Sulfonate Functionalisation of Transition Metal Complexes:

A Versatile Tool Towards Catalyst Recovery

Functionalisatie van Overgangsmetaalcomplexen met Sulfonaatgroepen: een Veelzijdige Strategie voor Hergebruik van Katalysatoren

(met een samenvatting in het Nederlands)

La Fonction Sulfonate: une Stratégie Polyvalente pour le Recyclage de Catalyseurs Basés sur des Métaux de Transition

(avec un résumé en français)

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PREFACE

The development of sustainable approaches to industrial processes is an important aspect of contemporary research in the field of homogeneous catalysis. Inherently, the separation, recuperation, and reuse of homogeneous catalysts have always been an issue. Now more than ever, the reuse of catalysts has become a major concern both from an economic and environmental point of view, and consequently the development of recyclable homogeneous catalysts is a very active field of research. Several conceptual strategies for catalyst recycling have been formulated over the years and several, including strategies for the immobilisation of catalysts on soluble macroscopic supports or for supported aqueous phase catalysis, have met many of the requirements for catalyst recovery and reuse. In particular, the immobilisation of enantioselective homogeneous catalysts on dendritic supports has proven to be a valuable approach to overcome the difficulties in recycling homogeneous catalysts. *Chapter One* of this thesis provides an overview of the different strategies that were investigated over the years to develop enantioselective dendritic catalysts. Besides the excellent activities and selectivities that these dendritic catalysts can achieve, their ease of recovery by means of nanofiltration or precipitation has greatly contributed to their success in synthetic chemistry. Further efforts should, however, be pursued towards the design of dendritic catalysts that continue to show reaction rates comparable to freshly made ones upon their consecutive reuse.

The aim of the work described in this thesis was to develop a methodology for the functionalisation of transition metal complexes with alkyl sulfonate groups. The interest in this moiety is manifold, yet our goal was to utilise this functional group as a handle for catalyst immobilisation and, accordingly, catalyst recovery.

As strong σ-donors and poor π-acceptors, *N*-Heterocyclic Carbene (NHC) ligands have become a very attractive family of ligands in homogeneous catalysis, bringing robustness and high reactivity to the catalyst. The design and synthesis of alkyl-sulfonate

functionalised NHC ligands have been investigated in *Chapter Two*. The electronic and structural properties of these sulfonato-NHC ligands was evaluated through the spectroscopic characterisation of their (NHC)-Rh(I) and (NHC)-Ir(I) complexes.

The affinity of ammonium groups for sulfonate moieties was the foundation to investigate the non-covalent immobilisation of NHC transition metal complexes on octa-cationic dendrimers. *Chapter Three* presents a convenient method for the preparation of metallodendrimers using a one pot procedure, including concomitant transmetallation and immobilisation reactions on NHC-metal complexes. The so-formed gold and rhodium metallodendrimers were used as catalyst in the hydration of alkynes and the hydrosilylation of ketones, respectively. A study of the gold metallodendrimer by means of DOSY NMR did shed further light on the dynamic exchanges during the catalytic reactions and the resulting structural modification of the catalyst. The rhodium metallodendrimer proved to be active in the hydrosilylation of ketones, albeit that an overall lower activity per rhodium centre was observed in comparison to its mononuclear counterpart.

A similar strategy was employed in *Chapter Four* for the synthesis of multimetallic dendrimers consisting of a hexammonium Dendriphos ligand and sulfonate-functionalised transition metal complex building blocks, and assembled via ionic interactions. The resulting homo- or hetero-multimetallic dendrimers comprise up to 13 metal fragments, whose structure was fully corroborated by means of NMR and ESI-MS analysis.

Chapter Five describes the synthesis of arene ruthenium(II) dimers functionalised with an alkyl sulfonate group, which were used in the synthesis of transition metal complexes with inverted solubility profiles. Specifically, the deprotection of the starting sulfonate esters conferred a very high hydrophilicity to the transition metal complexes, which enabled "immobilisation" of the complexes in water. A chiral diamine ligand was coordinated to the ruthenium metal centre and the resulting chiral complex was tested in the asymmetric hydrogen transfer of prochiral ketones in aqueous solvent. The catalyst showed an excellent reactivity and enantioselectivity for this reaction and could be easily recycled several times without loss of stereoselectivity.

Finally, the *Addendum* describes preliminary investigations on the use of a sulfonated (NHC)-Ag(I) complex described in this thesis as an antimicrobial agent. (NHC)-Ag(I)

complexes are commonly used as carbene transfer agent for the synthesis of other (NHC) transition metal complexes as is described in *Chapter Two* and *Chapter Three*. However, due to their electronic properties, these complexes have recently also been proposed to be used as antimicrobial agents, since silver is known for centuries to have bactericidal activity. The alkyl-sulfonate functionalised biscarbene silver complex was found to be active against various strains of bacteria.

CHAPTER ONE

Enantioselective Catalytic Dendrimers

ABSTRACT

The development of chiral transition metal complexes for asymmetric catalysis has seen the concomitant emergence of strategies for their recovery and recyclability in order to render these catalysts economically interesting for industrial applications. In particular, the synthesis of enantioselective metallodendrimers is an interesting approach that combines the advantages of both homogeneous and heterogeneous catalysis without violating the highly active and stereoselective properties of the parent catalyst. In this chapter, a comprehensive overview of the state of the art in enantioselective catalytic dendrimers is given with an emphasis on the catalytic and recyclability properties of these macromolecules.

1.1 Introduction

Because of its applications in organic synthesis, bulk and fine chemicals production, homogeneous catalysis is a very active area of research. In this area, efforts in ligand design and fine-tuning are being pursued to develop catalysts with improved catalytic performance, stability and selectivity. This phenomenon is even more marked in asymmetric catalysis where the use of efficient enantioselective catalysts is still increasing. Unfortunately, these optimised enantioselective catalysts are often expensive due to their sophisticated ligand and precious metal components. It is for this reason that the recovery and/or reuse of enantioselective catalysts are required in many cases to make them industrially attractive.

In order to overcome the difficulties of recovering homogeneous catalysts, several methods have been developed, among which aqueous and fluorous biphasic catalysis, the use of ionic liquids and supercritical carbon dioxide as reaction medium, and catalyst immobilisation on insoluble and soluble supports like dendrimers.[1-4] Dendrimers are large macromolecules with well-defined spherical or globular architectures that offer the advantages of being recoverable by precipitation, nanofiltration or ultrafiltration. In addition, dendrimers display enhanced solubility profiles as compared to other polymeric supporting materials. Figure 1 provides a schematic representation of the two main types of metal complex attachment to dendrimers. Core-functionalised metallodendrimers (right) have a metal complex encapsulated at the centre of the dendrimer. Conversely, peripherally substituted systems (left) incorporate multiple metal species on the outer dendritic surface.

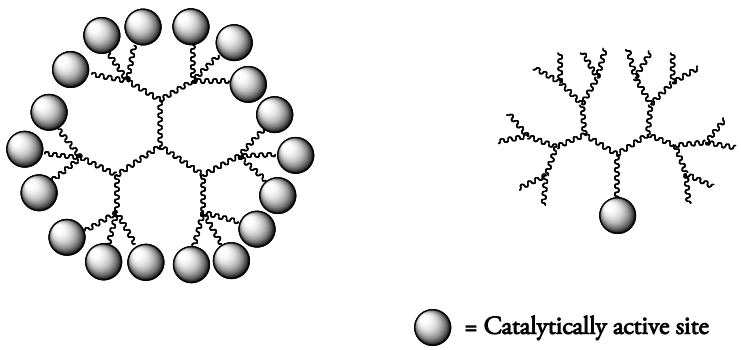

Figure 1. Attachment of catalysts at the periphery or at the core of the dendrimer.

