (Table 1). Similar trends were observed in CD and optical rotatory dispersion (ORD) studies—the CE at 240 nm (of the carbamate chromophore) and 250–270 nm (of the phenyl chromophore) both decreased as the generation number increased. This phenomenon was evident for all the amino acid dendrimer derivatives, but was most pronounced in the cases of the dendrimers bearing sterically hindered amino acids (*i.e.* *t*-Boc-L-lysine, *t*-Boc-L-phenylalanine, *t*-Boc-D-phenylalanine and *t*-Boc-L-tyrosine). This unexpected behaviour could not be explained by the reduction of the number of chiral chromophores with respect to the molecular weight of the dendrimer, as this ratio remains constant throughout the series (the number of the amino acid residues and the molecular weight double in each new generation). In addition, other factors such as concentration and temperature did not affect the optical rotation values observed for these dendrimers (identical rotations were observed at $c = 0.1$, 1 and 4 at

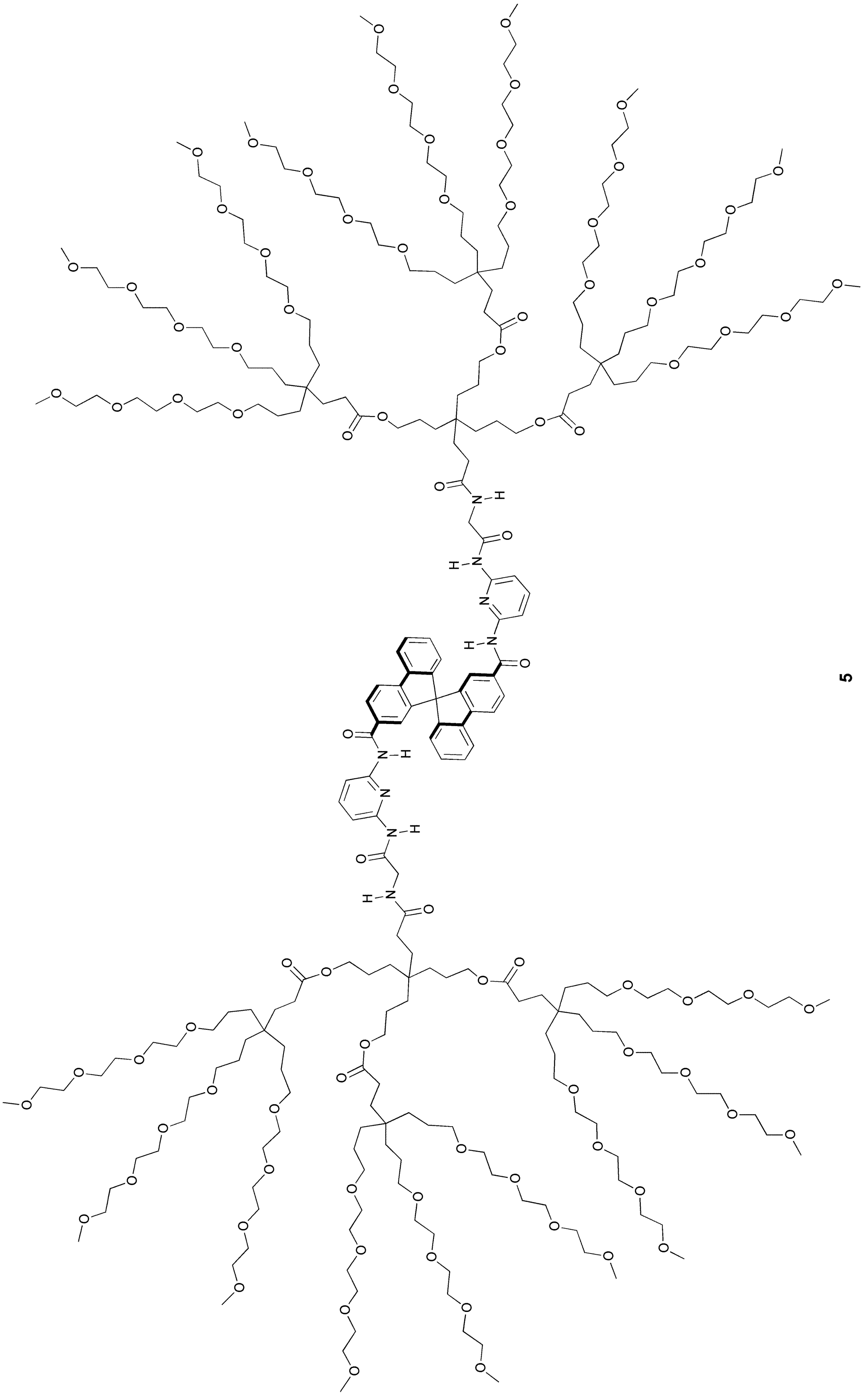

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Fig. 4 *Dendrocleft* **5**—an enantioselective receptor based upon a polyether dendrimer incorporating a 9,9′-spirobi[9*H*-fluorene] core.[54]

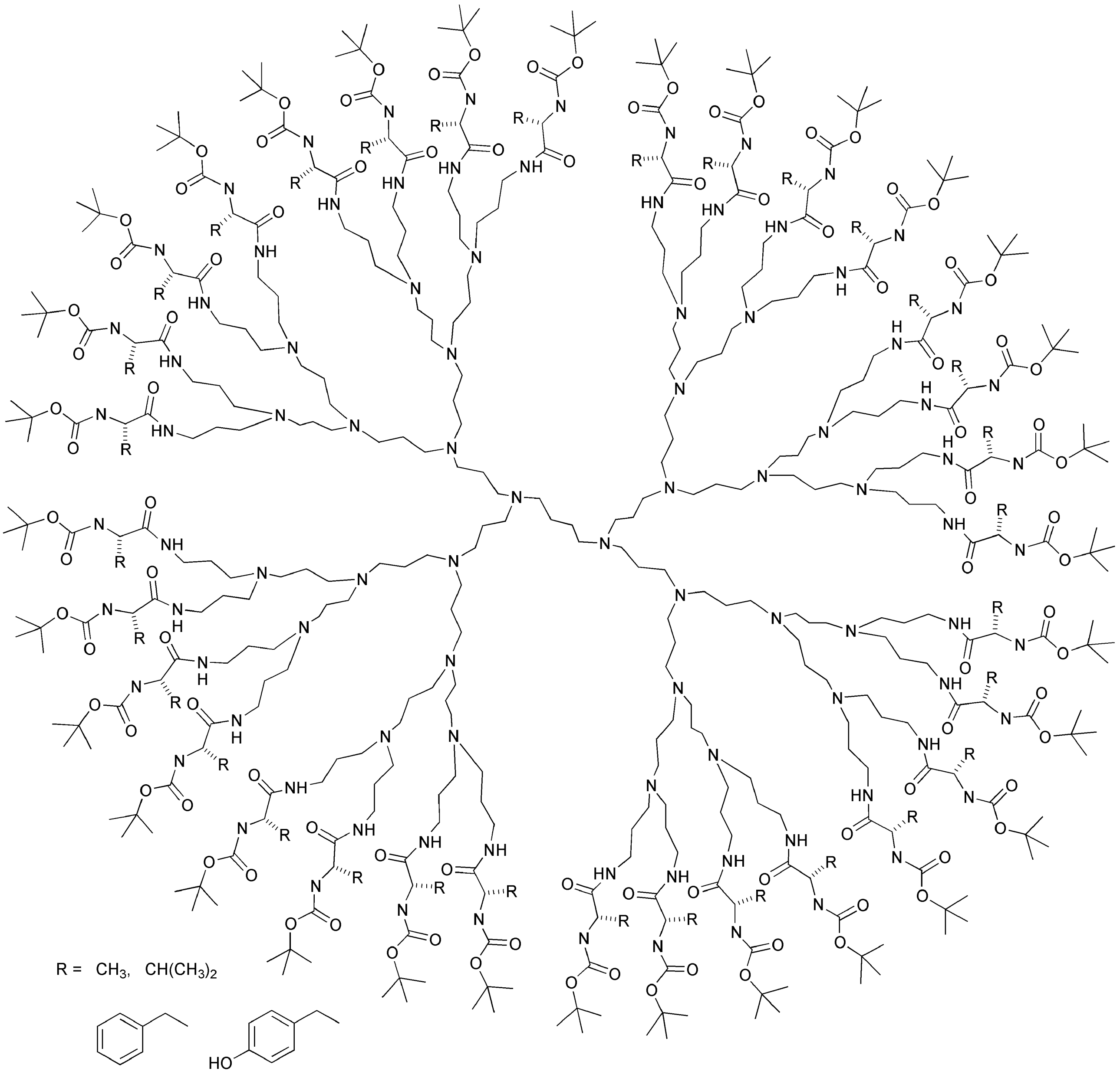

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Fig. 5 A chiral PPI dendrimer **6** peripherally functionalised with *tert*-butyloxycarbonyl (Boc) protected amino acids.[60]

different temperatures (20 and 55 °C)). Furthermore, chiral HPLC analysis on amino acids cleaved from the dendritic surface by hydrolysis revealed enantiomeric excesses greater then 96%, indicating that racemisation had not occurred during the amino acid coupling step to the PPI dendritic backbone. Interestingly, a significant dependence of the optical activity upon the solvent (studied in the case of the smaller dendrimers) was observed and this trend mirrored the solvent dependency of the optical rotation of the corresponding free amino acid.[43] In addition, magnetic resonance–relaxation studies upon these chiral PPI dendrimers revealed a decrease in the molecular motion in the case of the higher generation dendrimers (*i.e.* increase of the spin–lattice time (T_1) at higher generation). These spectroscopic data indicated that a change of the local environment around the peripheral amino acids was occurring at higher generations and was related to an increased packing density at the dendrimer surface. This peripheral dense packing is reinforced by multiple hydrogen bonding between the amide and carbamate groups of the amino acid and protecting group, respectively. The maintenance of the optical activity for each generation dendrimer when the carbamate moieties were replaced with acetal groups (that cannot form hydrogen bonds so readily), confirmed hydrogen bond formation at the PPI dendrimer surface. Since the chiroptical properties of the amino acid residues at the PPI dendrimer peripheral surface proved sensitive to the local environment, it was proposed that numerous chiral conformers are formed under non-equilibrium conditions, forced by the dense packing and hydrogen bonding. The different 'frozen conformations' of the protected amino

Table 1 Specific rotation of poly(propyleneimine) dendrimers peripherally modified with different amino acids

Generation number:	1	2	3	4	5
Number of end groups:	4	8	16	32	64
Surface amino acid group	Specific rotation $[\alpha]_D$/deg cm^2 g^{-1}[a]				
L-Alanine[b]	−24	−25	−26	−3	−14
L-Valine[b]	−39	−31	−27	−28	−22
L-Lysine[b]	−28	−8	−3	−1	0.0
L-Phenylalanine[b]	−11	−7	−2	−1	−0.1
L-Tyrosine[c]	+19	+9	+1	−0.2	−0.1

[a] $c = 1$. [b] Solvent = $CHCl_3$. [c] Solvent = DMSO.

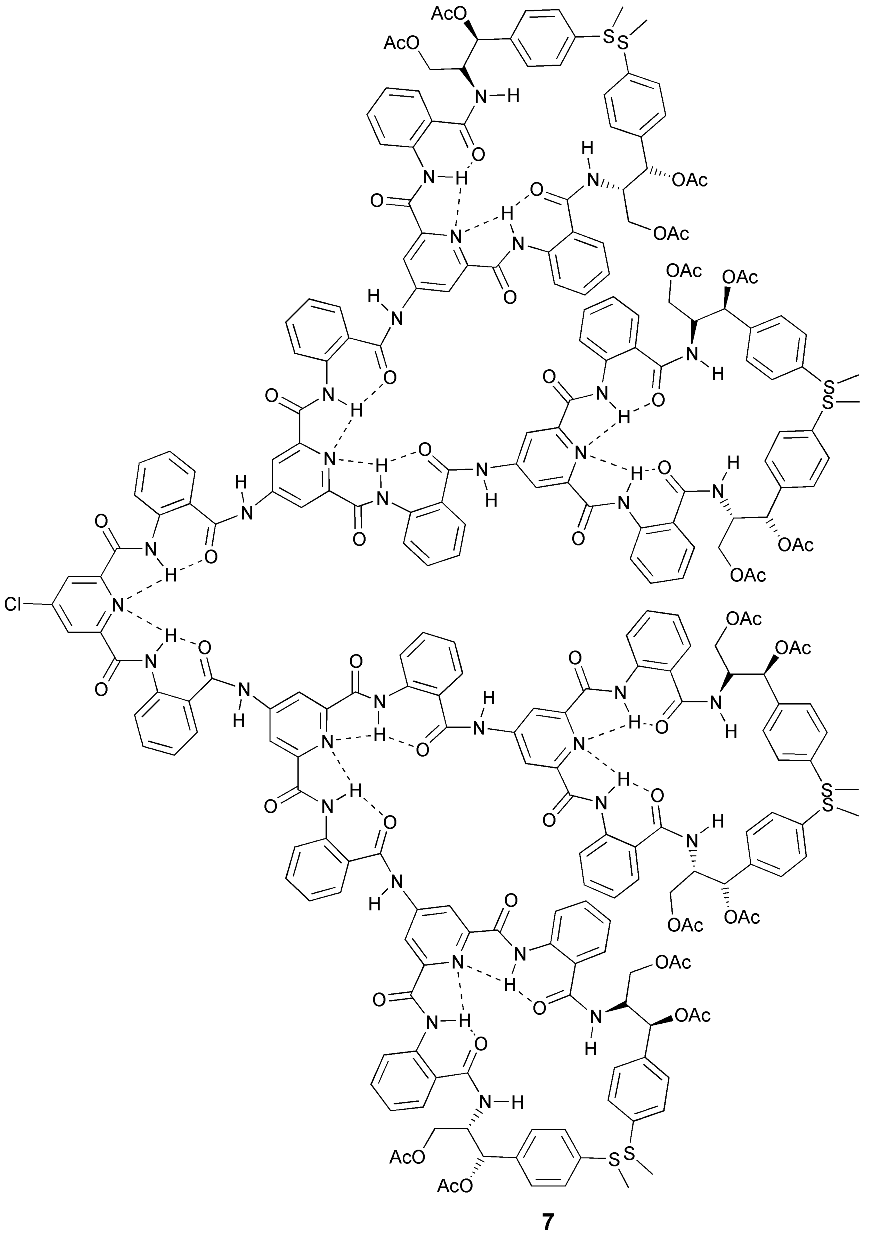
acid at the dendritic surface caused an internal compensation effect within the dendrimer thus leading to a decrease in the optical activity values observed. This theory was confirmed by coupling more rigid chiral moieties (such as camphorsulfonamide and camphanic amide whose chiroptical properties are independent from the local environment) to the peripheral surface of the PPI dendrimer backbone. In these cases the optical rotation values observed were constant for each generation number of the PPI dendrimer. The results obtained for these modified PPI dendrimers do not imply that the dendrimer surface possessing these rigid chiral units are not densely packed (especially at 5th generation), but that the packing does not have an effect upon the conformational equilibrium and thus all the chiral molecules are able to adopt the same conformation. Further proof of this theory arose from chiroptical studies on similar systems featuring flexible alkyl chains between the dendrimer surface and the amino acid. In these systems the optical rotation was maintained at every generation, indicating that dense packing is prevented by the flexibility of the alkyl spacer.

An interesting application of chiral PPI dendrimers of this type is their use as novel hosts or *dendritic boxes*, in which the presence of the densely packed and solid-like peripheral surface has been exploited.[56*b*,61] Several guest substrates have been encapsulated within the 5th generation PPI dendrimer that featured *t*-Boc-L-phenylalanine at the peripheral surface, however, the most intriguing results were obtained from the encapsulation of the achiral dye Rose Bengal. From detailed spectroscopic investigations, it was determined that several dye molecules could be encapsulated within each dendritic host; the maximum number that could be incorporated within the dendritic environment was four. CD analysis of the dendritic complex featuring one encapsulated Rose Bengal molecule revealed an induced CD spectrum with a negative CE. However, an exciton coupling was observed in the CD spectra when four molecules of Rose Bengal were encapsulated in the 5th generation PPI dendrimer, indicating close proximity and fixed orientations of the dye chromophores within the dendritic structure. These CD results suggest that even if the optical activity of the dendrimer is very small, a local chirality is still present. The induced circular dichroism (ICD) effect that was observed has been rationalised as the transfer of the local chirality from the surface to the encapsulated guest. Further in depth studies are necessary to determine how the chemical structure of the encapsulated guest and the chemical nature of the cavities relate to each other, in order to explain why, for example, induced exciton coupling occurs with certain guest systems and not with others (such as Eosin B, New Coccin and Rhodamide). PPI dendrimers have also been coupled at the surface with a wide variety of other chiral moieties. For example, Vögtle *et al.* introduced[62] enantiomerically pure 5-formyl-4-hydroxy[2.2]paracyclophane units at the peripheral surface of a series of PPI dendrimers, in order to exploit the ability of these systems to form metal complexes (*i.e.* with cobalt(II)) and potential new macromolecular chiral catalysts. The CD spectra of these macromolecules were in good agreement with the theoretically simulated spectra and the optical rotation values obtained were constant as the generation number increased. Similar results were obtained by Stoddart and Meijer *et al.* in a study of glycodendrimers that featured optically pure saccharide units anchored to the surface of peptide derived[63] or PPI dendrimers.[64] In both of these cases, the optical rotation remained nearly constant and the molar rotation values were found to be directly proportional to the number of saccharide units coupled to the dendritic periphery. Caminade and Majoral *et al.* studied[65] the chiroptical properties of phosphorus containing dendrimers with (*R*)- and (*S*)-α-methylbenzylamine at the surface. Three series of dendrimers were synthesised: in the first series, the peripheral aldehyde functionalities were converted into the corresponding imine system by reaction with the chiral methybenzylamine, in the second set, the imine groups were selectively reduced to form the desired secondary amine and in the third group, the secondary amines thus formed were coupled to a diphenylphosphine derivative to afford phosphino terminated dendrimers. The specific rotation values observed for these three series decreased slightly as the generation number of the dendrimer increased (a direct consequence of the diminishing contribution of the stereogenic groups to the molecular weight), whereas the molar rotation was found to increase exponentially with the generation number. However, when the molar rotation values obtained were divided by the number of stereogenic units, the optical characteristics were approximately constant for all the different dendrimer generations. From these studies, it is evident that each chiral terminal group behaved as an isolated independent molecule, whatever the generation number of the dendritic backbone. In addition, Majoral and co-workers have developed the synthesis of the highest generation dendrimer to date (up to the 11th generation) that possesses a peripheral chiral surface obtained by coupling phosphorus containing dendrimers with redox active asymmetric ferrocene units.[66] These ferrocene containing dendrimers exhibited the same chiroptical properties as described for the analogous phosphorus containing dendrimers that possessed chiral methylbenzylamine units at the peripheral surface (*vide supra*). Even in the case of the highest generation dendrimer, evidence of steric overcrowding at the peripheral surface was not found, and confirmation of the spacial freedom in these dendrimers arose also from electrochemical measurements that indicated minimal influence of the dendrimer size upon the redox properties of the ferrocene units.

