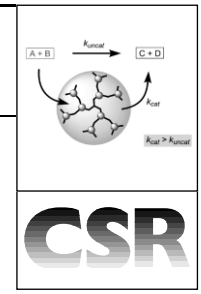
Catalysis inside dendrimers



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Catalytic sites can be placed at the core, at interior positions or at the periphery of a dendrimer. There are many examples of the use of peripherally functionalised dendrimers in catalysis and this subject has been thoroughly reviewed in the recent literature. This review is concerned only with dendrimer based catalysis involving catalytic sites at the core of a dendrimer and within the interior voids. In covering the significant achievements in this area, we have concentrated on examples that highlight key features with respect to positive and/or negative catalytic activity.

1 Introduction

Although Flory published a series of seminal papers describing the theoretical evidence for the formation of branched 3-dimensional molecules in 1941,[1] it was not until 1978 that Vögtle published the first synthesis of a controlled branched molecule.[2] This work was followed up in 1985 when Newkome and Tomalia independently published their results on a series of branched molecules they respectively termed arborols[3] and dendrimers[4] (the term dendrimer has now become the accepted name for this class of molecule). The field has now grown to such an extent that it is fair to say that dendrimers are an important new class of molecular architecture. Early attempts at dendrimer synthesis revolved around what is now known as the divergent approach (Fig. 1). The principle of this method involves growth from a central core, where branching is encouraged *via* a series of repetitive steps. This method is characterised by reactions occurring at an ever increasing number of sites, with the dendrimer being built up from the inside out. However, these characteristics soon led to problems with both purification and monodispersity. Nevertheless, relatively large dendrimers can be synthesised very quickly using this approach. More recently, Fréchet and Hawker have established a new synthetic technique that has been termed the convergent approach (Fig. 1).[5] Using this method the synthesis is started at what will ultimately become the outside of the dendrimer. The essential principle of this approach involves the synthesis of small dendrons or wedges, which can then be

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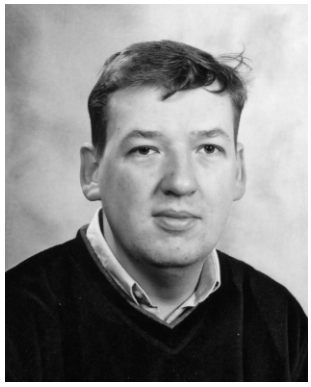

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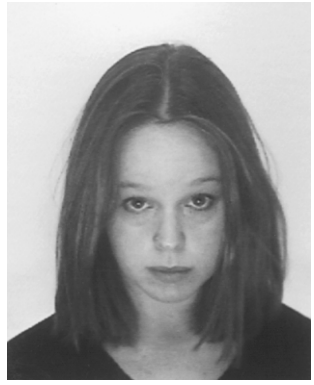

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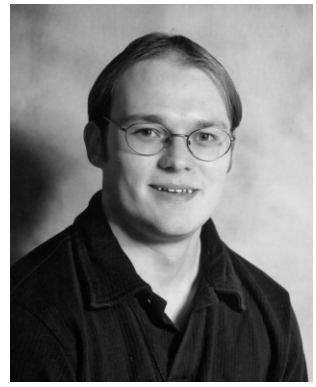

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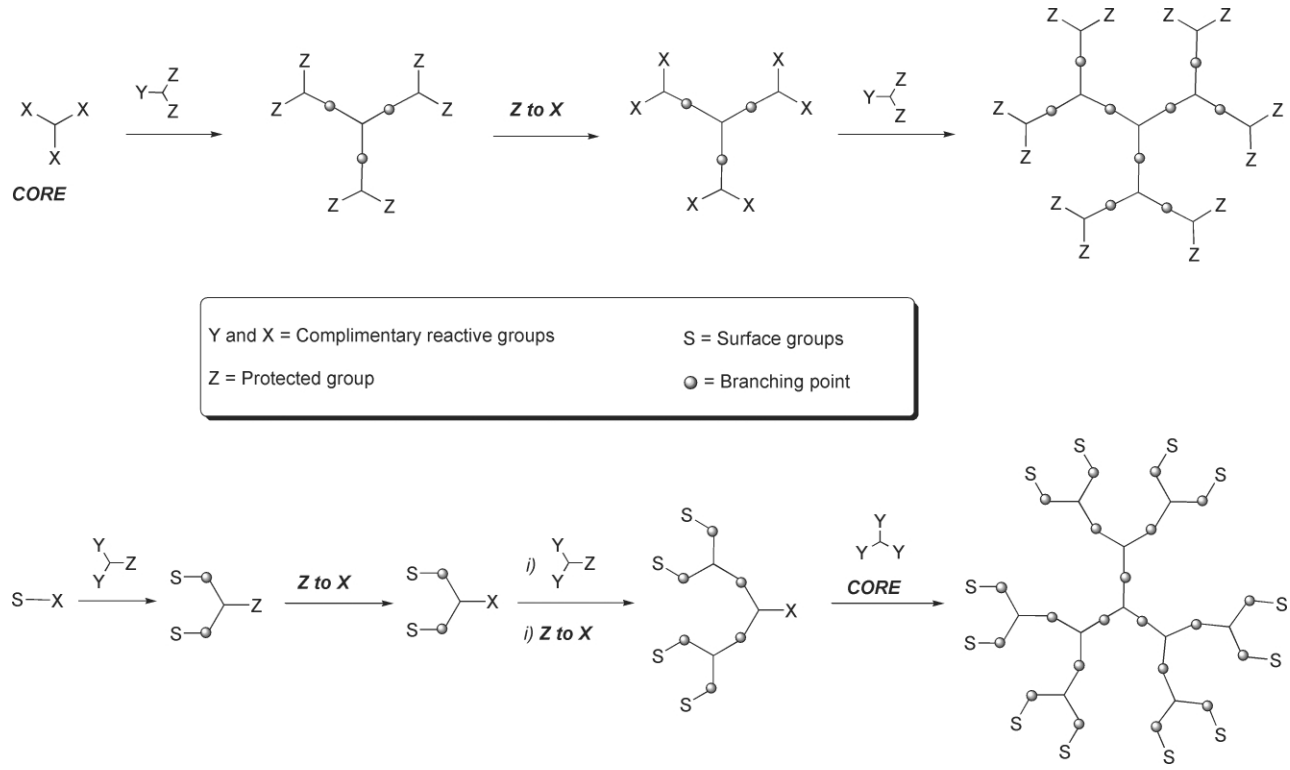


Fig. 1 Dendrimer synthesis, the divergent approach (top), and the convergent approach (bottom).

brought together on a central core to give the final dendrimer. This method is characterised by reactions occurring at only one site, the core or focal point. Unfortunately this focal point soon becomes masked by the growing dendrons. Consequently only relatively small dendrimers can be synthesised using this approach; even so, the purification and synthesis are easier and often more reliable than with the divergent approach.

During the early years, the area blossomed and dendrimers based on a variety of repeat units appeared: these included amides, amines, carbosilanes, siloxanes, esters, ethers, phenylacetylenes, various organometallics, amino acids and even nucleic acid based dendrimers.[6] In addition, secondary function was also incorporated into these systems. These included porphyrins, phthalocyanines, saccharides, mesogens, anionic and cationic groups and various chromophores.[6] Over the next few years more and more applied systems began to be developed and this area of applied research is now one of the most vibrant areas of dendrimer chemistry. Examples of such applications are many and diverse: they include encapsulation and solubilisation,[7] medicinal and biomimetic applications,[8] novel materials,[9] and the area that this review is concerned with, catalysis.

It was soon realised that by placing catalytic groups at the core, on the outside, or at intermediate positions within a dendrimer, various advantages over heterogeneous systems could be achieved. Heterogeneous catalysts are insoluble and reactions therefore take place at the interface between two phases. However, heterogeneous catalysts can easily be recovered *via* filtration; this is particularly important with respect to expensive catalysts. On the other hand, homogeneous catalysts are soluble in the reaction media and are therefore very efficient. Unfortunately, recovering these catalysts is not so easy; special and/or time consuming and expensive techniques are often required. What is desired, then, is a homogeneous catalyst that can be recovered by filtration. Early attempts to reach this goal concentrated on polymers that were soluble in the reaction solvent, but could be precipitated on addition of a second solvent. Unfortunately, polymer based catalysts were often ineffective because of leaching of the catalytic groups or unavailability of the catalytic group owing to uncontrollable polymer conformations. In an attempt to overcome these problems and obtain superior catalysts, chemists turned their attention to dendrimers. Dendrimers can be precipitated from solution, or if large enough, removed using membrane filters. In addition, it is also possible to incorporate catalysts at *controlled* sites within the dendrimer; this gives us a significant advantage over the uncontrollable and indefinable incorporation of catalysts within conventional polymers. Catalytic groups placed at the core of a dendrimer allow us to control the microenvironment around this catalytic group. Unfortunately, placing a single catalytic group at the core of a large dendrimer results in a low loaded system. One way of overcoming this disadvantage, while retaining the advantage of controlling the microenvironment around the catalyst, is to incorporate the catalytic groups throughout the interior of the dendrimer. Fig. 2 schematically shows these alternative approaches.

In addition, catalytic groups can be incorporated at the surface of a dendrimer. Catalytic groups at the surface are readily available for reaction, especially in larger dendrimers, which adopt a globular conformation with most terminal groups located at the surface. The loading on these systems is extremely high due to the inherent nature of dendrimer structures. There are many examples of the use of peripherally functionalised dendrimers in catalysis of reactions including the Kharash addition, hydrolysis, decarboxylation, Heck couplings, polyurethane formation, oxidation (bromides and thiophenes), allylic alkylation, Stille couplings, Knoevenagel condensations, Michael addition, nucleophilic addition, asymmetric hydrogenation, and so on. This is a broad and rapidly expanding subject, which has already been thoroughly reviewed in the recent literature.[10–14] This review is therefore going to concentrate on the significant achievements within the area of *internally* functionalised dendrimer catalysts. Rather than describe the achievements chronologically, similar topics are grouped together for clarity. The field of dendrimer based catalysis is an extremely active area, and much of the work follows a similar theme. We have therefore decided to focus on the significant achievements and to concentrate on examples that highlight key features with respect to a positive or negative catalytic activity.