Anchoring a catalyst on a dendritic support is expected to leave the catalytic properties of the homogeneous catalysts unaltered and to potentially improve the activity by modulating the catalyst microenvironment. In this context, the type of dendrimer used for immobilisation plays an important role as it can by its intrinsic nature or its molecular geometry have an impact on the activity of the catalyst.

In this introduction chapter, we present an overview of the work on enantioselective homogeneous catalysts immobilised on dendrimers, where we compile all the typical examples from the literature.[5-7] The overview is organised in distinctive sections based on the position of the metal center, either inside the dendrimer or on its surface. Next, the examples are classified according to the type of ligand that is used, where a difference is made between P-based, N-based, and O-based ligand, as well as between monodentate and bidentate ligands. All examples are discussed in terms of catalytic activity, enantioselectivity, and the comparison between non-immobilised and dendrimer-immobilised catalyst performance. Finally, the possibility to recover and reuse the dendrimer catalysts is discussed in terms of activity and stereoselectivity.

1.2 Dendrimer functionalisation at the core

1.2.1 Phosphorus-based ligands functionalisation

1.2.1.1 Bisphosphine ligands

In 1994 Brunner and co-workers were the first to report the synthesis of a chiral core-functionalised dendrimer.[8] Brunner proposed that the structure of such expanded phosphines (Figure 2) would allow chirality to be induced to the catalyst's pocket thanks to the space filling nature of the molecule and named these new molecules dendrizymes, as this concept is based on the resemblance to enzymatic systems.[9] The activity of the phosphines was tested in the rhodium-catalysed asymmetric hydrogenation of (α)-N-acetamidocinammic acid (see equation in Figure 2). The substrate was efficiently reduced but no significant enantiomeric excess was observed. The use of these ligands in the hydrosilylation of acetophenone and the cyclopropanation of styrene with ethyl diazoacetate did not show chiral induction either. Even though the chirality inducing effect of the 'dendrizymes' was disappointing, these studies represent the onset of many future studies in the field of enantioselective dendrimer catalysis.

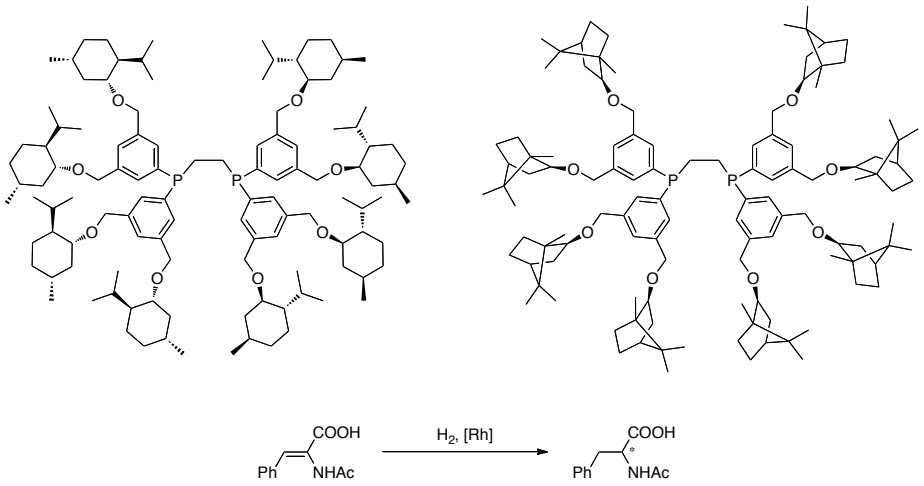

Figure 2. Brunner's example of dendritic phosphines.

In a communication by Fan and Chan *et al.*,[10] the authors report the synthesis of (*R*)-BINAP ligand derivatives decorated with polyether dendrons (so-called Fréchet dendrons) of different generations. The different generations of Fréchet dendrons are thought to increase the steric bulk around the metal center with increasing dendritic generation. The ligands **1-3** were used in the ruthenium catalysed asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)phenyl]acrylic acid (Figure 3) and showed complete conversion after 24 h with good enantioselectivities. Remarkably the enantiomeric excess increased while going from the first to the second generation (ligand **1** to **2**, 91.8 to 92.6 % ee) but with a slightly lower enantioselectivity when the third generation was used (ligand **3**, 91.6 % ee). The rate of the reaction increased as well with the size of the wedges, indicative of a positive dendritic effect. The catalysts were recycled by precipitation and reused without showing any decrease in activity or selectivity.

In a later report the same authors presented the synthesis of similar BINAP-ligands **4-7** bearing an alkyl chain at the periphery to provide specific solubility properties to the catalyst.[11] The ligands were used in the ruthenium-catalysed asymmetric hydrogenation of 2-phenylacrylic acid in an ethanol/hexane mixture that enabled an easy recovery of the catalyst by phase separation upon addition of water. The different catalytic systems displayed full substrate conversions after 4 h and good product enantioselectivities (84-91 % ee). However, upon recycling the catalyst with ligand **5** showed a decreased reactivity already after the first run.

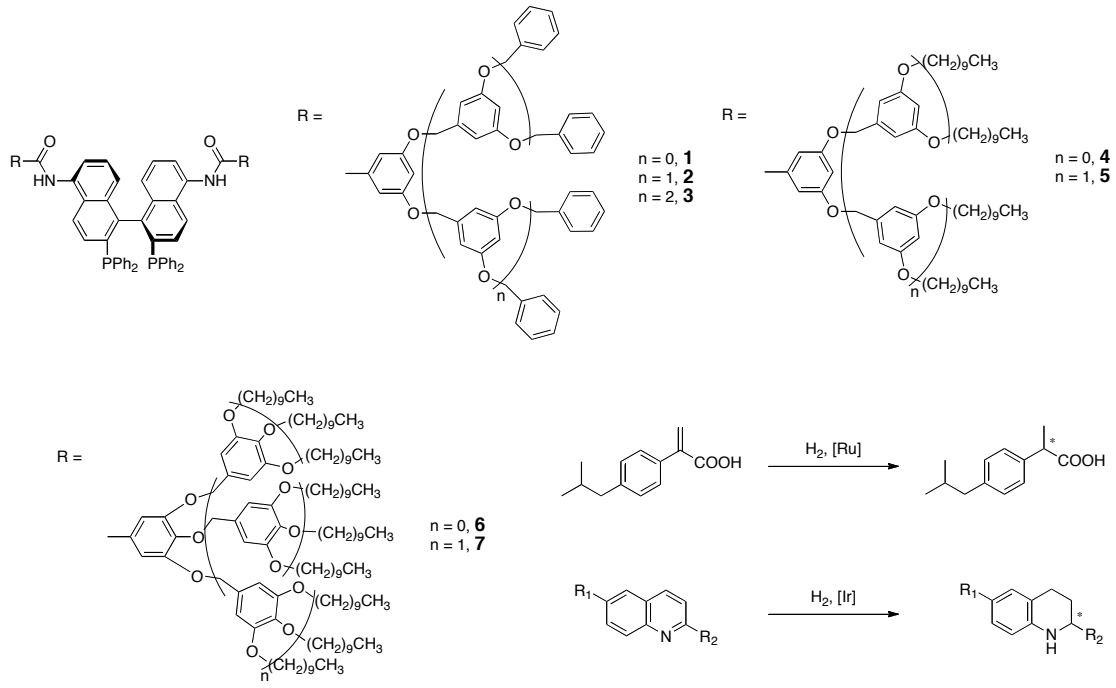

Figure 3. Dendritic BINAP ligands **1-7** developed by Fan's group.

