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Stereoselective Dendrimer Catalysis

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Abstract Enantioselection in a stoichiometric or catalytic reaction is governed by small increments of free enthalpy of activation, and such transformations are thus in principle suited to assessing "dendrimer effects" which result from the immobilization of molecular catalysts. Chiral dendrimer catalysts, which possess a high level of structural regularity, molecular monodispersity and well-defined catalytic sites, have been generated either by attachment of achiral complexes to chiral dendrimer structures or by immobilization of chiral catalysts to non-chiral dendrimers. As monodispersed macromolecular supports they provide ideal model systems for less regularly structured but commercially more viable supports such as hyperbranched polymers, and have been successfully employed in continuous-flow membrane reactors. The combination of an efficient control over the environment of the active sites of multi-functional catalysts and their immobilization on an insoluble macromolecular support has resulted in the synthesis of catalytic dendronized polymers. In these, the catalysts are attached in a well-defined way to the dendritic sections, thus ensuring a well-defined microenvironment which is similar to that of the soluble molecular species or at least closely related to the dendrimer catalysts themselves.

Keywords Dendrimers · Stereoselective catalysis · Homogeneous catalysis · Heterogeneous catalysis

Abbreviations

ALB	Al-Li-bis(binaphthoxide)
BICOL	9*H*,9′*H*-[4,4′]Bicarbazole-3,3′-diol
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-Bi-2-naphthol
COD	1,5-Cyclooctadiene
Danishefsky's diene	1-Methoxy-3-(trimethylsilyloxyl)buta-1,3-diene
DPEN	1,2-Diphenylethylenediamine
ee	Enantiomeric excess
G_x	Generation x (1, 2, 3, …)
Josiphos	1-[2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexyl-phosphine
NOBIN	2-Amino-2′-hydroxy-1,1′-binaphthyl
PAMAM	Poly(amido)amine
PPI	Poly(propyleneimine)
Pyrphos	3,4-Bis(diphenylphosphino)pyrrolidine
salen	Ethylenebis(salicylimine)
TADDOL	2,2-Dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol

1 Introduction

Homogeneous chiral catalysts are well-defined molecular systems that may display high activity and selectivity in catalytic reactions, combined with an excellent reproducibility of the experimental results. The production of chiral enantiomerically pure catalysts is expensive and thus catalyst recycling is an important practical objective. This challenge was recognized early on and has led to the development of supported molecular catalysts and, more recently, dendrimer catalysts [1, 2]. With the latter, catalyst recycling has been achieved using membrane reactors as well as catalyst precipitation and subsequent filtration, although frequently with deteriorating catalyst performance over time. This utilitarian aspect of dendrimer catalysis has provided the motivation for much of the work on chiral dendrimer catalysts. These have been generated either by attachment of achiral complexes to chiral dendrimer structures or by immobilization of chiral catalysts to non-chiral dendrimers, by methods described in more detail elsewhere in this monograph.

Dendrimer fixation may be achieved by attachment of catalysts at the periphery of dendrimers (Fig. 1a) in the way first established by van Koten, van Leeuwen and co-workers in their pioneering work on the Karasch reaction [3, 4]. The second possibility is the attachment of one or more dendritic wedges to the catalysts, which are then located at the core of the result-

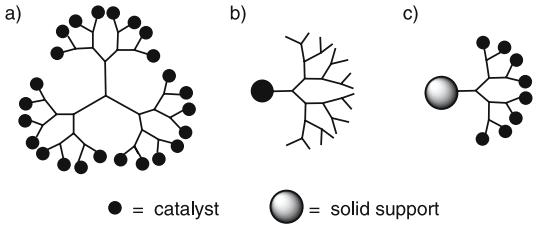


Fig. 1 Fixation of catalytic metal centres (represented by the *black spheres*) in exodendral (**a**) and endodendral (**b**) positions of dendrimers or on dendronized polymers (**c**)

ing functionalized dendrimers (Fig. 1b). The first example of such catalysts was reported by Brunner et al. ("dendrizymes"), who studied the influence of a chiral dendritic periphery on the performance of asymmetric cyclopropanation catalysts [5, 6]. Recently, a third type of chiral dendritic catalyst has been developed which is based on an insoluble polymer support loaded with dendritic wedges. These are functionalized by attachment of molecular catalysts to their periphery (Fig. 1c). The structures obtained following this strategy combine the well-defined dendritic architecture near the active sites of the catalytic phase with the ease of reuse characteristic of common heterogeneous catalysts.

Since enantioselection in a stoichiometric or catalytic reaction is governed by small increments of free enthalpy of activation [7], such transformations are particularly suited to assessing "dendrimer effects" which result from the immobilization of catalysts. In the assessment of such multi-site macromolecular catalysts, it is essential to establish whether the immobilized catalyst units retain their identity and are not altered by the nature of the dendrimer backbone. The linker and spacer units employed in the fixation of the catalysts may be crucial in this respect as well as the functional groups present in the dendrimer. Regarding the dendrimer core structure itself, the length and conformational rigidity of the branches and spacers are important factors when evaluating a dendritic catalyst. For immobilized asymmetric catalysts, even subtle conformational changes may significantly influence their stereoselectivity. The interplay of all these factors will generally determine detrimental or beneficial dendrimer effects on catalyst performance, which will be the focus of this overview of the field of asymmetric dendrimer catalysis.

2
Dendrimer Fixation of Chiral Catalysts

The underlying concept of Brunner's dendrizymes [5, 6] was the creation of a chiral dendritic architecture in the environment of a catalytic centre, which

should induce stereoselectivity in the same way as in enzymes. In metalloenzymes, in particular, the first coordination sphere of the metal centre is frequently achiral (see for instance the ubiquitous tris-histidine binding sites!), and the chiral induction is due to the chirality of the polypeptide protein structure which allows for chiral secondary interactions with the substrates. In contrast to the biological systems, the reaction performance of dendrimers containing a chiral dendritic backbone has been found to be unsatisfactory [8, 9]. This is thought to be due to the fact that the dendrimers that have been employed do not form well-defined secondary structures in the same way as polypeptides. Consequently, the arrangement of functional groups in the "second sphere" of the catalytic site, and thus their interaction with a potential substrate, remains ill-defined.

In view of the inefficiency of the chiral induction effected by chiral dendritic structures, most attention has been directed towards the covalent or electrostatic [10] fixation of established chiral mononuclear complexes to achiral dendritic cores or wedges. A number of efficient chiral dendrimer catalysts have been obtained, as will be discussed in the following sections. However, even in these cases particular care has to be taken to avoid the negative interference of functional groups in the dendrimer core with the attached catalytic sites. This aspect is thought to be important in the enantioselective ethylation of benzaldehyde with chiral dendrimer catalysts, for which both the chemical yields and the enantiomeric excesses were found to decrease with increasing generation of the dendrimers [8, 9]. Multiple interactions of the catalytic sites on the dendritic surface with the substrate at higher generations add to the observed negative effects. To relieve these interactions with the dendrimer end groups at the periphery of higher generations, the introduction of an alkyl chain as a spacer or the use of a rigid hydrocarbon backbone have been proposed [11].

3
Chiral Catalytic Sites at the Periphery of Dendrimers

3.1
Asymmetric Catalysis with Immobilized Phosphine-Based Catalysts

The first example of asymmetric rhodium-catalyzed hydrogenation of prochiral olefins in dendrimer catalysis was reported by Togni et al., who immobilized the chiral ferrocenyl diphosphine "Josiphos" at the end groups of dendrimers, thus obtaining systems of up to 24 chiral metal centres in the periphery (Fig. 2) [12–14]. The fact that the catalytic properties of the dendrimer catalysts were almost identical to those of the mononuclear catalysts was interpreted as a manifestation of the independence of the individual catalytic sites in the macromolecular systems.

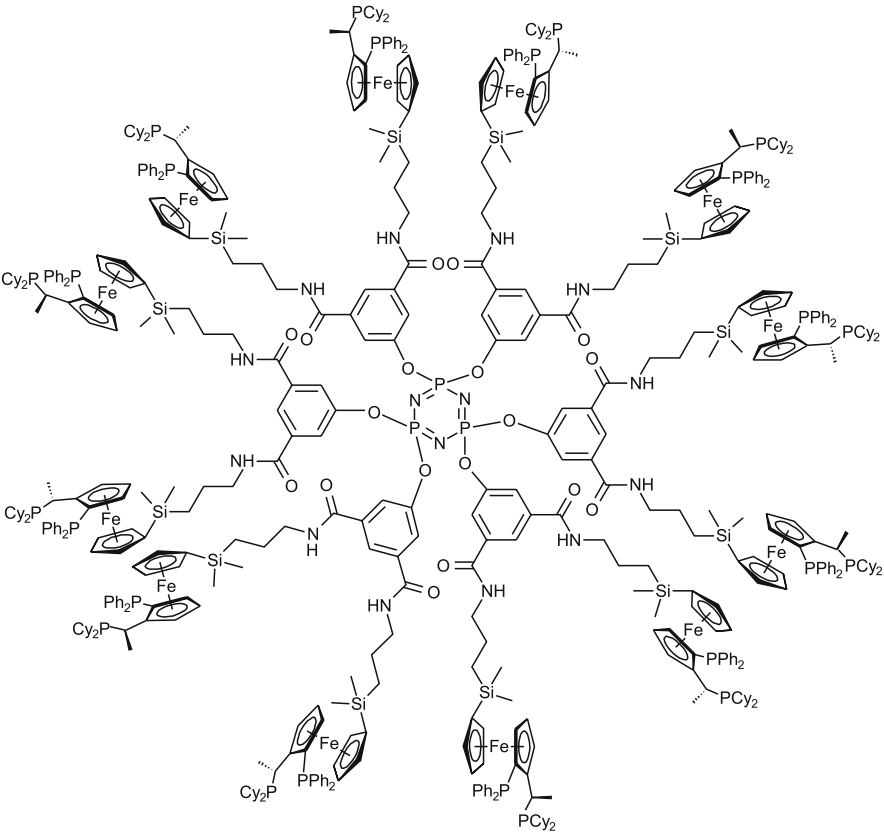


Fig. 2 Fixation of chiral "Josiphos" ligands to a first-generation dendrimer containing a cyclotriphosphazene core

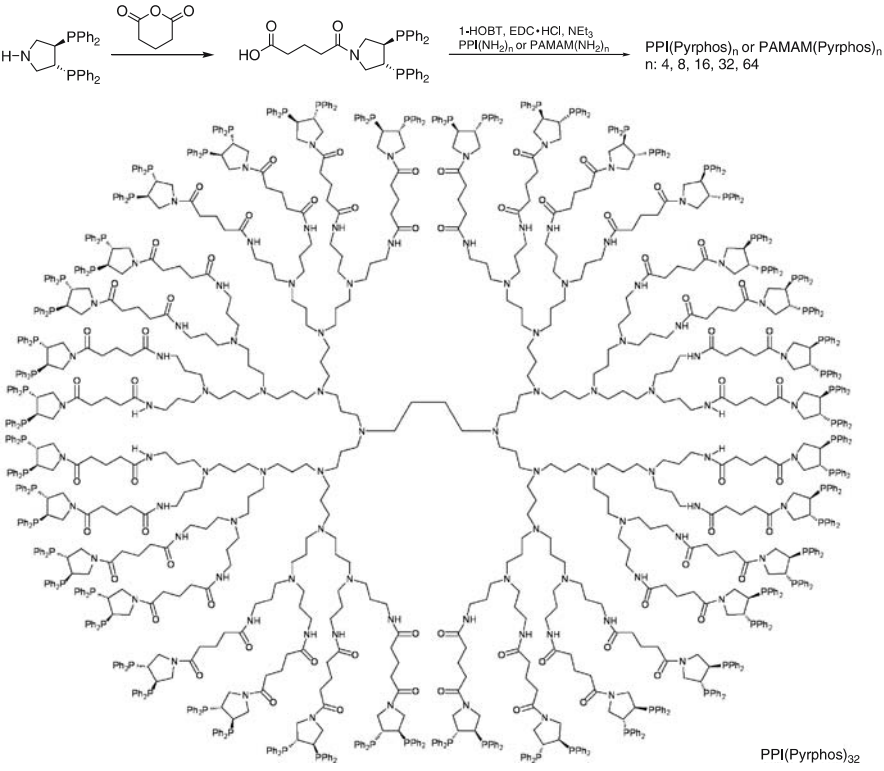
In a comprehensive study carried out by the same group, the asymmetric hydrogenation of dimethyl itaconate, asymmetric allylic substitutions and asymmetric hydroboration reactions catalyzed by the multi-Josiphos rhododendrimers were investigated [15]. The stereoselectivities obtained with the monodisperse dendrimer catalysts with up to 16 metal centres in the periphery were found to be very similar to those of the mononuclear reference systems. The authors concluded that the absence of negative dendrimer effects is probably the best possible result when cooperativity effects between single catalyst units do not play any relevant role. Small losses in selectivity, observed upon going to higher dendrimer generations, may be due to local concentration effects which become important, in particular, for cationic catalyst species.