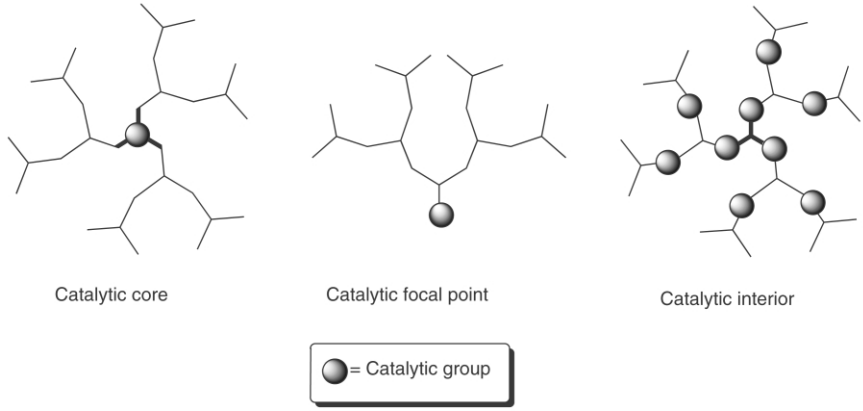


Fig. 2 The regions **within** a dendrimer where catalytic groups can be attached.

2 Catalysis at the dendrimer's core

Placing the catalytic group at the centre of a dendrimer allows spatial control of functionalities; this enables steric, photophysical and electrochemical properties to be controlled. Fréchet and co-workers were the first to demonstrate that a dendrimer's bulk and environment could be used to catalyse *and* control a chemical reaction. The group used the poly(aryl ether) dendrimer **1**, with an alkoxide group at the core, to initiate anionic ring opening polymerisations (Fig. 3).[15] The products obtained from these dendrimer assisted reactions were far superior to those yielded using a standard alkali metal alkoxide initiator. For example, when the dendrimer **1** was used as the initiator, high molecular weight polymers with very narrow polydispersities were obtained. This compares favourably to the low molecular weight polymers with extremely broad molec-

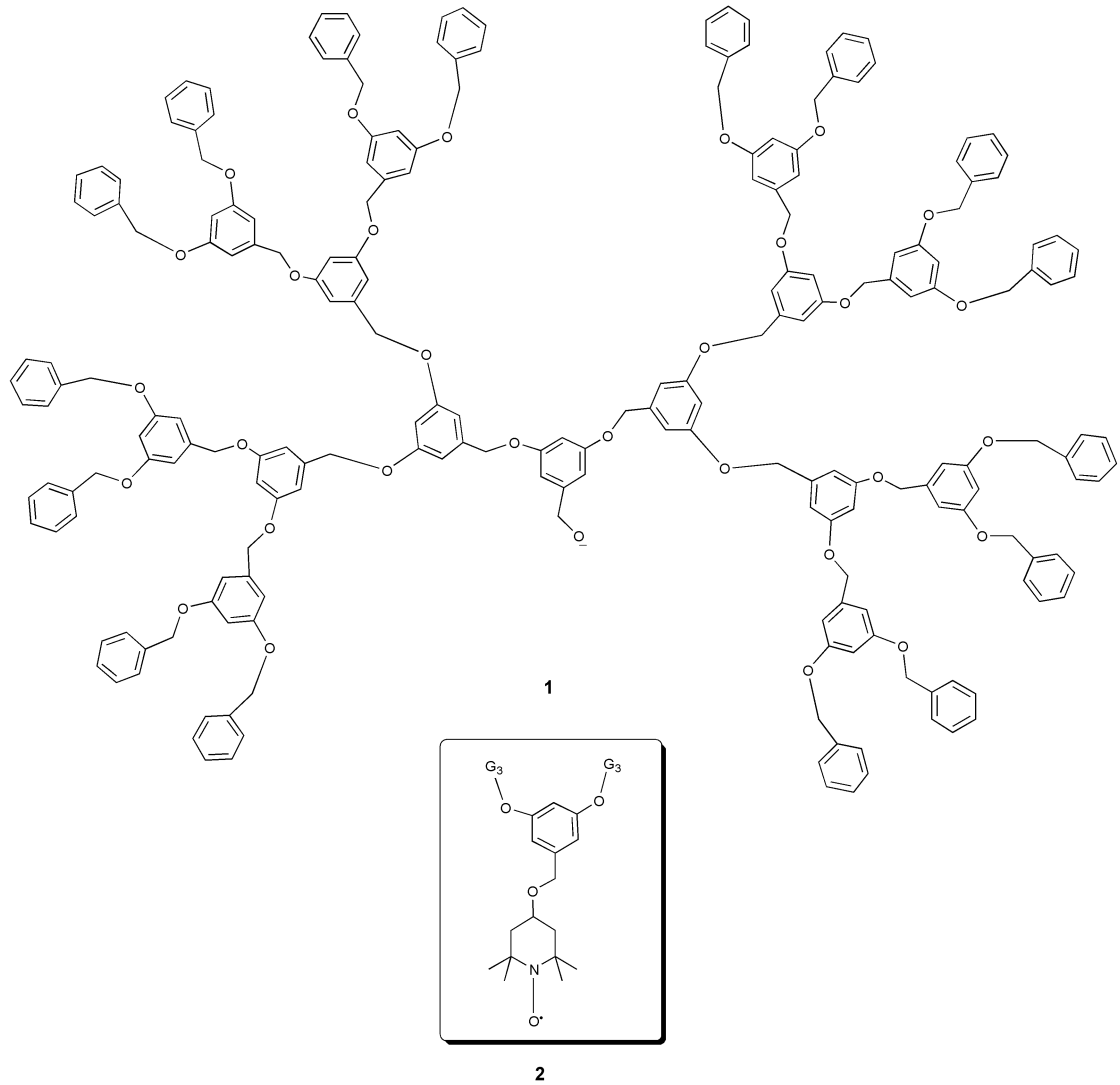


Fig. 3 Dendron with an alkoxide focal point used to initiate ring opening anionic polymerisation. A similar molecule with a TEMPO focal point (insert) was used to initiate a living radical polymerisation.

ular weight distributions being produced with simple metal alkoxide initiators. One of the reasons that low molecular weight polymers with large polydispersities are produced during metal alkoxide initiated reactions is that the reactive alkoxide group, which resides at the end of the growing polymer, reacts intramolecularly with another group on the same polymer chain (a side reaction known as '*backbiting*'); this results in short polymer chains. However, during the dendrimer initiated polymerisation, the reactive alkoxide group prefers to stay within the bulky aryl ether dendrimer, which encourages intermolecular reactions and significantly hinders any intramolecular '*backbiting*' side reactions. Another advantage of using dendrimer based initiators for anionic polymerisation is their solubility; the notorious insolubility of simple alkali metal initiators can often be the reason for disappointing yields and poor product characteristics. Fréchet has used a similar approach to control a living radical polymerisation, in which the radical initiator TEMPO **2** was placed at the dendrimer's centre. Using this approach, polymers with low molecular weights and low polydispersities were produced. The reason for the narrow molecular weight distribution is once again due to the radical group being retained within the dendrimer, which prevents radical–radical recombination. The yield of low molecular weight products was due to insolubility of the growing polymer dendrimer conjugate.[16]

Van Leeuwen *et al*. described the synthesis of three generations of carbosilane dendrimers that possessed ferrocenyl phosphorus donor atoms at their core.[17] These dendrimers were used as ligands for the palladium catalysed allylic alkylation reaction and the results of this study are displayed in Table 1. As the size of the dendrimer increases a corresponding reduction in yield occurs. This effect is due to more difficult mass transport with increasing steric bulk and is most pronounced when going from generation 2 to 3. However, the selectivity of the reaction (*i.e*. the ratio between *trans* and branched products) also changes as the size increases, and more of the branched product is obtained with the larger dendrimer ligands. The reason for this change in selectivity is a combination of effects. Firstly, the increased steric bulk of the larger dendrimer hinders nucleophilic attack on the palladium. Secondly, the apolar microenvironment within the larger carbosilane dendrimer may also account for the observed selectivity.

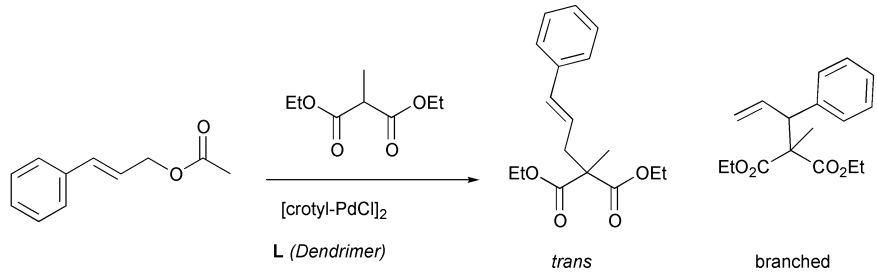
Brunner and Altmann also reported on the use of a series of low generation dendrimers with diphospho rhodium and copper complex units at their core for catalysis of hydrogenations and cyclopropanations respectively. These macromolecular catalysts not only retained their activity, but also displayed enhanced reactivity (although lower ee's were achieved relative to mononuclear analogues).[18] In a later study Chow and Mak described the synthesis and application of a series of dendrimers possessing bis(oxazoline)copper(II) catalysts at their core.[19,20] In this work Chow compares these dendrimers to metalloenzymes. The bis(oxazoline) unit **3** was synthesised and various dendrons added to give dendrimers up to the 3rd generation. In an alternative approach, dendrons were added to **4**, which was then cyclised to give the same bis(oxazoline) cored dendrimers (Scheme 1). Chow went on to apply these dendrimer as ligands for the copper catalysed Diels–Alder reaction shown in Scheme 2.

The aim was to determine the extent to which the dendrimer's polarity and steric factors affected the kinetics of catalysis. Using modified Michaelis–Menton kinetics and a Lineweaver–Burk analysis,[21] the rate constant and the binding of reactant **5** to the catalyst could be determined, as summarized in Table 2. By comparing the binding and rate constants, two important observations can be made. Firstly, as the dendrimer gets bigger, the binding constant decreases. This is due to steric factors that distort the geometry of the ligands, which therefore affects the binding of the dienophile to the catalyst. The second point of interest is that the rate constants remain the same for the zeroth-, first- and second-generation dendrimers, and it is not until the third-generation dendrimer is used that a drop in rate occurs. This sudden drop in activity is due to an increased steric barrier as the substrates try to approach the catalytic core. That is, a sudden change in the globular structure of the dendrimer occurs between generation two and three. This effect has been observed for the physical properties in a number of other dendritic systems.[22]

In an extension of this work[20] Chow investigated the effect of dendrimer size on intermolecular selectivity. For this study, the authors reacted one equivalent of cyclopentadiene with two equivalents of a 1 : 1 mixture of dienophiles of differing size in order to compare the effect of steric demand on product distribution. All four dendrimers (generation 0 to 3) were investigated, and in all cases the smaller dienophile reacted much faster than the larger dienophile. Therefore the dendrimers are able to offer some degree of steric selectivity during catalysis.