Ligands **1-3** were used in the asymmetric hydrogenation of quinoline derivatives catalysed by an iridium catalyst in a recent paper by Fan *et al.*[12] Full conversion and good enantiomeric excesses (85-90 % ee) were obtained after 1.5 h. The rate of the reaction increased with the dendrimer generation, reaching a TOF for the most hindered ligand **3** never achieved before for this reaction (1580 h^{-1}). This strong dendritic effect could not be explained by the authors, however they suggest that a shielding effect of the dendritic structure around the metal center might contribute to the rate enhancement.

In 2006, Fan *et al.* reported the synthesis of axially chiral dendritic bisphosphines derived from the bridged biphenyl phosphine ligand BIPHEP (Figure 4).[13] The ligands **8-10** were tested in the ruthenium-catalysed hydrogenation of β-ketoesters, in order to check the influence of the dendrimer generation on the catalyst activity. It was found that the size of the dendrimer had a major impact on the enantioselectivity, with the enantiomeric excess decreasing with dendrimer generation. At the same time the catalytic activity did not seem to suffer from the increased steric bulk. The authors could correlate this "dendritic effect" with the dihedral angle of the ligands, as it is known that a larger dihedral angle tends to give reduced enantioselectivity.

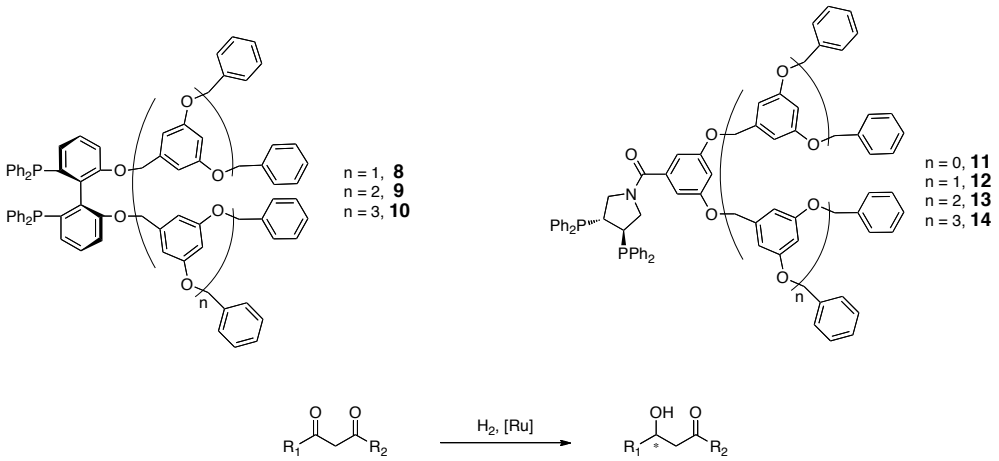

Figure 4. Other chiral bisphosphines dendritic ligands.

Fan and Chan also reported the synthesis of pyrphos ligands **11-14** modified at the focal point with dendritic Fréchet wedges (Figure 4).[14] The activity of the different generations of these chiral bisphosphine ligands was investigated in the rhodium catalysed asymmetric hydrogenation of α-acetamidocinnamic acid (reaction shown in Figure 2). When the reaction was performed in methanol/toluene, a clear decrease in reactivity was observed upon increasing the dendrimer generation (from 91 to 79 % conversion), however without loss of enantioselectivity (96.9 % ee). This effect was particularly flagrant when ligand **14** was used (only 20 % conversion was observed), suggesting a possible encapsulation of the active site and thus a more difficult diffusion of the substrate to the active site. To further assess this hypothesis, a series of dendrimers was synthesised with a more congested catalytic center, which displayed an even more decreased reactivity as well as a decreased enantioselectivity (from 96.9 to 94.6 % ee). The recyclability of ligand **13** showed a rapid decrease of reactivity without loss of enantioselectivity. In an extension of this work, Yi and coworkers reported the synthesis of dendritic ligands similar to **11-14,** decorated with alkyl chains at the periphery.[15] The recovery of these compounds was greatly improved compared to ligand **13** and the activity started to decrease only after the fourth cycle.

1.2.1.2 Monophosphine ligand

In 2008, Seco *et al.* published a report on the synthesis of P-stereogenic dendritic phosphines and their catalytic application in the palladium catalysed asymmetric hydrovinylation of styrene (Figure 5).[16] The authors were expecting an influence of the

specific catalytic environment on the activity and stereoselectivity of the catalyst depending on the dendrimer generation. The steric congestion around the metal center induced by the carbosilane dendrons is indeed believed to enhance the chiral induction by restricting the access to the metal centre. The steric bulk around the metal centre was first evidenced by the formation of an allyl palladium complex displaying diastereotopic protons in ^{1}H NMR, indicative of a high steric hindrance. The catalytic results reflect that increasing the dendrimer generation has a negative influence on the stereoselectivity, the best ee values being obtained with the least hindered ligand **15** (83 %), ligand **16** yielding up to 82 % ee, and only 73 % ee for **17**. The TOF steadily decreased while increasing the steric bulk around the metal centre, suggesting a negative dendritic effect on the activity of the catalyst.

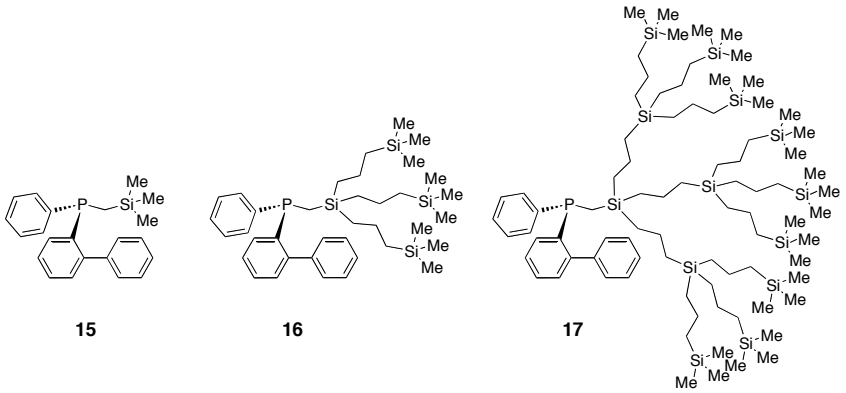

Figure 5. Chiral mono-phosphines **15**-**17** developed by Seco.

In a report by Klein Gebbink and coworkers, a new approach was investigated for the synthesis of chiral dendritic phosphine ligands.[17] In this case the chirality was induced by the presence of chiral Δ-Trisphat anions acting as counter ions for the six permanent positive charges present in the structure of the phosphine ligand (Figure 6). The influence of the steric bulk of ligand **18** on the activity and regioselectivity in the rhodium-catalysed hydroformylation of styrene was investigated with different dendrimer generations, evidencing a decrease of activity and regioselectivity in comparison to PPh_3 (*b:l* ratio is 10 *vs.* 21 for PPh_3). The stereoselectivity of **18** was also studied in the hydrogenation of dimethyl itaconate. In both reactions no significant enantiomeric excess was observed. The authors suggested that the chiral auxiliaries are located too far away from the metal center and that long-range effects are not occurring even when tight ion pairing is favoured in CH_2Cl_2 solution.