A series of chiral phosphine-functionalized poly(propyleneimine) (PPI) and poly(amido)amine (PAMAM) dendrimers was synthesized by reaction

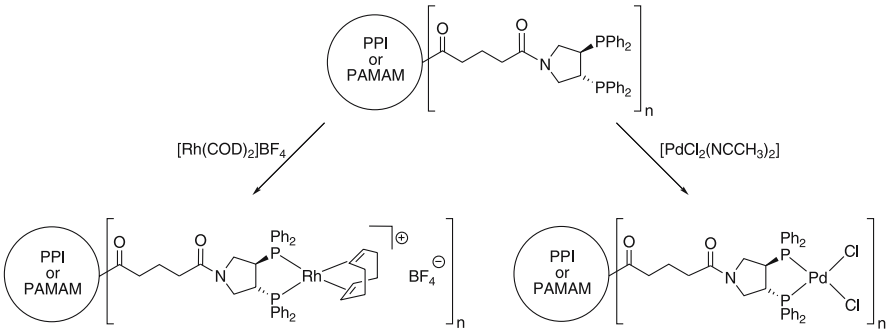
of carboxyl-linked C_2-chiral Pyrphos ligands (Pyrphos = 3,4-bis(diphenylphosphino)pyrrolidine) with 0th–5th-generation PPI (0th–4th-generation PAMAM) using ethyl-*N*,*N*-dimethylaminopropyl carbodiimide (EDC)/1-hydroxybenzotriazole as a coupling reagent (Scheme 1) [16]. The functionalized dendrimers were characterized by NMR spectroscopy, elemental analysis, and FAB and MALDI-TOF mass spectrometry, thus establishing their molecular masses of up to 20 700 amu for the PPI derivatives.

Metallation of the multi-site phosphines with $[Rh(COD)_2]BF_4$ (COD = 1,5-cyclooctadiene) or $[PdCl_2(NCCH_3)_2]$ cleanly yielded the cationic rhododendrimers or palladodendrimers, respectively, containing up to 64 metal centres (Scheme 2).

The relationship between the size/generation of the rhododendrimers and their catalytic properties was established inter alia in the asymmetric hydrogenation of *Z*-methyl-α-acetamidocinnamate and dimethyl itaconate. Generally, a decrease in activity of the dendrimer catalysts was observed on going to the higher generations for the PPI- and PAMAM-based dendrimers (Fig. 3).



Scheme 1 Synthesis of Pyrphos-functionalized PPI and PAMAM dendrimers by peptide coupling methods



Scheme 2 Metallation of the Pyrphos-functionalized PPI and PAMAM dendrimers

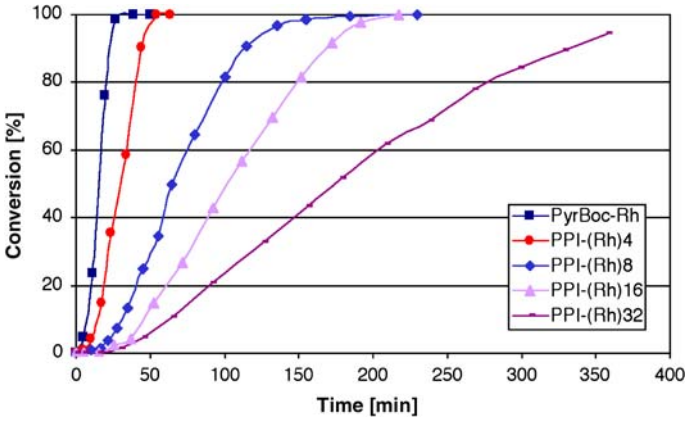


Fig. 3 Conversion curves for the asymmetric hydrogenation of *Z*-methyl-α-acetamidocinnamate for the different catalyst generations

However, for the Rh(COD) systems, the enantioselectivity in the hydrogenation of *Z*-methyl-α-acetamidocinnamate remained barely affected (Fig. 4) or decreased only slightly, depending on the chosen substrate.

In an effort to extend the use of the Pyrphos-derived dendrimers to asymmetric Pd-catalyzed coupling reactions, strongly positive selectivity effects were observed upon going to very large multi-site chiral dendrimer catalysts. This enhancement of the catalyst selectivity was observed in palladium-catalyzed allylic substitutions, such as that displayed in Scheme 3, which are known to be particularly sensitive to small changes in the chemical environment of the active catalyst sites [17].

The mononuclear catalyst [(Boc-Pyrphos)$PdCl_2$], which is very unselective for this transformation [9% enantiomeric excess (ee)], provided the point of reference for the subsequent studies with the dendrimer catalysts. This system and the metalladendrimers PPI(Pyrphos$PdCl_2$)$_4$ – PPI(Pyrphos$PdCl_2$)$_{64}$

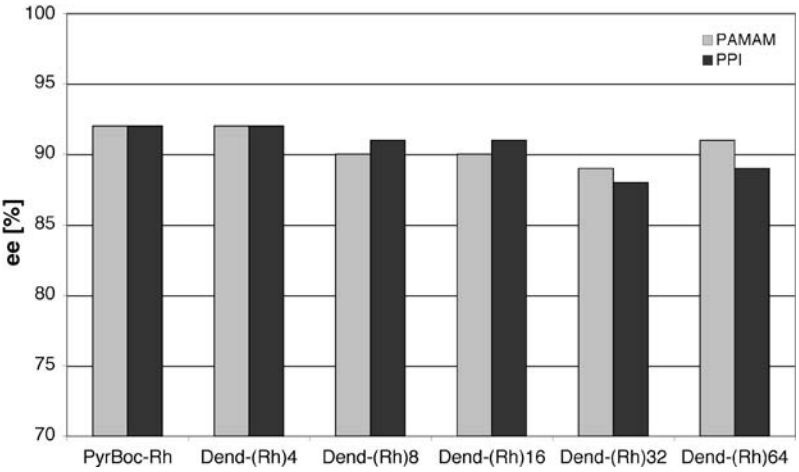
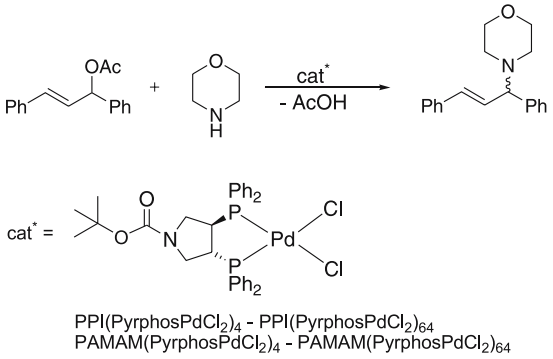


Fig. 4 Enantioselectivities for the different PPI- and PAMAM-derived catalyst generations in the hydrogenation of *Z*-methyl-α-acetamidocinnamate



Scheme 3 Asymmetric allylic amination of 1,3-diphenyl-1-propene-3-acetate catalyzed by Pyrphos-palladium complexes

and PAMAM(PyrphosPdCl$_2$)$_4$ – PAMAM(PyrphosPdCl$_2$)$_{64}$ in 0.3 mol % catalyst concentration were studied in the catalytic amination of 1,3-diphenyl-1-propene-3-acetate and gave the results displayed in Fig. 5.

A remarkable increase in catalyst selectivity was observed as a function of the dendrimer generation. This steady increase in ee values for the allylic amination was less pronounced for the PPI-derived catalysts [40% ee for PPI(PyrphosPdCl$_2$)$_{64}$] than for the palladium-PAMAM dendrimer catalysts, for which an increase in selectivity from 9% ee for the mononuclear complex to 69% ee for PAMAM(PyrphosPdCl$_2$)$_{64}$ was found. The same general trend was observed in the asymmetric allylic alkylation of 1,3-diphenyl-1-

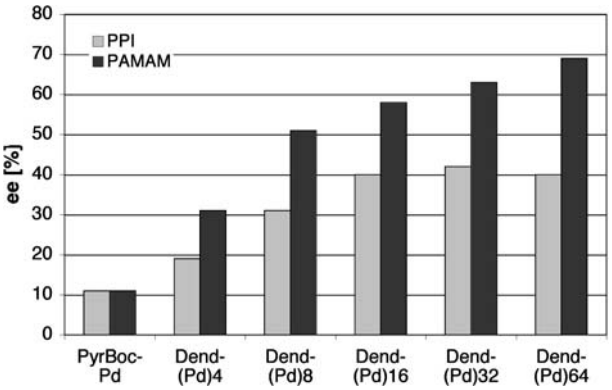


Fig. 5 Dependence of the enantiomeric excesses found for the allylic amination in Scheme 3 on the dendrimer generation for both precatalyst series PPI(PyrphosPdCl$_2$)$_4$ – PPI(PyrphosPdCl$_2$)$_{64}$ and PAMAM(PyrphosPdCl$_2$)$_4$ – PAMAM(PyrphosPdCl$_2$)$_{64}$

propene-3-acetate with sodium dimethylmalonate, which indicates that the results of the amination reaction may be typical for allylic substitutions in general [18–22].

The underlying mechanistic reasons for this strongly positive "dendrimer effect" are thought to be based on a dismutation reaction of the Pyrphos-palladium complexes, giving {(Pyrphos)$_2$Pd} sites which act as catalytic centres upon going to higher dendrimer generations. The latter effect is thought to be due to the high local catalyst concentration enforced by the attachment of the complexes to the dendrimer supports. The same selectivity effects were observed for the mononuclear species upon addition of a second equivalent of Pyrphos ligand.

3.2
Asymmetric Catalysis with Immobilized Non-Phosphine-Based Catalysts

The majority of studies into the catalytic behaviour of dendrimers with chiral catalytic centres at the periphery of the dendritic support have concerned non-phosphine-based catalysts. As has become apparent in these studies, the effect of the dendrimer fixation on the catalytic performance generally depends on the individual system. Factors such as the high local density of catalytic sites, the interaction of functional groups in the dendrimer backbone with the catalysts and the structural rigidity or flexibility of the dendrimers seem to play a role in many cases.

Jacobsen et al. reported a spectacular example of dendrimer-induced rate enhancement. They synthesized dendrimer-bound [Co^{II}(salen)] complexes (salen = ethylenebis(salicylimine)) with up to 16 catalytic sites, using PAMAM dendrimers as supporting materials (Fig. 6) [23]. In the hydrolytic kinetic

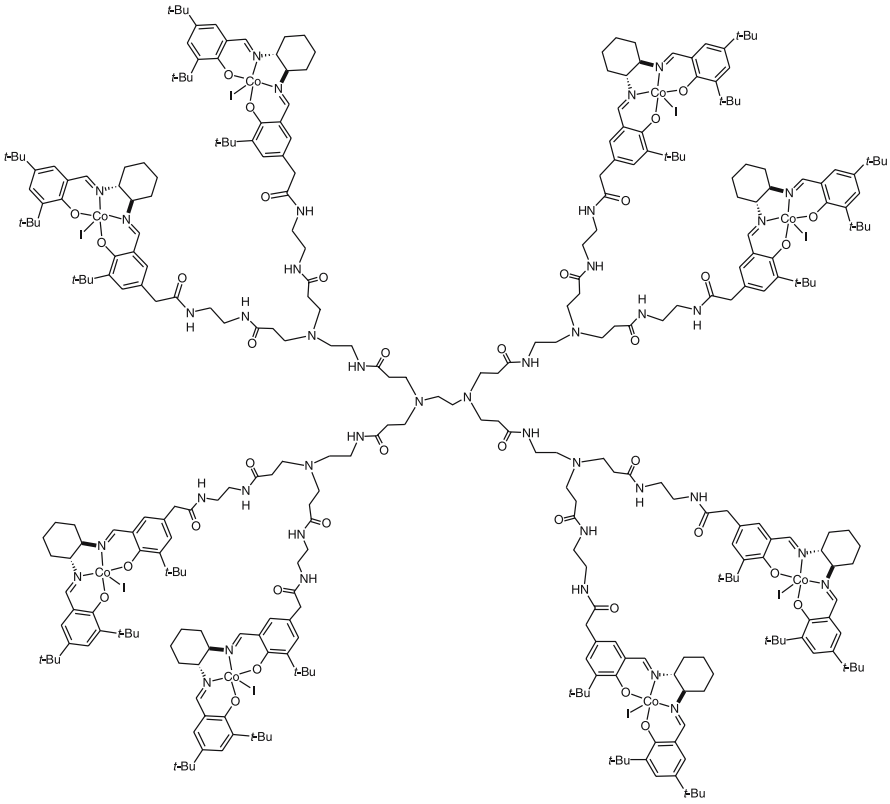


Fig. 6 The dendrimer-bound [Co(salen)] complexes studied by Breinbauer and Jacobsen

resolution (HKR) of terminal epoxides these catalysts exhibit significantly enhanced catalytic activity, in comparison with that of the mononuclear system. As had been shown previously, the kinetics of this reaction are second order in the concentration of the [Co(salen)] complex, a fact which was explained by a cooperative two-site mechanism. The dendrimer effect may therefore be attributed to the restricted conformation imposed by the dendrimer structure and the increase in the local effective molarity of [Co(salen)] units.