Folding processes in natural macromolecules responsible for biologically active tertiary structures are dominated by the formation of numerous weak non-covalent interactions (*i.e.* van der Waals forces, hydrogen bonding, π–π stacking interactions and solvophobic effect). In light of these natural phenomena, Parquette *et al.* have proposed[67] the use of non-covalent interactions—especially hydrogen bonding,[55] in order to induce secondary structural order within chiral dendrimers. Analogous studies have been reported on the control of intramolecular folding of linear oligomers[68] and the development of strong interfacial forces of attraction in polymer blends[69] through the formation of hydrogen bonds. In an initial study, the synthesis of monodendrons up to third generation based on 4-aminopyridine-2,6-dicarboxamide as the AB_2 branching monomer (and the primary source of hydrogen bonding) and chiral anthranilamide derivatives as the terminal groups has been reported. Hydrogen bonding interactions between the pyridine system and anthranilamide in conjunction with repulsive interactions between the carbonyl oxygen atoms of the amide groups direct the position of the two anthranilamide moieties in such a way that they reside above and below the plane of the assembly leading to the development of a helix. It has been proposed that dense packing, especially at higher generations, induces non-bonded interactions between adjacent terminal groups in a pair-wise fashion—this effect facilitates the transmission of the helical conformation across the surface of the dendrons, thereby leading ultimately to the formation of a single favoured helical conformation. This hypothesis was confirmed by investigating the chiroptical properties of these asymmetric dendrons in detail. ORD spectra were normalized for the concentration and the number of chiral units and revealed inconsistent chiroptical behaviour as the generation number of the dendritic components increased from the 0th to 1st, and from 2nd to 3rd generation. These studies revealed that not only the amplitude, but also the sign of the optical rotation changed significantly, suggesting that chiral substructures within the dendritic macromolecules contribute to the optical activity. Subsequent CD spectroscopic analysis confirmed this initial hypothesis. In the case of the 2nd generation dendron, an exciton coupled transition at 316 nm was observed, however, it was not evident in the CD spectra of the corresponding 0th and the 1st generation dendrons. This exciton coupling proved to be solvent and temperature dependent—an increase in the polarity of the solvent system and/or an increase in the temperature resulted in a decrease of the amplitude of the coupling transition. Similar CD spectral characteristics were observed for the 3rd generation dendron, but in this case the exciton coupled transition at 316 nm proved to be independent of the solvent polarity and the temperature. These observations indicated that hydrogen bonding and non-bonded repulsions dominate the folding ability of this dendron and contribute to the stabilization of the secondary structure at higher generations, with the preference for a single helical conformation. However, when the surface packing phenomenon does not predominate, favourable solvophobic effects in addition to low temperature environments are required to enhance the intramolecular packing and thus the helical conformation. The conformational order is intrinsically more stable in the case of the higher generation dendrons, and thus environmental parameters such as solvent polarity and temperature do not play a role. These successful preliminary results led to detailed investigations on derivatives of this type of dendron.[70] Consequently, anthranilamide 'turn' units were introduced not only at the peripheral surface of the dendrons but also as linker units between each generation shell (see **7** in Fig. 6). This modification led to the extension of the peripheral helicity into the internal branched regions of the dendrons, the result being more stable helical global structures. These conformational effects were confirmed by a variety of spectroscopic probes and indicated high stability of the secondary structure in both the 2nd and 3rd generation dendrons—in both cases the stable dendritic conformations were solvent and temperature independent. In these dendrimers, both the internal and peripheral shells fold into biased M-type helical conformations as a consequence of the terminal groups. This is the first example of a well-defined asymmetric secondary structure occurring in a dendrimer system induced by chiral units located at the surface.

2.3 Dendrimers constructed from an achiral core and constitutionally different branches

Chiral dendrimers can also result from coupling an originally achiral core unit to constitutionally different branches. Meijer



7

Fig. 6 An anthranilamide based dendron **7** that is capable of exhibiting peripheral and internal helicity as a consequence of directed intramolecular hydrogen bonding.[70]

et al.[71] were the first to study the chiroptical properties of dendrimer of this type. The racemic dendrimer synthesis involved coupling of a pentaerythritol core to different generations of aromatic polyether (Fréchet-type) dendrons (see **8** in Fig. 7). ^{1}H NMR spectroscopic studies revealed that the resultant dendrimers possessed stratified structures, and ordering of this nature was evident clearly when $CDCl_3$ was employed as the solvent: the benzylic methylene protons of each different dendrons resonated as sharp and separate singlets. The presence of resolved signals in the ^{1}H NMR spectra for such similar methylene protons could not be caused by differentiation of the electronic properties of each of the constitutionally different dendrons by the chiral core. Therefore, Meijer proposed that these macromolecules adopt an overall chiral shape in solution, whose structure depends on the solvent system used (for example, in stark contrast to $CDCl_3$, the benzylic methylenes resonate as unresolved signals in C_6D_6 and C_6D_5N). Unfortunately, these dendrimers could not be isolated in their enantiomerically pure form even when chiral HPLC analysis was employed. The inability to resolve the enantiomeric forms of the polyether dendrimers using chiral HPLC analysis was justified by consideration of the different 'dimensions' of chirality between the stationary phase, whose chirality is expressed at a molecular level, and the macroscopic chirality of the hyperbranched macromolecules.[72] The Eindhoven-based group[73] has also prepared closely related chiral dendritic macromolecules (**9a** and **9b** in Fig. 7) in the (*R*) and (*S*) pure forms employing the chiral glycerol derivative (*S*)-solketal as the starting material. Surprisingly, optical rotation, ORD and CD analysis of these non-racemic glycerol derivatives revealed the lack of any detectable optical activity. Molecular modelling studies revealed that the two enantiomers have very similar conformations, and the chirality is in effect 'hidden'. This was the first reported case of recognized *cryptochirality* (*i.e.* the lack of detectable optical activity in structurally chiral compounds) related to dendrimer architectures. The significant conformational freedom and the similarity of the electronic properties of the different dendrons effected the minimisation of the optical activity to a value so small that is 'unmeasurable' with the available analytical methods at present.[31]

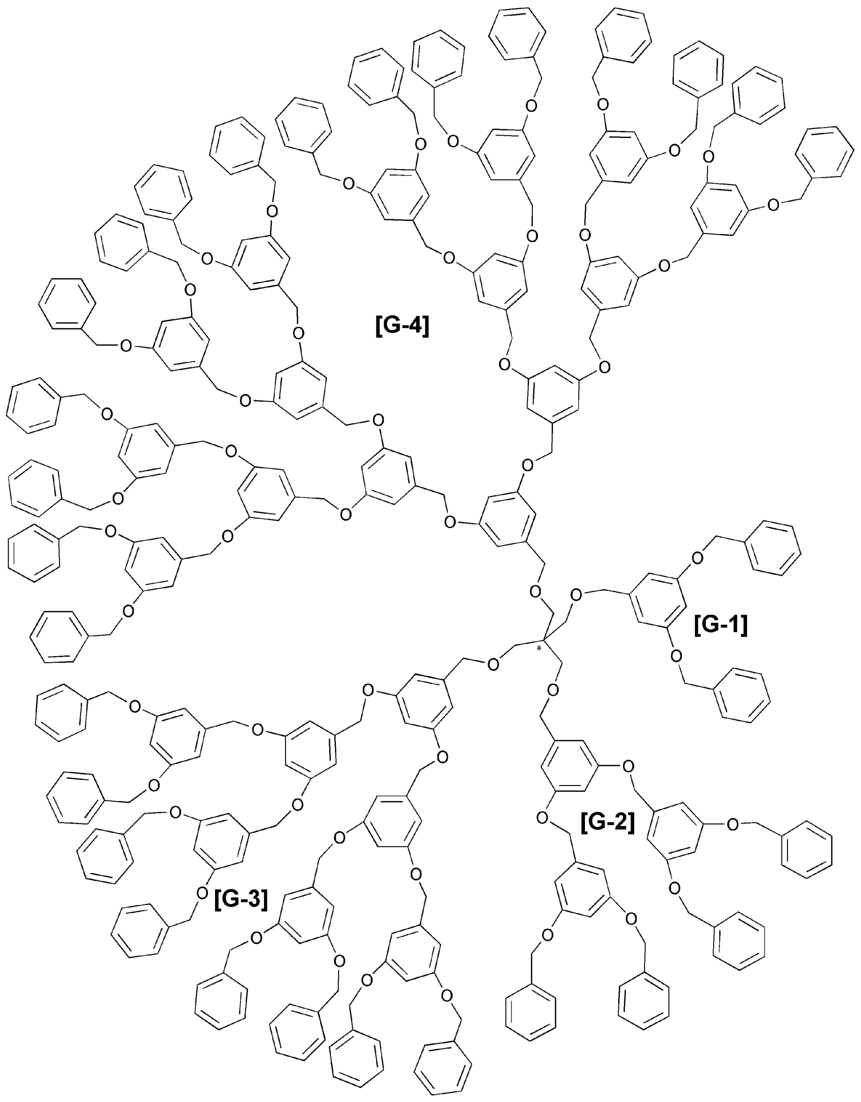
Additional studies have been carried out by Meijer and co-workers in this area that involve the synthesis of enantiomerically pure dendrimers that feature enhanced structural rigidity in comparison to **9a** and **9b**.[74] These rigid branched macromolecules were obtained by coupling the same (*S*)-solketal core with aromatic polyether dendrons that were constructed from a 2,6-dibenzoyloxy repeat unit rather than the corresponding 3,5-dibenzoyloxy monomer (*i.e.* the Fréchet system), in order to encourage back-folding within the dendritic arms. Remarkably, this rigidified dendrimer exhibited a very small, but measurable optical activity $[\Phi]_D^{rt} = +0.8$ ($c = 2.2$, CH_2Cl_2) in sharp contrast with **9a** and **9b**. The optical activity diminishes at elevated temperatures (*ca.* 30 °C) and a weak signal at 280 nm in the CD spectrum is observed at 15 °C. These results indicated the presence of an induced chiral conformation from the core to the polyether dendritic wedges, thus confirming that a certain level of rigidity is required in chiral dendrimers in order for chirality to be exhibited in branched macromolecules of this type.

2.4 Dendrimers featuring chiral branched units

Biomacromolecules such as proteins feature several levels of structural order (typically *via* non-covalent interactions[52c] or reversible covalent links) that determine the final three-dimensional conformation that is ultimately responsible for that system's specific biological function.[75] In order to design efficient biomimetic macromolecules, detailed understanding of the structural ordering processes must first be attained. However, as part of this investigative process and as a direct result of the complexity of these natural macromolecules, there is the need for model systems that resemble closely biological structures. As a consequence of their macromolecular dimensions and the synthetic ability to control the structure and globular morphology, dendrimers possessing chiral branches represent excellent candidates as potential protein mimics.[76] In addition, the introduction of chiral branched units into dendritic architectures should result in the development of non-symmetrical macromolecular conformations and provide chiral cavities useful for asymmetric catalysis, chiral recognition and resolution processes.

In order to study in more details the effects of chiral units on the chiroptical activity of dendrimers, Chow *et al.* described[77] chiral dendritic copolymers bearing more then one type of chiral unit. Dendrimers up to the 2nd generation that were based on tartaric acid derivatives as the chiral spacer unit (in both D- and L-forms) between phloroglucinol branching units were prepared. By combining the chiral tartrate units of both configurations, they obtained heterochiral (**10** and **11**) and homochiral (**12**) dendrimers (Fig. 8). The first interesting observation was that the^{1}H NMR and^{13}C NMR spectra of the diastereomeric dendrimers were almost superimposable, indicating that the central and peripheral phloroglucinol ring of the diastereoisomers possessed nearly the same chemical microenvironment irrespective of the absolute configuration of the chiral branches. In addition, preliminary study of the chiroptical properties revealed that each of the dendritic chiral units was independent and contributed to the overall molar rotation with the same absolute value. In fact, the molar rotation was found to be proportional to the number of tartrate units in excess inside the dendritic structure. However, CD analysis exposed key chiroptical features that were not revealed by the initial polarimetric studies. Two CE bands were observed for the all dendrimers, one at 200 nm that was assigned to a $\pi \rightarrow \pi^*$ transition of the *tert*-butylphenoxy group in the surface, and another band centred on 210 nm that was attributed to a $\pi \rightarrow \pi^*$ transition of the phloroglucinol moieties. The intensity and sign of the CE at 200 nm was proportional to the number and configuration of the tartrate units present in each diastereoisomer, confirming the results obtained from studies of molar rotation. However, the absorption at 210 nm did not follow this trend and exhibited unusual characteristics. Direct comparison of the CD spectral data that were obtained for the diastereoisomers **10** and **11** containing D- and L-tartrate spacer units in an inverted ratio and in different positions, revealed that the cancellation effect was most effective when the opposite chiral units were both present in the same layer. The authors suggested that the outer tartrate layers of the dendrimer were 'chiroptically slightly different' from the inner layers.

Similar results were obtained[78] by Lellek *et al.* who prepared chiral dendrimers using 1,1′-binaphthol unit derivatives of different configuration as the dendritic building blocks. As observed[77] by Chow and co-workers in the case of the polytartrate dendrimers, the molar rotation and the specific rotation values for the binaphthol-based dendrimers obeyed a linear relationship with respect to the number of chiral monomer units. However, by comparing the CD spectral data of the different generation dendrimers with calculated values predicted by superimposing the CD curves of the single monomer units, a different behaviour was observed. In the case of the 1st and 2nd generation homochiral dendrimers, a significant hypochromic effect was observed at 252 nm (related to the $\pi \rightarrow \pi^*$ transition of the aromatic chromophore). In contrast, this effect was not observed for the heterochiral dendrimers. The explanation could not be rationalised by direct consideration of the change of the torsional angle of the binaphthol unit,[44] as both the series of molar rotation and optical rotation data did not reveal significant differences from



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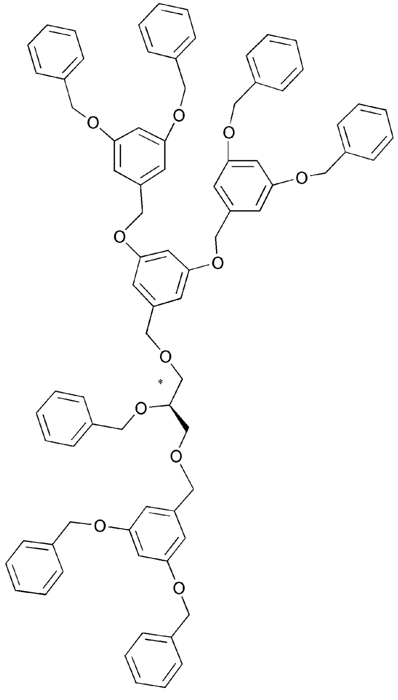
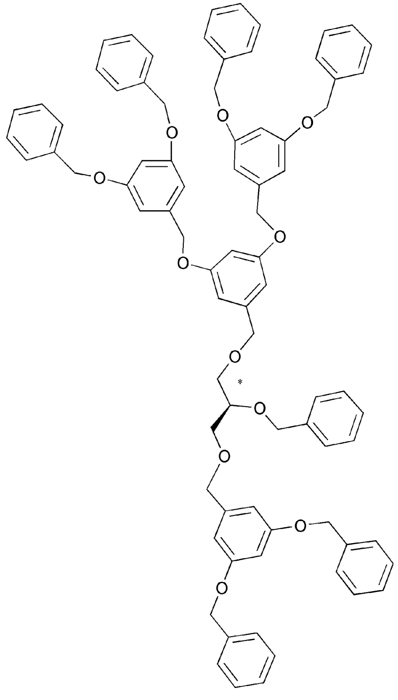
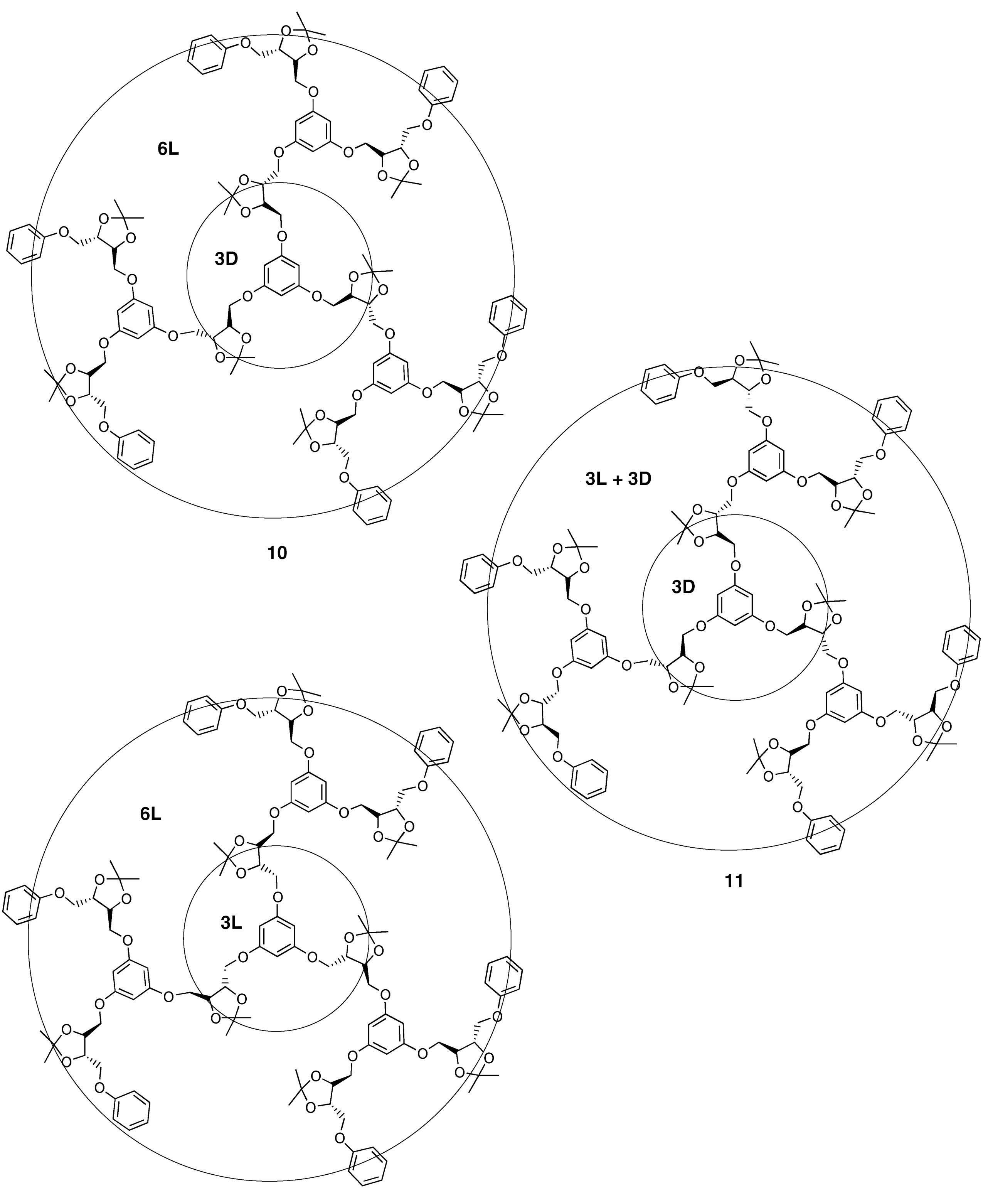


9a



9b

Fig. 7 *Cryptochiral* dendrimers[71–73] featuring flexible aromatic polyether (Fréchet type) dendrons coupled to either pentaerythritol (**8**) or (*S*)-solketal (**9a** and **b**) core units.