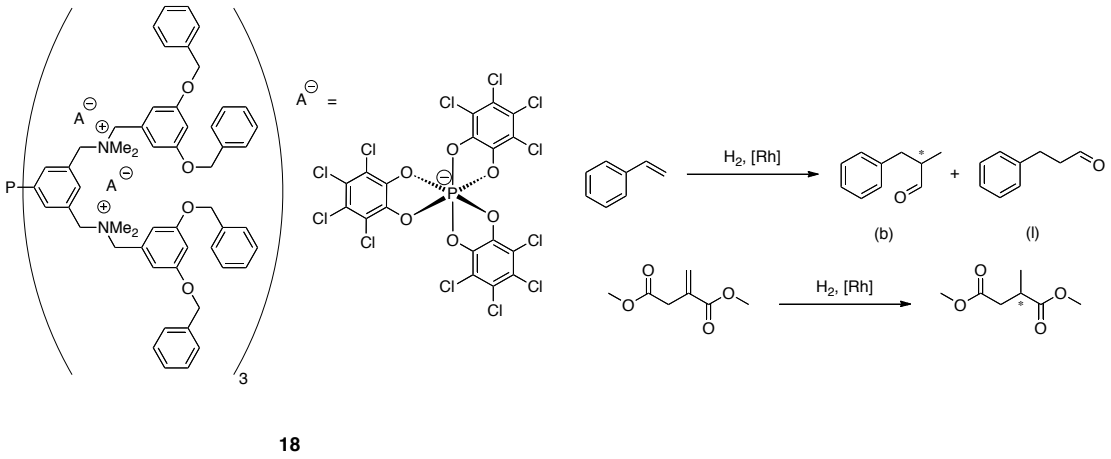

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Figure 6. Chiral *Dendriphos* ligand **18** developed by Klein Gebbink.

1.2.1.3 Phosphite and phosphoramidite based ligand

In 2008, Fan *et al.* reported on the synthesis of chiral monophosphite ligands **19**-**24** assembled by means of complementary hydrogen bonding between a dendritic Hamilton receptor and a barbituric acid derivative functionalised with a monophosphite moiety (Figure 7).[18]

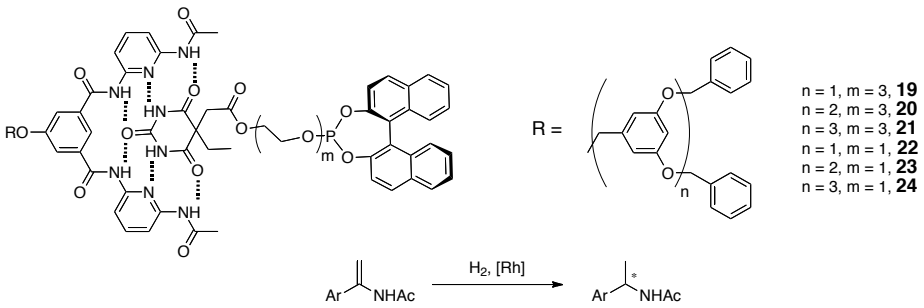

Figure 7. Fan's chiral dendritic phosphite ligand.

These dendritic ligands were employed in the rhodium-catalysed asymmetric hydrogenation of α-phenylenamide and α-dehydroamino acid esters (see reaction in Figure 2). Interestingly, the enantioselectivity in these reactions improved with dendrimers of higher generation (from **19** (80 % ee) to 20 (82 % ee) and from **20** to **21** (86 % ee)). On the other hand, ligands **22**-**24** bearing a shorter linkage displayed a reduced reactivity and enantioselectivity (88 % conversion and 64 % ee) compared to ligands **19**-**21** and the free ligand (100 % yield-93 % ee) in the hydrogenation of α-phenylenamide. It is thought that this negative dendritic effect is induced by the

increased steric bulk. The catalyst formed with ligand **21** was efficiently recycled and did not show deactivation even after five times.

Since the discovery that chiral monodentate ligand based on a BINOL backbone can be as efficient as the reknown bidentate BINAP ligands, a lot of efforts have been pursued in order to fine tune the selectivity and activity of this type of ligands, in particular in the development of chiral phosphoramidite ligands.

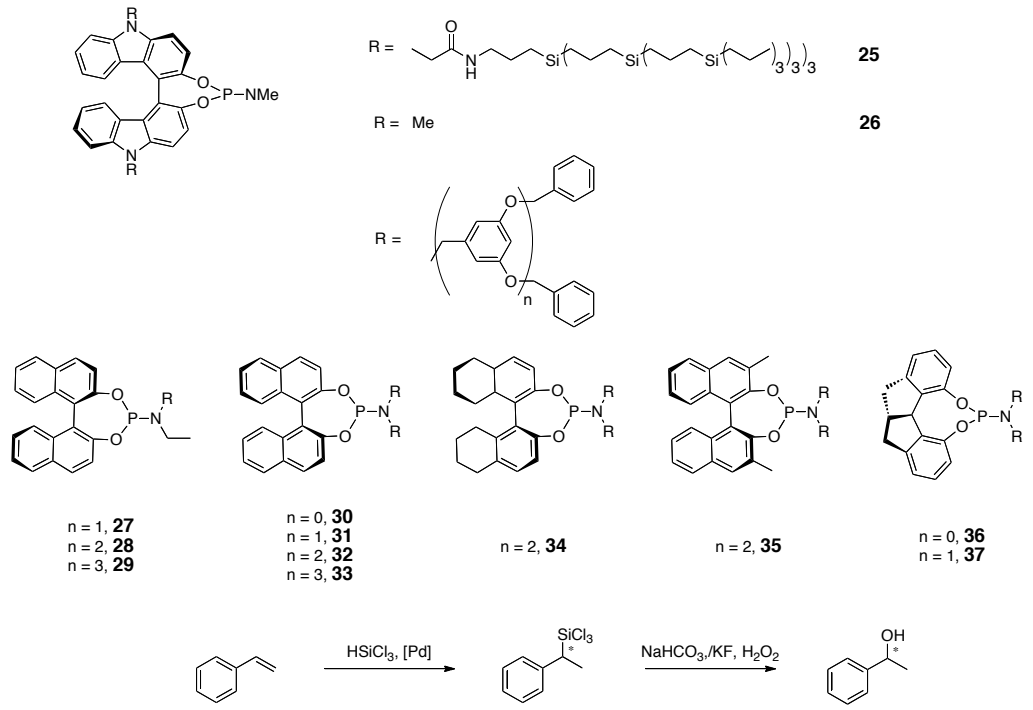

Figure 8. Dendritic phosphoramidite ligands developed by Reek and Fan.

Ligands **25-26**, developed by Reek *et al.*,[19] were the first examples of chiral dendritic phosphoramidites ligands synthesised starting from the BICOL backbone (BICOL = bicarbazolediol, carbazole equivalent of BINOL), which can be readily functionalised with carbosilanes dendritic wedges. These two ligands were tested in the rhodium-catalysed hydrogenation of methyl 2-acetamido cinnamate (see reaction in Figure 2) and compared with the very active and enantioselective MonoPhos ligand.[20] Ligand **25** showed a comparable reactivity to MonoPhos and the non-dendritic ligand **26**, indicating that the steric bulk has no negative effect on the reactivity of the catalysts. Likewise, the enantioselectivity in the reaction was not affected by the attachment of the ligand to the dendritic carbosilane scaffold (ee: **25**, 95 %; **26**, 93 %; MonoPhos, 95 %). Shortly after the report by Reek, Fan *et al.* published several reports on the synthesis of

chiral dendritic phosphoramidites ligands (compounds **27**-**37**, Figure 8) and their use in the rhodium catalysed asymmetric hydrogenation of pro-chiral alkenes (methyl 2-acetamido cinnamate, enamides and dimethyl itaconate, see reactions in Figure 2, 7 and 6 respectively) and palladium-catalysed hydrosilylation of styrene (Figure 8).[21-23] The approach developed involves a functionalisation of the phosphoramidites with Fréchet wedges on the nitrogen atoms, despite the established fact that the substituents on the nitrogen play an important role in the enantioselectivity. In the hydrogenation of methyl 2-acetamido cinnamate, ligands **27**-**29** exhibited a good reactivity and an even higher enantioselectivity than with the MonoPhos ligand (97.5 % vs. 95 % ee). On the other hand, a prolonged reaction time and higher H_2 pressure than with MonoPhos or **25** were required for **27**-**29**. Hydrogenation of α-dehydroamino acid esters and dimethyl itaconate gave satisfying results with similar or better enantioselectivities than MonoPhos (ee: 97.0-97.7 % vs. 93.6 %), with no evidence of the influence of the dendritic wedges on the activity of the catalyst. The modification of the chiral backbone in ligands **30**-**37** had no significant influence on the enantioselectivity in the hydrogenation of methyl 2-acetamido cinnamate with a rhodium catalyst. The authors could demonstrate though that a higher generation of dendrimer improved the stereoselectivity of the catalyst with other α-dehydroamino acid esters and enamides. Recycling experiments with ligand **32** showed a good recyclability of the catalyst by precipitation without loss of reactivity up to the fifth run. Ligands **30**, **32**, **35** and 3,3' substituted derivatives were also tested in the hydrosilylation of styrene.[23] Ligand **30** exhibited a moderate reactivity and enantioselectivity (20 % conversion, 11 % ee), while the introduction of steric bulk by substitution on the 3,3' position, as in **35**, increased the reactivity (>95 % conversion, 43 % ee), in particular with bulkier subsitutents like phenyl, naphtyl or phenanthryl.