Soai et al. developed poly(amidoamine), poly(phenylethyne) and carbosilane dendrimers containing chiral β-amino alcohols on their periphery (Fig. 7) [11, 24–28]. These systems were studied as catalysts for the enantioselective addition of dialkylzinc reagents to aldehydes and *N*-diphenylphosphinylimines. The different kinds of supporting dendritic structures gave rise to varying catalytic activities and selectivities. The functionalized PAMAM dendrimers of generations 0 and 1, bearing four and eight sites of chiral amino alcohols, catalyzed the addition of dialkylzinc derivatives to *N*-diphenylphosphinylimines with only moderate enantioselectivity com-

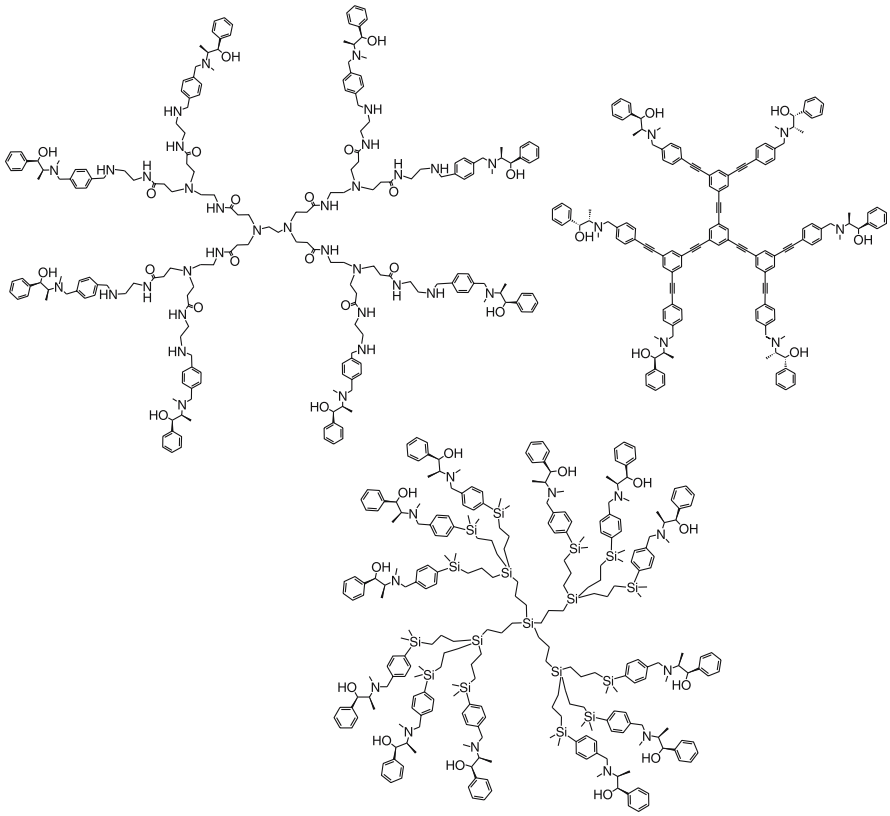


Fig. 7 The dendrimer-immobilized chiral amino alcohols studied by Soai et al. in the asymmetric alkylation of prochiral carbonyl compounds with dialkylzinc reagents

pared to the monomeric system. To obtain appreciable catalytic conversions, an excess of the zinc reagent was needed in each case, which is due to the fact that the nitrogen and oxygen atoms of the PAMAM skeleton coordinate to the zinc. The authors concluded that this led to a change of the conformation of the chiral dendrimers, which was thought to be the reason for the subsequent decrease in selectivity.

In order to avoid this unfavourable effect of the functional groups in the dendrimer structure, a rigid hydrocarbon backbone without heteroatoms was synthesized. Dendrimers with poly(phenylethyne) backbones, bearing three and six ephedrine derivatives at the periphery, were studied in the alkylation of aldehydes and *N*-diphenylphosphinylimines and proved to be highly enantioselective catalysts. For example, the system containing six catalytic sites catalyzed the addition of diisopropylzinc to aldehydes with enantioselectivities of up to 86% ee. As a third backbone a polycarbosilane dendrimer was used, which is chemically inert and more flexible than the poly(phenylethyne)

structure. The chiral dendrimers, bearing four and 12 ephedrine moieties catalyzed the reaction of diisopropylzinc with 3-phenylpropanal with even higher enantioselectivities (up to 93% ee).

Chan et al. synthesized first- and second-generation dendrimers containing up to 12 chiral diamines at the periphery (Fig. 8) [29]. Their ruthenium(II) complexes displayed high catalytic activity and enantioselectivity in the asymmetric transfer hydrogenation of ketones and imines. Quantitative yields, and in some cases a slightly higher enantioselectivity compared to those of the monomeric systems (up to 98.7% ee), were obtained.

In 2002, Sasai et al. reported the synthesis of dendritic heterobimetallic multi-functional chiral catalysts, containing up to 12 1,1′-bi-2-naphthol (BINOL) units at their terminal positions (Fig. 9) [30]. On treating these functionalized dendrimers with $AlMe_3$ and *n*-BuLi, insoluble metallated Al-Li-bis(binaphthoxide) generation *x* (G_x-ALB) catalysts were obtained, which showed moderate catalytic activity in the asymmetric Michael reaction of 2-cyclohexenone with dibenzyl malonate (Scheme 4).

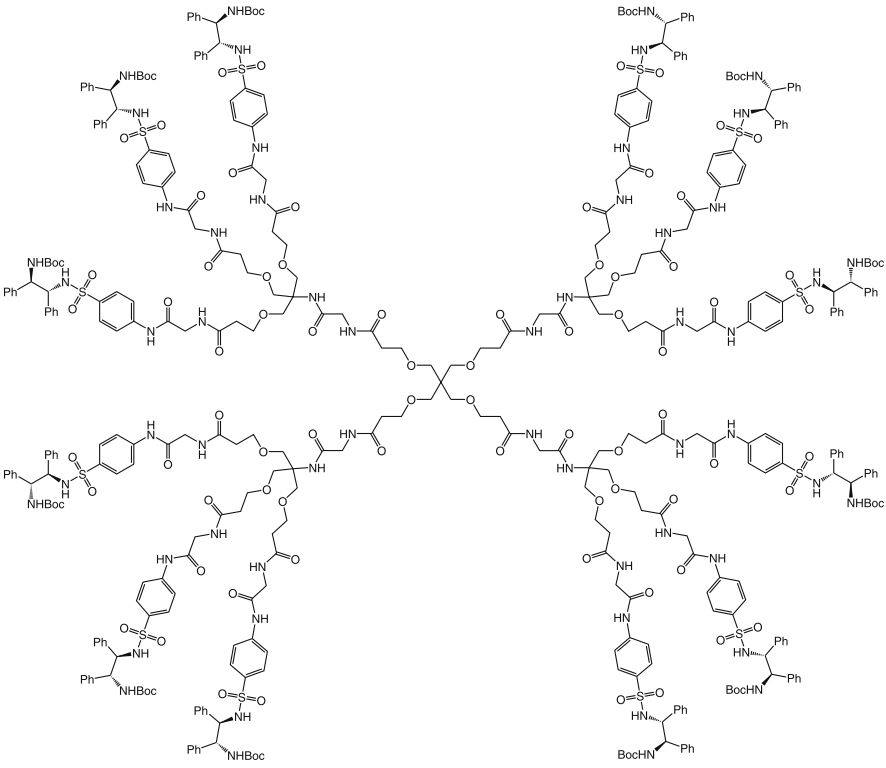


Fig. 8 (*R*,*R*)-1,2-Diphenylethylenediamine attached to the periphery of dendrimers. Metallation with ruthenium(II) precursors gave efficient transfer hydrogenation catalysts

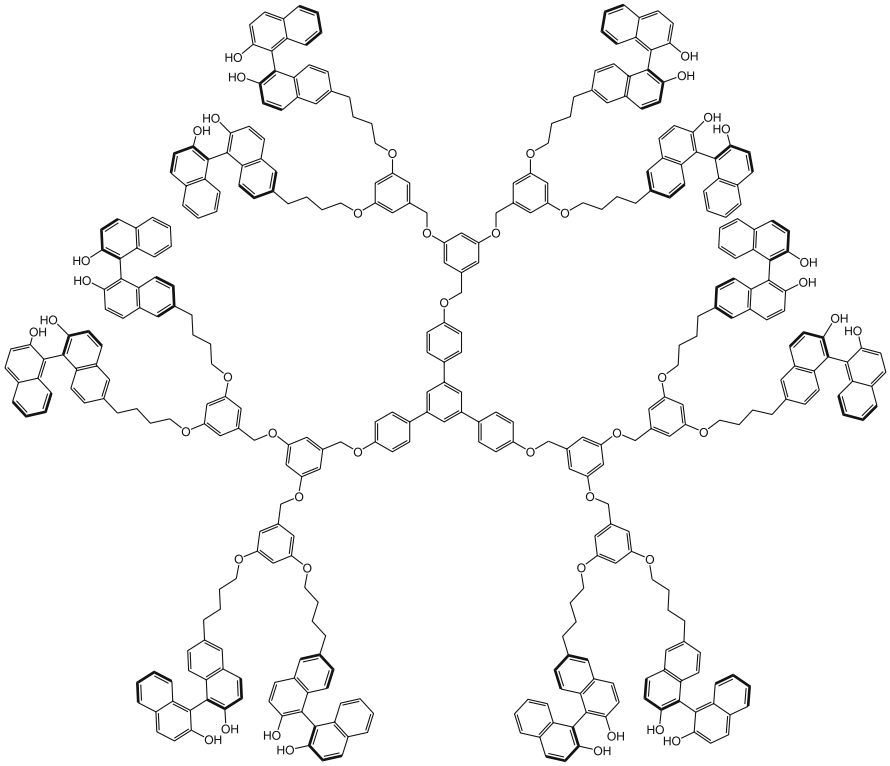
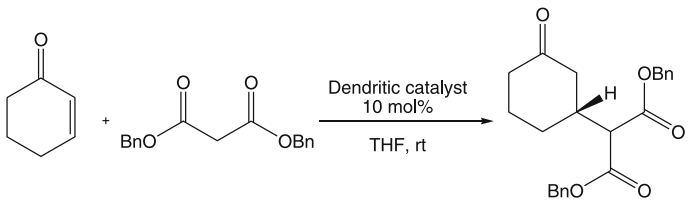


Fig. 9 Chiral BINOL ligands attached to the periphery of a poly(aryl ether) dendrimer



Scheme 4 Asymmetric Michael reaction of 2-cyclohexenone with dibenzyl malonate catalyzed by the metallated dendrimer shown in Fig. 9

Using the first-generation dendritic ALB as catalyst, the Michael adduct was obtained with 91% ee and in 63% yield after 48 h. Under similar conditions, the G_2 dendritic ALB gave the product with 91% ee in 59% yield. The dendritic catalysts could be recycled and reused twice, giving comparable results. It is notable that a catalyst derived from randomly introduced BINOLs on polystyrene resin only gave an essentially racemic product.

Another multi-centred BINOL derivative used in asymmetric Lewis acid catalysis should be mentioned in this context. In 2002, Chow et al. reported the preparation of the G_0 and G_1 generations of chiral 1,1′-binaphthalene-based dendritic ligands, using an oligo(arylene) framework as rigid supporting material (Fig. 10) [31]. Their corresponding aluminium complexes were shown to induce slightly higher reactivity and enantioselectivity than those of a monomeric 1,1′-binaphthalene catalyst in the Diels–Alder reaction between cyclopentadiene and 3-[(*E*)-but-2-enoyl]-oxazolidin-2-one. In the absence of intramolecular interactions among the catalytic centres, the catalyst reactivity and reaction enantioselectivity were found to be independent of the dendrimer generation.