10

11

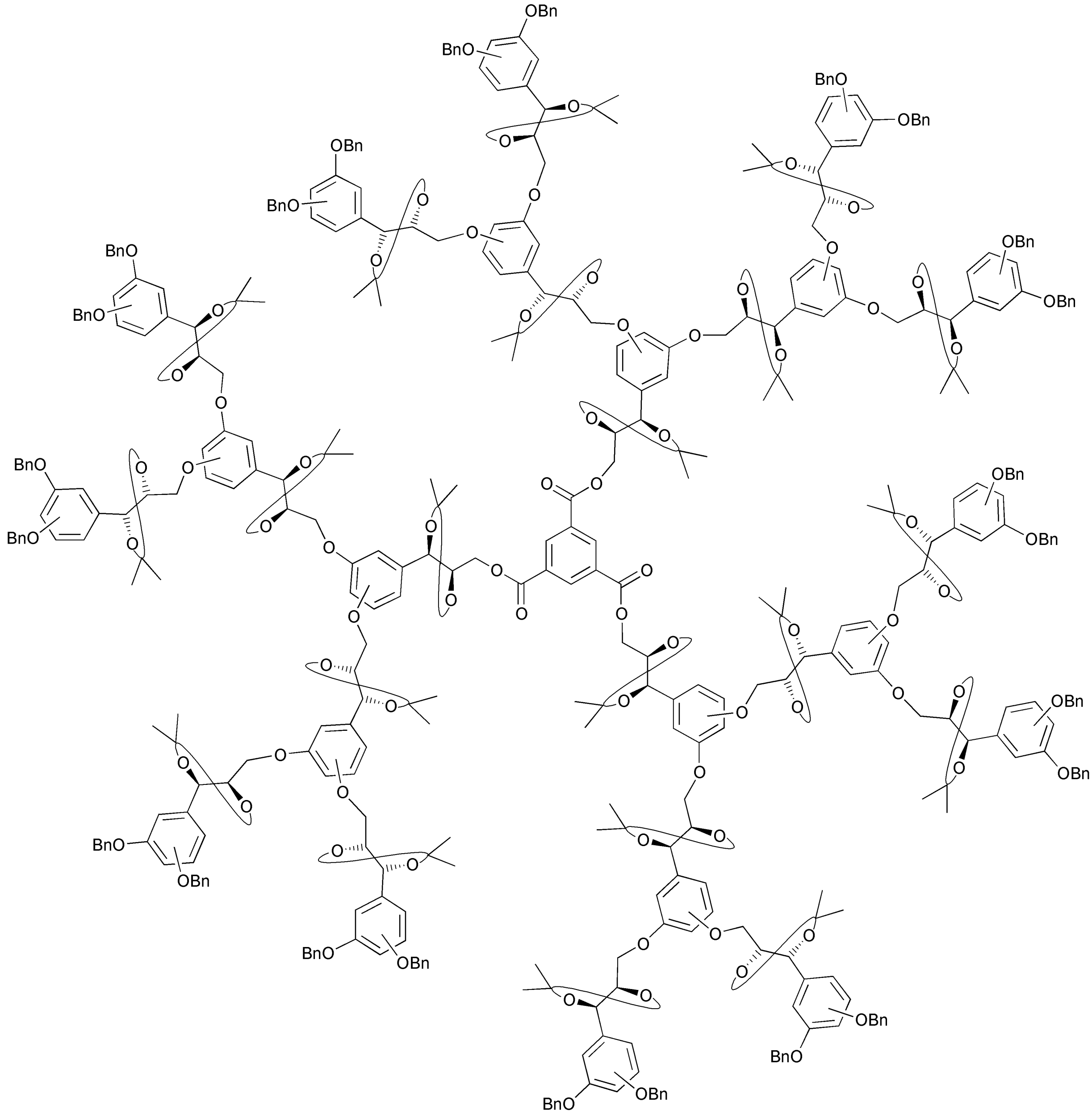
12

Fig. 8 Hetero- (**10** and **11**) and homochiral (**12**) dendrimers[77] incorporating tartaric acid linker units and phloroglucinol branching moieties.

the expected values. The authors attributed this anomalous spectral behaviour to the formation of intramolecular hydrogen bonds (between the amide bonds and unshared electron pair in the heteroatoms of the macromolecule) and thus the homochiral diastereoisomer developed an internal organization that led to a different conformation with respect to the heterochiral diastereoisomer.

Rosini, Brandi and co-workers reported[79] the synthesis of chiral dendrimers that were based on chiral (*trans*-3,4-dihydroxypyrrolidine) branched units and different benzenepolycarboxylic acids as the core. These studies revealed that both the molar rotation and CD spectral data of dendrimers that incorporated benzene-1,3,5-tricarboxylic acid as the central core were not in agreement with the contribution of the single chiral units. This finding led the authors to suggest that the chiral units were not independent of each other and an induction of chiral conformation may be occurring.

Similar results were described by Liskamp *et al.* who prepared[80] chiral dendrimers based on optically pure phenylalaninol. By studying the chiroptical properties of these chiral



13

Fig. 9 A chiral dendrimer **13** constructed from optically pure hydrobenzoin based branched units.[82]

dendrimers, the value obtained from the division of the molar rotation data by the number of chiral units was not constant as the dendrimer increased from the 1st to the 3rd generation. The authors attributed this result to interactions between the chiral units within the dendritic architecture. Completely different results were obtained by Sharpless *et al.*[81] who described the synthesis of chiral dendrimers up to 4th generation that featured benzene-1,3,5-tricarbonyl trichloride as the central core and asymmetric diol branching units derived from styrene. In this case, the molar rotation was proportional to the number of chiral units present, indicating the absence of chiral secondary structure.

The contrasting data obtained from the above studies indicate clearly the complexity and problems of the interpretation of chiroptical properties of dendrimers possessing chiral branching unit. McGrath *et al.* described[82] the synthesis of a novel dendritic structure containing optically pure hydrobenzoin based chiral branching units (see **13** in Fig. 9), in order to generate asymmetric functional cavities with the potential to bind guest molecules.[83] When the molar rotation values obtained for the chiral 1st, 2nd and 3rd generation dendrimers were divided by the number of chiral units present in the hyperbranched architecture and compared with the molar rotation of a single hydrobenzoin unit, significant differences in the optical behaviour were revealed.[42,84] This result could be interpreted as a possible indication of the presence of conformational chiral substructures in the dendritic branches. However, more detailed analyses of the structure revealed that constitutional changes of the chiral hydrobenzoin units when incorporated in the dendritic system could also cause these effects. By considering the molar rotation of different model compounds resembling the chiral hydrobenzoin units in different positions within the dendrimer (close to the core, at the branches and at the surface), the calculated overall molar rotation was much closer to the observed value (agreement between 4.5 and 15%).

In addition, the CD spectra recorded for the chiral dendrimers revealed that the magnitude of the CE band at 203 nm (corresponding to the π → π* transition of the aromatic ring) was proportional to the number of chromophores present and no exciton coupling was observed indicating possible interactions between independent chromophore units. Similar results were obtained in a related study investigating the influence of the position of chiral hydrobenzoin units within the dendritic structure on the chiroptical properties of dendrons up to 4th generation.[85] When the chiral unit was located within the internal shells of the chiral dendrimer, it was observed that the influence on the molar activity was greater then when situated at the periphery or at the central core. However, comparison of these optical analyses with those of suitable model hydrobenzoin compounds revealed that chiral substructures were not formed. These results suggest that the individual contributions of the chiral subunits to the overall optical activity of the hyperbranched macromolecule *cannot* be considered independent of their position within the dendritic structure. In fact, chiral subunits that are situated close to the central core moiety possess different constitutions from those located at the branches or at the peripheral surface. Consequently, the optical activities for dendrimers of this type do not follow defined trends as the generation number of the dendrons increases, and this anomalous behaviour has been attributed to constitutional changes of the dendritic macromolecules, rather than to induced chiral secondary substructures. Similar results have been observed[86] by Frejd *et al.* who described the synthesis of dendrimers incorporating chiral aromatic bis- and tris-amino acids. Significant deviations were observed between the experimentally determined molar rotation values and CD spectra and the predicted data (obtained by consideration of the single chiral units). However, further refinement of the structures of the model compounds enabled a better agreement between the observed and calculated values of both molar rotation and CD spectra.

2.5 Chiral dendrimers incorporating a chiral core, asymmetric branching units and optically active peripheral surface groups

In addition to the different variants of chiral dendrimers that have been described above, several dendritic systems exist that feature a chiral core, asymmetric branching units and optically active peripheral surface groups (or *fully* chiral dendrimers).

The first example of a dendrimer that contains just chiral units was described[87] by Denkelwalter *et al.* who synthesised poly(α,ε-L-lysine) dendrimers using a divergent approach. After this, the synthesis of several other dendrimer systems that were based on optically active natural building blocks (*i.e.* amino acids,[33] carbohydrates[34] and nucleosides[35]) have been reported. However, only few extensive studies of the chiroptical properties for systems of this type have been detailed in the literature. For example, Tam *et al.* have described[88] the efficient synthesis of fully chiral dendrimers that were based upon a tetravalent lysinil core peptide and peptide segments containing 20 amino acids each. The study of the chiroptical properties of these hyperbranched peptides revealed that exciton coupled CE in the CD spectra (corresponding to helical peptide conformations) were enhanced in the case of the multi-peptide arm dendrimers in comparison to the analogous single strand peptide sequences. These CD data indicated an interesting case of cooperative interactions between dendrimer branches with resultant formation of a highly stable global helical conformation. Recently, Maitra *et al.*[89] have reported the synthesis of the first bile acid-derived chiral dendrons (up to the 2nd generation) that possess nanometre-sized dimensions. In contrast to the polypeptide dendrimers described above, chiral secondary structures were absent in these bile acid hyperbranched polymers as revealed by consideration of the molar rotation values—these chiroptical properties were found to be directly proportional to the number of bile acid units present. Similar results were obtained[90] by Hirsch *et al.* who described the synthesis of depsipeptide-based dendrimers. The chiroptical studies revealed that the molar rotation behaviour of these depsipeptide-based dendrimers correlated with the sum of the dendrimers' constituent chiral building blocks.

The first example of an induced conformational chiral substructure for fully chiral dendrimers was reported[91] by Seebach *et al.* who detailed the convergent construction of dendrimers incorporating derivatives of chiral tris(hydroxymethyl)methane units (see **1** in Fig. 10) derived from poly[(*R*)-3-hydroxybutanoic acid].[92] Seebach observed that when the chiral core with configuration (*R*,*S*,*R*) was coupled with chiral dendrons of the 1st generation with *either* the (*R*) or (*S*) configuration at the benzylic stereogenic centre, the reaction proceeded in an efficient manner. However, when the same (*R*,*S*,*R*) core was coupled with the 2nd generation chiral dendrons, only the branches with (*S*) configuration at the benzylic stereogenic centres afforded the trisubstituted product (**14**), whereas, even under the most forcing conditions, the dendron with (*R*) configuration afforded only the disubstituted product (**15**). However, the same central core featuring elongated spacers (aromatic or aliphatic) reacted efficiently with both 1st and 2nd generation dendrons, with either (*R*) or (*S*) configurations at the benzylic centres of the branches. Remarkably, when both the 2nd generation dendrons with either (*R*) or (*S*) configuration were coupled to the central chiral core that possessed the opposite configuration (*S*,*R*,*S*) triply branched dendrimers were produced. Related investigations involving combinations of diastereomeric 2nd generation polyether dendrons of this type and a variety of analogous chiral core systems have revealed a degree of variability in the reaction efficiencies between chiral core and dendrons—some combinations led to the efficient formation of the fully substituted dendrimers whereas other dendron/core combinations did not. In some of these systems, the only configuration that differs is that at the central core, thereby suggesting that a unique macromolecular recognition process is in operation, affording either a 'fit' or 'misfit' of the chiral components. Detailed studies of the chiroptical properties of these hyperbranched macromolecules were carried out in order to obtain an insight into this fascinating diastereoselectivity phenomenon. These investigations revealed that the specific rotation and molecular ellipticity of all the dendrimers synthesised as part of this study were comparable to the predicted values (calculated by simple addition of the values obtained from model compounds that were structurally related to the building blocks in different positions within the dendritic system). The only exception of this series of fully chiral dendrimers was the 2nd generation dendrimer with (*R*,*S*,*R*) configuration at the central core and the dendrons possessing the (*S*)-configuration at the benzylic centres (**14**), whose specific rotation and molecular ellipticity deviate clearly from the values predicted and possess an inverted sign (from negative to positive). This result could further indicate the presence of preferred macroscopic chiral conformation that contributes to the optical activity. In order to probe this unusual behaviour in more detail, Seebach incorporated trifluoromethyl groups in close proximity to the chiral centres of the tris(hydroxymethyl)methane units to enable ^{19}F NMR spectroscopic analysis to be employed.[93] By using (*S*)-4,4,4-trifluoro-3-hydroxybutanoic acid, the 1st and 2nd generation dendrimers were prepared and the ^{19}F NMR spectra of these branched systems not only revealed definable differences between the inner CF_3 groups and those located at the periphery (as also indicated by ^{1}H NMR spectroscopic analysis), but also aspects that were not evident in previous spectroscopic studies. In the case of 1st generation dendrimer based upon the central core possessing (*S*,*R*,*S*) configuration, the ^{19}F nuclei of the CF_3 groups resonated as a doublet. However, in the case of the diastereomeric dendrimer (differing only for the configuration at the central core) three of the possible six ^{19}F signals were observed. Similar results were obtained for the 2nd generation dendrimer *even* after incorporation of an elongating biphenyl spacer between the chiral units that was based on the central core with (*S*,*R*,*S*) configuration. For this dendrimer

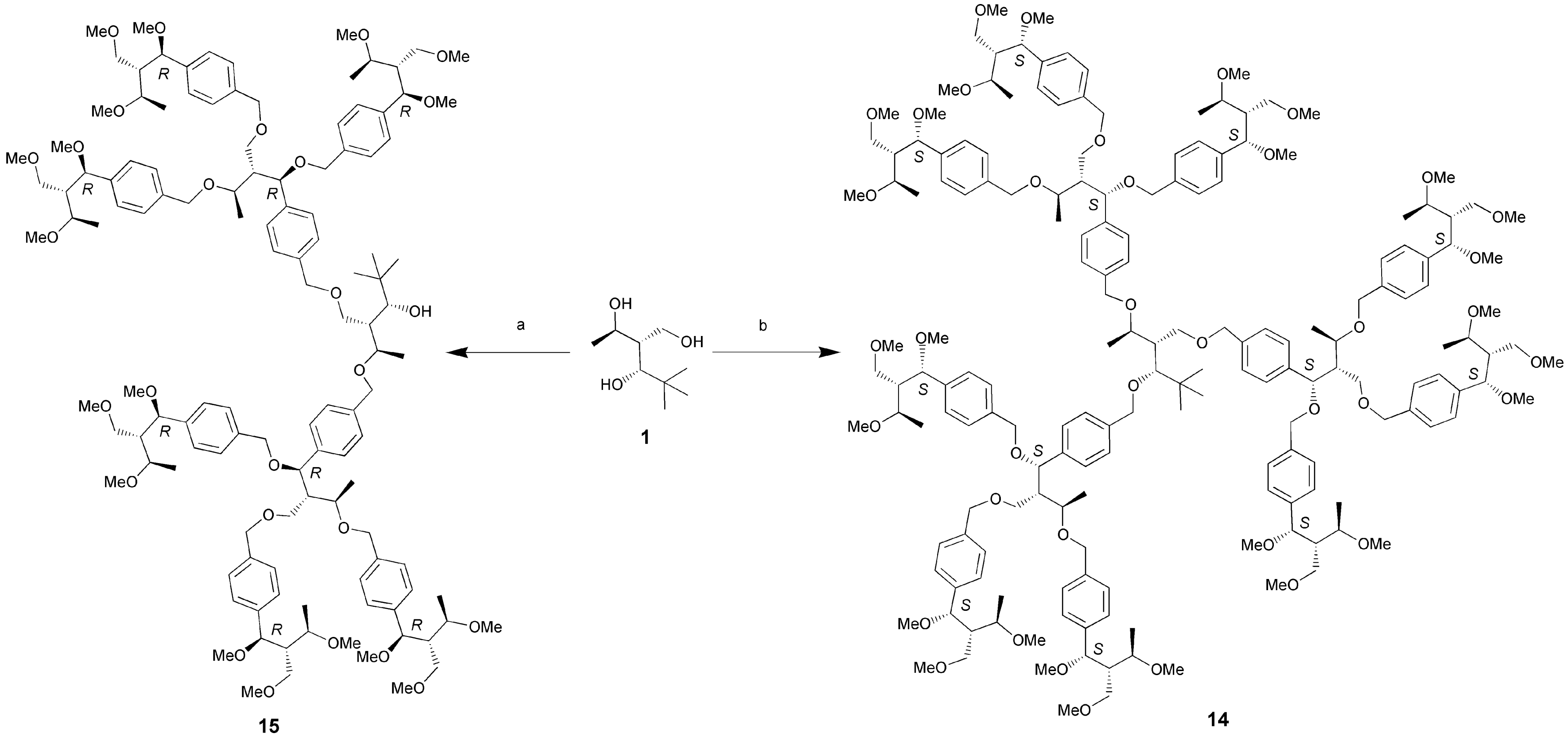


Fig. 10 An intriguing case of diastereoselectivity was exposed by Seebach and co-workers[91] during the synthesis of chiral polyether dendrimers **14** and **15**.

derivative, ^{19}F NMR spectroscopic analysis revealed the presence of four of the possible six signals corresponding to the inner CF$_3$ groups and eight of the possible eighteen signals were observed for the CF$_3$ groups at the periphery of the dendrimer. This spectroscopic data indicated that CF$_3$ groups within the dendrimer system were subject to different environments and exhibited constitutional heterotopicity. Scanning tunnel microscopy[94] (STM) was also employed to obtain further structural information on the dendrimers that had exhibited diastereoselectivity in this study. The double substituted dendrimers of both configuration [(*R*,*S*,*R*) core coupled to the branches with (*R*) or (*S*) configuration at the benzylic centres] were each separately deposited onto an electrically conducting surface as a thin film. In the STM images obtained, different shapes were evident for the different double-branched diastereoisomers, thus confirming the formation of denser packing for the dendrimer with branches with (*R*) configuration with respect to the one with (*S*) configuration.