1.2.2 Nitrogen based ligand functionalisation

1.2.2.1 Chiral diamines

After the discovery by Noyori *et al.* of the outstanding properties of (*S*, *S*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine, (*S*, *S*)-TsDPEN, as ligand in the ruthenium catalysed asymmetric transfer hydrogenation (ATH),[24] efforts have been pursued towards the synthesis of recyclable dendritic analogues for application in asymmetric catalysis. In 2001, Deng and coworkers reported on the synthesis and application of

chiral dendritic ligands **38**-**41**, which were synthesised by a three steps procedure involving the condensation of Fréchet type dendrons with amine functionalised (*S*, *S*)-TsDPEN (Figure 9).[25] The activity of these different ligand generations was tested in the asymmetric transfer hydrogenation of acetophenone with [RuCl(*p*-cymene)]$_2$ as the metal precursor. No significant influence of the dendrimer generation on the activity and the stereoselectivity of the catalyst was observed compared to those of the monomeric ligand (i.e. 97 % conversion in 20 h with 97.2 % ee vs. 99 % conversion in 20 h and 97.2 % ee). The catalysts formed with ligands **40** and **41** were recovered at the end of the reaction by precipitation and reused up to six times showing a decreasing reactivity, however without loss of enantioselectivity up to the fifth run for **40** and to the sixth run for **41**. In an extension of this work, the same group reported on the synthesis of similar ligand structures and their use in ATH with prochiral ketones, imines and activated alkenes.[26] A good activity and enantioselectivity was exhibited by these dendritic ligands, again very similar to the monomeric ligand.

The Deng group published two further consecutive reports on the development of dendritic ligands for catalytic ATH applications.[27, 28] Ligands **42**-**48** were synthesised by introduction of the dendritic functionality on the phenyl rings of the 1,2 ethylene diamine as opposed to the amino-functionalised vicinal diamines ligands **38**-**41**.[25, 26] The ligands were used in the ATH of the benchmark substrate acetophenone as well as of more challenging substrates like imines and alkenes. The authors noticed a slight influence of the dendrimer generation on the activity of the catalyst in the ATH of acetophenone when the reaction was performed in the presence of [RuCl(*p*-cymene)]$_2$. Ligand **44** showed a first drop in activity, which enhanced upon further increase of the steric bulk, i.e. the dendritic generation, however without loss of enantioselectivity (96.1 %).[28] The same observation was made when the reaction was performed with (*S*)-BINAP-RuCl$_2$, along with a loss of stereoselectivity though (82 % ee).[27] The authors attribute this loss of reactivity to the structure of the ligands, which changes from an extended to a more globular conformation as the steric bulk induced by the dendritic wedge generation increases. In both reports recyclability studies of the catalysts by precipitation gave satisfactory results and the catalysts could be recycled without loss of stereoselectivity up to five times (up to 94 % ee), however with a decrease in activity that can be ascribed to metal leaching as determined by ICP analysis.[28]

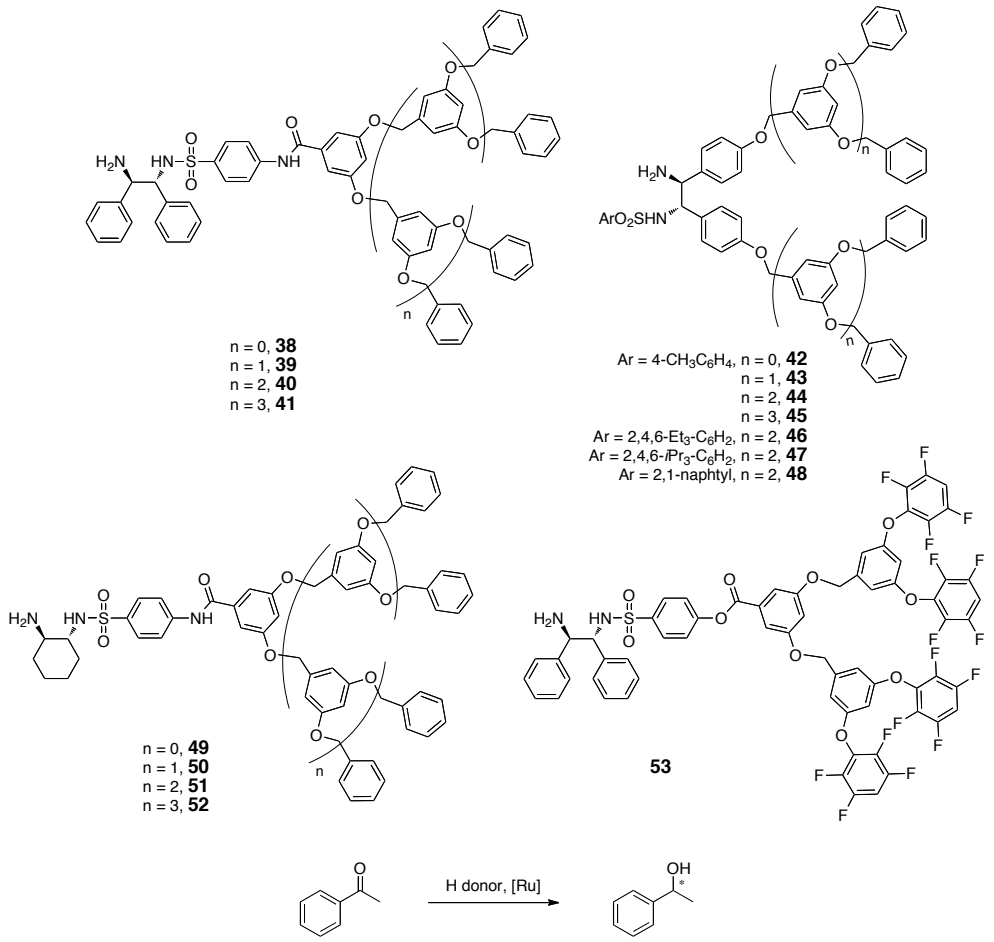

Figure 9. Chiral dendritic diamine ligands.

In their search for chiral catalysts with enhanced recyclability, the group of Deng also developed dendritic ligands **49**-**52** comprising a chiral 1,2-diaminocyclohexane core, which were synthesised in a similar fashion as ligands **38**-**41**.[29] The ligands were tested in the ruthenium and rhodium catalysed ATH of prochiral ketones and showed a decreased reactivity under various reaction conditions when the steric ligand **52** was used. No influence of the dendritic generation was observed; the ligands **49**-**51** performing equally well as the monomeric ligand both in terms of activity and enantioselectivity, with conversions superior to 99 % and ee values ranging from 85-96 % depending on the conditions used for the reaction. The ligands also performed well when the reaction was performed in water with either a ruthenium or rhodium metal precursor. The enantioselectivity using the rhodium metal precursor was higher under these conditions than with ruthenium (96% ee vs. 88% ee). The recyclability of ligand **50** by precipitation from water with hexane showed remarkable results as the catalyst could be reused up to six times in the rhodium catalysed ATH without loss of

stereoselectivity, while only a slight decrease in reactivity was observed. Interestingly, the authors mention that the recyclability of **50** in organic solvents compared to that of **40** or **41** is very limited; the authors noted that the reactivity dropped drastically after the second use with a conversion of 46 % (the first use gave a conversion of 99 %) and only 7 % after the third use.