Recently, Majoral et al. described the synthesis of a third-generation phosphorus-containing dendrimer possessing 24 chiral iminophosphine end groups derived from (2*S*)-2-amino-1-(diphenylphosphinyl)-3-methylbutane (Fig. 11) [32]. The dendritic catalyst was tested in allylic substitution reactions, using *rac*-(*E*)-diphenyl-2-propenyl acetate or pivalate as substrates. The observed enantioselectivities were good to excellent (max. 95% ee) in all reactions. After completion of the catalytic reaction, the catalyst could be reused at least twice after precipitation and filtration. A slight decrease

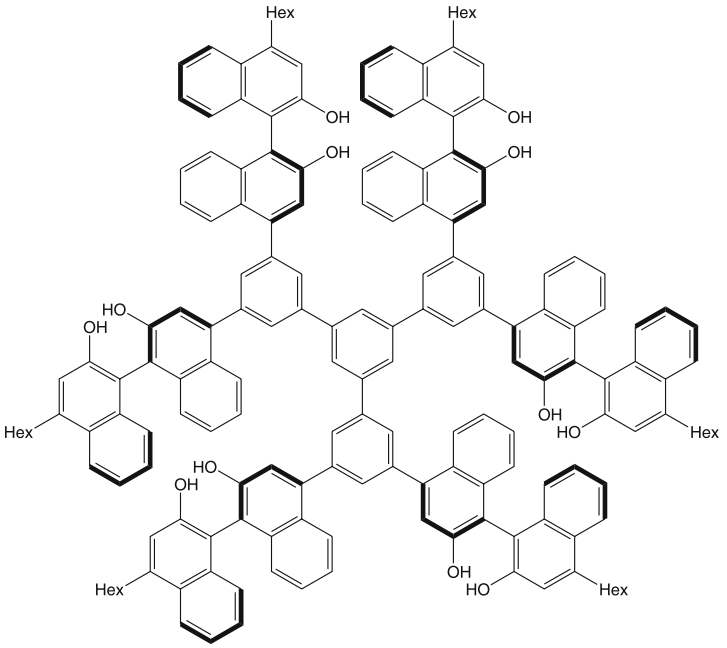


Fig. 10 BINOL units attached to polyaryl cores used as ligands for Al^{III}-catalyzed asymmetric Diels–Alder reactions

of the enantioselectivity was observed (first reuse 94% ee, second reuse 92% ee) and, as shown in Fig. 12, a diminished activity was found for the third run.

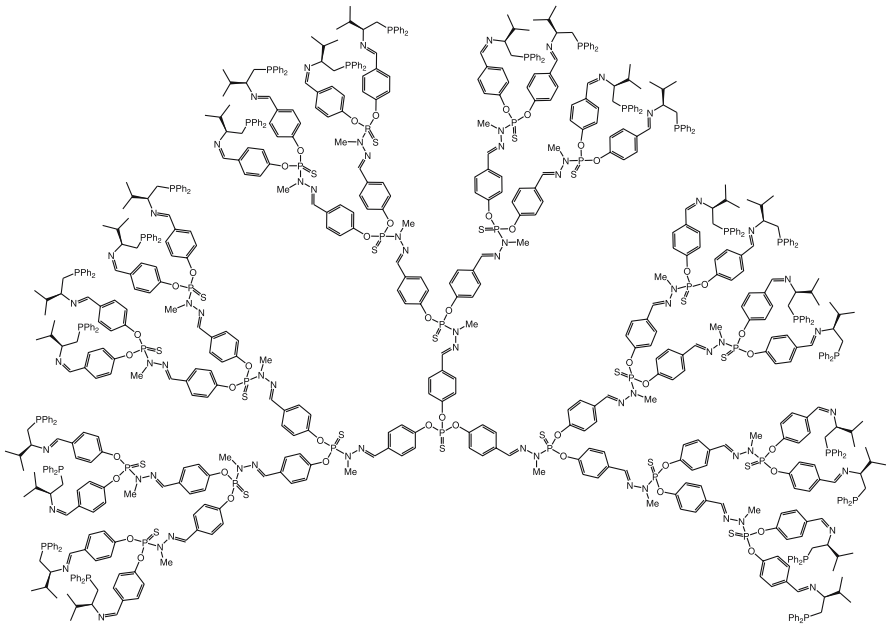


Fig. 11 The chiral dendrimers used by Majoral et al. for enantioselective allylic substitution catalyzed by palladium

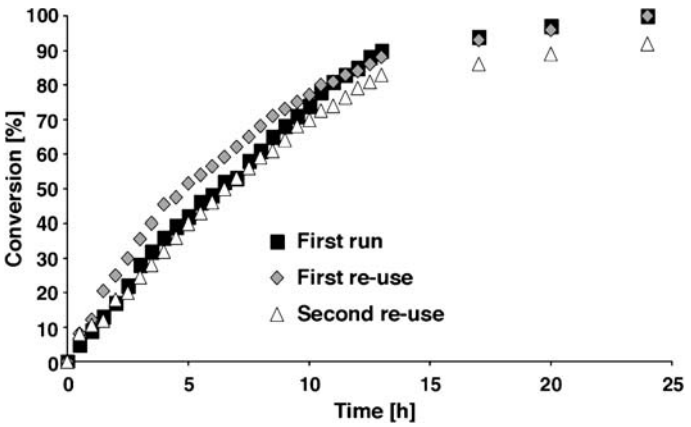


Fig. 12 Asymmetric allylic substitution catalyzed by the palladated dendrimer shown in Fig. 11 [32]

3.3
A Special Case: Enantioselective Borohydride Reduction of Ketones in the Periphery of Chiral Glycodendrimers

In all the examples of exodendrally functionalized enantioselective dendrimer catalysts, the active sites in the periphery of the support were well-defined immobilized molecular catalysts. An alternative is provided by the possibility of attaching chiral multi-functional molecules to the end groups of dendrimers which, due to their high local concentrations, may interact more or less strongly with an achiral reagent and thus induce enantioselectivity in a transformation of a prochiral substrate. Asymmetric induction thus occurs by way of a chiral functionalized microenvironment for a given reaction.

An interesting example of this kind of stereoselective dendrimer catalysis has been reported by Rico-Lattes et al., who prepared glycoden-

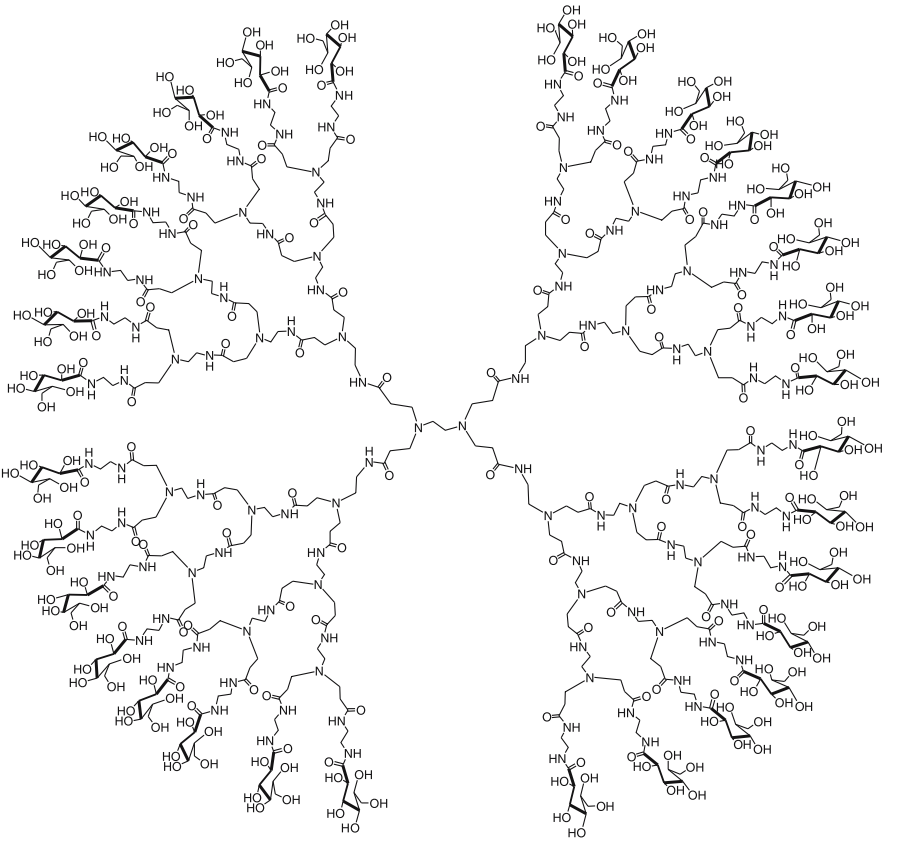


Fig. 13 Third-generation glycol-PAMAM dendrimers studied as microenvironments for the enantioselective reduction of prochiral ketones with sodium borohydride

drimers based on poly(amido)amines of generations 1–4 and gluconolactone (Fig. 13) [33–37]. These glycodendrimers were examined as catalysts for the reduction of prochiral ketones, using sodium borohydride as reducing agent. The corresponding chiral alcohols were isolated in high yields and had enantiopurities of up to 100% ee.

In water, the highest stereoselectivities were obtained by using the fourth-generation amphiphilic dendrimer, whereas, under heterogeneous reaction conditions in THF as solvent, the third-generation dendritic catalyst proved to be the most selective.

To explain this different behaviour, mechanistic studies of the system were performed with the aid of molecular modelling, ^{13}C NMR spectroscopy, induced circular dichroism, a systematic variation of the reaction parameters, and variation of the molecular structure of the sugar moieties and of the linking units. These studies established that under homogeneous reaction conditions (water), the main factor influencing the enantioselectivity is probably the ordering and specific orientation of the ketone at the chiral interface. Under heterogeneous conditions in THF the situation appears to be more complex.

4
Asymmetric Catalysis in the Core of Dendrimers: Catalysts Attached to Dendritic Wedges

Brunner's concept of attaching dendritic wedges to a catalytically active metal complex represented the first example of asymmetric catalysis with metal complex fragments located at the core of a dendritic structure [5, 6]. Important early examples of catalysts in core positions were Seebach's TADDOL systems (TADDOL = 2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol) [38, 39]. In general, the catalytic performance of such systems was either unchanged with respect to the simple mononuclear reference system or significantly lower. In no case has the potential analogy of this core fixation and the existence of efficient reactive pockets in enzymes been vindicated. This may be due to the absence of defined secondary structures in the dendrimers that have been employed to date.

4.1
Chiral BINAP- and BINOL-Based Dendrimer Catalysts

Two interesting reports by Chan and co-workers of dendritic core-functionalized Ru-BINAP (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) catalysts, which were employed in asymmetric hydrogenations and which were fully recoverable, have appeared recently [40, 41]. In particular, such dendrimers containing long alkyl chains in the periphery were synthesized and

employed for asymmetric hydrogenation using a mixture of ethanol/hexane as reaction medium (Fig. 14).

This binary solvent system provided complete miscibility of the phases over a broad range of reaction temperatures and avoided the use of water during the catalytic conversion, with its established negative effects on the enantioselectivity [41]. Phase separation after complete reaction was induced by the addition of small quantities of water, and the recycling of the catalyst could be readily achieved. Remarkably, attachment of the dendrimer to the BINAP system did not lead to a decrease in selectivity.