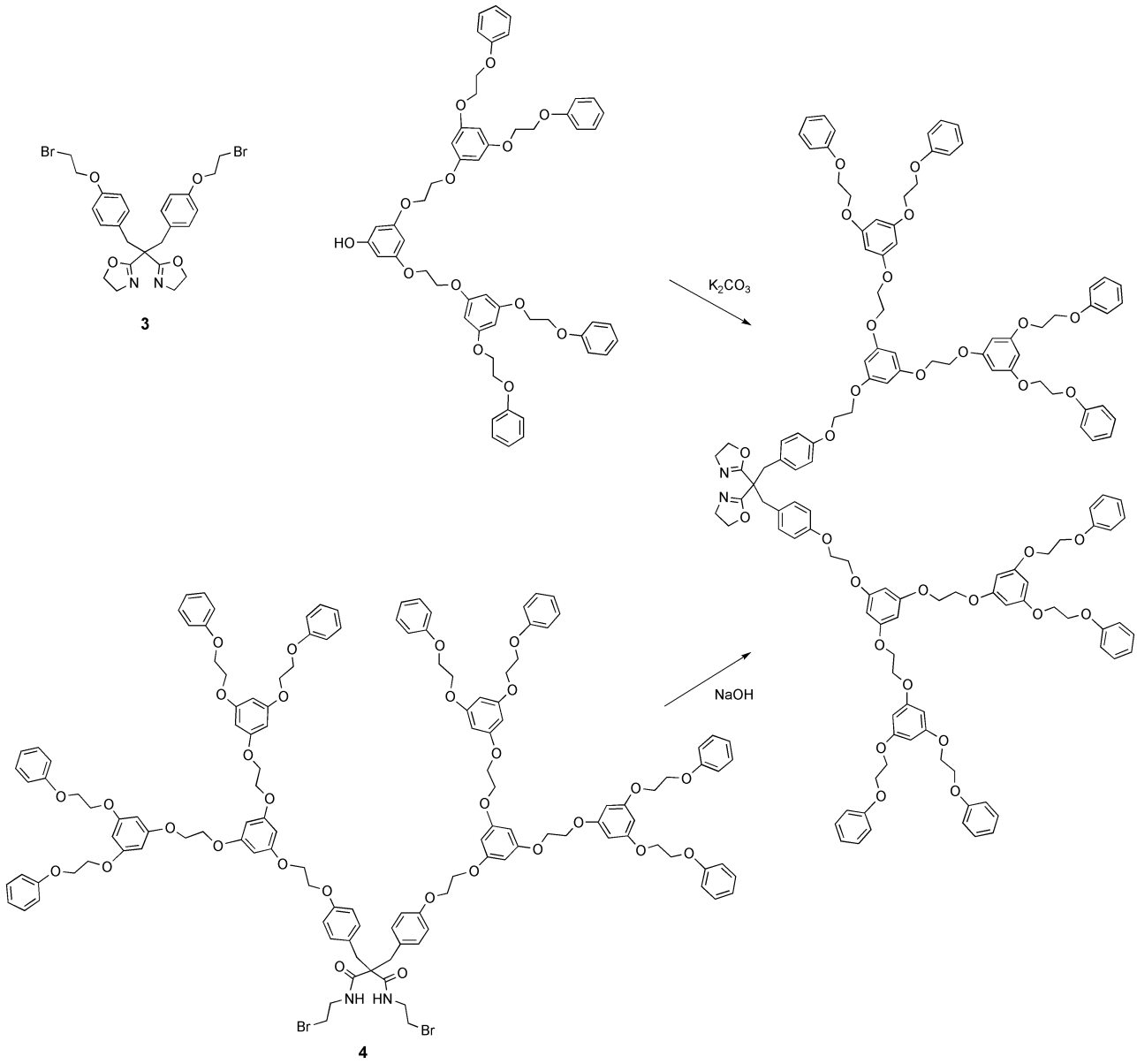
This idea of sterics controlling selectivity has also been explored by Moore and Suslick who applied ester-linked dendrimers with metalloporphyrin cores as shape selective catalysts. These manganese–porphyrin dendrimers were synthesised up to the 2nd generation and their ability as shape selective oxidation catalysts was studied.[21,23] The UV–vis absorption spectra of these dendrimers were similar to that of the simple porphyrin, but were blue shifted. This was thought to be due to the dendrimer creating a localised region of low

Table 1 Product distribution obtained during an allylic alkylation reaction when different dendrimer catalysts are used

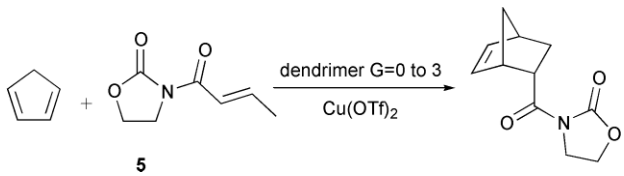


L (dendrimer)	Conversion (%)	*trans* Product (%)	Branched product (%)
—	8	96	4
dppf[a]	72	90	10
G = 1	76	88	12
G = 2	58	87	13
G = 3	17	79	21

[a] dppf = 1,1′-bis(diphenylphosphino)ferrocene.



Scheme 1 The two routes Chow used to construct the 2nd generation bis(oxazoline) centred dendrimer.



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Scheme 2 The Diels–Alder reaction chosen by Chow to investigate dendrimer catalysis.

Table 2 Binding and rate constants for the catalysed Diels–Alder reaction shown in Scheme 2

Catalyst	Binding K_c/M^{-1}	Rate $10^3k/M^{-1}\ s^{-1}$
G = 0–$Cu(OTf)_2$	10.4	3.3
G = 1–$Cu(OTf)_2$	9.8	3.3
G = 2–$Cu(OTf)_2$	7.8	3.2
G = 3–$Cu(OTf)_2$	5.7	1.9

polarity around the porphyrin (similar effects have been reported for zinc dendrimer porphyrins). Epoxidation experiments were performed using the dendrimer metalloporphyrins shown in Fig. 4 and iodosylbenzene as the oxygen donor. The first set of experiments was designed to test the intramolecular regioselectivity of these dendritic catalysts; various compounds containing two separate alkene functionalities were therefore subjected to the oxidation conditions. In most cases, the dominant reaction pathway involved oxidation of the least substituted alkene functionality, the results of which are shown graphically in Fig. 5. A second set of experiments was then developed to test the ability of these catalysts to distinguish intermolecularly between 1 : 1 mixtures of different alkenes (Fig. 5).

The cyclic alkenes are oxidised up to three times more effectively than the larger cyclic alkenes. This is contrary to the fact that we would expect the more electron rich (*Z*)-cyclooctene to exhibit greater reactivity during epoxidation than the simpler 1-alkenes. In addition, excellent oxidation stability was observed for the dendrimer metalloporphyrins. Under the conditions used, only 10% of the catalyst activity had degraded after 1000 turnover cycles. A closely related system was developed by Kimura *et al.*[24] In this case a cobalt(II) phthalocyanine was used as the dendritic core. The authors demonstrated how electron transfer reactions at the centre of the dendrimer were slowed as a result of dendritic shielding. These dendritic cobalt(II) phthalocyanines catalysed the oxidation of 2-mercaptoethanol (to the corresponding disulfide) with a similar activity to the parent phthalocyanine. In addition, these

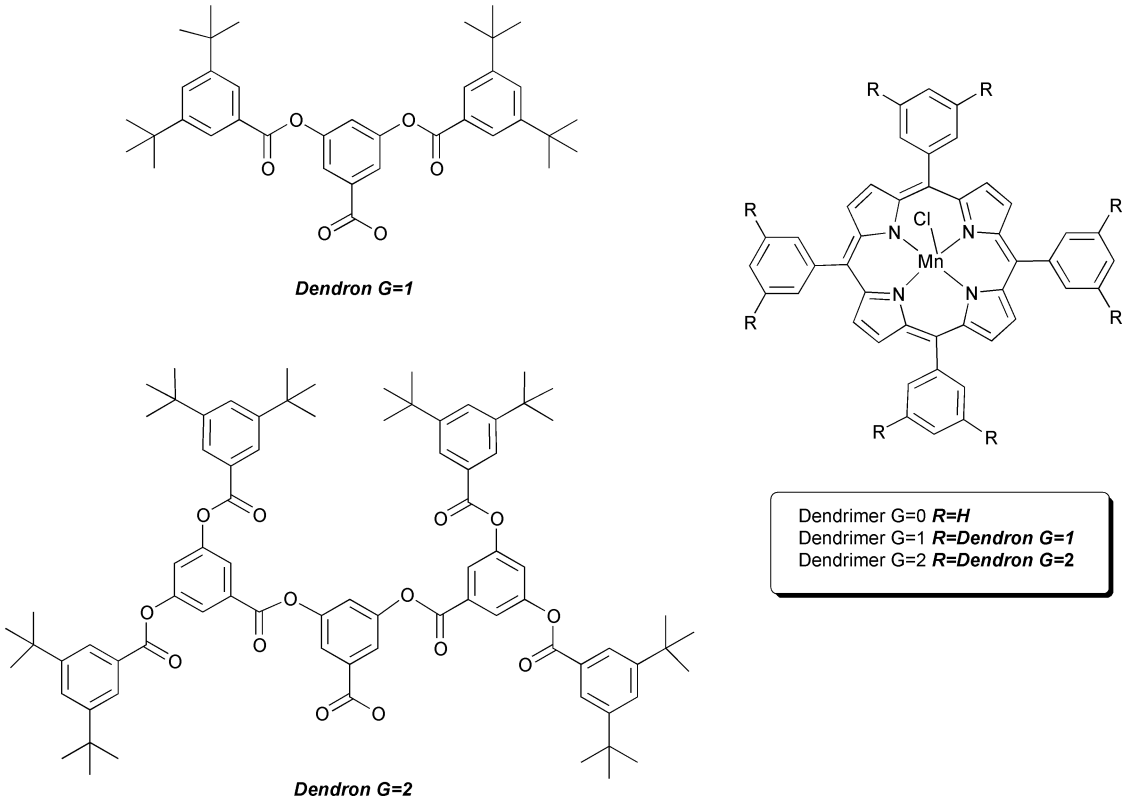


Fig. 4 Porphyrin cored dendrimers used as shape and size selective epoxidation catalysts.