In 2010, Wang and coworkers reported on the synthesis of a fluorinated TsDPEN derived ligand (**53**) and its application in the ruthenium-catalysed ATH of prochiral ketones in an aqueous medium.[30] Ligand **53**, which was synthesised in a six-step procedure with an overall yield of 65 %, exhibited a good catalytic activity and enantioselectivity (93%) in water. The presence of tetrabutylammonium iodide further improved the enantioselectivity of the reaction to 97 % ee. By a precipitation method, the catalyst could be recovered at the end of the reaction and reused up to an unprecedented 26 times without loss of activity and stereoselectivity. The authors suggested that this exceptional stability of the catalyst (no metal leaching was observed by ICP analysis) can be ascribed to the introduction of fluorine atoms on the ligand, thus conferring robustness to the ligand and to the catalyst.

1.2.2.2 Proline-based ligands

Proline-based ligands represent another important type of easily accessible chiral ligands have been well studied for their application in asymmetric catalysis. Their derivatisation with dendritic wedges has been investigated by several groups, in particular by Zhao and coworkers. In 2005, they reported on the synthesis of ligands **54**-**57** and their application in the enantioselective addition of organozinc reagents to aldehydes (Figure 10).[31] This topic had been already studied by Bolm *et al.* in 1996 using a chiral pyridyl alcohol ligand decorated with Fréchet dendrons.[32] However, no other effect of the dendrimer on the activity of the catalyst was demonstrated and a slight decrease of stereoselectivity of the dendritic ligands compare to the monomeric pyridyl alcohol was found. With the proline-based ligands, very good activities and stereoselectivities were obtained for the reaction of *p*-chlorobenzaldehyde with Et_2Zn in the presence of 20 mol% ligand. Ligands **54**-**56** gave better ee values than the monomeric species (98 % ee vs. 94 % ee), except for the highest generation dendrimer **57** that exhibited a slightly reduced enantioselectivity (91 % ee). Ligand **56** was recovered by precipitation at the end of the reaction and was recycled at least five times without a decrease in activity and

stereoselectivity. Substituted benzaldehydes were efficiently transformed into the corresponding diaryl alcohol with the use of the dendritic proline liagnds. Aliphatic aldehydes, on the other hand, were converted with lower selectivity and lower efficiency (77 % conversion and 65 % ee).

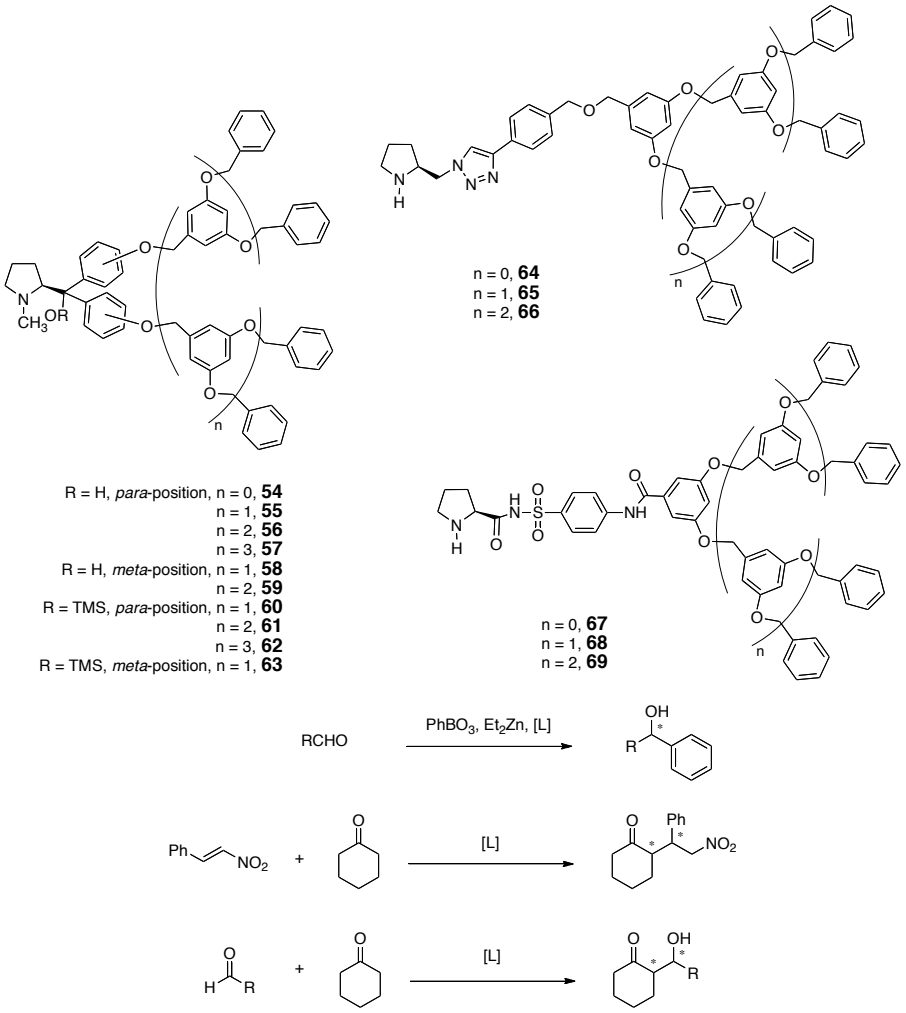

Figure 10. Chiral proline-derived dendritic ligands **54-69**.

The use of ligands **54-57** and **58-59** as asymmetric organocatalysts was further investigated in the enantioselective reduction of ketones,[33] the enantioselective epoxidation of enones[34], and the asymmetric reduction of indolones and tetrolones.[35] The modified counterparts **60-63** were used in the organocatalytic asymmetric Michael addition of aldehydes to nitrostyrenes[36] and in a tandem cyclopropanation/Wittig reaction of α, β-unsaturated aldehydes with arsonium ylides.[37] These ligands showed a great versatility in their application and in all cases exhibited good activities and stereoselectivities (78-99 % ee). Recovery and reuse of these ligands by means of

precipitation was possible without loss of activity up to five consecutive runs. The synthesis of pyrrolidine-derived ligands **64**-**66** decorated with Fréchet dendrons via click chemistry was reported by Gao and coworkers.[38] These organocatalysts were tested in the Michael addition of ketones to nitroolefins and exhibited a good activity (up to 99 % conversion) and stereoselectivity (up to 95 % ee) as well as a good recyclability with a little loss of reactivity after six runs (80 % conversion and 90 % ee).

In 2006, Zhao *et al.* reported the synthesis of proline-derived ligands **67**-**69** functionalised with dendritic wedges and their application as organocatalysts in the asymmetric direct aldol reaction in water (Figure 10).[39] The authors hypothesised that these chiral amphiphilic ligands would assemble in water with the hydrophobic reagents, keeping the reaction site away from water and thus enabling a high asymmetric induction. The aldol reaction proceeded as expected, yielding the product in good yields with high stereo- and enantioselectivity, especially with ligand **68** (*anti/syn* 99:1, 99 % ee). This same ligand was used in a recycling test and could be recycled by precipitation up to four times without a decrease in activity and stereoselectivity.