In a related approach, Fan et al. synthesized a series of dendritic BINAP-Ru/chiral diamine ((*R*,*R*)-1,2-diphenylethylenediamine; DPEN) catalysts for the asymmetric hydrogenation of various simple aryl ketones (Fig. 15) [42]. The resulting systems displayed high catalytic activity and enantioselectivity and allowed facile catalyst recycling. In the case of 1-acetonaphthone and

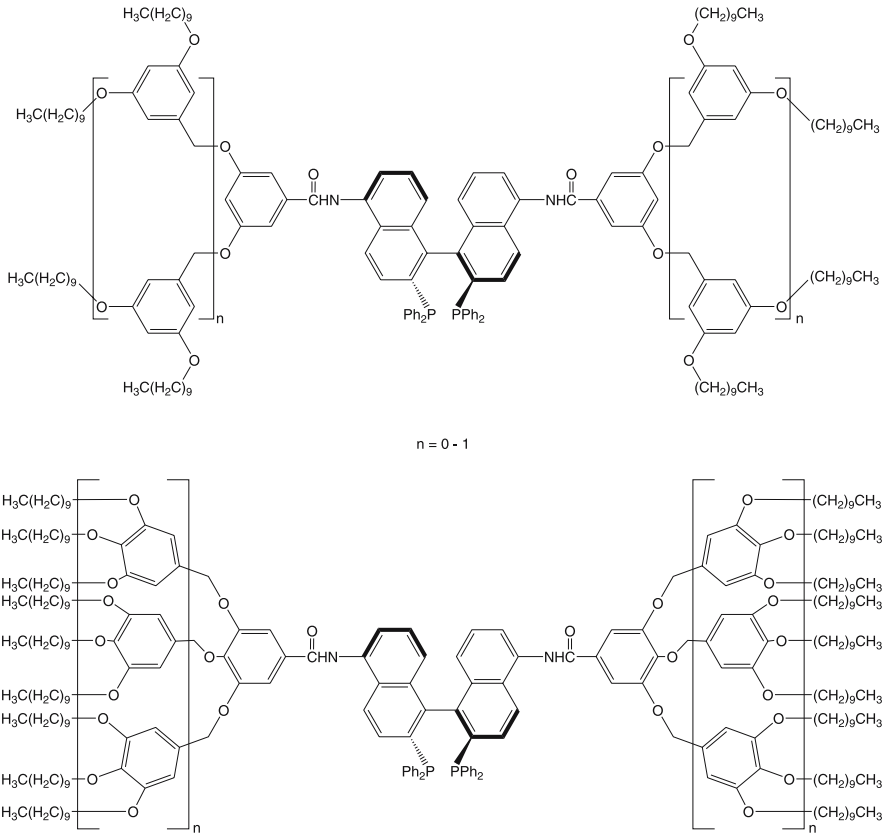


Fig. 14 BINAP core-functionalized dendrimers containing long alkyl chains in the periphery

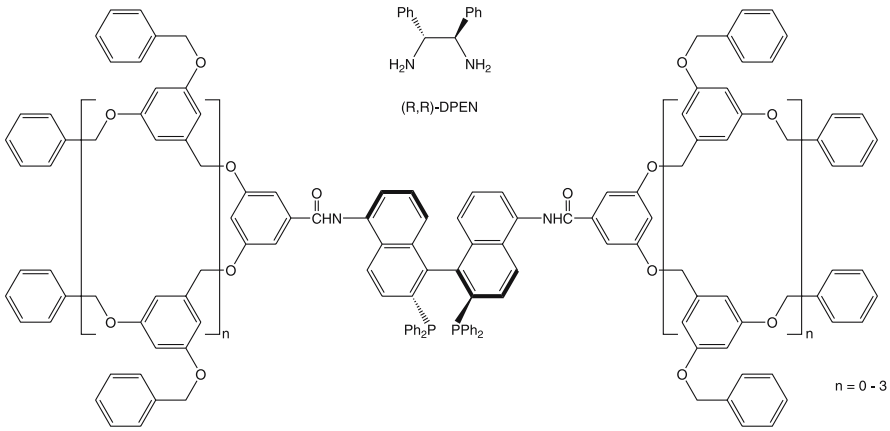
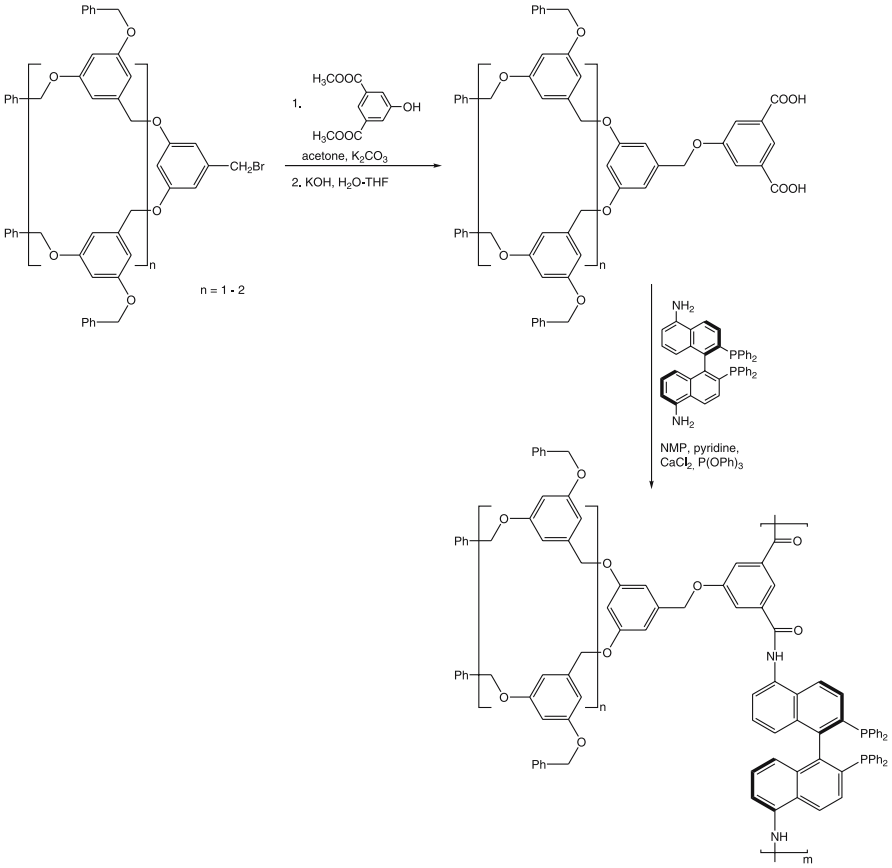


Fig. 15 BINAP ligand functionalized with poly(aryl ether) dendritic wedges



Scheme 5 The dendronized polymeric BINAP ligands studied by Fan et al.

2′-methylacetophenone, ee values of up to 95% were observed, which are comparable to the enantioselectivity reported by Noyori under similar conditions and higher than those of the heterogeneous poly(BINAP)-Ru catalyst reported by Pu and co-workers [43].

The same group also developed optically active dendronized polymeric BINAP ligands (see also Sect. 5) as a new type of macromolecular chiral catalyst for asymmetric hydrogenation. They could be synthesized by condensation of 5,5′-diamino-BINAP with dendritic dicarboxylic acid monomers (Scheme 5) [44].

These polymeric Ru(BINAP) catalysts exhibited high catalytic activity and enantioselectivity (up to 92%) in the hydrogenation of simple aryl ketones, which is very similar to the results obtained with the corresponding parent Ru(BINAP) as well as the Ru(BINAP)-cored dendrimers referred to above. Unsurprisingly, they found that the pendant dendritic wedges have a major impact on the solubility and the catalytic properties of the polymeric catalysts, which could be easily recovered from the reaction mixture by simple precipitation.

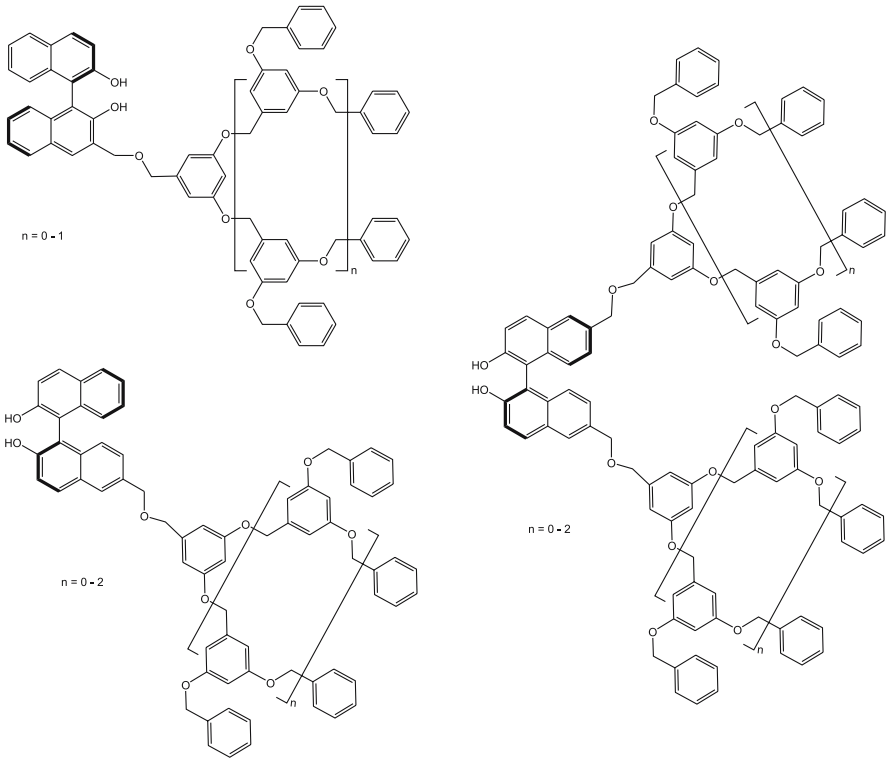
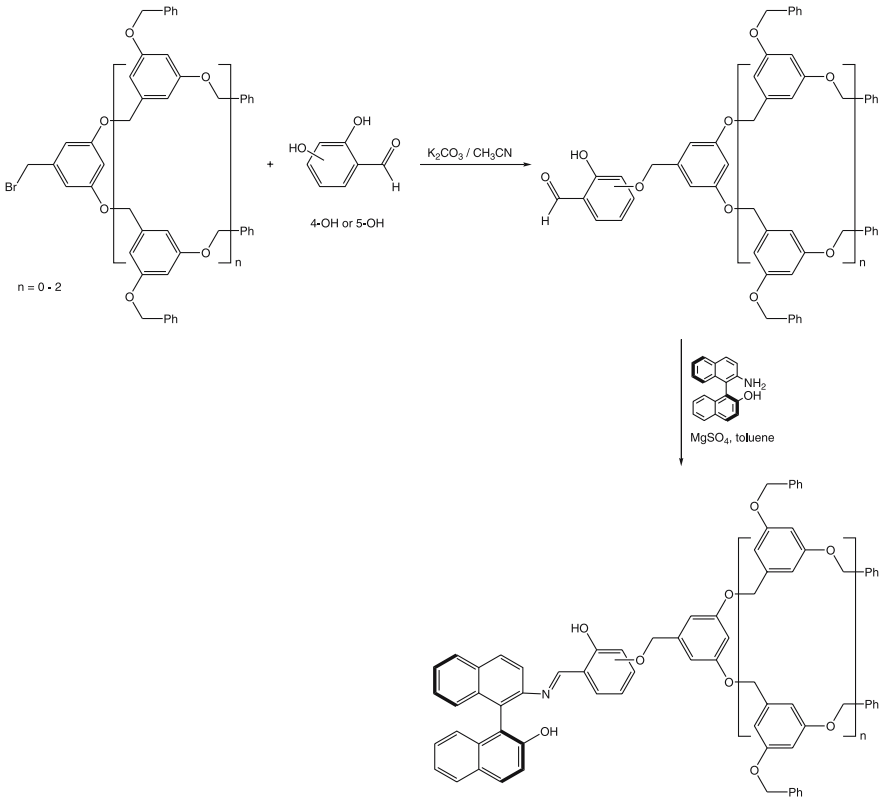


Fig. 16 BINOL ligands bearing dendritic poly(aryl ether) wedges

In 2003 Fan et al. synthesized three types of new chiral BINOL ligands (Fig. 16), bearing dendritic wedges located at the 3-, 6,6′- and 6-positions of the binaphthyl backbone in order to study the effect of the linking position and generation of the dendritic wedges on the catalyst properties [45, 46]. These new ligands were tested in the enantioselective Lewis acid catalyzed addition of diethylzinc to benzaldehyde, and high conversions (up to 99%) and enantioselectivities were observed. A marked effect of the positions of attachment for the linkers as well as the dendron generation on the enantioselectivity and/or activity was found for all three types of dendritic catalysts. Among these systems, the catalyst bearing poly(aryl ether) wedges in the 6,6′-positions of BINOL gave the highest enantioselectivity (up to 87% ee).