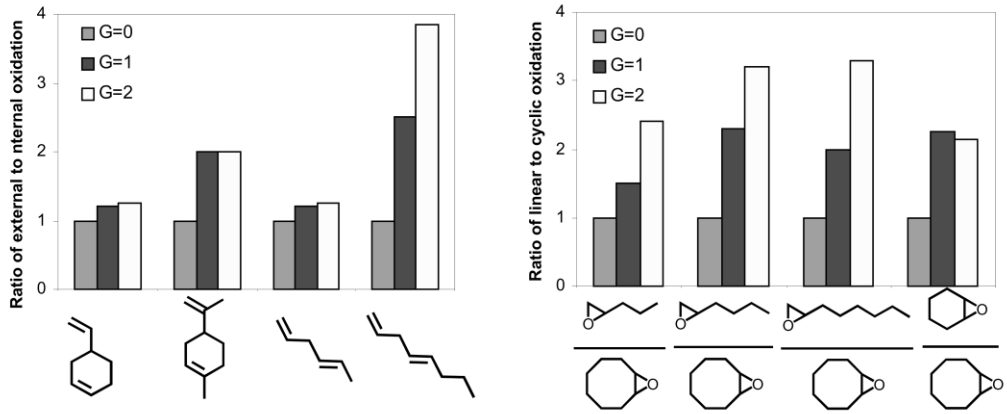
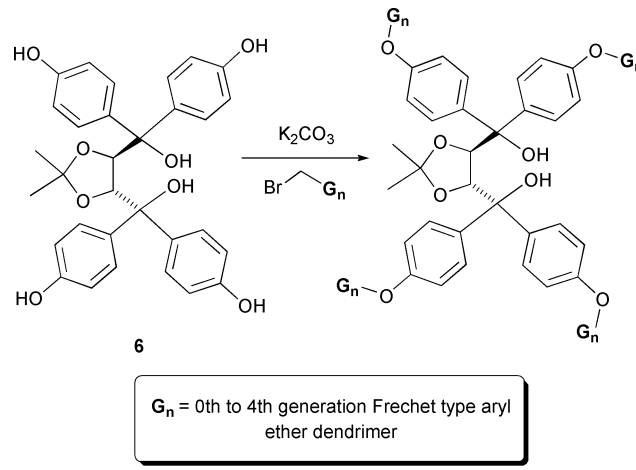


Fig. 5 Product distribution obtained for intermolecular epoxidations as the fraction formed from the least hindered double bond (left) and ratios for intramolecular epoxidations (right). Both graphs are normalised with respect to the G = 0 dendrimer catalysts.

systems demonstrated enhanced stability due to the shielding effect of the dendritic structure.

Seebach *et al*. have published a number of papers that have investigated the catalytic properties of a series of dendrimers with chiral TADDOL [(*R*,*R*)-α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol] ligands at their core.[25] These dendrimers were constructed by adding 'Fréchet-type' dendrons to the tetraphenol TADDOL core unit **6** (Scheme 3). TADDOL containing dendrimers of the zeroth to the fourth generation were constructed.

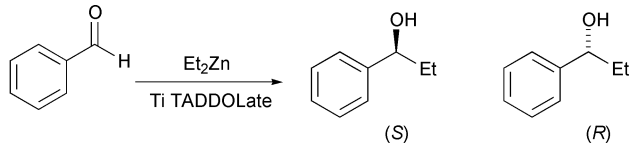
The influence of the dendritic branches on the catalytic activity and stereoselectivity of the TADDOL based dendrimer ligands was investigated; the results are summarised in Table 3. The reaction chosen was the titanium–TADDOLate catalysed addition of diethylzinc to benzaldehyde. Once again, the dendrimeric structure has an affect on the outcome of the catalysed reactions. As the dendrimer ligands get larger, a decrease in yield occurs and this is most pronounced when going from the 3rd to the 4th generation dendrimer. The reduction in yield can be attributed to steric problems associated with mass transport and substrate access to the catalytic site.



Scheme 3 Seebach's TADDOL cored catalytic dendrimers.

However, a small change in enantioselectivity can also be observed as the dendrimer ligands become larger.

Table 3 Stereoselectivity of the TADDOL based dendrimer ligands used during the Ti catalysed addition of diethylzinc to benzaldehyde



TADDOLate	Conversion (%)	*S* : *R* ratio (%)
TADDOL	100	99 : 1
TADDOL G = 0	99	98 : 2
TADDOL G = 1	97	98 : 2
TADDOL G = 2	96	98 : 2
TADDOL G = 3	94	96 : 4
TADDOL G = 4	47	94 : 6

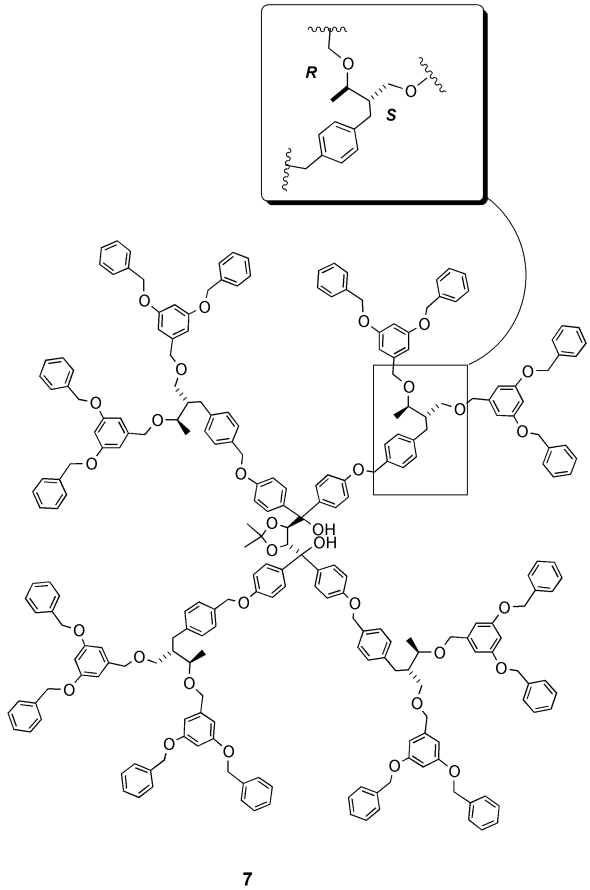
In an extension of this work, Seebach and Sellner have gone on to construct similar dendrimers containing chiral groups within their branches.[26] These were constructed in an effort to determine whether or not remote chiral groups could influence the stereoselectivity of the catalysed reaction occurring at the core of the dendrimer (Fig. 6). Once again the enantioselective addition of diethylzinc to benzaldehyde was used as the test reaction. On carrying out the reaction using the TADDOLate chirally *branched* dendrimers **7** and **8** (both generation 2), no effect on stereoselectivity could be observed when compared to the simpler TADDOLate chiral dendrimer (generation 2) described above. A similar result was obtained by Brunner who attempted to affect the stereochemical outcome of chiral hydrogenation reactions using rhodium catalyst complexed to the core of a dendrimer with chiral peripheral units.[27]

This may not seem surprising when it is considered that the additional chiral groups are now 16 atoms away from the reactive/titanium centre of the dendrimer. Nevertheless, the same group had earlier demonstrated the potential of remote chiral effects in dendrimer based asymmetric catalysis. Seebach had earlier developed a series of dendrimers that possessed chiral arms around a catalytic core; these molecules were able to catalyse enantioselective protonation reactions, despite the fact that the nearest chiral groups were 12 atoms away from the reactive centre.

More recently, Seebach *et al*. have described how these *homogeneous* dendritic catalysts can be incorporated within a polymer bead and used to great effect as *heterogeneous* catalysts.[28] The dendrimer **9** contains vinyl groups on the surface, which were used as cross linkers during the copolymerisation of styrene to yield polystyrene beads with a diameter of about 400 μm (in their non-swollen state). The resulting polymers were then complexed with $Ti(OCHMe_2)_4$ to give the necessary Ti–TADDOLate catalysts. These catalysts were once again tested during the enantioselective addition of diethylzinc to benzaldehyde. Surprisingly, these polymerised heterogeneous catalysts seemed to outperform the equivalent non-polymerised dendritic catalyst **10** in terms of enantioselectivity and rate (Fig. 7). It can be hypothesised that this increase in rate is due to control of the polar environment around the catalyst (*i.e*. the change in local polarity around the catalyst stabilises the transition state).

It can also be argued that the rigid and open structure around the catalyst means that reactants and products can diffuse freely in and out of the polymer, thus increasing the rate of reaction. Another advantage of these polymeric dendritic catalysts is that they can easily be recovered *via* filtration and used again. Seebach reports that no drop in enantioselectivity occurred after 20 reaction cycles.

Other groups have adopted a similar approach towards asymmetric catalysis. For example, Bolm *et al*. reported the use



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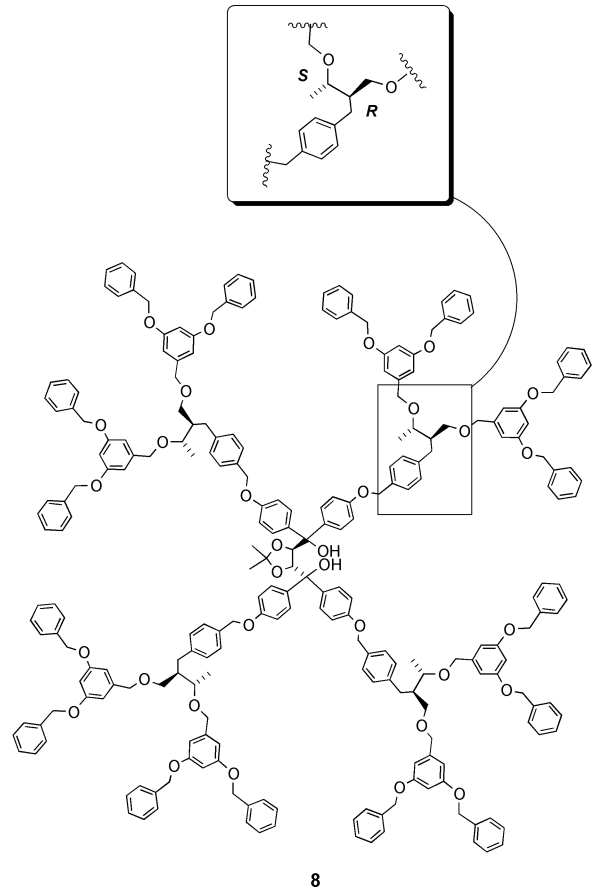