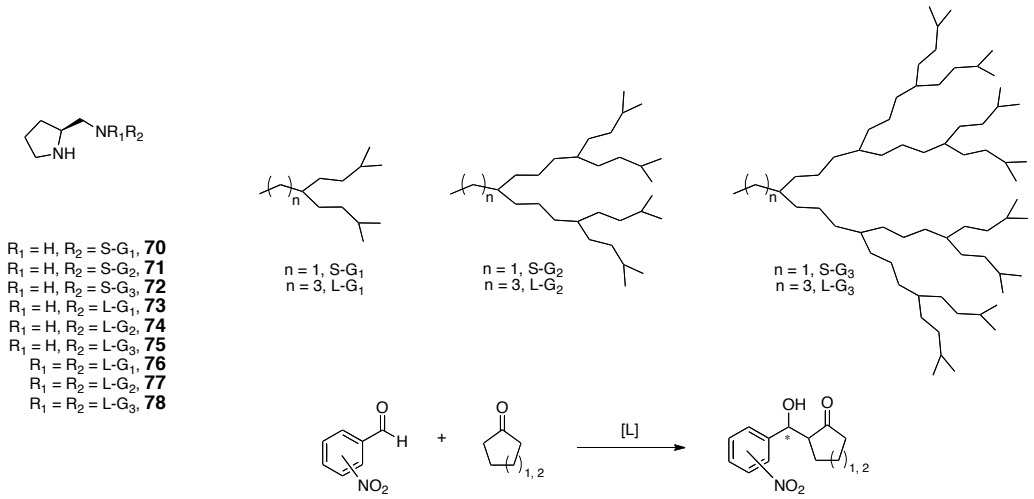

Figure 11. Amphiphilic dendritic organocatalysts.

In a similar approach, Chow *et al.* synthesised three series of proline-derived chiral dendritic organocatalysts for the application in aqueous asymmetric catalysis (Figure 11).[40] The functionalisation of the proline with hydrophobic hydrocarbon dendrons was expected to induce the formation of emulsions in water and to enhance the reactivity and selectivity during the catalytic reaction. The authors found that the properties of these compounds are indeed mainly due to their ability to form emulsions in water and that

compounds **71**, **74**, and **77** are best suited to catalyse asymmetric aldol reactions and nitro-Michael additions, for which they exhibited a good reactivity (78-87 % conversion), diastereoselectivity (*syn*/*anti* > 90:10) and enantioseectivity (80-84 % ee). The authors also showed that the catalysts could be recovered by solvent partitioning with heptane/methanol in which little decrease in reactivity and selectivity was found until the fifth run.

1.2.2.3 Oxazoline based ligands

In 2002, Moberg and coworkers investigated the functionalisation of oxazolines with dendritic wedges.[41] Pyridinooxazolines and bisoxazolines were functionalised with achiral and chiral polyester dendrons to yield the ligands **79**-**89**, which were used in a palladium catalysed allylic alkylation (Figure 12). Ligands **84**-**89** showed a enantioselectivity similar to the parent ligand (76-80 % vs. 79 % ee) and no specific influence of the dendritic wedges on the reaction was observed. On the other hand, ligands **79**-**83** showed a better enantioselectivity than their monomeric counterpart (94 % vs. 79 % ee). The catalytic activity of the bulkier ligand **80** was quite low; i.e. only 10 % of product was obtained after prolonged reaction time. Furthermore, the introduction of a chiral dendron on the oxazoline core moiety (ligands **81**-**82** and **87**-**88**) had no beneficial influence on the enantioselectivity (79 % ee, as for the parent ligand).

Fan *et al.* reported on the synthesis of the chiral bisoxalines ligands **90**-**92** functionalised with different generations of polyether dendrons (Figure 12).[42] In combination with $Cu(OTf)_2$, these ligands were used as Lewis acid catalysts in the enantioselective aldol reaction of benzaldehyde with a silyl enol ether in aqueous solvent. ligands **90**-**92** exhibited a good reactivity (75 % conversion) but moderate stereoselectivity (*syn*/*anti* = 2.1/1 and 60 % ee). A slight increase in product enantioselectivity was observed for higher dendritic generation. The catalysts were recovered at the end of the reaction by precipitation, however the recycled catalyst gave lower yields 40 %) and ee values (30 % ee) compared to the freshly prepared catalysts.
The same approach was pursued by Du and coworkers by the functionalisation of a slightly different bisoxazoline core with Fréchet dendrons (not shown).[43] These ligands were applied in the asymmetric alkylation of indoles with nitroalkenes and showed an activity similar to the monomeric ligand (93-99 % vs. 96 % conversion). The dendritic generation had no significant influence on the enantioselectivity but a slightly decreased

reactivity was observed when the steric bulk was increased (93 % conversion for the bulkier dendritic ligand vs. 99 % for the less hindered dendritic ligand).

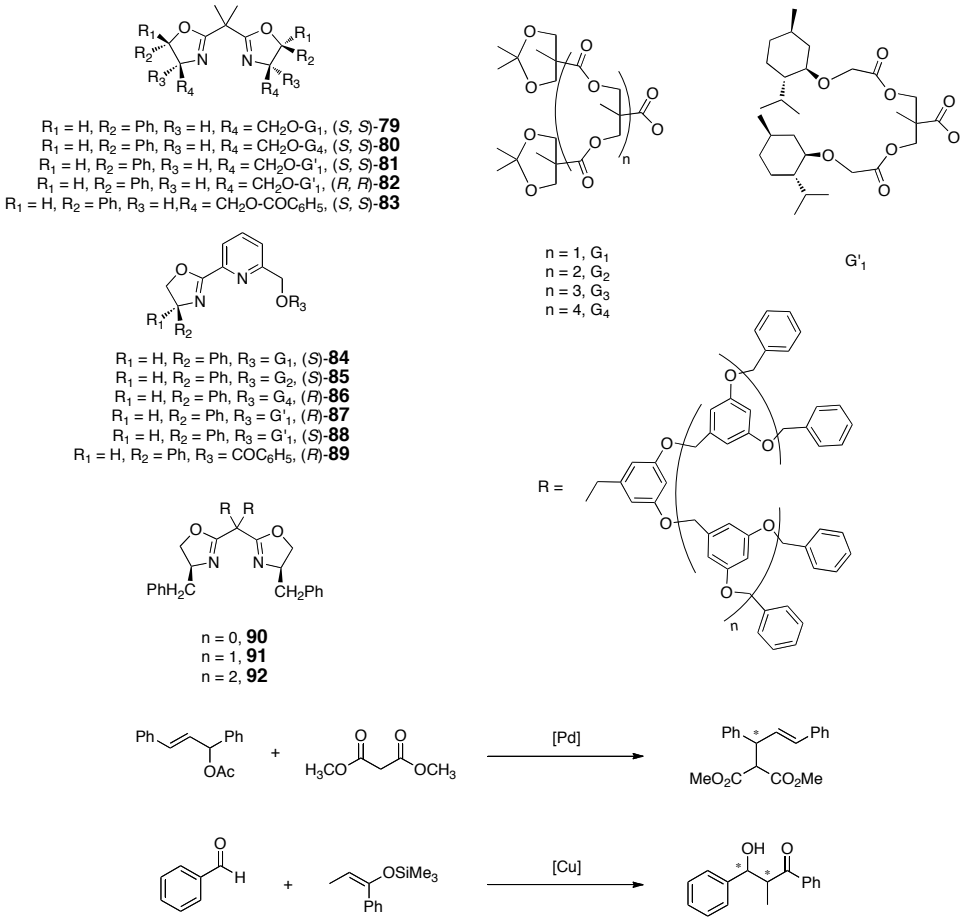

Figure 12. Oxazoline-based dendritic ligands.