Considering that steric factors prevented the preparation of higher generation dendrimers featuring triple branched building blocks, the synthesis of fully chiral dendrimers with double branched building blocks was carried out.[95] Consequently dendrons up to the 5th and dendrimers up to the 4th generations were prepared. In these systems diastereoselectivity was not observed and the specific rotation values closely resembled the predicted values. However, detailed CD spectroscopic studies revealed aspects that the preliminary polarimetric investigations did not demonstrate. Chloroform and *tert*-butyl methyl ether were employed as the solvents in these studies and CD analysis of the solutions thus formed revealed a constant rise of the negative CE at 242 nm as the generation number of the dendrimer increased—this was attributed to the incremental contribution from the benzene chromophores. However, when the CD spectra were recorded using CH$_3$CN as the solvent, the profile of the absorption bands and sign changed as the molecular weight increased, especially between the 2nd and 3rd generation dendrimers. A contribution of chiral substructures might have caused this behaviour and this effect appears to be sensitive to the analysis conditions used.

A characteristic of dendrimers that has been recognized as the major impediment to the formation of chiral conformational order is the highly flexible nature of the branched units.[19*a*,74] Highly flexible dendrons lead to the development of compact 'amorphous' tertiary structures without a dominant, well-defined stable conformation and the incorporation of chiral carbon centres alone within the dendritic architecture has not proved to be sufficient to infer stable global chiral conformations upon branched macromolecules.

One approach that has been adopted in light of the above observation is the reduction of the flexibility of dendritic branches. This route to more rigid dendrimers has been employed by Weintraub and Parquette,[96] who constructed unsymmetrical (although formally *achiral* macromolecules) branches in order to restrict mobility within the resultant dendron and favour specific conformations. In a series of aromatic polyether dendrons, a compact unsymmetrical 2,3-pattern was utilised instead of the characteristic 3,5-pattern found in Fréchet-type dendrons, and thus a desymmetrised dendritic analogue of the latter system was obtained. The absence of symmetry in these dendritic derivatives was evident by consideration of the^{1}H NMR spectral analysis, whereby the resonances corresponding to the benzylic methylene groups and terminal methyl ester groups appear as partially resolved singlets. The most interesting finding was revealed by structural analysis of the lowest energy conformer indicating that the dendritic components are arranged in helical coiled conformations toward the focal point of the dendrimer. This hypothesis was reinforced by the differences observed in the gel permeation chromatographic (GPC) retention volumes between the 2,3-branched dendron and its isomeric 3,5-analogue. The 2,3-branched systems exhibited longer retention times upon analysis and thus lower molecular weights in comparison to the Fréchet-types systems, indicating that the asymmetric aromatic polyether branches assume more compact globular morphologies in the solvent system used (THF). An alternative approach for the incorporation of rigid chiral units into dendritic structures has been presented by McDonnell *et al.* who constructed[97] conformationally rigid metallodendrimers using the self-assembly of enantiomerically pure [Ru(diimine)$_3$]$^{2+}$ with 1,10-phenanthroline-5,6-dione and 1,10-phenanthroline-5,6-diamine ligands. A controlled synthetic strategy was used to afford hexameric and decameric assemblies from monomers possessing the same configuration (*i.e.* $\Lambda^6\Lambda^3\Lambda$-Ru$_{10}$ and $\Delta^6\Delta^3\Delta$-Ru$_{10}$) (whereby the $\Lambda^6\Lambda^3\Lambda$ and $\Delta^6\Delta^3\Delta$ notations used refer to the stereochemistry of the ruthenium atoms in the outer or middle generation layers and the central core of the dendritic assembly) or with a mixture of different configurations (*i.e.* $\Lambda^6\Delta^3\Lambda$-Ru$_{10}$). Remarkably, these assembled dendritic structures proved to be very robust, stable to heat, acid or base and chromatographic purifications. CD analysis of these ruthenium complexes revealed that the magnitude of the signals was directly proportional to the number of metal chromophores in excess within each of the respective macromolecular assemblies and no exciton coupling (that would indicate the presence of a rigid conformation formed between two chromophores) was observed. However, this result was not attributed to the lack of topological and conformational differences between the rigid hexameric and decameric assemblies, but to possible weak electronic coupling between the chromophores.[98] This suggestion was confirmed by electric birefringence measurements, revealing that the two diastereoisomers $\Lambda^6\Lambda^3\Lambda$-Ru$_{10}$ and $\Lambda^6\Delta^3\Lambda$-Ru$_{10}$ possess different colloidal behaviours, that ultimately depend on the macromolecular topology. Molecular modelling studies also revealed that the two diastereoisomers assume different conformations: a propeller-like conformation for $\Lambda^6\Lambda^3\Lambda$-Ru$_{10}$ and disk-like arrangement for $\Lambda^6\Delta^3\Lambda$-Ru$_{10}$. These chiral macromolecules have been considered analogous to proteins, as they exhibit specific tertiary structures as a consequence of their primary structural sequence. The presence of deep clefts in the dendritic framework, as evident from the molecular modelling studies, suggest that these chiral assemblies could be employed in molecular recognition processes.

3. Dendrimers and catalysis

One of the most promising developments related to dendrimer research is the preparation of novel and efficient catalytically active hyperbranched macromolecules. The application of soluble polymers in the field of catalysis[99] has been thoroughly explored as a direct consequence of the numerous advantages related to anchoring catalytic species to polymeric supports—especially if the macromolecular support is soluble[100] in the reaction medium employed. In comparison to mononuclear homogeneous counterparts, these macromolecular support systems have been found to be more stable and less corrosive or toxic.[25] Homogeneous polymeric catalyst performances are dependent upon several factors: (1) the physical and chemical properties of the catalytic sites; (2) the distribution of the catalytic sites across the polymeric backbone and their consequent accessibility to the reagents and substrates. High polymer viscosity and densely coiled polymer conformations limit the accessibility of the catalytic sites to the reagents and consequently afford low diffusion rates for substrates and products alike, in general leading to inefficient catalytic processes. Therefore, the efficiency of polymeric-supported catalysts is ultimately governed by the conformation of the polymer chain that in turn is dependent upon the temperature and the solvent system employed. In addition, the proposed advantage of using polymer supported catalysts in order to ease the recovery and re-use through membrane filtration[26] could be compromised by the polymer's viscosity and non-persistent nanoscopic size characteristics as a consequence of their rheological properties.[25] Therefore, an ideal polymeric catalyst should be highly active and selective, but also highly soluble in the solvent used while adopting a conformation that permits easy access/egress to/from the catalytic sites for the substrates/products, respectively. Additionally, the polymer support must also maintain a stable three-dimensional shape and size under a range of solvent and temperature conditions in order to facilitate efficient catalyst recovery and recycling.

As a consequence of the unique structural and chemical properties of dendritic macromolecules, these hyperbranched systems differ significantly from traditional linear polymers.

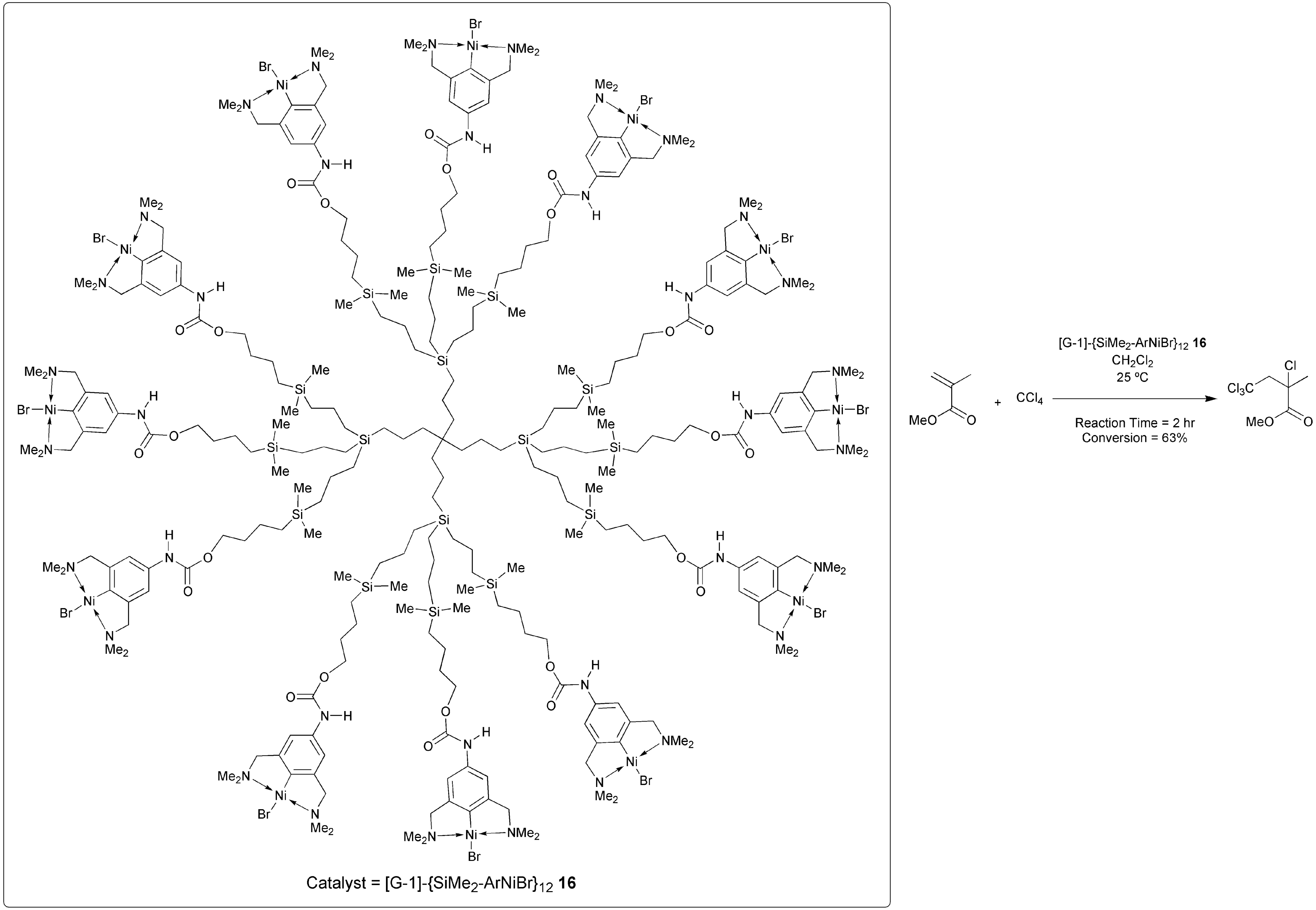
Dendrimers also possess persistent and controllable dimensions (1–100 nm), controllable topologies, are monodisperse in nature ($M_w/M_n \leqslant 1.0005$), and the possibility exists to fine-tune the dendritic structure and solubility characteristics by incorporation of specific functionalities in predetermined positions (*vide supra*).[1,4] All of these features render dendrimers as attractive alternatives in the development of new materials that combine the main advantages of both homogeneous and heterogeneous catalysts: (1) excellent solubility in common organic solvents (*advantage of homogeneous catalysts*); (2) minimally-entangled structure (unlike linear polymers), therefore the catalytic sites are easily accessible to the substrates leading to high catalytic activity (*advantage of homogeneous catalysts*); (3) ease of removal from the reaction media by membrane and ultrafiltration techniques as a direct result to their large size when compared to the products (*advantage of heterogeneous catalysts*). In an analogous fashion to chiral dendrimers, catalytic sites can be incorporated[101] within dendritic structure in several ways: (1) at the central core (or focal point of dendritic wedges); (2) at branching points; (3) at the peripheral surface of dendrimers.

3.1 Peripherally functionalised dendritic catalysts

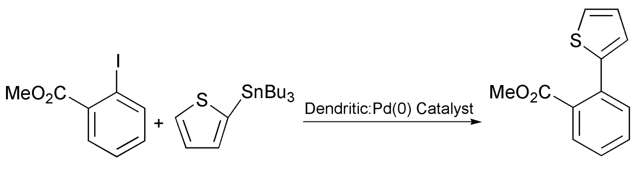
The first example of a dendrimer employed as a catalyst support was reported by van Koten and co-workers in 1994.[102] The preparation of 0th and 1st generation polysilane dendrimers functionalised with diaminoarylnickel(II) complexes at their peripheral surfaces (see **16** in Scheme 1) and their use as homogeneous catalysts in Kharasch-type additions of polyhalogenoalkanes to olefins (shown for methyl methacrylate and carbon tetrachloride) was described. In comparison to the monomeric counterpart, a reduction (20–30%) in the catalytic activity was observed when the dendritic catalysts were employed. However, the potential application of physical separation methods (*i.e.* filtration) was described for these hyperbranched systems. This seminal report revealed several attractive and potentially beneficial aspects of the use of dendrimers in catalysis and consequently, numerous dendritic catalysts have since been described in the literature.

Peripherally functionalised dendrimers possess several potential advantages over conventional linear polymeric supports. Numerous catalytic sites are located at the periphery of the dendrimer and are subject to minimal detrimental chain entanglement effects from the hyperbranched macromolecule. These multiple catalytic sites are thus freely available to interact with substrates and reagents alike and this accessibility enables reaction rates that are comparable to those of homogeneous monomeric counterparts. For example, Reek and van Leeuwen *et al.* have described[103] recently the preparation of carbosilane or PPI dendrimers that bear covalently and non-covalently anchored diphosphine ligands for metal binding. ([η^3-C_3H_7)$PdCl_2$] was then mixed with the polydiphosphine dendrimers to form multi-component palladium complexes whose efficacies were tested in the allylation substitutions reactions with a variety of suitable substrates. All the dendritic complexes exhibited high catalytic activities—for example, use of the 4th generation PPI dendrimer complex possessing 32 non-covalently anchored phosphine ligands[104] led to 80% conversion in the allylic amination of crotyl acetate with piperidine after just 10 minutes—approximately the same reaction rate was observed for the corresponding monomeric diphosphine complex. Reetz *et al.* reported[105] the use of PPI dendrimers up to the 3rd generation bearing bidentate diphenylphosphane ligands at the surface that are capable of forming complexes with metals such as nickel, palladium and rhodium. The palladium complex catalysts formed by treatment with [$Pd(Cl_2)(PhCN)_2$] were employed in preliminary studies of Heck couplings of bromobenzene and styrene to form the corresponding stilbene. Conversions between 85–90% and turnover numbers (*i.e.* number of moles of product produced per mole of catalyst employed) up to 50 were observed for the dendritic catalyst. In contrast, turnover numbers of just 16 were obtained for the analogous monomeric ligand under identical experimental conditions. These studies indicate that dendritic catalysts of this type can manifest even higher catalytic activities in comparison to their monomeric counterparts, and this enhancement was attributed to the higher thermal stability of the dendritic complex thus avoiding the decomposition of the palladium complexes. Similar results were obtained[106] by Caminade *et al.* who prepared phosphorus containing dendrimers up to the 3rd generation that were 'coated' with palladium diphosphine complexes and tested them in the Stille coupling of methyl 2-iodobenzoate with 2-(tributylstannyl)thiophene (Scheme 2). In the case of the 3rd generation dendrimer, not only was the catalytic activity higher when compared to the monomeric palladium–ligand complex[107] $(Ph_3P)_2PdCl_2$ (*i.e.* 95% conversion in 2.5 hours *versus* 81% after 20 hours), but also the stability of the palladium–ligand complex was increased—the production of inactive precipitates that contained palladium were not detected when the dendritic catalyst were used.