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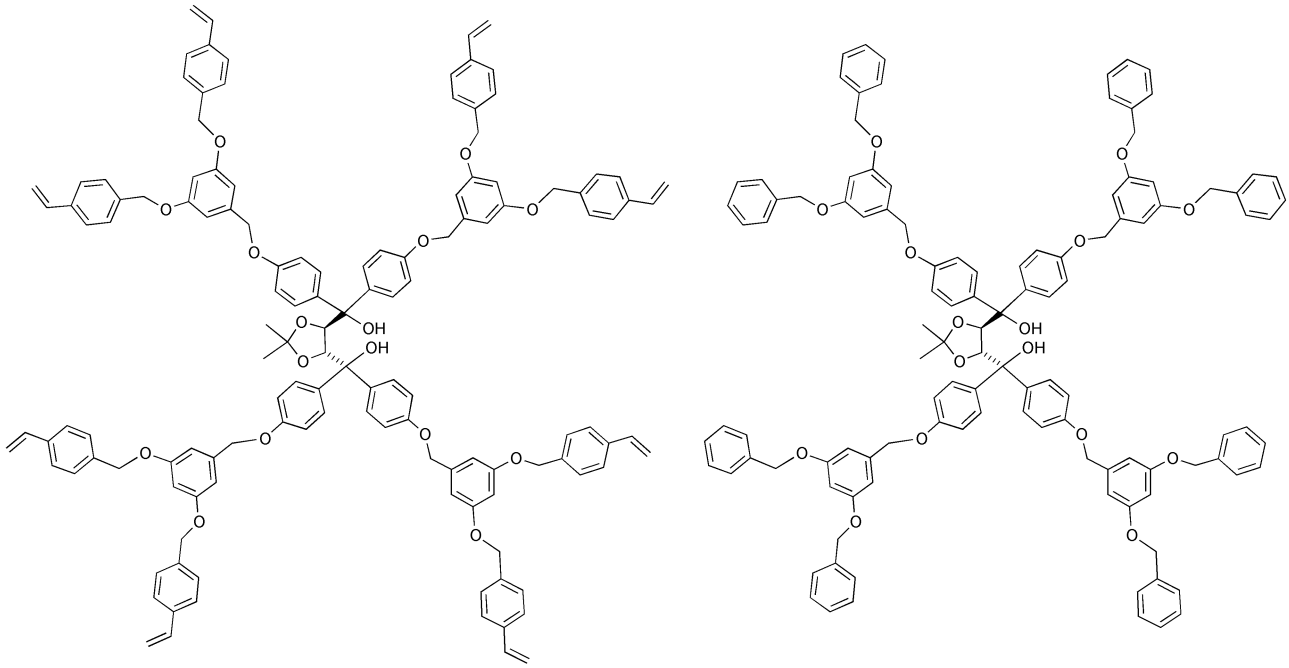
Fig. 6 Chiral TADDOLs with remote chiral groups.



9 **10**

Fig. 7 Chiral TADDOL **9** with polymerisable surface groups.

of Fréchet type dendrimers with chiral pyridyl alcohol ligands at their core.[29] These dendrimers were again applied as chiral ligands for the enantioselective addition of diethylzinc to benzaldehyde. The enantioselectivity obtained for these macromolecular systems was almost the same as that obtained for the monomeric ligand (85% ee for the dendrimer as opposed to 88% ee for the monomeric ligand). However, the dendritic based ligand is large enough to be recovered and reused. Bolm also used a similar series of dendritic ligands with chiral amino alcohols at their cores for asymmetric borane reductions of acetophenones. Monomeric ligands, G0, G1, G2 and G3 were all studied, and the best enantioselectivity was obtained for the intermediately sized G2 ligand, even when compared to the monomeric amino alcohol. For example, an ee of 87% was recorded for the monomeric ligand whilst an ee of 91% could be obtained with the G2 ligand. This was rationalised by arguing that the G0 and G1 ligands were too small and flexible, whereas the G3 dendritic ligand was too large to allow adequate access to (and release from) the core.[30]

The idea that a dendrimer with a catalytic core can represent a mimic of pyruvate oxidase was exemplified by a group of scientists led by Diederich from the ETH in Zurich.[31]The group synthesised dendrimer **11** and its water-soluble derivative **12**, both of these macromolecules contain a catalytic cyclophane at their core. It has been shown that similar molecules, termed *dendrophanes*, are able to bind arenes and steroids within their macrocyclic core *via* π–π and/or simple hydrophobic interactions. Host–guest exchange kinetics of the guest molecules bound within the dendrophane were found to be very fast, with first order decomplexation rates of around 10^3 s^{-1}; this makes dendrophanes very attractive with respect to catalysis. The catalytic dendrophanes **11** and **12** also contain the thiazolium group on the ridge of the macrocycle; these groups are capable of catalysing the oxidation of aromatic aldehydes into aromatic esters. Diederich chose to study the oxidation of naphthalene-2-carbaldehyde (see insert in Fig. 8) because it binds to the centre of the dendrophanes with a binding constant of around 300 M^{-1}. This affinity is similar to that measured for the corresponding non-dendronised cyclophane **13**; this indicates that the binding is not hampered by the dendrimer branches. Therefore, as dendrimers **11** and **12** provide a favourable environment with respect to polarity (without causing a detrimental effect on the binding affinity), then an increase in the rate of reaction was expected when using dendrophane. Initially the results were not encouraging: a reduction in the rate of reaction was observed (compared to that measured using the simple cyclophane catalyst **13**) when dendrophanes **11** or **12** were used as a catalyst. The authors postulated that this reduction in activity might be due to a different step in the reaction pathway being rate determining (*i.e.* the dendrimer may slow down an electron transfer step, this step then becomes rate determining). Alternatively, the branches within the dendrimer and the steric environment may unfavourably affect other transition states in the multistep process.

3 Catalysis within the dendrimer's interior

The interior regions of a dendrimer can provide a localised environment suitable for binding and catalysis. For example, it has been demonstrated that water-soluble dendrimers can 'dissolve' small hydrophobic molecules within their interiors in much the same way that a micelle can.[32] This provides a mechanism for the concentration of reactive species within a small localised and controlled microenvironment (any increase in concentration will be accompanied by an increase in the rate of reaction). It can therefore be envisaged that many traditionally based organic reactions could be catalysed in bulk aqueous solution.

In our group we have recently demonstrated that the interior voids of a dendrimer can be utilized in a similar manner in which the hydrophobic interior of a micelle can be used to bind and catalyse reactions between hydrophobic guests.[33] In our study, we measured the rate of an aminolysis reaction between the PAMAM dendrimer **14** with 64 terminal amine groups and *p*-nitrophenyl acetate, and compared this rate to that obtained when 64 equivalents of the simpler monomeric amine, *N*-acetylethylenediamine, were used (Fig. 9).

Aminolysis reactions were carried out in buffered water at pH 8.5 and initial rates of 1×10^{-8} M s^{-1} and 4×10^{-10} M s^{-1} were obtained for the dendrimer **14** and *N*-acetylethylenediamine respectively, which corresponds to a 25-fold rate enhancement with **14**. This rate enhancement can be attributed to two

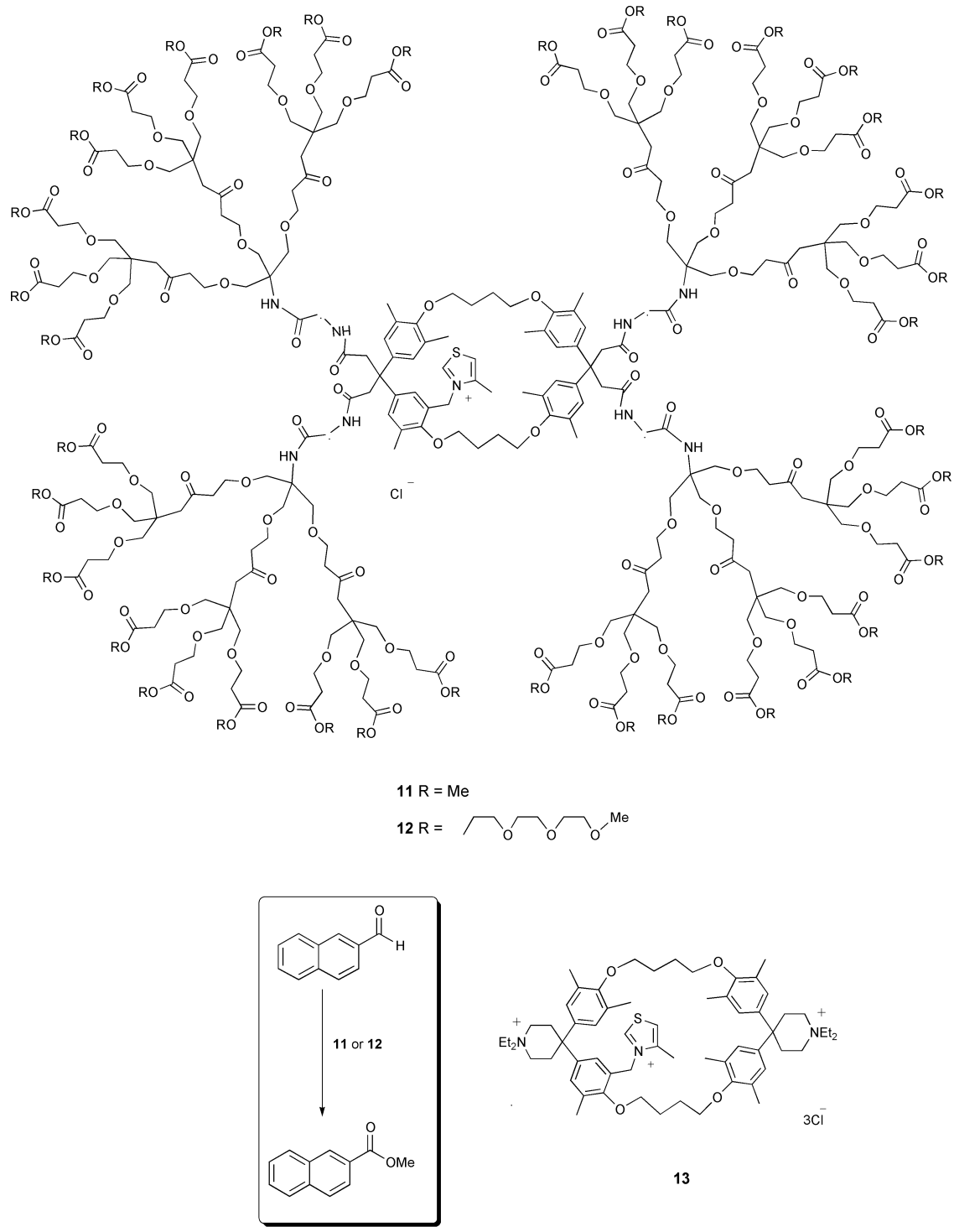


Fig. 8 A biomimetic dendrimer used to catalyse the oxidation of naphthalene-2-carbaldehyde (insert).

factors. Firstly, the dendrimer is acting as a static micelle, and is solubilising the hydrophobic *p*-nitrophenyl acetate within the outer hydrophobic region of the dendrimer. Once bound the *p*-nitrophenyl acetate group is held in close proximity to the reactive amine groups on the surface. This leads to an increase in effective molarity of the two reactive partners (the amine and the *p*-nitrophenyl acetate). This increase in concentration contributes significantly to the increased rate. A second factor involves the internal amide groups. These are able to stabilise the high-energy tetrahedral intermediate as it forms, which lowers the activation barrier and therefore accelerates the reaction (Fig. 10). More recent studies using a series of dendrimers ranging in size from generation 0 to 5 have supported this analysis. Although dendrimer **14** is not a true catalyst (since the dendrimer is irreversibly acylated during the reaction), this example illustrates the point that rate enhancement occurs as a result of the dendrimer's internal environment.