The dendritic 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN)-derived Schiff base ligands, displayed in Scheme 6, have been applied in the titanium-



Scheme 6 NOBIN derivatives bearing dendritic poly(aryl ether) wedges. These systems have been studied in the titanium-catalyzed hetero-Diels–Alder reaction of Danishefsky's diene with aldehydes

catalyzed hetero-Diels–Alder reaction of Danishefsky's diene (1-methoxy-3-(trimethylsilyloxyl)buta-1,3-diene) with aldehydes [47]. These reactions afforded the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-ones in quantitative yields and with excellent enantioselectivities (up to 97% ee). The disposition of the dendritic wedges and the size of the dendron in the ligands were found to have significant impact on the enantioselectivity of the catalytic reaction. The recovered catalysts could be reused without further addition of titanium reagent or a carboxylic acid additive for at least three cycles, retaining similar activity and enantioselectivity throughout the process. The other important observation has been the high degree of asymmetric amplification for the dendritic system.

4.2 Pyrphos-Based Catalysts Bearing Dendritic Wedges

In 2004, Chan et al. reported the synthesis of dendritic ligands bearing the chiral Pyrphos ligand at the focal point of Fréchet-type polyether dendrons (Fig. 17) [48]. The relationship between the primary structure of the dendrimer and its catalytic properties was established in the Rh-catalyzed hydrogenation of *Z*-methyl-α-acetamidocinnamate. For the systems containing the first- and second-generation dendritic wedges, high enantioselectivities (up to 98% ee) were observed. The third-generation catalyst gave lower enantioselectivity (95% ee) and a significantly decreased rate of conversion. Upon

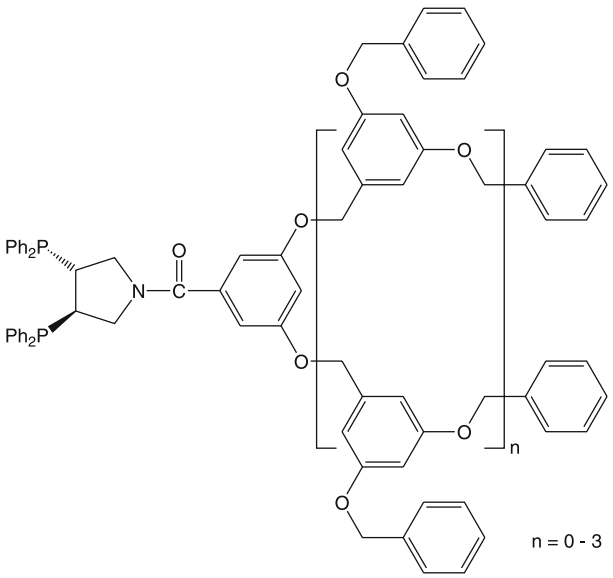


Fig. 17 A Pyrphos derivative bearing an *N*-bound poly(aryl ether) dendron

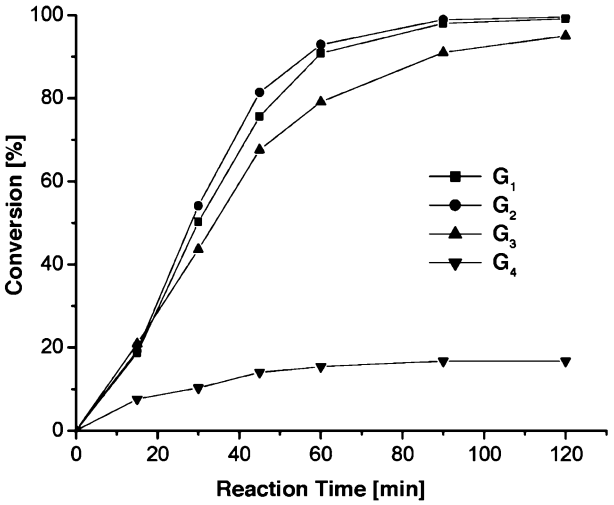


Fig. 18 Conversion curves for the Rh-catalyzed hydrogenation of *Z*-methyl-α-acetamido-cinnamate using the dendritic catalysts displayed in Fig. 17 [48]

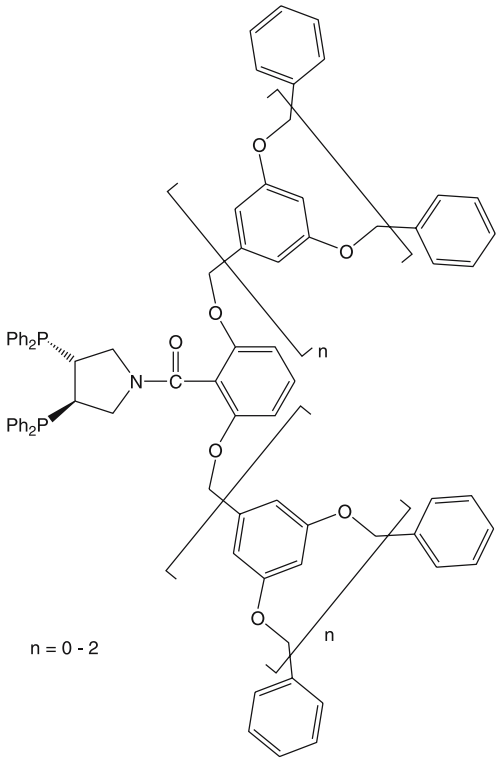


Fig. 19 Dendronized Pyrphos ligands bearing backfolded poly(aryl ether) dendrons

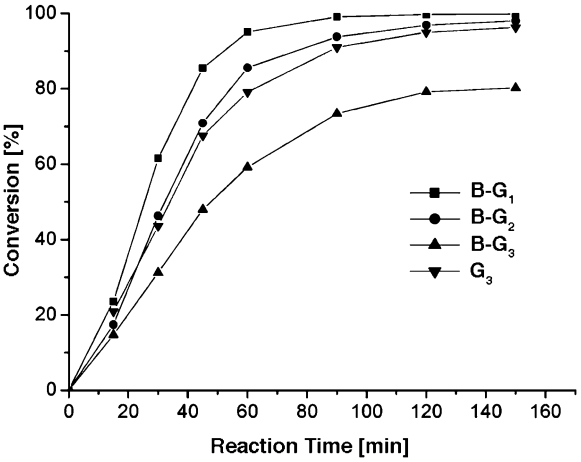


Fig. 20 Conversion curves for the Rh-catalyzed hydrogenation of *Z*-methyl-α-acetamidocinnamate using ligands bearing the backfolded poly(aryl ether) dendrons displayed in Fig. 19. (B-G_x) compared with that of the third-generation catalyst displayed in Fig. 17 (G_3) [48]

going from generation 3 to 4, the dendritic catalyst almost completely lost its activity (Fig. 18).

This gradual decrease in reactivity is thought to be due to the increased steric shielding of the metal centre by the attached dendron on going to higher generations. To demonstrate this particular effect, Chan et al. designed "backfolded" dendrons by modifying the branching pattern of the dendritic wedges (Fig. 19). These backfolded linkages were expected to increase the degree of steric congestion around the catalytically active core. The conversion curves for the hydrogenations catalyzed by these backfolded dendrimers are represented in Fig. 20. Although the first-generation dendrimer displayed the same behaviour as the reference system in Fig. 17, the sterically demanding wedges of the higher-generation dendrimers significantly influenced the reactivity of these catalysts. This effect was most pronounced upon going from generation 2 to 3, a behaviour which is consistent with the effective encapsulation of the active core by the backfolded dendrimer. Furthermore, unlike the systems discussed above, the enantioselectivity of the Rh-catalyzed hydrogenation decreased for the higher dendrimer generations.

4.3 Dendrimer-Fixed Chiral Diamine-Based Catalysts

As for the exodendrally functionalized dendrimer catalysts (Sect. 3.2), chiral diamine ligands have also been the objects of study in the investigation into the catalytic behaviour of core-functionalized dendrons.

Deng et al. synthesized chiral diamine dendritic ligands using (*S*,*S*)-DPEN as ligand system and Frechét-type dendritic wedges as supporting material (Fig. 21) [49]. Asymmetric transfer hydrogenation reactions were studied using acetophenone as the model substrate. Compared with the monomeric Ru[(*S*,*S*)-DPEN] complex, a slightly enhanced reactivity was observed for the dendritic catalysts, as well as high enantioselectivities (> 96% ee).

Following up this work, the same group recently published the synthesis of "hybrid" dendritic ligands containing a combination of dendritic chiral DPEN and Fréchet polyether dendrons (Scheme 7) [50]. The solubility of these hybrid dendrimers was found to be controlled by the polyether dendron. Compared with the simple core-functionalized systems displayed in Fig. 21, the hybrid dendrimers showed similar catalytic activity but reduced recyclability.

Another possibility to immobilize the DPEN ligand is the functionalization of the phenyl rings, as exemplified in Fig. 22 [51–53]. The Ru-catalyzed hydrogenation of acetophenone was chosen as a test reaction, using 2-propanol and toluene in a 1 : 1 ratio as solvent system. The enantioselectivities of the first- and second-generation dendritic catalysts were comparable to that of Noyori's catalyst. However, the third-generation catalyst gave lower enantioselectivity (84%) and significantly decreased activity (45% conversion, 1 mol % catalyst) under the same conditions, even at a higher temperature (50 °C, 51% conversion and 88% ee). The sudden loss of activity for the third-generation dendritic catalyst may be thus attributed to the change in dendrimer conformation, from an extended to a more compact globular structure with increase of the steric requirements of the dendritic branches. This "encapsulation" of the active species by the dendrimer provides a barrier

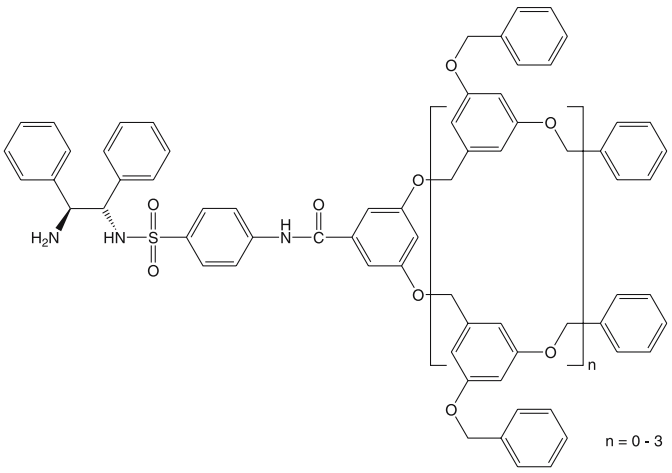
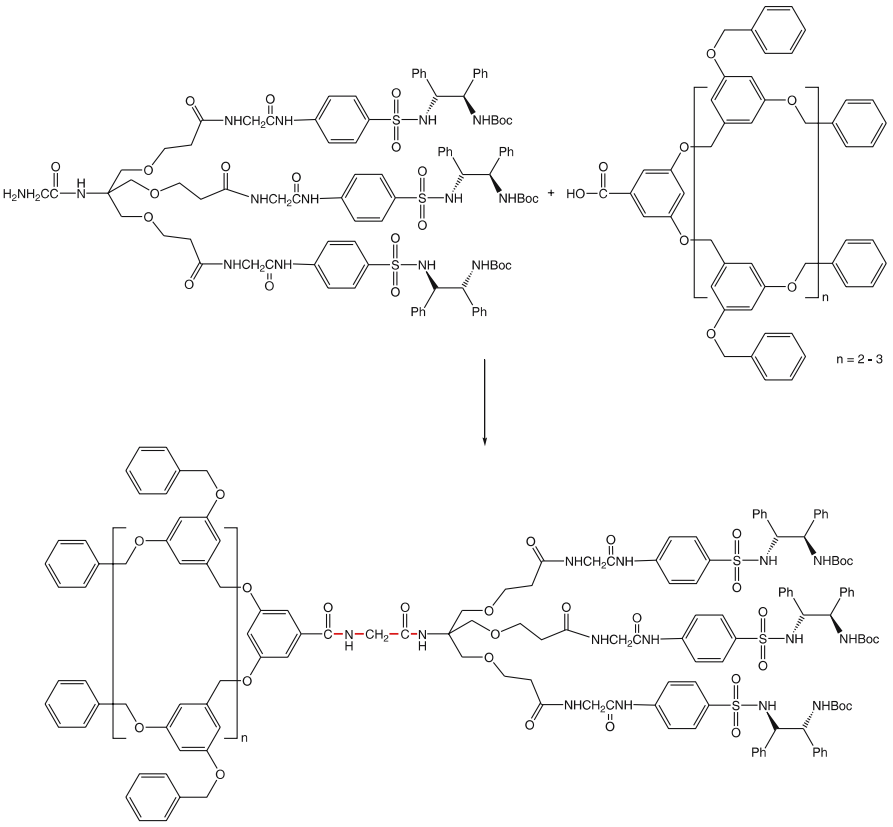


Fig. 21 A chiral diamine ligand attached to poly(aryl ether) dendrons



Scheme 7 "Hybrid" dendritic diamine ligands for Ru-catalyzed asymmetric transfer hydrogenation

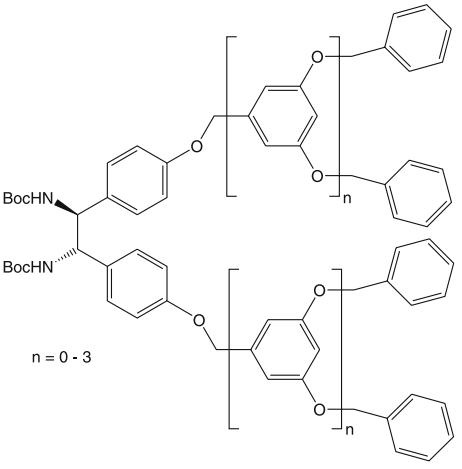


Fig. 22 Attachment of poly(aryl ether) dendrons to the phenyl substituents in the backbone of DPEN

to the diffusion of the substrate into the catalytically active core of the dendritic catalyst. Upon increase of the hydrogen pressure to 70 atm, complete conversion within 20 h was achieved.