Positive and negative co-operative effects have been described for peripherally functionalised dendritic catalysts as a consequence of the presence of a high concentration of catalytic sites within close proximity to each other at the surface of the dendritic structure. High local catalyst concentrations of peripherally functionalised dendrimers could be useful if the desired modification of the substrate proceeds *via* a mechanism that requires simultaneous use of two catalytic sites. Therefore, in terms of entropic factors alone, a peripherally functionalised dendrimer bearing a high density of catalytic sites should enhance the activity in comparison to monomeric species.[108] For example, Ford *et al.* have described[109] the use of polyether dendrimers (up to the 3rd generation) bearing quaternary ammonium cations at the surface as catalysts for the decarboxylation of 6-nitrobenzoisoxazole-3-carboxylate and the hydrolysis of *p*-nitrophenyl diphenyl phosphate.[110] In terms of activity per catalytic site, the higher generation polyether dendrimers were found to be more efficient in comparison to the smaller dendrimers thus indicating a potential positive co-operative effect between the peripherally located ammonium cations. However, deactivation of catalytic metal–ligand complexes has also been observed when high local concentrations of catalytic species[111] are employed and thus detrimental site poisoning could occur in peripherally functionalised dendritic catalysts. Several examples have been reported regarding such deactivation processes in the case of dendrimers containing transition-metal ligands as catalytic species at the surface. For example, Majoral, Chaudret and co-workers described[112] the reduction of the reactivity of diphospinoruthenium complexes at the peripheral surface of phosphane based dendrimers towards the



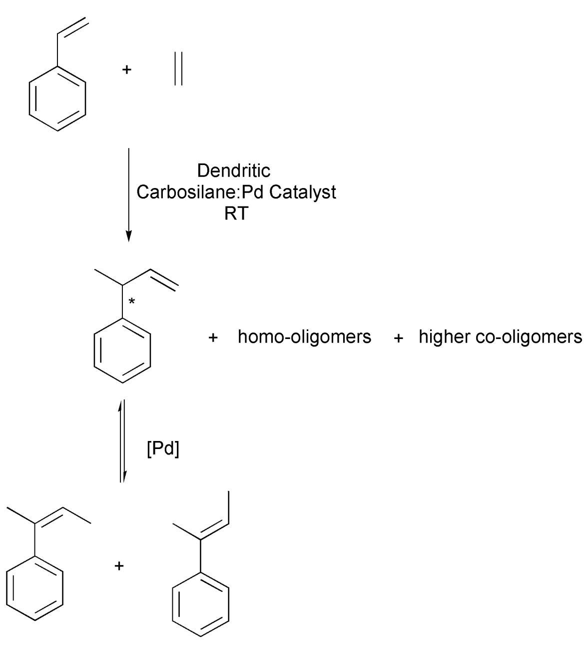
Scheme 1 The polysilane dendritic catalyst **16** described[102] by van Koten and co-workers—the first example of a dendritic catalyst system and was utilised in the Kharasch-type addition of a variety of polyhalogenoalkanes to olefin substrates.



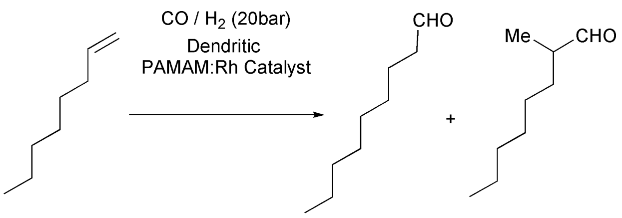
Scheme 2 Use of phosphorus-based metal–dendritic complexes in Stille coupling methodologies.[106]

reactions of CO or olefin insertion in comparison to the monomeric counterparts. This phenomenon could arise either from the steric bulk at the surface of the dendrimer (thereby inhibiting diffusion of the reactants) or from the stabilization of the complex by several functionalities present in the dendrimer. Vogt, van Koten and co-workers have also described[113] carbosilane dendrimers bearing different phosphino-carboxylic acid esters at the peripheral surface capable of forming palladium complexes for use in the hydrovinylation of styrene (Scheme 3). In comparison to the monomeric palladium complexes, the 0th and 1st generation dendrimers exhibited reduced catalytic activity indicating catalyst deactivation as a consequence of the close proximity of large numbers of palladium metal centres.

Another related case of dendrimer catalyst deactivation of this type has been reported recently by the same research group,[114] whereby carbosilane dendrimers functionalised with tridentate [$C_6H_2(CH_2NMe_2)_2$-2,6-(*R*)-4] ligands at the surface were prepared. Subsequent exhaustive complexation with nickel(II) and application of these dendritic metal complexes in the Kharasch addition of polyhalogenated alkanes to olefins revealed a dramatic drop (~70%) in the catalytic activity between the 0th and 2nd generation dendritic catalysts. A purple-brown precipitate was formed in these catalytic studies indicating that the active nickel(II) metal centres were oxidised to the corresponding nickel(III) species resulting in the formation of less soluble mixed multi-valence dendritic complexes. As a direct consequence of the proximity effect at the dendritic surface, interaction of nickel(II) sites with neighbouring sites enabled the formation of mixed-valence nickel(II)–nickel(III) complexes capable of competing for substrate radicals.[115] However, it was possible to maintain the catalytic activity for higher generation dendritic catalysts with performances comparable to the monomeric sites by increasing the spatial separation between the nickel-sites, *via* insertion of longer branches.[116] Analogous structural modifications have been made[117,118] to the hyperbranched component in other dendritic catalyst systems possessing reactive centres at the peripheral surface in order to reduce the congestion around the peripheral surface and therefore enhance the catalytic activity. Several studies reported in the literature have shown that steric effects not only influence the catalytic activity but also the intramolecular and intermolecular regioselectivity of a reaction.[119] Xi *et al.* have prepared[120] PAMAM dendrimers up to the 3rd generation that featured phosphine–rhodium(I) complexes at the surface, and tested them as catalysts in the two-phase hydroformylation of styrene and oct-1-ene (Scheme 4). The ratio of the branched : linear products was determined as 15 : 1 for the styrene hydroformylation, in comparison to the ratio 6 : 94 that was obtained using the simple monomeric ligand–rhodium(I) complex. In contrast, lower regioselectivity was observed for oct-1-ene (1 : 2 branched : linear). Cole-Hamilton and co-workers[119c] showed that when a dendritic catalyst based on a polyhedral oligomeric silsequioxane cores with up to 16 diphenylphosphine ligands coupled to rhodium at the surface were used for the reaction of hydroformylation of oct-1-ene, a higher ratio linear/branched product respect to the monomer ligand was found (l/b = 14 *versus* 3–4). This positive dendritic effect was explained as a consequence of the steric crowding at the dendritic surface that favour the formation of bidentate eight-membered ring between PPh_2 and rhodium, and the ring formation enhances the linear selectivity in hydroformylation reactions.



Scheme 3 Selective hydrovinylation of styrene using carbosilane dendritic catalysts.[113]



Scheme 4 A two-phase hydroformylation reaction that is catalysed by rhodium-complexed water-soluble PAMAM dendrimers.[120]

The majority of dendritic catalysts reported so far have featured transition metal complexes. The combination of the unique structural features of dendritic architectures with the plethora of organo-transition metal complex catalysts, has opened up the development of novel catalytic systems.[121] However, several dendritic catalyst systems have been described that do not contain transition metal ligand complexes as the catalytic species.[110,122] For example, Hawker, Fréchet and co-workers reported[123] the synthesis of catalytically active polyether aromatic dendrimers (up to the 4th generation) bearing tetradecyl units at the surface that behave in a reverse micellar fashion. In this case, the polyether dendrimer possesses a hydrophilic interior environment that is able to stabilise polar transition states and a hydrophobic exterior that is able to drive the products away from the catalytic site.[124] This catalyst was successfully tested in the reaction of E1-type eliminations from tertiary alkyl halides, with a complete conversion obtained within 24 hours and at low catalysts loading (0.57%).

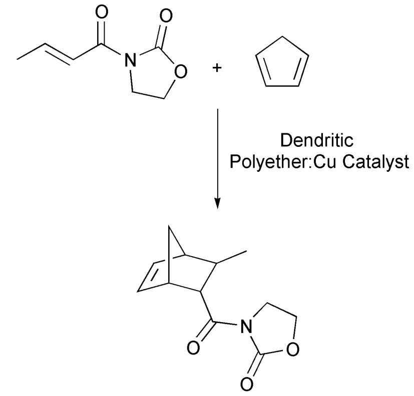
A common practical problem in organic synthesis is the use of water-soluble reagents in the chemical modification of water-insoluble substrates. A solution to this problem has been the use of co-solvent or phase transfer catalysts that bring incompatible reagents and substrates in close contact.[125] van den Broeke *et al.* reported[126] the preparation of a series of PPI dendrimers bearing perfluoroctanoyl groups at the surface. These dendrimers also behave as inverse micelles and are excellent phase transfer catalysts for the halogen exchange reaction of benzyl chloride into benzyl bromide and for the esterification of oxalic acid with pentafluorobenzyl bromide in supercritical CO_2 and water.

3.2 Central core functionalised dendritic catalysts

In contrast to peripherally functionalised dendritic catalysts, central or focal point functionalised dendrimers offer several different properties that are related mainly to site isolation phenomena created by the hyperbranched environment. For example, incorporation of a single catalytic site within monodisperse and well-defined dendritic architectures represents one potential route to enzyme models (so-called *dendrienzymes*[127])—the catalytic activity and substrate selectivity of enzymes are not only related to the precise structure of the catalytic site but are also determined by the surrounding peptide structure. Such effects can be mimicked 'easily' by dendrimers *via* precise control in the construction of the hyperbranched architecture.[128] The phenomenon of site isolation within dendrimers can be extremely advantageous especially for catalytic species that are deactivated in the presence of excess ligand sites or by negative cooperative effects (as evident in several peripherally-functionalised dendrimers, *vide supra*). For example, van Koten *et al.* described[129] the preparation of a dendritic catalyst featuring a single 'pincer' $2,6\text{-}[(CH_2NMe_2)_2\text{-}4\text{-}NR_2]$ ligand at the focal point of aromatic polyether dendrons up to the 2nd generation. The catalytic activity of this dendritic ligand system was tested in the Kharasch addition of CCl_4 to methyl methacrylate and revealed comparable activities to that of the non-dendritic catalytic ligand systems. These results differed markedly from those obtained when related dendritic catalyst systems bearing multiple nickel complexes at the peripheral surface were used (*vide supra*).

Another successful example of core-functionalised dendritic catalysts has been reported by Majoral *et al.* who described[106] the preparation of phosphorus containing dendrimers featuring a ruthenium complex at the central core. Dendritic catalysts of this type were tested on the Michael addition between ethyl cyanoacetate and diethyl ethylidenemalonate. The catalytic activity observed for the dendritic catalyst system was comparable to the single monomeric unit, however, the possibility to recycle the catalyst by precipitation without significant loss of catalytic activity after recovery proved advantageous.

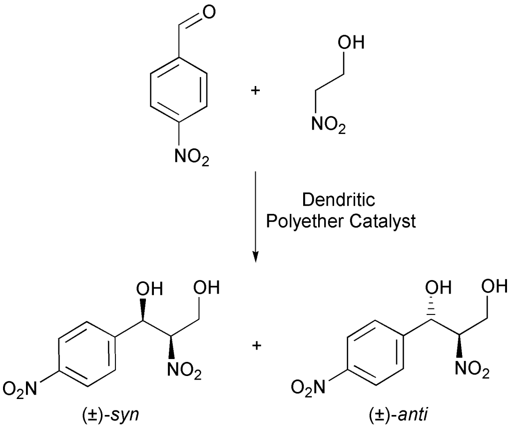
A variety of detailed studies on core-functionalised dendritic catalysts have revealed that the increase of the generation number leads to a detrimental effect upon the catalytic activity. This general trend is attributed to restricted access of the reagents and substrates involved to the active site at the core. For example, Diederich *et al.* prepared[130] novel dendritic catalysts based on a thiazoliocyclophane core as the catalytic site coupled to poly(ether amide) dendrons up to 2nd generation, in order to mimic the natural thiamine diphosphate dependent enzymes. The oxidation rates of aromatic aldehydes to the corresponding carboxylic esters catalysed by the novel *dendrienzyme* was slower (between 50 and 130 times depending on the groups at the dendrimer surface) than those observed when the monomeric ligand system was employed. This decrease in reaction rates (as the generation number of the dendritic component increased) was attributed to steric hindrance within the reactions' transition states, despite favourable micropolarity characteristics at the cyclophane active site. Chow *et al.* described[131] the preparation of copper(II) bis(oxazolidine) complexes that were coupled to aromatic polyether dendrons up to the 3rd generation. These dendritic catalysts were tested in the Diels–Alder reaction between cyclopentadiene and crotonyl amide (Scheme 5) and it was observed that the rate constant of the rate limiting step (*i.e.* the reaction of the complex dienophile–catalyst with the diene), remained the same when 0th to the 2nd generation dendrimers were employed, but then decreased dramatically in the case of 3rd generation dendritic catalyst. This result was attributed to a detrimental increase of the steric repulsion between the large dendritic wedges of 3rd generation that induced back-folding of the hyperbranched arms toward the catalytic core in order to relieve the overall steric strain of the system, thereby decreasing the accessibility at the central catalytic core.



Scheme 5 A Diels–Alder reaction between cyclopentadiene and a dienophile that is catalysed by a polyether dendrimer that features a bis(oxazoline)copper(II) complex at the central core.[131]

Cossío *et al.* have prepared[132] dendrimers based on a triethanolamine core with aromatic polyether Fréchet type dendrons up to the 3rd generation. These dendritic catalysts were utilised in the Henry reaction (Scheme 6) and it was observed that the smaller generation dendritic catalysts enabled high conversion (85–95%) to the nitroaldol products after only 4–6 hours, whereas, in the case of the higher generation systems, the same conversion required two days.

Reek and van Leuween[103] described the preparation of carbosilane dendrimers containing 1,1′-bis[diphenylphosphino]-ferrocene (dppf) ligand at the core. After forming the corresponding palladium complex, these dendritic catalysts were tested in the allylic alkylation of 3-phenylallyl acetate with diethyl 2-sodio-2-methylmalonate. Almost total conversion of the substrates was observed for each of the dendritic catalysts, however, the reaction rate decreased as the generation number of the dendritic component increased, evident by examination of the turnover frequency (number of moles of product per moles of catalyst per hour) that dropped from 752 for the 1st generation catalyst to 168 for the 3rd generation dendrimer. However, despite the decrease in the catalytic activity, these dendritic catalysts revealed interesting regioselectivity as the ratio branched/linear product increased from the 1st to the 3rd generation. This effect was attributed to the change in the local polarity at the core of the dendrimer as a consequence of the larger apolar dendritic shells. In contrast, the same group have shown[101] that when related carbosilane dendrimers possessing a single dppf ligand at the central core (see **17** in Fig. 11) were



Scheme 6 The nitroaldol reaction between 4-nitrobenzaldehyde and 2-nitroethanol that is catalysed by Fréchet-type dendrimers featuring an amino core unit.[132]

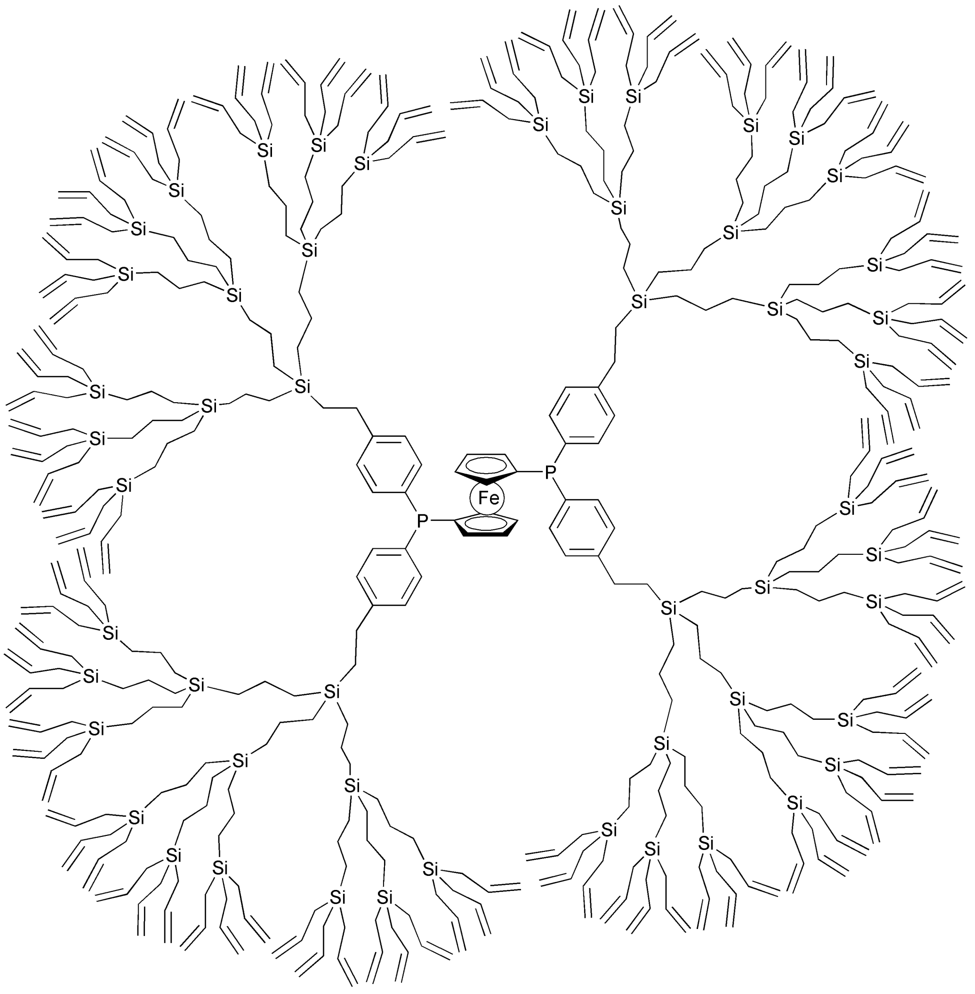


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Fig. 11 A polysilane dendritic catalyst **17** featuring a bis[diphenylphosphino]ferrocene central core unit that is used in the hydroformylation of oct-1-ene.[101]

complexed with rhodium and tested in the hydroformylation of oct-1-ene, the activity of the catalyst was not detrimentally affected by increasing size of the hyperbranched ligand.