Ford and Pan have also described the synthesis and catalytic properties of a static micellar dendrimer that possesses a neutral hydrophilic periphery and a positively charged interior, **15** (Scheme 4).[34] Accessibility to the interior of dendrimer **15** was studied by investigating the conformational dynamics of the dendrimers arms, in a range of solvents, using ^{13}C NMR T_1 measurements. These studies revealed that a greater rotational freedom existed for the alkyl chain in non-polar solvents, such as chloroform, whereas in polar solvents like methanol, a greater rotational freedom existed for the triethyleneoxymethyl ether chain. This clearly demonstrates that solvent molecules, rather than the dendrimer chains, affect the motion of the outer

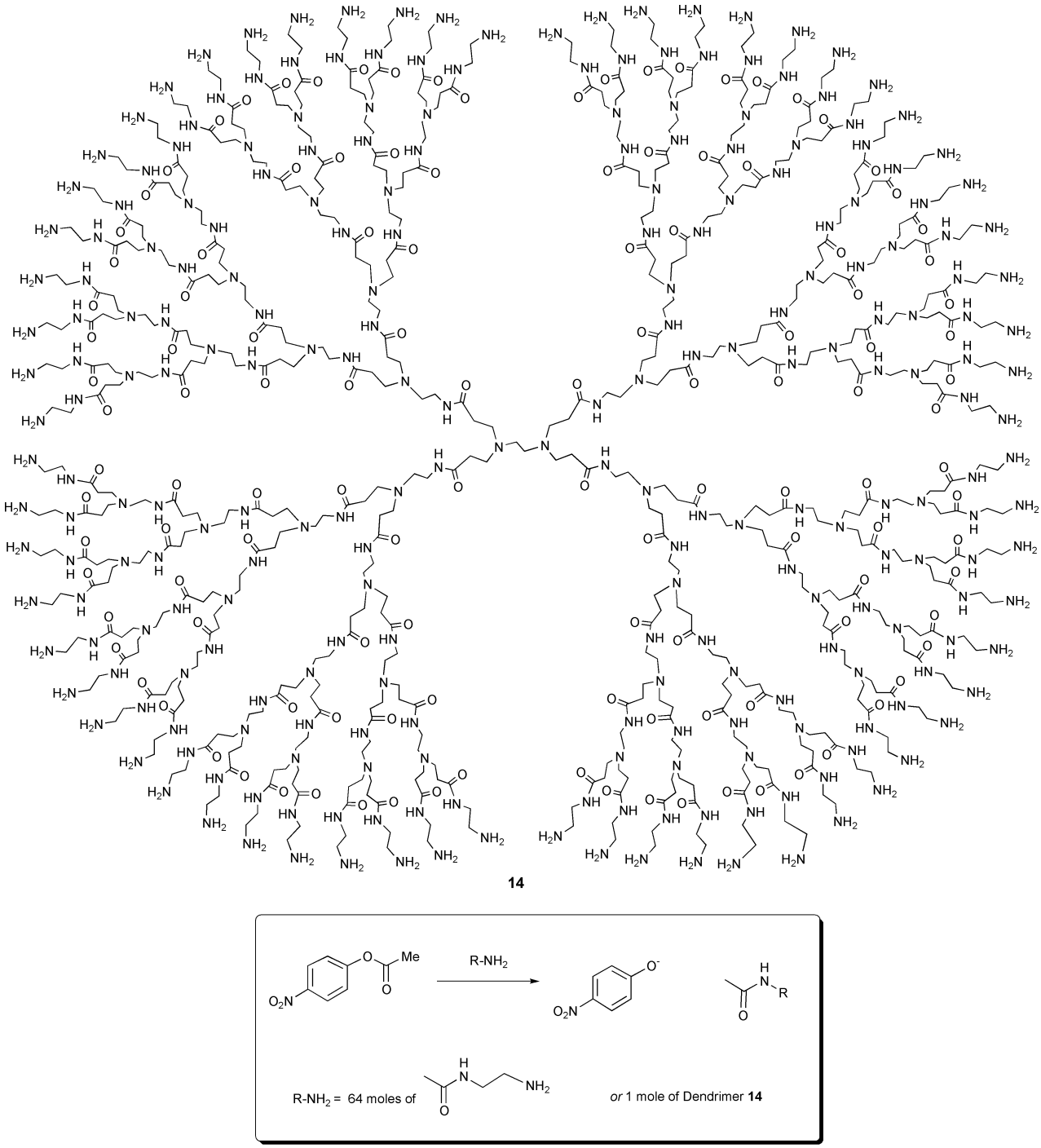


Fig. 9 The PAMAM dendrimer **14** was used to accelerate an aminolysis reaction 25 times faster than an equivalent amine concentration of *N*-acetylethylenediamine (shown in the insert).

arms; this therefore indicates good solvation along the outer chains (*i.e.* solvent access). Ford also demonstrated that inclusion complexes between hydrophobic molecules and the dendrimer **15** could form in water.[35] UV analysis of these complexes showed that the guests were bound in a similar environment to that found in a quaternary ammonium micelle. For example, an aqueous solution of Reichardt's dye and the dendrimer **15** had a λ_{max} at 576 nm, which is almost identical to the λ_{max} obtained with cetyltrimethylammonium micelle.

Having established solvent accessibility and hydrophobic binding, Ford then went on to apply dendrimer **15** as a catalyst for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate (Scheme 5). In water the reaction is slow due to hydrogen bonding between the solvent and the carboxylate anion. However, in the presence of dendrimer **15**, the rate increased nearly 500 fold. This increase in rate is due to substrate binding within the dendrimer where it is less hydrated and in close proximity to the stabilising ammonium group.

Kimura *et al*. recently described the synthesis of dendrimers that possessed 32 water-soluble poly(*N*-isopropylacrylamide) polymer chains on their outer surface.[36] The resulting water-soluble macromolecules were able to bind catalytic Co(II) phthalocyanine groups within their internal voids. This binding is the same as the hydrophobic binding that occurs when micelles 'dissolve' hydrophobic groups within their interiors. These dendrimer phthalocyanine complexes were then successfully employed as aqueous based catalysts for the oxidation of 2-mercaptoethanol. Van den Broeke and co-workers described one particularly interesting application of dendrimers as static micelles.[37] They applied poly(propyleneimine) dendrimers modified with perfluorooctanoyl end groups as novel phase transfer catalysts for reactions involving supercritical carbon

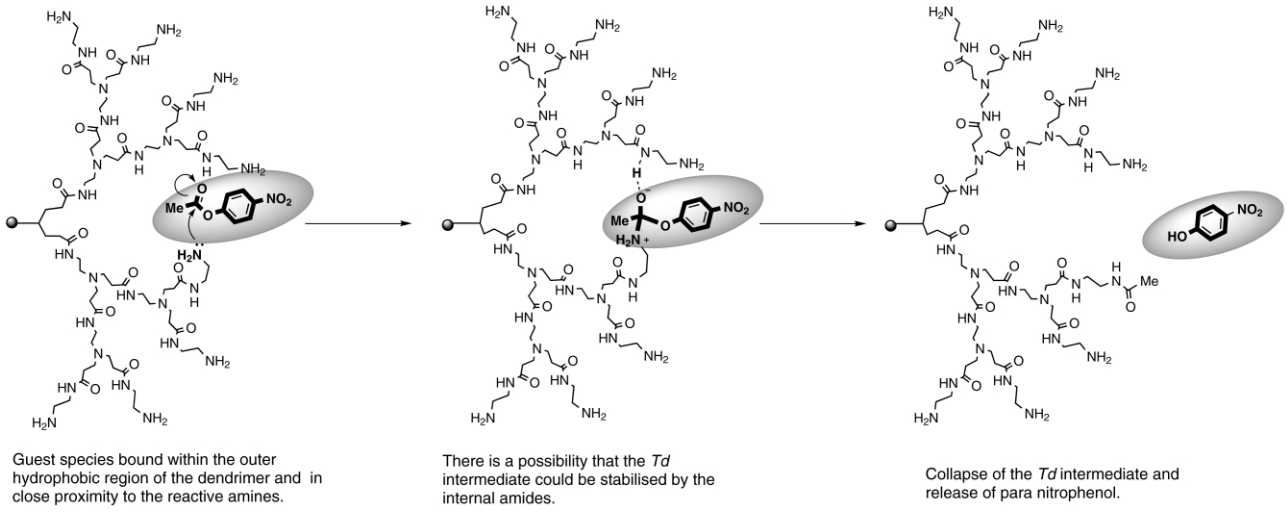
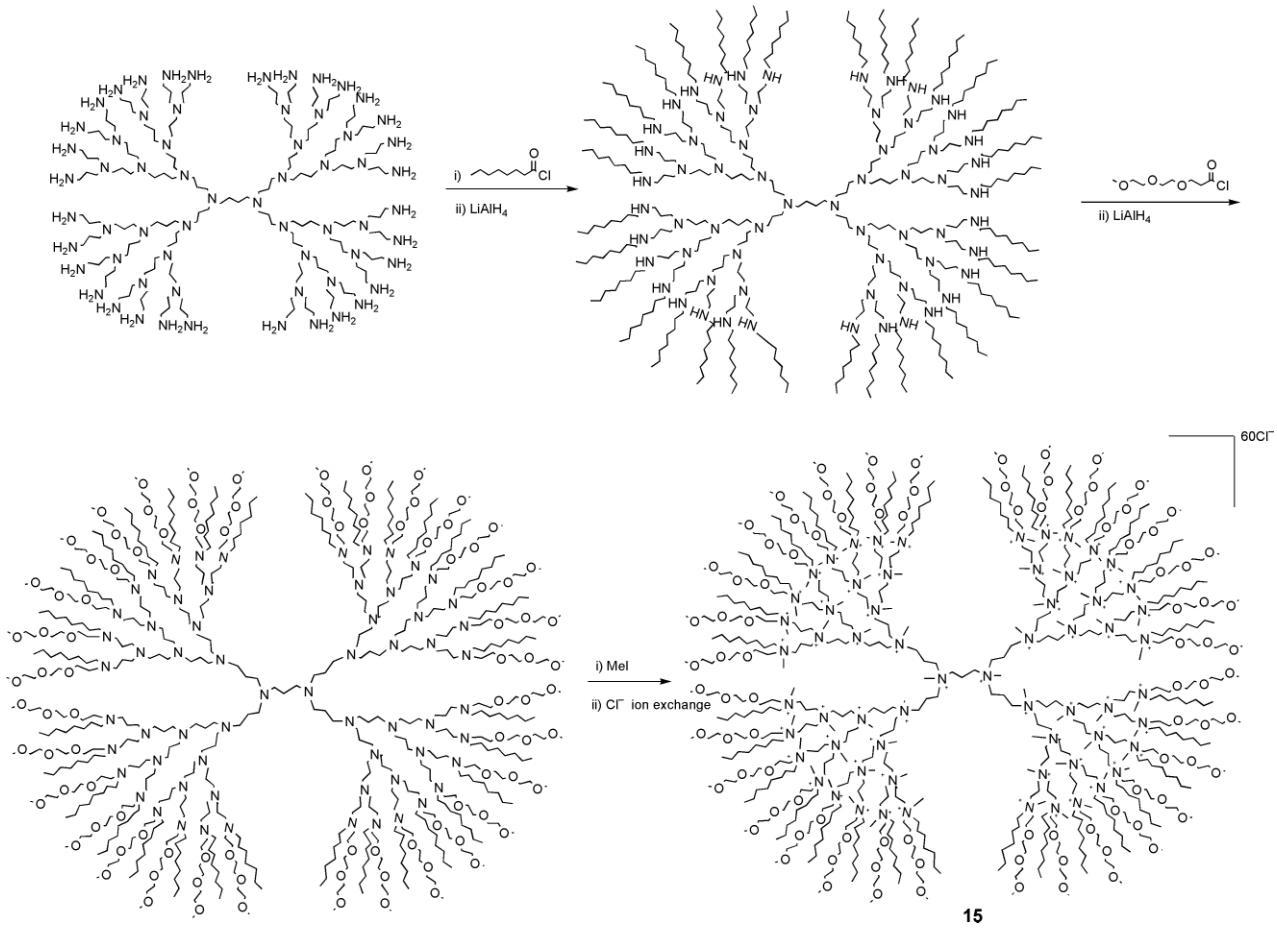
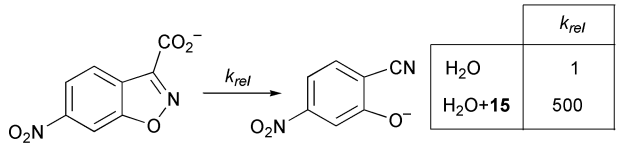