4.4 Dendritic Bisoxazoline-Based Chiral Catalysts

In 2003, Chen and Fan synthesized a series of copper(II) complexes with chiral bis(oxazoline) ligands, which were disubstituted by Fréchet-type polyether dendrons at the carbon atom linking the two oxazolines (Fig. 23) [54]. These complexes were used as Lewis acid catalysts in enantioselective aldol reactions in aqueous media. High yields but only moderate enantioselectivities were obtained, which were comparable with those resulting from the corresponding small molecular catalysts. In fact, the dendritic substituents, which were assumed to affect the structure of the active site, did not decrease the enantioselectivity or the yield but gave slightly higher enantioselectivities and yields for the higher dendron generations.

Malmström and Moberg attached first- to fourth-generation dendritic substituents based on 2,2-bis(hydroxymethyl)propionic acid and (1*R*,2*S*,5*R*)-methoxyacetic acid to 2-(hydroxymethyl)pyridinooxazoline and bis-[4-(hydroxymethyl)oxazoline] compounds (Fig. 24) [55]. These new ligands were assessed in palladium-catalyzed allylic alkylations. The first type of ligands gave rise to enantioselectivities similar to that of a simple benzoyl ester derivative, whereas the latter type of ligands afforded products with higher selectivity than the analogous benzoyl ester. In general, the activity of the dendritic catalysts decreased with increasing generation.

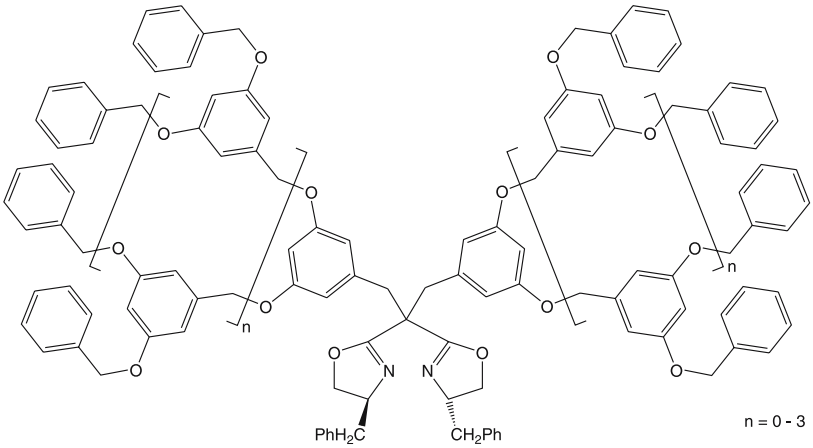


Fig. 23 The dendronized bisoxazolines studied by Chen and Fan

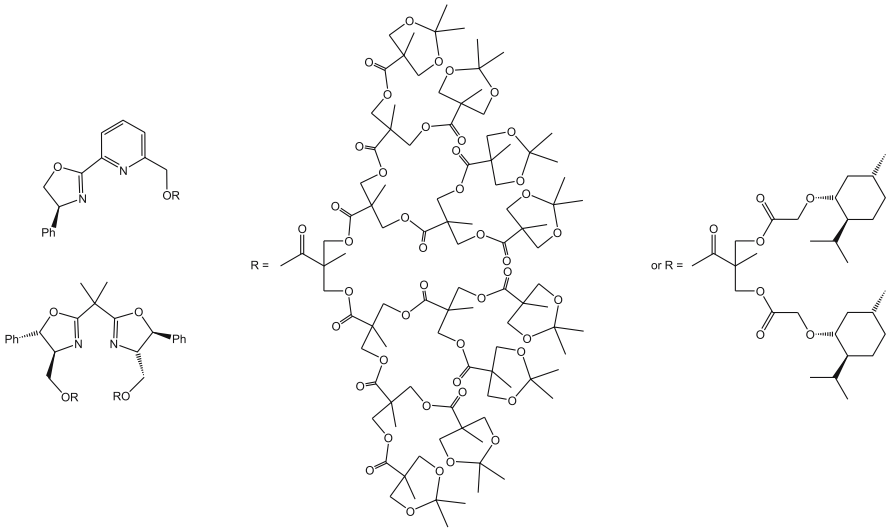


Fig. 24 The dendronized oxazoline ligands studied by Moberg et al.

4.5
Other Ligand Systems and Biphasic Catalysis

A series of chiral dendritic ligands derived from cinchonidine and Fréchet-type dendritic wedges up to generation 3 have been reported by van Koten et al. (Fig. 25) [56]. These dendritic ligands were tested as catalysts in the biphasic alkylation of *N*-(diphenylmethylene)glycine isopropyl ester with benzyl bromide (Scheme 8). The highest enantioselectivities (76% ee) were observed for the second-generation catalysts in aqueous 25% NaOH or aqueous 50% KOH as reaction media. Comparing the whole series of dendron

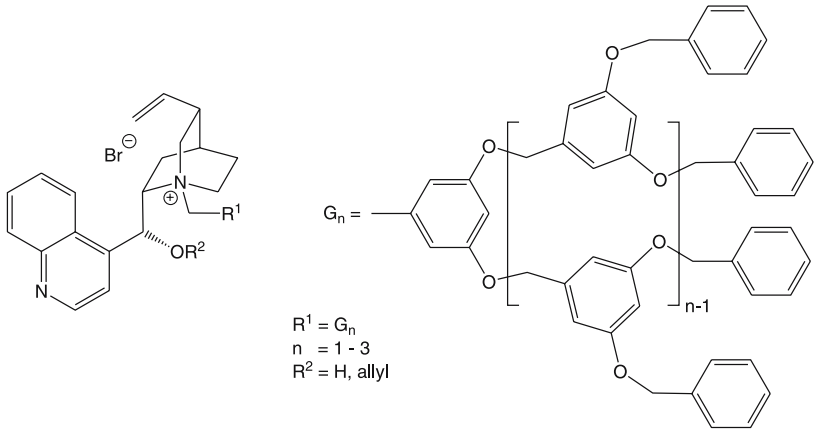
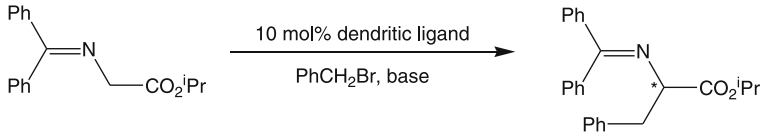


Fig. 25 Dendronized catalysts for asymmetric catalytic alkylation in a biphasic system



Scheme 8 Asymmetric alkylation of *N*-(diphenylmethylene)glycine isopropyl ester with benzyl bromide catalyzed by the dendronized catalysts shown in Fig. 25

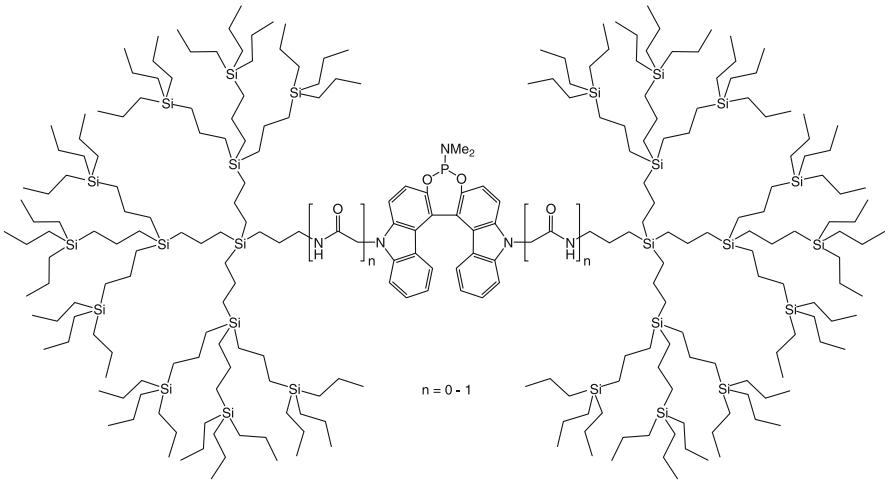


Fig. 26 A dendronized BICOL rhodium catalyst developed by Reek et al.

generations, it appears that the increase in steric hindrance due to the bulkiness of the dendritic wedge seems to have little effect on the enantioselectivity in this process.

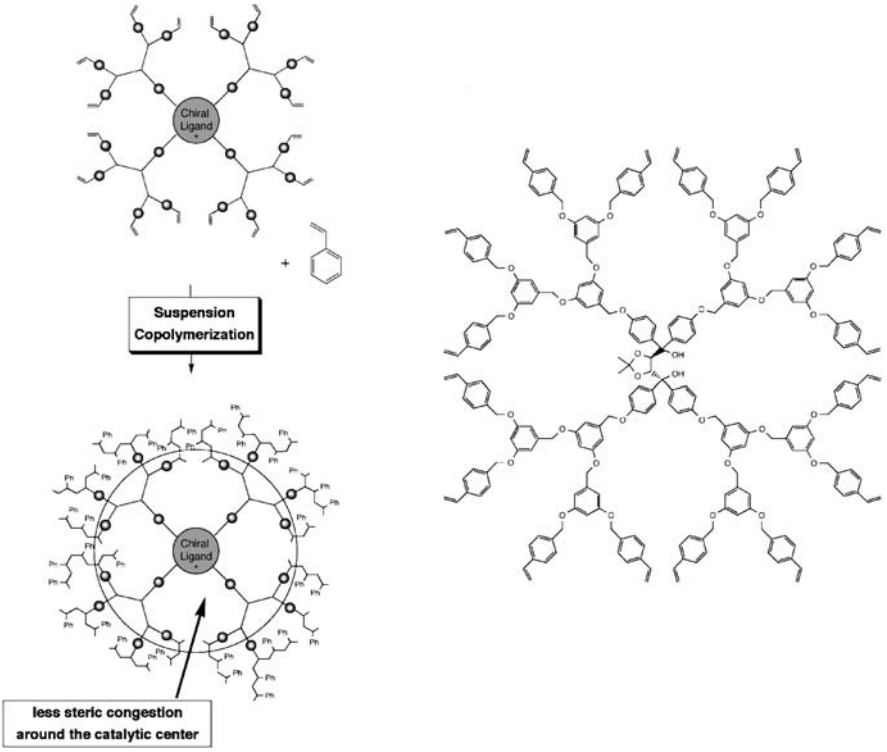
Recently, Reek et al. published the synthesis of a 9*H*,9′*H*-[4,4′]bicarbazole-3,3′-diol (BICOL)-based chiral monodentate phosphoramidite ligand, which was functionalized with two different third-generation carbosilane dendritic wedges (Fig. 26) [57]. As reference reaction in the catalytic study, the rhodium-catalyzed asymmetric hydrogenation of *Z*-methyl-α-acetamidocinnamate was chosen. Using a ligand-to-rhodium ratio of 2.2 led to enantioselectivities which were comparable to the results obtained using the parent BINOL-derived monodentate phosphoramidite MonoPhos.

5
Polymer-Supported Chiral Dendritic Catalysts

Both the activity and the selectivity of heterogeneously immobilized molecular catalysts are frequently reduced with respect to the performance of

their soluble analogues used under homogeneous conditions. The reasons for this are manifold, and include hindered diffusion processes or a significant change in the preferred conformations within the ligand shell of the catalytic moiety. A way out of this dilemma may be the use of dendronized polymers in which the catalysts are attached in a well-defined way to the dendritic sections, thus ensuring a well-defined microenvironment which is similar to that of the soluble molecular species or at least to the dendrimer catalysts themselves.