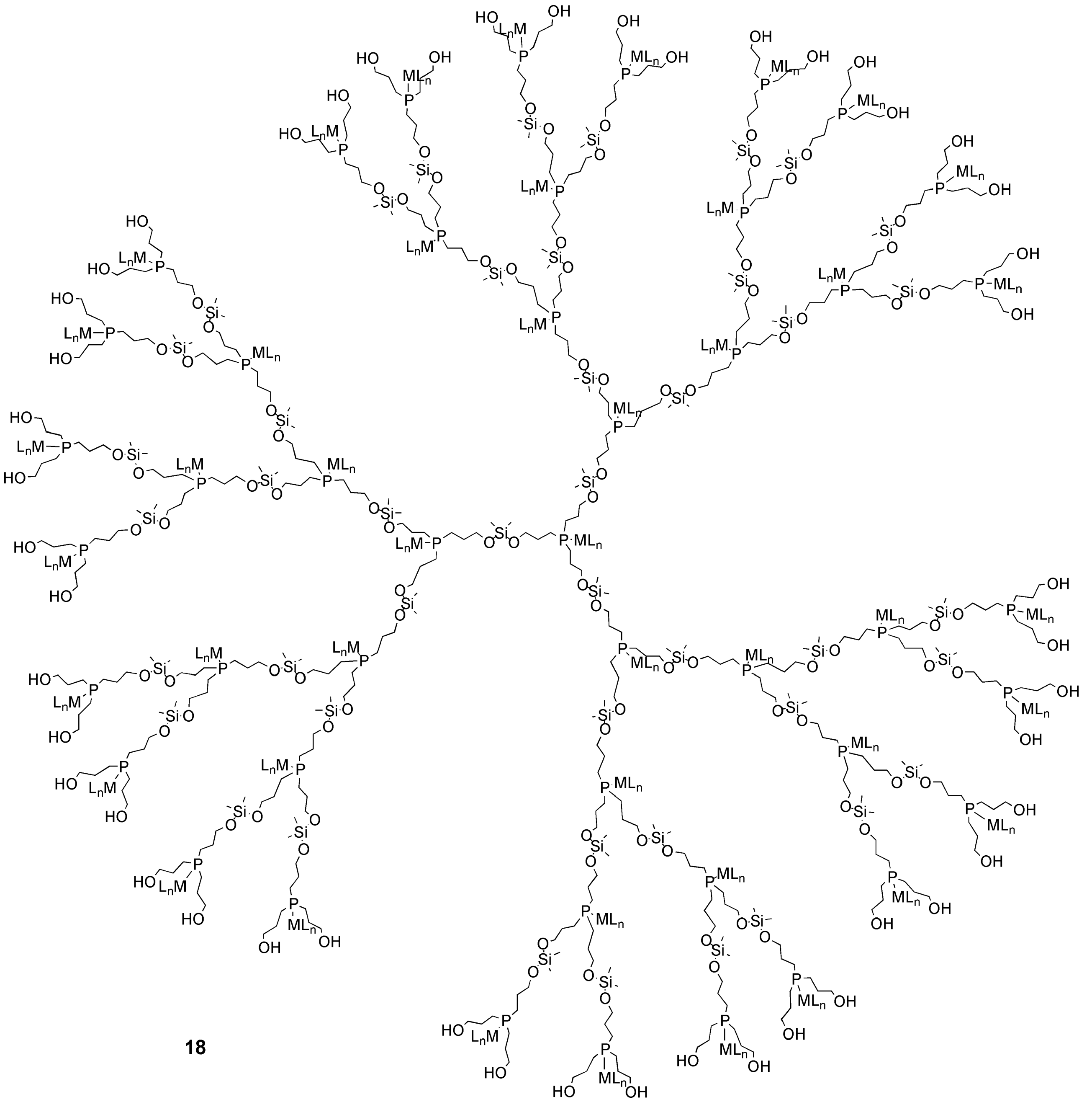
Suslick, Moore and co-workers have studied[133] porphyrin core functionalised dendritic catalysts and this work has revealed intra- and intermolecular selectivity in the epoxidation of olefins. By using several non-conjugated dienes they observed that epoxidation proceeded more rapidly at the less hindered double bond of the diene. Similarly, when mixtures of different alkenes were epoxidised using this dendritic catalyst the less hindered alkene were converted at a faster rate. These results were rationalised by consideration of the steric influence of the bulky dendritic system surrounding the manganese(III)–porphyrin core. It has been proposed[27,134] that a key structural feature in successful dendritic catalysts is the combination of the active site with apolar dendrons, however, this study demonstrates that polar dendritic structure may also prove advantageous.[135]

Though dendritic catalysts featuring organometallic catalytic sites have been extensively studied, simple polyether dendrons with a hydroxyl focal point have proven to be very useful as catalytic initiators in polymerisation processes.[136] For example, Fréchet and co-workers[137] prepared dendritic alkoxide macro-initiators for use in the anionic ring opening polymerisation of ε-caprolactone. Despite the bulk of the initiator, efficiencies were maintained ($\sim 100\%$). This type of initiator has been considered particularly suitable as a consequence of the enhanced solubility properties and the prevention of 'backbiting' directly related to the bulky nature of the initiator. Indeed, larger polyether initiators prevented the termination of the ring opening polymerisation by shielding the growing chain, thereby obtaining high molecular weight polyesters with relatively low polydispersity indices ($M_w/M_n \approx 1.07$).

3.3 Dendritic catalysts featuring catalytic sites at branched points

The majority of dendritic catalysts reported in the literature feature catalytic sites at either the surface or at the central core/focal point. However, it is also theoretically possible to distribute catalytic sites throughout *all* of the dendritic structure and few examples have been described to date. Kakkar *et al.* have prepared[138] dendritic wedges featuring phosphine units as branching points that are capable of binding metals such as rhodium (see **18** in Fig. 12). Rhodium metallodendrimers thus formed were catalytically active in the hydrogenation of decene and larger dendrimers of this type (up to the 3rd generation) exhibited activities comparable to the monomeric rhodium–phosphine complexes.

DuBois *et al.* prepared[139] analogous hyperbranched structures with tertiary phosphine ligands at the branching points and the surface of dendrimer. These tertiary phosphine dendrimers were then converted into the corresponding palladium complexes and their catalytic properties were studied in the electrochemical reduction of CO_2 to CO—the reaction rates obtained for these macromolecular catalysts were comparable to those of the analogous molecular palladium



18

Fig. 12 A metallodendrimer **18** (M = Rh) reported[138] by Kakkar and co-workers that incorporates phosphine ligand sites in the branched units.

based catalysts. However, these preliminary studies did not ascertain whether the performance of these dendritic catalysts stemmed from the catalytic units at the periphery or from those located in the interior of the dendrimer.

3.4 Recyclable dendritic catalysts

As mentioned earlier in this section, one significant advantage of the use of dendritic catalyst systems with respect to the corresponding homogeneous mononuclear counterparts, is the potential to separate and reuse the hyperbranched catalysts from the reaction mixture at the end of the reaction by ‘simple’ physical processes (*i.e.* nano- or ultrafiltration) as a consequence of the nanosize dimensions of dendrimers. Several recoverable dendritic catalyst systems have been described that employed either precipitation[106,140] or membrane filtration processes[129,141] in order to separate the products from the macromolecular reagent. Membrane reactors have also been investigated as an alternative approach to the recycling of dendritic catalysts.[26] Since the first reports of membrane reactors,[142] highly selective membrane materials have been developed that are able to specifically retain relatively small compounds (*i.e.* mass cut-off 400 Da). Consequently, membrane reactors have already been used successfully in continuous processes involving the separation of polymer-supported homogeneous catalysts.[143] However, dendrimers represent even more suitable systems for the application of this type of reactor as a direct consequence of their globular-type morphologies (Fig. 13).

The use of membrane in a continuous process involving dendritic catalysts offers several advantages for technical and industrial applications. For example, fresh catalyst can be supplemented in a continuous process—such methods are difficult in the case of fixed bed reactors. In addition, the concentration of the reactant can be kept constant with the time and thereby the steady state of the reaction can be maintained. Ultimately, the overall effect is the achievement of higher turnover numbers in systems of this type in comparison to optimised conditions in a batch reaction and easy removal of the catalyst thus avoiding expensive purification steps *without*

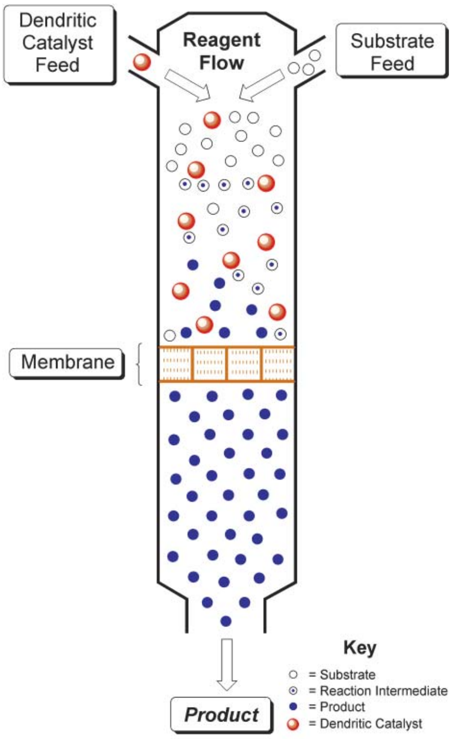
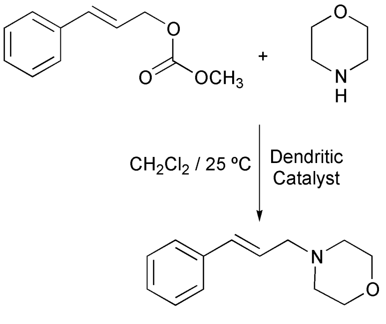


Fig. 13 A schematic representation of a selective continuous membrane reactor.

losing the advantages of homogeneous catalysis. To date, only a few examples of the application of dendritic catalysts in combination with continuous membrane reactors have been described in the literature. Brinkmann and co-workers detailed[144] the application of PPI dendrimers (3rd and 4th generation) bearing palladium–diphenylphosphane complexes as the catalysts in a continuous membrane reactor format for allylic substitution reactions (Scheme 7). As a result of the PPI dendrimers' molecular weight ([G-3] = 10 212 g mol^{-1} and [G-4] = 16 199 g mol^{-1}) and low viscosity characteristics, these dendritic catalysts possessed retention factors in a SELRO MPF-50™ membrane up to 0.999. However, in the case of the 3rd generation PPI dendrimer, only low conversions were observed ($\sim$12%) after 60 residence times (*i.e.* the time needed to fully replace one membrane reactor volume). This result was attributed to leaching of the palladium species during the reaction. In contrast, use of the 4th generation dendrimer catalyst led to initial conversion factors of 100% that decreased to 75% after 100 cycles. The different results obtained were not attributed to the characteristics of the dendritic catalysts but to the different reactions conditions used for the two separate experiments. van Koten *et al.* have described[116] the application of carbosilane dendrimers bearing tridentate ligands for nickel binding at the surface (*vide supra*) in combination with a continuous membrane reactor for use in the Kharasch addition of polyhalogenated alkanes to olefins. The retention factors observed for the 0th and the 1st generation catalysts when a SELRO MPF-50™ nanofiltration membrane was used were high (97.5% and 99.75%, respectively). However, during this continuous process, detrimental precipitate formation involving the catalyst was observed. Precipitation was prevented by the addition of tetrabutylammonium bromide implying that the ammonium additive interacts competitively with the membrane surface preventing adsorption (and consequent deactivation) of the catalyst. This result demonstrates that the compatibility between the membrane system and the type of catalyst is an important factor and requires optimisation before using continuous catalytic processes. Reek and van Leuween[103] have applied core functionalised dendritic catalysts in a continuous process for the first time. Carbosilane dendrimers containing a palladium–dppf catalytic core were prepared (*vide supra*) and, remarkably, when applied in a continuous flow membrane reactor exhibited a rapid growth in catalytic activity during the first 30 minutes that stabilised to a constant conversion rate over the following 8 hours. These results were in stark contrast with those obtained when analogous carbosilane dendrimers bearing peripheral surface catalyst moieties based on covalently or non-covalently anchored palladium–phosphine complexes were used. In the case of these peripherally functionalised dendritic catalysts, an initial high conversion ratio (80%) was observed followed by a dramatic decrease of the catalytic activity (as a result of deactivation of the palladium catalyst). The hypothesis that core functionalised dendritic catalysts are more stable in comparison to dendritic systems bearing numerous active sites at the peripheral surface as a consequence of the shielding effect of the dendrimer's backbone is supported by the above studies. Further studies are necessary relating to the use of dendritic catalysts in continuous membrane reactors, in order to optimise procedures of this type but these initial studies clearly indicate the potential of this methodology.



Scheme 7 Use of PPI dendrimer bearing palladium–phosphine complexes in allylic substitution reactions.[144]

4. Dendrimers in asymmetric catalysis

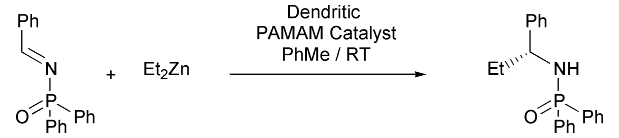
In the past 30 years, considerable effort has been dedicated to the discovery and development of new effective catalysts for asymmetric synthesis.[145] Soluble chiral metal complexes are used commonly, however, consideration of the costs involved has often restricted the use of such reagents on large scales. Numerous studies have been carried out in order to investigate the recovery and recycling of such expensive asymmetric catalysts in order to decrease the economic impact of their application. One approach has been to immobilise chiral homogeneous catalysts on insoluble inorganic[146] or organic polymers[147] to facilitate separation of the catalyst from the reaction media. The main problems associated with polymeric supports of this type is the limitation of mass transport to/from the active sites (*vide supra*). Consequently, solid supported catalyst exhibit slow catalytic rates, decreased activity and/or selectivity arising from subtle structural changes and diminished mobility of the attached complexes. An elegant alternative to these solid supported systems has been the application of liquid–liquid biphasic systems[148] where the chiral catalysts are selectively dissolved in one of the liquid phases. This phase transfer approach has enabled the chiral species to maintain the optimum catalytically active three-dimensional conformation and, therefore their chiral selectivity. Simple phase separation methods then permit efficient catalyst recovery and reuse. Another solution to the problem of catalyst separation consists of anchoring the asymmetric catalysts onto a soluble polymeric support so as to preserve the activity and selectivity of the parent catalyst species.[149] The solubility of these supported catalyst systems enables relatively easy diffusion of solvent and substrates within the polymer support thereby facilitating higher catalytic activity with respect to the insoluble polymer supported catalyst systems described above. In addition, as a consequence of the polymeric component, this type of catalyst can be easily recovered by precipitation or membrane filtration.

In a similar fashion, multiple copies of an asymmetric metal ligand site have been incorporated within dendritic scaffolds to afford soluble macromolecular catalysts possessing high loadings. As a consequence of the regular structure of dendrimers, the individual chiral environments of the asymmetric metal ligand sites are approximately the same, whereas in linear polymer supported catalysts this is not the case. The key question posed of these novel hyperbranched catalyst systems is do they offer effectively the same (or higher) stabilities and enantioselectivities with respect to the parent homogeneous monomeric catalytic species? Preliminary results obtained from studies of symmetric dendritic catalysts are very promising (*vide supra*). The next section will describe the use of dendritic catalysts in asymmetric synthesis. In a similar manner to the dendritic catalysts already described in Section 3, dendritic catalysts for use in asymmetric transformations have been constructed using two main approaches: i) peripherally functionalised chiral dendrimers, and ii) core functionalised chiral dendrimers.

4.1 Peripherally functionalised chiral dendritic catalysts

One of the first example describing the incorporation of chiral ligands at the surface of dendritic structure was reported[150] by Meijer *et al.* in 1995, who prepared PPI dendrimers up to the 5th generation that were functionalised with chiral β-amino alcohol groups at the surface. The series of modified PPI dendrimers featuring the same concentration of amino alcohol end groups (same total number of catalytic units) were tested in the enantioselective addition of diethylzinc to benzaldehyde. The yield of the secondary alcohol varied between 70 and 85% for the series of different generation catalysts. However, the enantiomeric excess (% ee) of the product decreased gradually as the generation number of the PPI catalyst increased (ranging from 11% ee for the model compound butylamine (possessing a single chiral unit) to 0% ee for the highest generation dendrimer featuring 64 catalytic units). This result was in agreement with the chiroptical data obtained from the PPI dendrimers bearing *t*-Boc-L-phenylalanine at the surface, where the molar rotation values decreased as the generation number of the dendritic component increased. These results were explained by consideration of the dense packing occurring at the dendritic surface (especially in the cases of the higher generation dendrimers), leading to diminished flexibilities of the chiral peripheral groups (*vide supra*). As a consequence, the chiral catalytic units adopt several conformations affording differences in the stereochemical course of the reaction. A similar result was obtained[151] when PPI dendrimers were functionalised at the surface with (*R*)-phenyloxirane. The enantiomeric excess for the same reaction dropped from 36% (for the model compound with one catalytic unit) to 7% for the 5th generation dendrimer. Also this study demonstrates the detrimental effect of steric crowding when large and bulky high generation dendrimers are employed in catalysis. As described in related studies (*vide supra*), this problem may be circumvented by the introduction of flexible spacers between the dendritic surface and the catalytic chiral units in order to reduce steric congestion.[19a]

Soai *et al.* prepared[152] small PAMAM dendrimers that featured ephedrine-based chiral catalytic ligands anchored to the surface *via* amino- or imino-linkages. The dendritic catalysts were employed in the enantioselective addition of diethylzinc to several *N*-diphenylphosphinylimines (Scheme 8) and their catalytic characteristics were compared to those of diamine and diimine model compounds that incorporated two chiral catalytic sites. The diamine and diimine model catalysts exhibited product yields up to 54% with % ee values as high as 92%, whereas when the 0th and 1st generation dendritic catalysts were employed significantly lower yields (18–32% for [G-0] and 8–12% for [G-1]) and % ee values (40–43% for [G-0] and 30–39% for [G-1]) were obtained. The results of this study were attributed to unfavourable interactions occurring between the ephedrine-based catalytic ligands at the dendrimers' surface enabled by the flexible dendritic backbone. In addition, an excess of the alkylating agent was required since the amine residues present in the dendrimer detrimentally co-ordinate to this reagent, thereby complicating the purification of the desired alkylated *N*-diphenylphosphinylimines. The same group[153] subsequently reported an improved dendritic catalyst system that overcame these practical problems. Poly(phenylacetylene) dendrimers up to the 2nd generation possessing chiral β-amino alcohols at the peripheral sites were synthesised and tested as catalysts in the same reaction as described above. In the case of the 1st generation dendrimer, different yields and enantioselectivities were obtained that were dependent on the location of the chiral ligand (*meta* or *para*) upon the terminal aromatic residues of the dendritic backbone. In the case of the dendrimers featuring *para*-substituted β-amino alcohol ligands, yields of 73–80% and % ee values between 89–94% were obtained, whereas in the case of the *meta*-substituted catalysts, comparable yields were observed (62–84%), but the enantioselectivity had decreased. This behaviour was explained by consideration of the close proximity of the *meta*-substituted β-amino alcohol catalytic sites to the bulky dendritic backbone and thus potential steric restrictions enforced upon the transition-state. In the case of the 2nd generation dendrimer, comparable yield (74–79%) and enantioselectivity (85–90% ee) were observed, and after recovery by purification on silica gel it could be reused without a considerable loss of enantioselectivity. Similar results were obtained by testing the same catalysts in the enantioselective addition of diethylzinc to benzaldehyde and naphthaldehyde[153b]—both 1st and 2nd generation dendrimers exhibited enantioselectivities from 80–86% ee. These results showed that the use of a more rigid and inert backbone is effective in preventing unfavourable intramolecular interaction between the catalytic sites and the necessity to use an excess of the alkylating agent.