Fig. 10 The three proposed steps involved in the dendrimer assisted aminolysis reaction.



Scheme 4 Synthesis of water-soluble dendrimers with internal ammonium groups capable of stabilising negatively charged groups.



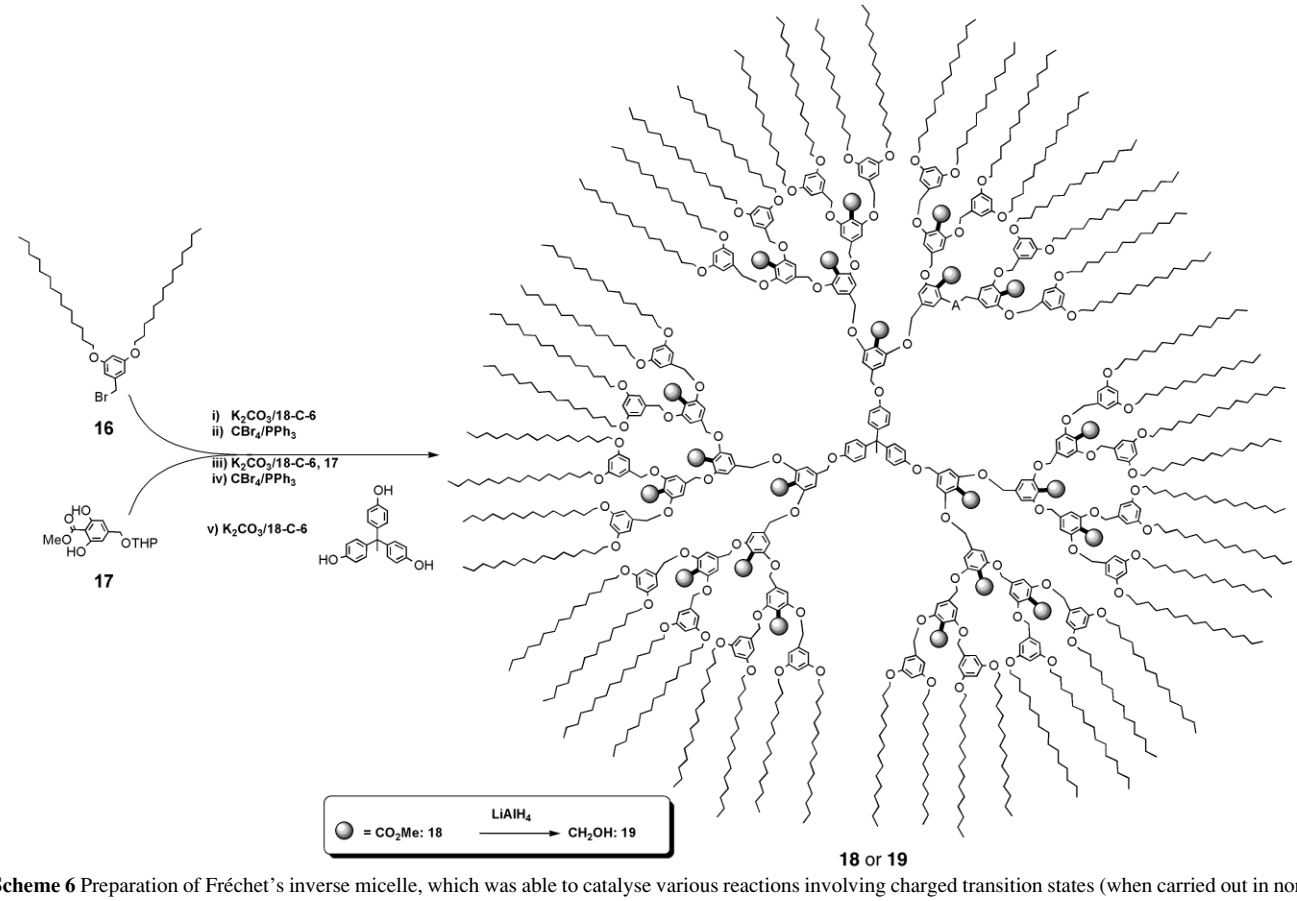
Scheme 5 The decarboxylation of 6-nitrobenzisoxazole-3-carboxylate can be catalysed by dendrimer **15**.

dioxide. One of the main problems with supercritical carbon dioxide is the low solubility of standard phase transfer reagents. In their work they successfully applied perfluorooctanoyl functionalised dendrimers as soluble transfer agents for the S_N2 halogen exchange reaction of benzyl chloride into benzyl bromide, using supercritical carbon dioxide as the solvent (for these experiments the dendrimeric architecture is more akin to that of an inverted micelle). These perfluorooctanoyl functionalised dendrimers speeded up the halogen exchange reaction fivefold, although this is not a huge acceleration, it clearly demonstrates the potential of this approach.

Fréchet and co-workers have described the synthesis of unimolecular dendritic inverted micelles that possesses reactive groups within their interiors.[38,39] These dendrimers (similar to **18** and **19**) were synthesised from the two building blocks **16** and **17** using a standard convergent approach (Scheme 6). The internal ester groups were either left intact or converted to

benzyl alcohol functionalities *via* facile reduction with $LiAlH_4$. These polar groups were included so as to provide a stabilising region within the interior of these dendrimers. The aim being to increase the rate of S_N2 and E1 type reactions, where positively charged transition states, or planar cationic intermediates can be stabilised in polar environments or solvents. Initially, S_N2 reactions involving the alkylation of pyridines with various alkyl halides were studied. Specifically, a faster rate could be observed for the reaction of methyl iodide with pyridine in the presence of the dendritic inverse micelle **18**. For example, a 50% conversion could be observed after 7 days for the dendrimer catalysed reaction, whereas for the control reaction (pyridine, methyl iodide and benzyl chloride), 0% conversion was obtained over the same time. The authors noted that the dendritic reverse micelle **19** with internal hydroxymethyl groups was a far superior catalyst to the parent dendrimer possessing methyl ester moieties. For the E1 elimination reaction, the preparation of alkenes from secondary and tertiary alkyl halides was chosen as the test reaction. The explicit reaction selected was the reaction of *tert*-butyl iodide with sodium hydrogen carbonate (because an acid is generated during the reaction, a scavenger base was added to prevent cleavage of the benzyl ethers). Once again the dendritic inverse micelle was an effective catalyst, however, on this occasion the rate of reaction was much faster than that observed for the S_N2 reaction described above. Complete conversion to the products was achieved after 48 hours, whilst a 0% conversion was observed for the control reaction. After these reactions the dendritic catalyst was recovered and analysed; no fragmentation or degradation could be detected. Once recovered the dendritic catalyst could be re-used many times without any loss in activity or structural integrity, which demonstrates the unique nature of these dendrimeric architectures.