The combination of an efficient control over the environment of the active sites in a multi-functional catalyst and its immobilization within an insoluble macromolecular support was pioneered by Seebach et al. In their approach, the chiral ligand to be immobilized was placed in the core of a polymerizable dendrimer, followed by copolymerization of the latter with styrene as shown in Scheme 9 [58]. In this way, no further cross-linking agent was necessary, since the dendrimer itself acted as cross-linker. The dendritic branches are thought to act as spacer units, keeping the obstructing polystyrene backbone



Scheme 9 Dendronized TADDOL ligands which are cross-linked to form a dendritic network [58]

away from the catalytic centres and leading to better accessibility, and thus to enhanced catalytic activity.

A series of styryl-substituted TADDOL derivatives with flexible, rigid or dendritically branching spacers between the TADDOL core and the styryl groups have been prepared and used as cross-linkers in styrene suspension polymerization, leading to polymer beads ca. 400 μm in diameter. These in turn were loaded with titanate, and used for the Lewis acid catalyzed addition of Et_2Zn to PhCHO as a test reaction. A comparison of the enantioselectivities and degrees of conversion (both up to 99%) showed that these polymer-incorporated Ti-TADDOLates were highly efficient catalysts for this process. The best performance over 20 cycles of the test reaction was obtained with the TADDOL bearing four first-generation Fréchet branches with eight peripheral styryl groups. The enantioselectivity, the rate of reaction and the swelling factor were essentially unchanged after numerous operations carried out with the catalytic beads and a degree of loading of 0.1 mmol TADDOLate/g polymer, with or without stirring. The rate of conversion for the dendritically polymer-embedded Ti-TADDOLate was greater than that found for the corresponding monomer.

Seebach et al. also prepared salen derivatives carrying two to eight styryl groups for cross-linking copolymerization with styrene [59]. The salen cores were derived either from (*R*,*R*)-diphenylethylenediamine or (*R*,*R*)-cyclohexanediamine, and the styryl groups were attached to the salicylic aldehyde moieties using Suzuki or Sonogashira cross-coupling reactions, as well as phenol etherification with dendritic styryl-substituted Fréchet-type benzylic branch bromides. Subsequent condensation with the diamines provided the chiral salens (Fig. 27). These polymer-bound Mn and Cr complexes were used as catalysts for the stereoselective epoxidation of phenyl-substituted olefins, as well as for catalyzed dihydropyranone formation from Danishefsky's diene and aldehydes.

There are several remarkable features of these immobilized salens, notably the fact that the dendritic branches do not appear to decrease the catalytic activity with respect to the complexes in solution. Moreover, the reactions with dendritic catalysts incorporated in polystyrene gave products of essentially the same enantiopurity as those observed in homogeneous solution, with the dendritically substituted or with the original Jacobsen–Katsuki complexes. Some of the Mn-loaded beads were stored for a year without loss of activity. Especially, the biphenyl- and acetylene-linked salen polymers gave Mn complexes of excellent performance, which after ten catalytic runs showed no loss of enantioselectivity or degree of conversion.

In another example of the dendronization of solid supports, Rhee et al. described the design of silica-supported chiral dendritic catalysts for the enantioselective addition of diethylzinc to benzaldehyde (Fig. 28) [60–62]. The immobilized dendritic systems were formed in two different ways: one by stepwise propagation of dendrimers and the other by direct immobilization

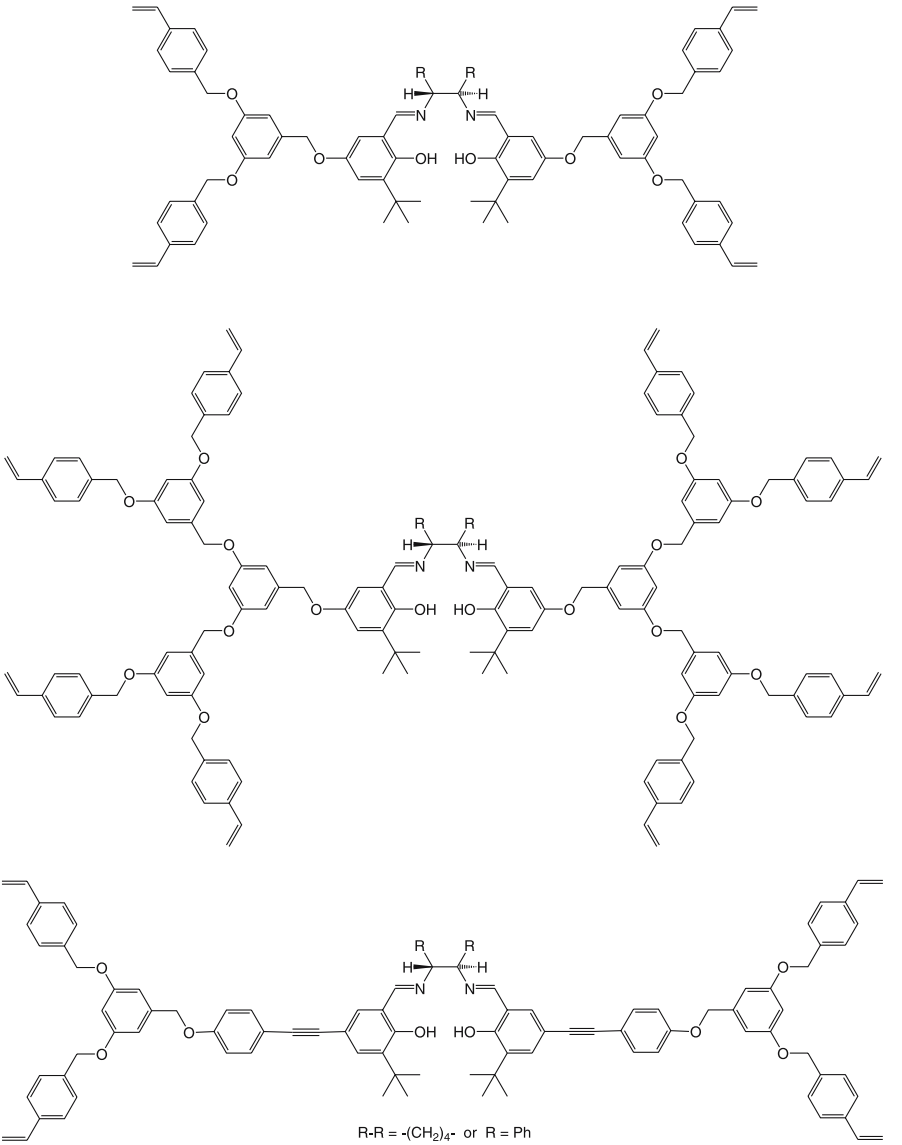


Fig. 27 Dendronized salen ligands which were subsequently immobilized by cross-linking of the styryl units

of the complete dendrimers on silica. From the former alternative, i.e. the dendrimer catalyst preparation by stepwise propagation of dendrimers on silica, symmetric hyperbranching was found to be a prerequisite in order to suppress the unfavourable racemic reaction taking place on the naked surface. Moreover, the control of hyperbranching was important not only to retain the

accessibility of the active sites, but also to relieve the multiple interactions between the chiral active sites. In the alternative method of dendrimer catalyst preparation by direct immobilization of preformed dendrimers on silica, the participation of surface silanol groups in the racemic reaction first had

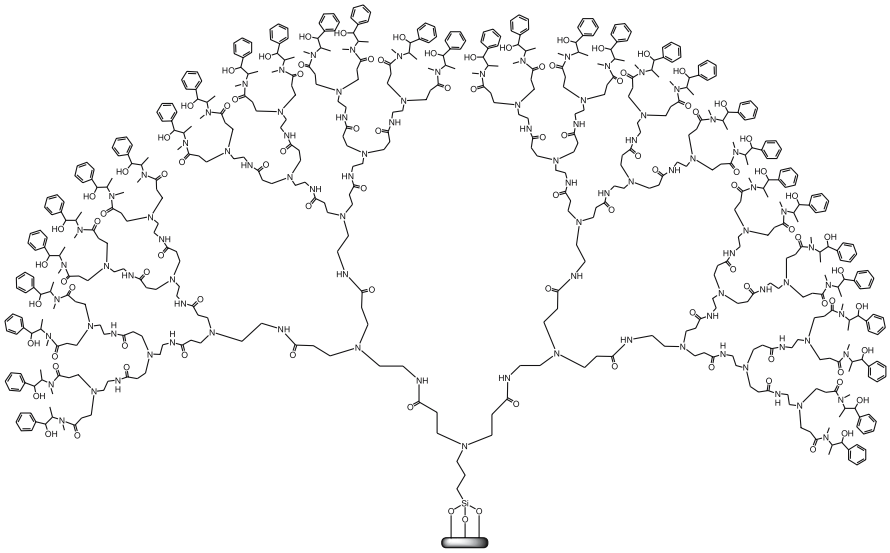


Fig. 28 Dendronization of a silica support

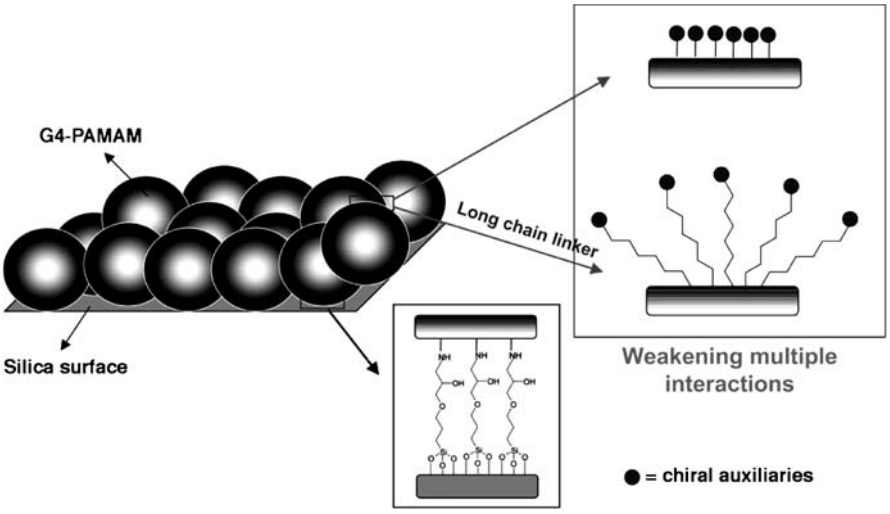


Fig. 29 Effect of the linker chain lengths on the intermolecular interaction of catalytic dendrimers immobilized on silica supports [62]

to be effectively suppressed by appropriate functionalization. The substitution of terminal end groups with a long alkyl chain was found to suppress the multiple interactions between the active sites (Fig. 29).

Finally, homopolymers of bis(oxazoline) ligands have been used to prepare efficient catalysts for cyclopropanation reactions. However, the reduced accessibility to most of the bis(oxazoline) moieties along with the high substitutional lability of copper(I)/(II) leads to a low degree of metal loading. As a consequence, the transmission of chiral information from the metallated polymer is inefficient. The use of suitable dendrimers as cross-linkers in the polymerization process allows a higher level of metallation.

In 2003, Mayoral et al. proved that by using this strategy, the productivity of chiral cyclopropanes per molecule of chiral ligands immobilized on a dendrimer greatly increased, which led to an improvement in the ligand economy and the chirality transfer [63].

6
Conclusion and Outlook

As has been emphasized at the beginning of this overview of asymmetric dendrimer catalysis, the kinetically controlled stereoselection depends on very small increments of free activation enthalpy. It is therefore an excellent sensitive probe for "dendrimer effects" and will continue to be studied in this fundamental context. As monodispersed macromolecules, chiral dendrimer catalysts provide ideal model systems for less regularly structured but commercially more viable supports such as hyperbranched polymers.

However, the results obtained in recent years have also established that the structural characteristics of the established dendrimer systems, such as the absence of a well-defined secondary structure, have limited the development of efficient abiotic enzyme mimics based on dendrimers. To achieve this ambitious goal, more efforts in dendrimer synthesis will be necessary. The use of dendritic catalysts in biphasic solvent systems has only just begun and appears to be a particularly fruitful field for further developments. These utilitarian aspects aside, it is the aesthetic attraction of these topologically highly regular macromolecules that continues to fascinate those working in the field of dendrimer catalysis.

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