Scheme 8 Enantioselective addition of diethylzinc to *N*-diphenylphosphinylimines using PAMAM-based chiral catalysts featuring ephedrine at the peripheral surface.[152]

Another very powerful enantioselective catalyst system is that based upon the (α,α,α′,α′-tetraryl-1,3-dioxolane-4,5-dimethanol (TADDOL) ligand.[154] In common with other homogeneous catalysts, the metal–TADDOL ligand system suffers from inefficient separation from the products/substrates. Seebach *et al.* proposed several alternatives: the incorporation of these ligands on soluble or insoluble polymeric supports,[155] or incorporation within a dendritic structure either at the central core (*vide infra*) or at the surface. Dendrimers have thus been prepared that contain either three or six TADDOL ligands at the surface. These homogeneous catalysts were tested in the enantioselective addition of diethylzinc to benzaldehyde and enantioselectivities comparable to the original monomeric ligand were obtained (94% ee). However, since the dendrimer bearing six ligands possessed a molecular weight of only 3833 Da, it could not be separated efficiently from the products by ultrafiltration methods—more labour intensive column chromatography proved effective to this end.[156]

Chiral ferrocenyl moieties have proven to be very efficient catalyst systems in a number of asymmetric reactions[157] and consequently Pugin and co-workers have studied[158] the efficacy of species of this type when located upon a dendritic scaffold to solve the notorious problem of catalyst recovery. Two structurally-related series of dendritic catalysts were synthesised: one series incorporated a 1,3,5-substituted aromatic tricarboxylic acid unit and the other possessed an adamantane-1,3,5,7-tetracarboxylic acid residue as the central core. Ferrocene ligands were coupled to the different core units to afford the corresponding 1st generation dendrimers, and when an aromatic dicarboxylic acid was employed as the branching units, 2nd generation dendrimers were obtained. In the case of both the 1st and 2nd generation dendrimers, an alkyl amine chain was inserted between the peripheral catalytic units and the dendritic surface in order to introduce higher flexibility and avoid detrimental steric interactions between the substrate receptor sites of the ferrocene catalyst. Treatment with the metal complex $Rh(COD)_2BF_4$ led to the active catalyst that was then tested in the asymmetric hydrogenation of dimethyl itaconate. Total conversion of the substrate was observed for each of the dendritic catalysts used and the enantioselectivities obtained were comparable between the different generations (98.7 and 98.1% ee for [G-1] and [G-2], respectively). As a consequence of the nanosize dimensions of dendrimers of this type ($\sim$3 nm for the 2nd generation catalyst), preliminary separation experiments have determined that these systems can be retained by commercially available nanofiltration membranes, but further studies are necessary to assess the potential application of these novel ferrocenyl dendritic catalysts in continuous processes. In a related work, the same group[159] prepared 1st generation dendrimers based on cyclotriphosphazene or tetraphosphazene central core systems that bear multiple ferrocenyl groups at the surface (possessing 12 and 16 units, respectively). The ability to construct dendrimers possessing very high concentrations of catalytic sites at the peripheral surface even at low generation is one advantage of using these unusual phosphazene-based core units. After formation of the catalytically active rhodium-complexes, these dendrimers were used in the hydrogenation of dimethyl itaconate. Enantiomeric excess values of the product up to 98% ee were observed when both dendritic systems were used and these results are comparable to the % ee values obtained when the monomeric ferrocenyl ligand system is employed. These results indicate that despite the high local concentration of ferrocenyl units at the dendrimers' periphery, these catalytic sites were in effect acting independently.

Reports of co-operative binding effects within dendrimers that incorporated recognition elements such as amino acid or carbohydrates[160] prompted Jacobsen and co-workers to study[161] potential co-operative interactions between catalytic units in dendritic architectures. PAMAM dendrimers up to the 3rd generation were functionalised with cobalt(II)–salen complexes at the surface (see **19** in Fig. 14) and tested in the asymmetric ring opening of epoxides (Scheme 9). The 2nd generation dendritic catalysts effected up to 50% conversion of the epoxide used with % ee values greater then 98%, whereas, in contrast, the monomeric cobalt(II)–salen complex (under identical reaction conditions with a catalyst loading of 0.015 mol %) did not afford measurable conversion even after 40 hours. The enhanced reactivity of the dendritic catalyst (*positive dendritic effect*) was justified by co-operative interactions between the numerous cobalt(II)-salen complexes,[162] especially in consideration of the mechanistic studies revealing that the asymmetric ring opening of epoxides involves co-operative and bimetallic processes.[163] Inspired by studies of the use of chiral micelles in asymmetric catalysis,[164] Rico-Lattes and co-workers reported[165] the synthesis of PAMAM dendrimer systems up to the 3rd generation that featured non-racemic glucose units at the surface. These systems were tested as catalytic unimolecular micelles in the reduction of prochiral ketones by sodium borohydride in water. The apolar nature of the ketones used meant that the desired transformations could not be performed in water, however, the water-soluble dendritic micelles encapsulate the prochiral ketones within the hydrophobic interior and enable close contact with the reagents in water. High asymmetric induction was observed (up to 99% ee) with concomitant efficient conversion (90–97%) of difficult ketone substrates such as acetophenone. Remarkably, it was also observed that the same reaction could be performed in a heterogeneous fashion using THF as the solvent. Under these conditions, the dendritic micelles are rendered insoluble, however, the reduction of the prochiral ketones was effectively carried out with comparable enantioselectivities and yields. This was the first example of a dendrimer used in asymmetric synthesis in a *heterogeneous* manner in order to enable ease of recovery and consequent recycling of the hyperbranched macromolecule by simple filtration methods.

4.2 Asymmetric dendritic catalysts featuring chiral cores

The three-dimensional structures of dendrimers, coupled with specific functionalities present within the hyperbranched scaffold have enabled these macromolecules to be used in enzyme mimic studies. From consideration of recent examples of shape selective encapsulation of guests into the cavity of dendrimers[166] and the behaviour of achiral molecules bound within a 'dendritic box',[61] it is apparent that the interiors of dendrimers are suitable environments in which to carry out asymmetric synthesis. Brunner *et al.* reported[167] a dendritic catalyst system that was based on an achiral catalytic core surrounded by chiral branching units. The structure of these organometallic dendritic catalysts was based upon either a diphosphine or diimine ligand core and branched substituents containing optically active groups at the surface in order to create an asymmetric environment to the achiral ligand necessary for asymmetric synthesis. Thus a *dendrienzyme* was prepared based on a diimine ligand consisting of pyridine aldimine derived from (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol for metal binding surrounded by (1*R*,2*S*)-ephedrine or L-aspartic acid. Subsequent complexation with copper(I) triflate afforded the active dendritic catalyst and these were tested in the cyclopropanation of styrene with ethyl diazoacetate. Low % ee ($\sim$10%) was exhibited by the dendritic catalyst, however, use of the parent pyridine aldimine ligand system afforded negligible asymmetric induction. This result indicated that the chiral dendritic pocket had slightly increased the enantioselectivity of the reaction. In a related study, the same group prepared[168] a dendritic phosphine ligand consisting of a central diphosphine core for metal binding and a layer of 3,5- or 2,5-disubstituted arenes with chiral bornyloxy or chiral menthyl units at the surface. Subsequent formation of the rhodium complex by treatment with $Rh(COD)Cl_2$ produced chiral dendritic catalysts that were then tested in the hydrogenation of acetamidocinnamic acid and hydrosilylation of acetophenone. The catalysis of the reactions using the phosphine ligands in conjunction with the 3,5-disubstituted arenes proved faster then those performed using the parent diphosphine ligand, whereas, when the 2,5-disubstituted arenes were employed the rate of reaction dramatically decreased (by a factor of 300 in comparison to the parent ligand). It has been proposed that the presence of *ortho*-substituents on the aromatic branched units reduces the accessibility of the substrates to the core unit because of steric factors. In general, the enantioselectivities of these transformations were extremely low on account of the high flexibility of the ligands. Different diphosphine based *dendrienzymes* have also been prepared,[169] with 1,2-bisphosphanylbenzene ligand at the central core

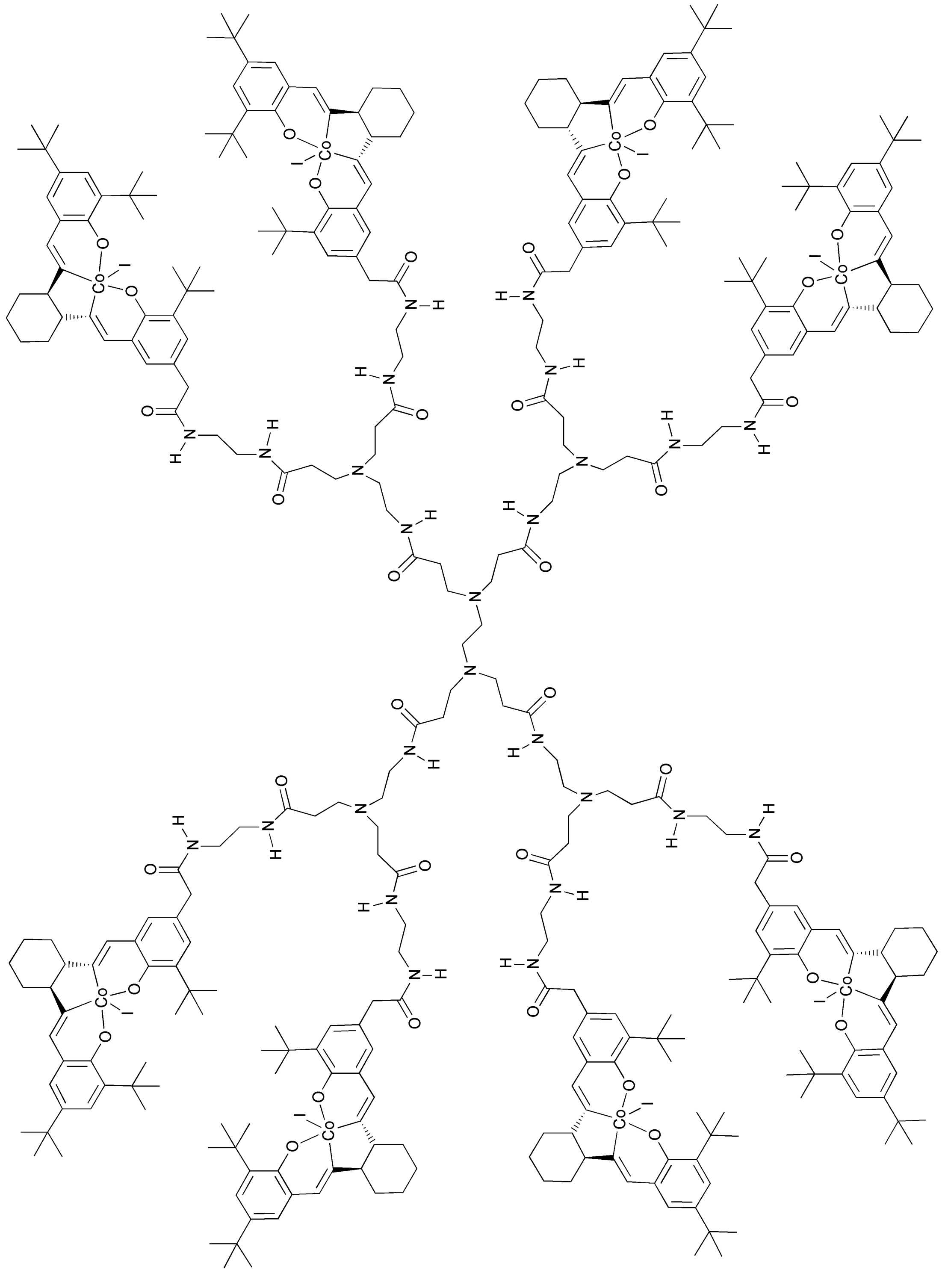


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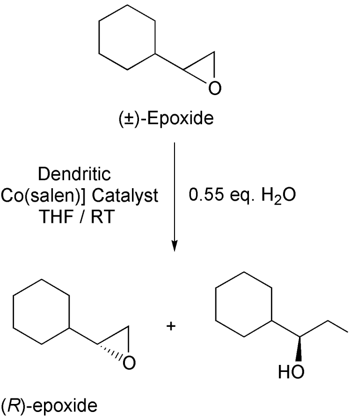
Fig. 14 A PAMAM dendrimer bearing multiple cobalt(II)–salen complexes at the peripheral surface **19** for use in the asymmetric ring opening of epoxides.[161]



Scheme 9 Use of a PAMAM dendrimer bearing multiple cobalt(II)–salen complexes at the peripheral surface **19** in the ring opening of epoxides.[161]

coupled to different optically active acrylate or methacrylate derivatives (such as (*R*)-(+)-*N*-methyl-*N*-(1-phenylethyl)acrylamide, (1*S*,2*R*,5*S*)-(+)-menthyl acrylate and (1*S*)-*endo*-(−)-bornyl acrylate). These chiral catalysts were used in the hydrogenation of (*Z*)-α-acetamidocinnamic acid, the hydrosilylation of acetophenone and the allylation of 1,5-dimethylbarbituric acid. In all of these transformations, acceptable yields were obtained (from 54 to 91%), however, the optical induction was very poor (*i.e.* only 8.6% ee for the hydrogenation reaction). The poor stereoselectivities obtained in these studies were justified with the lack of appropriate rigidity of the chiral arms of the dendritic catalyst necessary to maintain the macroscopic chirality. Further developments in this area led to the preparation[170] of other diphosphine ligands containing 1,2-bisphosphanylbenzene or ethylene ligands coupled to aromatic branching units with aldehyde-based substituents capable of forming Schiff bases with different peripheral chiral units, such as (*S*)-leucinol, (*R*)-1-cyclohexylethylamine, and (*S*)-valinol. After formation of the metal complex with transition metals such as palladium, rhodium or nickel, these dendritic catalysts were used in the same reactions as described above. Slight improvements in the enantioselectivities were observed only for the hydrosilylation reaction (∼18% ee) when the dendritic catalyst featured ethylene bridging ligands. Recent studies by the same group[171] have described the synthesis of a new diphosphine ligand that features a chiral *trans*-1,2-disubstituted cyclopentene bearing two phosphorus atoms as the binding sites for either polyaldehyde aromatic dendritic extensions (with CHO-groups in *ortho*- or *meta*-positions) bearing different chiral amino alcohols (*i.e.* D- and L-valinol, L-leucinol) (see **20** in Fig. 15) or to polyether aromatic dendritic structures with bulky borneol groups at the surface. The presence of chiral units both at the central catalytic centre and at the dendritic surface offers the possibility to study the source of optical induction. After formation of palladium complex, the dendritic catalysts were used in the enantioselective allylation of 1,5-dimethylbarbituric acid with allyl acetate (Scheme 10). Higher enantioselectivities were observed (10–20% ee) when polyaldehyde aromatic dendritic units possessing *meta*-substituents were used and the direction of the optical induction seemed to be determined by the (1*S*,2*S*) chelate structure of the central diphosphine ligand and not from the stereochemistry of the surface groups. Improved results were obtained when the corresponding rhodium dendritic complex was employed in the hydrogenation of α-acetamidocinnamic acid. High enantioselectivities (90–96% ee) were observed in comparison to the results obtained by using single diphosphine ligand (only 23% ee). As in the previous example the direction of the optical induction was determined largely by the stereochemistry of the central chiral ligand, as an excess of the (*S*)-enantiomer (96% ee) was obtained when using (1*R*,2*R*) diphosphine structure and an excess of the (*R*)-form (94% ee) was obtained when using the core of opposite configuration. However, when the catalysts were tested in the enantioselective hydrosilylation of acetophenone, a larger influence of the peripheral groups to the stereochemistry of the products was observed. In fact using the *meta*-substituted ligand in conjunction with D-valinol at the surface, a % ee of 23% was found for the (*S*)-enantiomer, but this value dropped to 12% when the peripheral group D-valinol was exchanged for the enantiomeric L-form.