Crooks and his group from the Texas A&M University demonstrated that PAMAM dendrimers terminated with 64 OH groups could be used to encapsulate between 12 and 60 positive platinum ions within their interiors.[40] These noble metal nanoparticles were synthesised by absorbing a known amount of Pt(II) into the dendrimer and then reducing the ions with BH_4^-. UV spectroscopy was used to precisely characterise these particles. The UV spectrum of $PtCl_4^{2-}$ shows a peak at 216 nm. When known amounts of dendrimer are added a new peak appears at 250 nm. This peak increases in intensity as more dendrimer is added, the intensity of this peak is proportional to the number of Pt(II) ions in the range 0–60 and can therefore be used to control the loading. An isosbestic point at 234 nm can also be seen as more dendrimer is added, which is indicative of a ligand exchange reaction (*i.e.* replacement of the chloride ligands with the tertiary nitrogens within the dendrimer). Control experiments confirm that the Pt(II) ions are complexed within the dendrimer, rather than coordinated to the peripheral OH groups. Finally, X-ray photoelectron spectroscopy of the dendrimer–Pt_{60} complex indicates a Pt : Cl ratio of 1 : 3, which suggests that complexation of $PtCl_4^{2-}$ is accomplished by replacement of a single chloride ligand with a tertiary nitrogen. Platinum is the most effective practical catalyst for the reduction of O_2, an important reaction in fuel cells. The authors therefore attempted to apply their dendrimers as catalysts for the electrochemical reduction of O_2. Using a silver electrode coated with metal free dendrimer, and in the presence of O_2, a small current having a peak potential of −150 mV was recorded. However, when silver electrodes modified with the dendrimer–platinum complex (Pt_{60}) were used, a much stronger catalytic effect was recorded and the peak potential shifted to a positive value of 75 mV; this indicates a substantial catalytic effect.[41] Importantly, these results demonstrate that the surface of the



Scheme 6 Preparation of Fréchet's inverse micelle, which was able to catalyse various reactions involving charged transition states (when carried out in non-polar media).

dendrimer is accessible to reactants and can exchange electrons with the underlying electrode surface. Crooks went on to construct other dendrimer nanoparticles using a variety of metals, including Cu, Pd, Ru and Ni. The spectroscopic properties of these metal–dendrimer complexes were similar to those observed for the Pt–dendrimer complexes described above. Of these, the most interesting were the 4th generation palladium based dendrimers, which showed excellent potential as homogeneous and size selective hydrogenation catalysts. The G4–Pd and the larger G8–Pd complexes (Fig. 11) were both

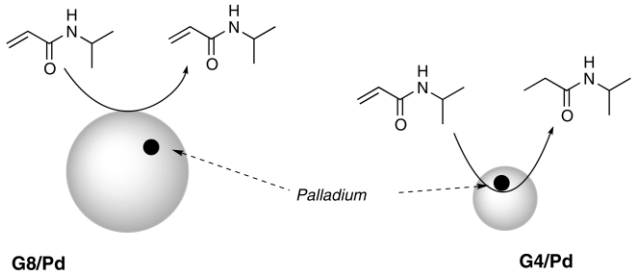


Fig. 11 Size selective dendrimers. The bulky acrylamide is too big to penetrate the congested surface of the large palladium containing G8 dendrimer and therefore no reaction takes place (left). However, there is less congestion at the surface of the smaller G4 dendrimer (right) and the bulky acrylamide group is able reach the catalytic palladium units inside and reduction can take place.

used as catalysts for the reduction of *N*-isopropylacrylamide and allyl alcohol. The G4–Pd complex catalyses both these reactions efficiently, with turnover numbers of 372 and 218 obtained for the reduction of acrylamide and allyl alcohol respectively. These numbers are comparable to those obtained using polymer bound Ru catalysts. However, when the larger G8 dendrimer is used efficiency drops, and turnover numbers of 17 (for the reduction of acrylamide) and 134 (for the reduction of the alcohol) are obtained. Comparison of these values with those obtained using the smaller G4 dendrimer indicates a massive 95% reduction in efficiency for the acrylamide reaction, whilst only a 32% drop was observed for the reduction of the allyl alcohol.

The reason for this difference in efficiency can be ascribed to the size of the substrate (the *N*-isopropylacrylamide or the allyl alcohol) and the steric crowding on the surface of the dendrimer. The catalyst is buried within the dendrimer and the substrate must first penetrate the dendrimer's outer shell before any reactions can take place. Clearly, the larger *N*-isopropylacrylamide unit cannot pass through the outer layer of the dendrimer, however, the smaller allyl alcohol unit is still able to efficiently penetrate the dendrimer's surface and reach the catalytic groups (Fig. 11).[36] Once again this is a good demonstration of how a dendrimer's architecture can be used to good effect to control size and shape selective reactions; such selectivity is not possible using polymer bound catalysts.

4 Conclusions

Most of the examples described in this review demonstrate that profound effects on regio- and stereoselectivity can occur when catalytic groups are embedded within a well defined and controlled dendrimeric environment. Other examples have shown how the physical properties of the interior of a dendrimer can catalyse reactions. In these cases it is the nature of the microenvironment (*i.e.* polar or non-polar), and/or the nature of the incorporated groups that catalyse the reaction. At the moment the industrial and commercial exploitation of dendrimer based catalysis is limited by the difficulty in synthesising these complicated molecules. Nevertheless, there are a number of unique advantages that can only be obtained from dendrimer based catalysis, which may eventually warrant their use in a number of specialized industrial applications. These advantages include the ability to carry out reactions in a controlled microenvironment, therefore allowing the use of bulk solvents that are cheaper and/or environmentally more acceptable (*i.e.* water). Another particularly important advantage of using a dendrimer based approach, is that catalysis occurs homogeneously; reactions are therefore faster and more efficient than those carried out using related polymer methods (dendrimers are easily recovered from reaction media *via* membrane filtration or precipitation).[42] In addition, these catalysts may offer us the best method for obtaining regioisomers that are not normally obtained using conventional catalytic techniques.

5 References

1 P. J. Flory, *J. Am. Chem. Soc*., 1941, **63**, 3096.
2 E. Buhleier, W. Wehner and F. Vögtle, *Synthesis*, 1978, 155.
3 G. R. Newkome, Z. Yao, G. R. Baker, V. K Gupta, P. S. Russo and M. J. Saunders, *J. Am. Chem. Soc*., 1986, **108**, 849.
4 D. A. Tomalia, H. Baker, M. Hall, G. Kallos, S. Martin, J. Roeck, J. Ryder and P. Smith, *Polym. J*., 1985, **108**, 849.
5 C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc*., 1990, **112**, 7638.
6 G. R. Newkome, C. N. Moorefield and F. Vögtle, *Dendritic Molecules*, VCH, Weinheim, 1996.
7 J. F. G. A. Jansen and E. W. Meijer, *J. Am. Chem. Soc*., 1995, **117**, 4417.
8 D. K. Smith and F. Diederich, *Chem. Eur. J*., 1998, **4**, 1353.
9 G. B. Gorman, *Adv. Mater*., 1997, **9**, 1117.
10 G. van Koten and J. T. B. H. Jastrzebski, *J. Mol. Catal. A: Chem*., 1999, **146**, 317–323.
11 G. E. Ooestrom, J. N. H. Reek, P. C. J. Kramer and P. W. N. M. van Leeuwen, *Angew. Chem., Int. Ed*., 2001, **40**, 1828–1849.
12 M. A. Hearshaw, A. T. Hutton, J. R. Moss and K. J. Naidoo, *Adv. Dendritic Macromol*., 1999, **4**, 1–60.
13 D. Astruc and F. Chardac, *Chem. Rev*., 2001, 2991.
14 D. Seebach, A. K. Beck and A. Heckel, *Angew. Chem., Int. Ed*., 2001, **40**, 92–138.
15 L. Gitsov, P. T. Ivanova and J. M. J. Fréchet, *Macromol. Rapid Commun*., 1994, **15**, 387.
16 K. Matyjaszewski, T. Shigemoto and J. M. J. Fréchet, *Macromolecules*, 1996, **29**, 4167.
17 G. E. Oosterom, R. J. van Haaren, J. N. H. Reek, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Chem. Commun*., 1999, 1119.
18 H. Brunner and S. Altmann, *Chem. Ber*., 1994, **127**, 2285.
19 C. C. Mak and H.-F. Chow, *Macromolecules*, 1997, **30**, 1228.
20 C. C. Mak and H.-F. Chow, *J. Org. Chem*., 1997, **62**, 5116.
21 P. Bhyrappa, J. K. Young, J. S. Moore and K. S. Suslick, *J. Am. Chem. Soc*., 1996, **118**, 5708.
22 J. F. J. A. Jansen and E. W. Meijer, *J. Am. Chem. Soc*., 1995, **117**, 4417.
23 P. Bhyrappa, J. K. Young, J. S. Moore and K. S. Suslick, *J. Mol. Catal. A: Chem*., 1996, **113**, 109.
24 M. Kimura, Y. Sugihara, T. Muto, K. Hanabusa, H. Shirai and N. Kobayashi, *Chem. Eur. J*., 1999, **5**, 3495.
25 P. B. Rheiner and D. Seebach, *Chem. Eur. J*., 1999, **5**, 3221.
26 H. Sellner and D. Seebach, *Angew. Chem., Int. Ed*., 1999, **38**, 1918.
27 H. Brunner, *J. Organomet. Chem*., 1995, **500**, 39.
28 D. Seebach, A. K. Beck and A. Heckel, *Angew. Chem., Int. Ed*., 2001, **40**, 92.
29 C. Bolm, N. Derrien and A. Seger, *Synlett*, 1996, 387.
30 C. Bolm, N. Derrien and A. Seger, *Chem. Commun*., 1999, 2087.
31 T. Habicher, F. Diederich and V. Gramlich, *Helv. Chim. Acta*, 1999, **82**, 1066.
32 L. J. Twyman, A. E. Beezer, R. Esfand, M. J. Hardy and J. C. Mitchell, *Tetrahedron Lett*., 1999, **40**, 1743.
33 L. J. Twyman and I. K. Martin, *Tetrahedron Lett*., 2001, **42**, 1123.
34 Y. Pan and W. T. Ford, *Macromolecules*, 2000, **33**, 3731.
35 K. Vassilev, J. Kreider, P. D. Miller and W. T. Ford, *React. Funct. Polym*., 1999, **41**, 205.
36 M. Kimura, M. Kato, T. Muto, K. Hanabusa and H. Shirai, *Macromolecules*, 2000, **33**, 1117.
37 E. L. V. Goetheer, M. W. P. L. Baars, L. J. P. van den Broeke, E. W. Meijer and J. T. F. Keurentjes, *Ind. Eng. Chem. Res*., 2000, **39**, 4634.

38 M. E. Piotti, C. Hawker, J. M. J. Fréchet, F. Rivera, J. Dao and R. Bond, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, 1999, **40**, 410.
39 M. E. Piotti, F. Rivera, R. Bond, C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc*., 1999, **121**, 9471.
40 M. Zhao and R. M. Crooks, *Adv. Mater*., 1999, **11**, 217.
41 M. Zhao and R. M. Crooks, *Angew. Chem., Int. Ed*., 1999, **38**, 364.
42 G. Van Koten and J. T. B. H. Jastrzebski, *J. Mol. Catal. A: Chem*., 1999, 317–323.