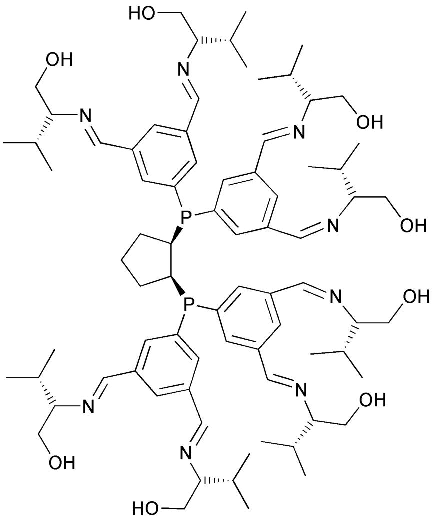


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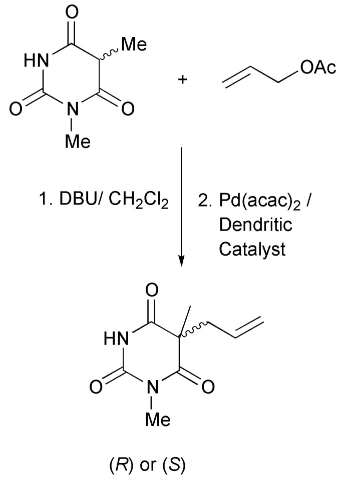
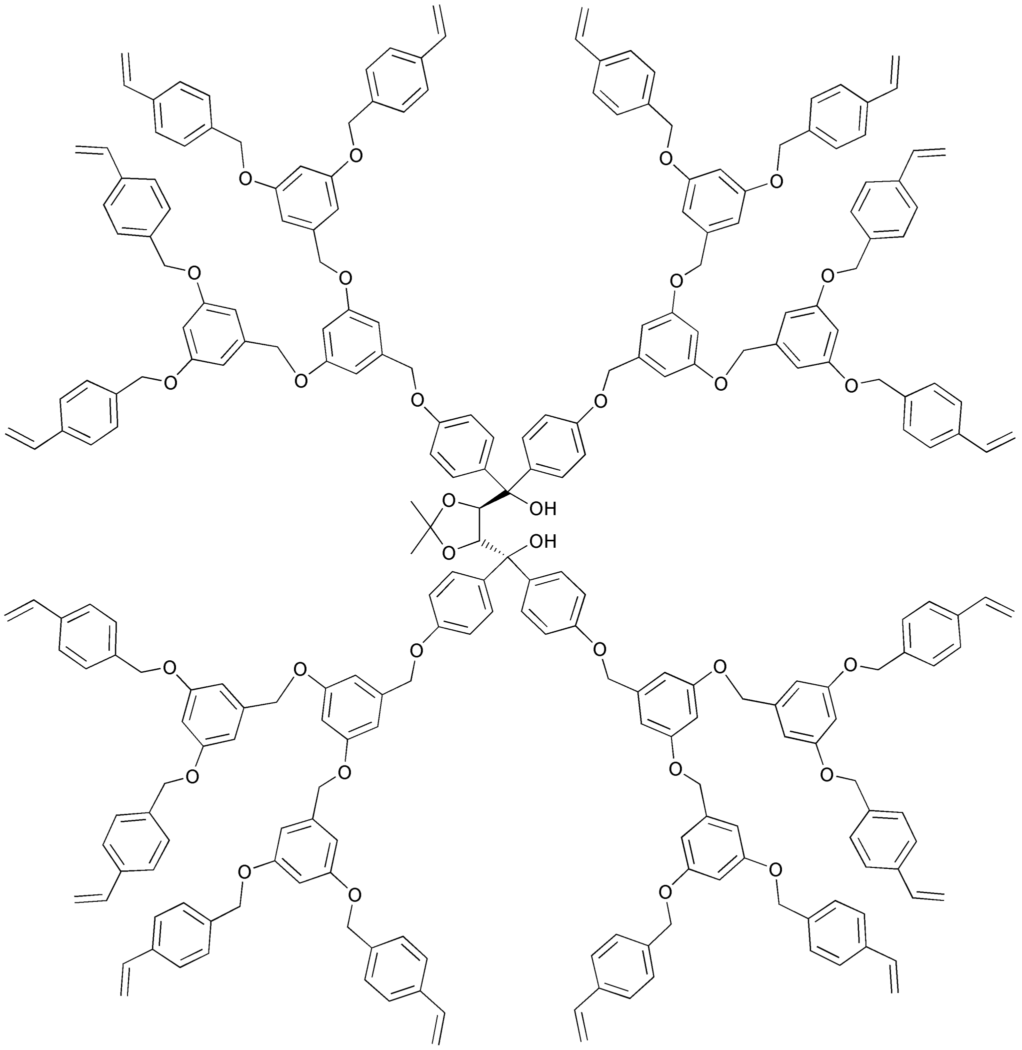
Fig. 15 A polyimine 'dendrienzyme' **20** that is effective in the asymmetric allylation of barbituric acid derivatives.[171]

As part of the study of TADDOL–based catalysts (*vide supra*), Seebach *et al.* have synthesised[172] a dendritically-substituted TADDOL unit possessing peripheral styryl groups to afford a polystyrene resin that contains catalytically-active hyperbranched cross linkers (see **21** in Fig. 16). As a consequence of the conformationally flexible dendritic spacers between the chiral ligands and the rigid polystyrene backbone, these dendritic cross-linked insoluble polymers were expected to possess accessible TADDOLate sites (in contrast[155] to an analogous polymer resin containing TADDOL units). After doping the new cross-linked polymer with $Ti(OCHMe_2)_4$, this active heterogeneous resin catalyst was tested for its efficacy in the enantioselective addition of diethylzinc to benzaldehyde. The enantioselectivity of this process was similar to the



Scheme 10 The asymmetric allylation of barbituric acid derivatives using a polyimine 'dendrienzyme' **20**.[171]



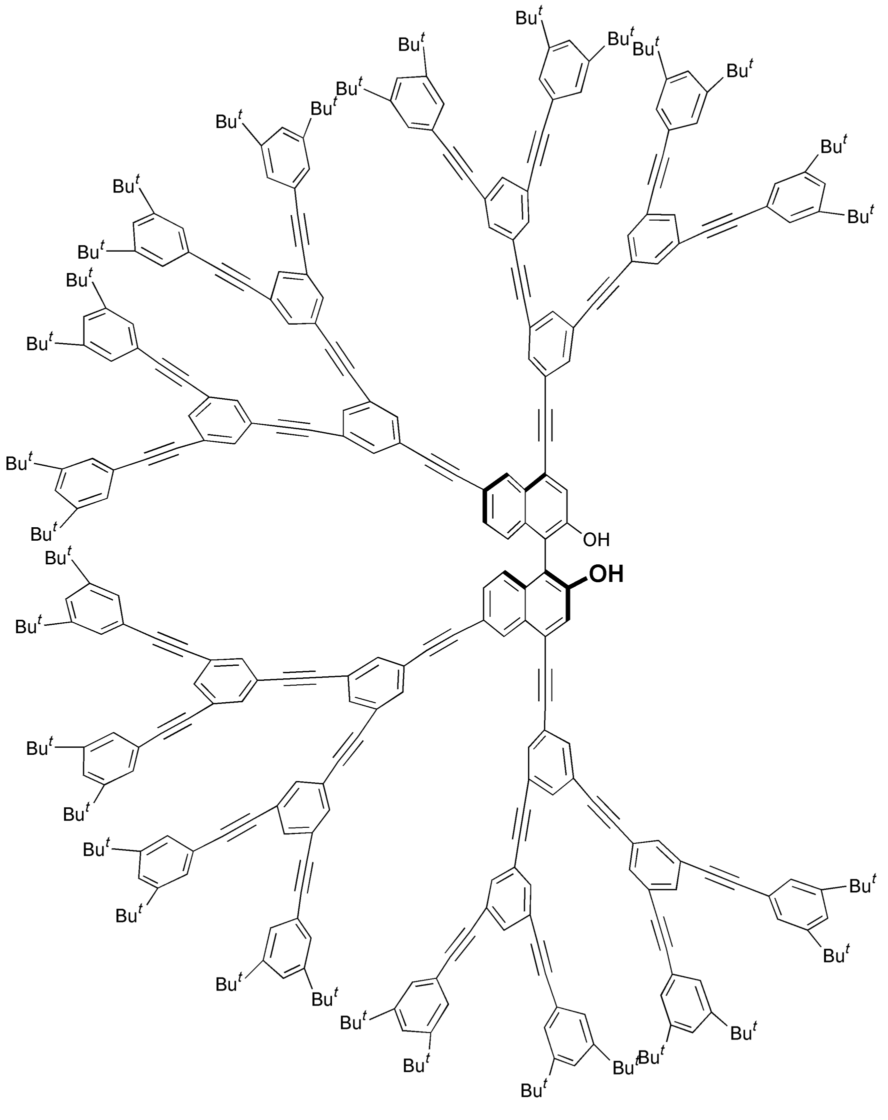
21

Fig. 16 An example of a flexible dendritic cross-linking agent **21** that features a chiral TADDOL ligand at the central core.[172] Subsequent polymerisation of this cross-linking agent with styrene affords a macroporous polymer that is then used as a catalyst in the enantioselective addition of diethylzinc to benzaldehyde following activation with $Ti(OCHMe_2)_4$.

homogeneous analogue (98% *versus* 96% ee) *even* after 20 cycles. The generation number of the dendritic structure did not affect the enantioselectivity, however, this factor increased by decreasing the percentage content of the TADDOL-dendritic cross-linker (*i.e.* decreasing the cross-linking density). The conversion rates of benzaldehyde using these heterogeneous resin catalysts were comparable to the homogeneous dendritic TADDOL or monomeric TADDOL species. These results confirm that, although secured within an insoluble cross-linked polymer, the catalytic ligands are easily accessible as a consequence of the dendritic linker system.

The catalytic activity of dendrimers that contain central TADDOL cores have also been studied by the same group.[173] Two dendritic structures have been employed in these studies: the central TADDOL ligand was been coupled to either aromatic polyether (Fréchet type) dendrons (up to the 4th generation) or to chiral branches derived from 3-hydroxybutanoic acid. In a similar fashion to the TADDOL-based resins, the two series of dendritic catalysts were tested, after formation of the catalytically active titanium-complex, in the addition of diethylzinc to benzaldehyde. The rate of the reaction and enantioselectivity of the homogeneous aromatic polyether dendrimer catalysts up to the 2nd generation were comparable to the values observed for the monomeric TADDOL complex (98% ee), however, both factors decreased as the generation number of the branched component increased—most likely a direct consequence of steric crowding. The study of the catalytic properties of the TADDOL ligand covalently bound within chiral branches is particularly interesting as this study would reveal whether the presence of chiral branching units of opposite configuration would influence the enantioselectivity of the reaction. Detailed optical studies elucidated that the selectivity was the same for the two dendritic diastereoisomers, with the same direction of optical induction [(*S*) : (*R*), 8 : 2]. In addition, the rate of reaction was almost the same as that observed for the monomeric titanium–TADDOL complex, indicating that the presence of dendritic branches up to the 2nd generation, *regardless* of whether they contain additional stereogenic centers, did not influence the catalytic performances of dendritic titanium–TADDOL complex system. This effect is not universal, as demonstrated by the same group when studying[174] the catalytic properties of the chiral ligand (*S*,*S*)-1,4-bis(dimethylamine)-2,3-dimethoxybutane (DDB) coupled to polyether aromatic (Fréchet type) dendrons through a chiral spacer. The resultant dendritic catalysts were tested in the enantioselective addition of methanol to methyl phenyl ketene. The enantioselectivity of the dendritic DDB catalyst was higher compared to the monomeric DDB ligand (18 *versus* 8% ee). However, the stereoselectivity decreased as the temperature was increased in contrast to the constant % ee value observed for the monomeric DDB ligand system. In this catalyst system, the flexible chiral branches influence the stereoselectivity of the reaction. In addition, the non-linear temperature dependence of the stereoselectivity could result from a change in the active conformation of at least one of the chiral branches.

Optically active (*S*)-1,1′-bi-2-naphthol has found many applications in several field such as chiral recognition, material sciences and asymmetric catalysis.[175] Pu *et al.* studied the catalytic properties of binaphthol (BINOL) unit coupled to rigid poly(phenylacetylene) dendrons (see **22** in Fig. 17) in the addition of diethylzinc to benzaldehyde.[50] The dendritic BINOL catalysts revealed high substrate conversions in comparison to the monomeric BINOL ligand (98 *versus* 37%), however, the enantioselective effect was very low in both cases. The high yield exhibited by use of the dendritic BINOL catalyst was attributed to the favourable tendency of binaphthol ligands to form stable zinc complexes when diethylzinc was added to the reaction mixture. In presence of monomeric BINOL, aggregates occur in solution as a result of intermolecular Zn–O–Zn bond formation that leads to the reduction of the Lewis acidity of the zinc metal centre.[176] In contrast, aggregates of this type cannot form when the binaphthol ligand is incorporated within a bulky dendritic structure, and this leads to an increased Lewis acidity of the zinc metal centre. After addition of titanium isopropoxide, total conversion of benzaldehyde with significant improvement of the product enantioselectivity values were obtained (up to 90% ee), using the dendritic BINOL catalysts (comparable with the monomeric BINOL catalysts). These results indicated that despite the bulk of the dendritic component surrounding the catalytic centre, the benzaldehyde substrate could still access it easily. An advantage of these dendritic BINOL catalysts was the possibility of recovery from the reaction media by precipitation with methanol. In a related area, Yamago and co-workers studied[49] the catalytic properties of (*R*)-binaphthol ligands coupled to aromatic polyether dendrons up to the 4th generation. After formation of metal complex with Ti by treatment with titanium isopropoxide, the active catalysts were tested in the allylation reaction of benzaldehyde and allyl stannane. Remarkably, the 2nd and 3rd generation catalysts demonstrated higher rate of reaction respect to the 1st generation dendritic and monomeric BINOL catalysts. These results contrast the general observation that the catalytic activity decreases as the generation number of core functionalised dendritic catalyst increased (*vide supra*). The enantioselectivity were very similar for the dendritic BINOL and the parent monomeric species (~92% ee) indicating that both the selectivity and the reactivity of these catalysts are not influenced in a negative fashion by the bulkiness of the dendritic structure. A similar result was obtained by Fan *et al.* who synthesised[140] dendritic catalysts containing a



22

Fig. 17 An efficient dendritic catalyst **22** that is constructed from rigid poly(phenylacetylene) dendrons and a chiral binaphthol core.[175,50]

ruthenium–chiral diphosphine (BINAP) complex as the catalytic core coupled to aromatic polyether (Fréchet type) dendrons up to the 3rd generation. The catalytic activity and the enantioselectivity of the dendritic catalysts were tested in the asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)phenyl]acrylic acid. Complete conversion was obtained after 20 hours and enantioselectivity values up to 92% ee were obtained. All the dendritic catalysts were more efficient in comparison to the parent BINAP complexes, and the rate of the reaction increased as higher generation dendritic catalysts were employed. These results were interpreted by consideration of the effect that the increased steric bulk of the dendritic wedges had upon the dihedral angle of the two naphthalene rings in the ruthenium–BINAP complex, thus leading to faster conversion rates and enhanced enantioselectivities. In addition, in a similar way to the BINOL catalysts, the BINAP dendritic catalysts could be recovered easily by precipitation with methanol and then reused (up to three times) while maintaining the same activity and enantioselectivity. Bolm *et al.* prepared[177] dendritic catalysts containing (*S*)-pyridyl alcohol derivative at the focal point and polyether aromatic (Fréchet type) dendrons up to the 2nd generation in order to study the influence of the enlarged structure on the catalytic properties of the chiral ligand in the enantioselective addition of diethylzinc to a range of aldehydes. It was found that when 5% mol of the dendritic catalyst or of the monomeric ligand was used, the enantioselectivity of the dendritic catalyst was only 2–3% less than that for the monomeric counterpart (86% ee). Even when the generation number was increased, no significant change of the % ee was found. The same group prepared[178] dendritic catalysts based on two types of polyether aromatic dendritic structure, one derived from 3,5-dihydroxybenzyl alcohol (Fréchet type dendrons) and the other containing an alkyl spacer derived from 4,4-bis(4′-hydroxyphenyl)pentanol. Both dendrons were coupled separately at the focal point to the (*S*)-2-amino-3-(*p*-hydroxyphenyl)-1,1-diphenylpropan-1-ol chiral ligand. These dendritic catalysts were tested in the enantioselective borane reduction of several prochiral ketones. In general, the ketone conversion was achieved in good yield ($>75\%$) and the enantioselectivities were comparable to the value obtained with the monomeric ligand (81–96% ee). Significantly, when 10% mol of the dendritic catalyst containing the elongated alkyl spacer were used higher % ee were obtained (91%) in comparison to when stoichiometric amounts of the monomeric counterpart were used (87%). In general, the dendritic catalysts possessing the alkyl spacer performed better then those derived from Fréchet type dendrons, most probably as a result of the relatively higher rigidity of the dendritic backbone derived from the 3,5-dihydroxybenzyl alcohol units. A similar result has been obtained by Deng *et al.* in a recent study[179] on the catalytic activity of the chiral ligand (*S*,*S*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine coupled to polyether aromatic dendrons in the ruthenium catalysed transfer hydrogenation of prochiral ketones. The dendritic catalysts performed better than the related monomeric ligand, with comparable enantioselectivity ($>96\%$) and enhanced reactivity even at higher generation (up to the 4th) (98–99%). This result was in contrast with the decreased catalytic activity observed when the same chiral ligand system was incorporated in a polymeric matrix. In addition the dendritic catalyst revealed high stability as only after the 5th reuse the activity decreased from 99 to 52%. Recently, Hirsch *et al.* described[180] the preparation of a new class of dendritic catalysts comprising buckminsterfullerene C_{60} with three chiral bis-oxazolidine groups as the chiral catalytic core and polyether aromatic (Fréchet type) dendrons up to the 2nd generation. The copper–bis-oxazolidine complexes of these systems were used as catalysts for the cyclopropanation of styrene with ethyl diazoacetate. These preliminary studies found that the stereoselectivity of these fullerene based dendritic catalysts were very low compared to those obtained with other bis-oxazolidine catalysts.

4. Conclusions

This review has covered the recent developments in the fields of dendritic macromolecules, in particular concentrating upon the advances in chiral dendrimers and their applications in catalysis. As this review was written, it has become quite clear that dendrimers are no longer mere synthetic curiosities for organic and polymer scientists alike. In the past decade, advances in the synthetic design of dendrimers have enabled these fascinating macromolecules to be targeted for use in a diverse range of hi-tech applications such as light harvesting, drug delivery and catalysis. Dendrimer chemistry now receives world wide recognition, several dedicated symposia have been held and the topic of this review was inspired by the recent ACS national congress meeting held in San Diego. It is quite apparent from this symposium and this study that dendrimers will continue to have an impact upon new functional materials in the future.

Acknowledgement

We would like to thank the University of Reading Research Endowment Trust Fund for a Research Studentship (to B. R.).

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