1.2.3 Oxygen-based ligands

1.2.3.1 TADDOL-derived ligands

In two consecutive reports from 1999, Seebach *et al.* presented the synthesis of core-functionalised TADDOL dendrimers. [44, 45] The TADDOL center was decorated by four Fréchet dendrons in **93**-**97** and by four chiral polyether dendrons in **98** and **99** (Figure 13). These dendrimers were used as ligands in the synthesis of titanium taddolates, which in turn were employed as catalysts in the asymmetric addition of Et_2Zn to benzaldehydes (see reaction in Figure 10). Compounds **93**-**99** all showed a good stereoselectivity (89-97 % ee) for this reaction, which was found to be comparable to the performance of the monomeric TADDOL ligand (98 % ee). Much like in several of the previous examples, the enantioselectivity dropped slightly upon increase of the dendrimer generation. This

observation was also true for the activity of the catalyst, for which a marked decrease between the activity of **96** and **97** was observed (94 % vs. 47 % conversion, respectively). No influence of the chiral dendrons **98-99** on the stereoselectivity was demonstrated.

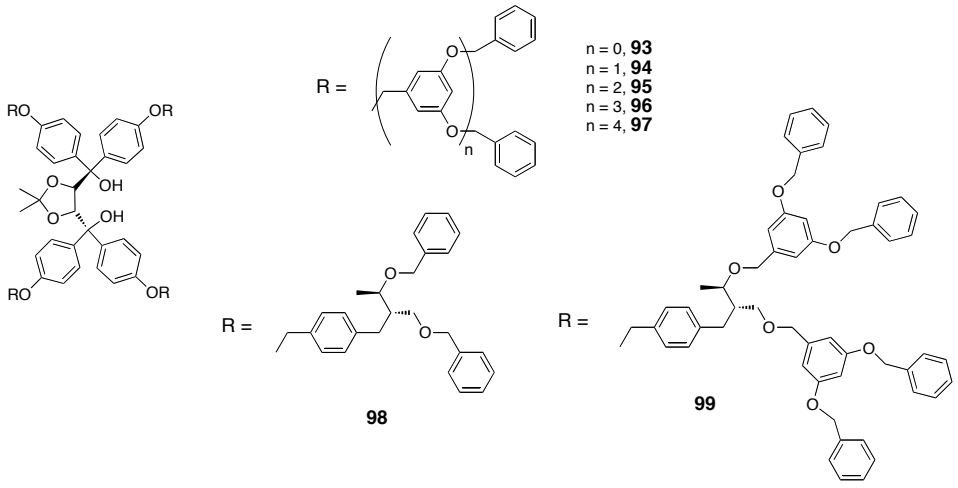

Figure 13. Seebach's TADDOL derived dendrimers.

1.2.3.2 BINOL-derived ligands

In 1998, Yamago and coworkers reported the synthesis of BINOL derivatives decorated with dendritic polyether dendrons (Figure 14).[46] Ligands **100-102** were used in the titanium-catalysed allylation of aldehydes using allyl stannane and showed a poor activity (18-36 % conversion) for this reaction, albeit with good enantioselectivities (88-92 % ee) similar to what was reported for BINOL (89 % ee). This preliminary work on BINOL derivatives paved the way for other groups to further investigate the influence of dendritic wedges on the activity of BINOL-based catalysts.[47, 48] Ligands **100-110** were tested in the titanium catalysed asymmetric addition of diethyl zinc to benzaldehyde (see reaction in Figure 10). All dendritic catalysts were found to be very active for this reaction (>99 % conversion) giving 77 to 87 % ee. Variations in dendron branching point (R_1/R_4 position vs. R_2/R_3 position) or dendrimer size had limited to no influence on the overall catalytic performances in these cases.

Ding et al. described the synthesis of the NOBIN-derived ligands **111-116** bearing Fréchet dendrons (Figure 14).[49] The authors employed these dendritic ligands in titanium-mediated enantioselective Hetero-Diels-Alder reaction (HDA) on Danishefsky's diene with aldehydes. The reactions proceeded with high efficiency and good enantioselectivity (94-97 % ee), though the best results were obtained with ligands

carrying Fréchet wedges that are branched on the meta-position (ligands **114-116**). For ligands **111-113**, the enantioselectivity was influenced by the increasing dendrimer generation, with the enantioselectivity ranging from 92 % for **111** to 75 % ee for **113**. The authors also showed that catalyst **115** could be recycled by precipitation and reused in up to three catalytic runs with a slightly decreasing reactivity (99 to 90 % conversion for the first to the third run).

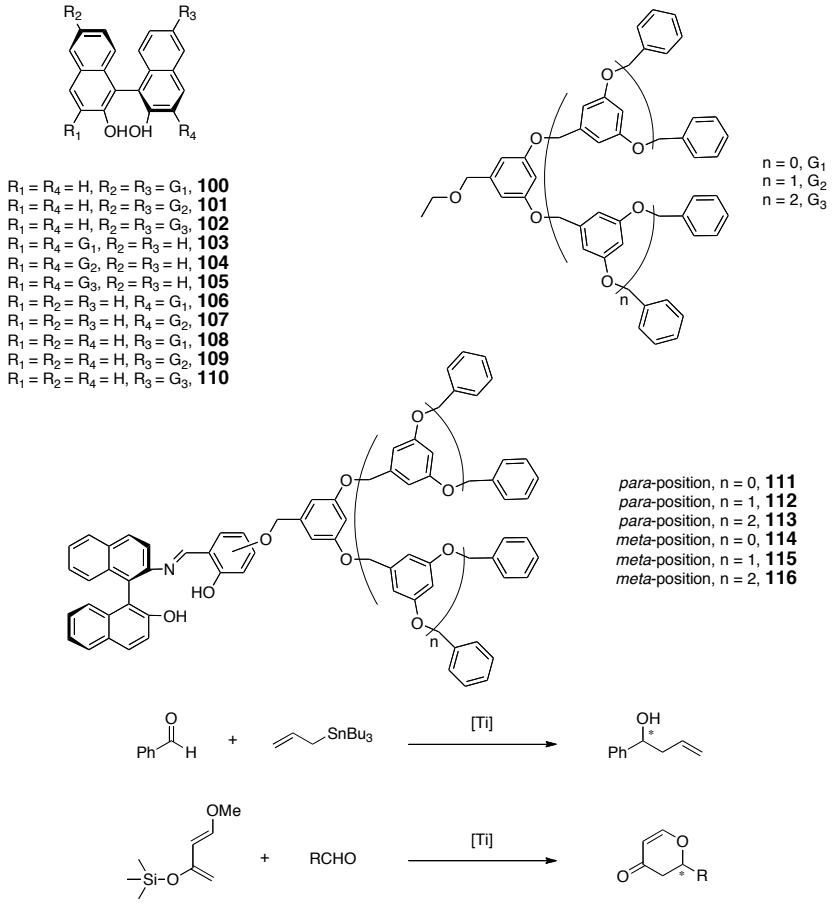

Figure 14. BINOL and NOBIN-derivatived dendritic ligands.

1.2.4 Other functionalisation

The groups of Van Koten and Majera described the synthesis of cinchonidine-derived ammonium salts and their application as phase transfer catalyst (Figure 15).[50] The different ligands **117-123** were used as phase transfer catalyst in the biphasic alkylation of *N*-(diphenylmethylene)glycine isopropyl ester with benzyl bromide. A study on the effect of the different generations of dendrimers on the catalytic activity showed no correlation between the dendrimer size and the enantioselectivity. Overall reaction

rates were found to range between 44-76 % ee without an apparent trend. The recyclability of compounds **119** and **121** were tested by performing the reaction in a membrane dialysis tube, which was used as a "tea bag" in which the reaction could take place and which could be easily transferred to a next reaction batch. Both compounds performed in a similar manner as the fresh catalyst for the first two rounds, while **119** showed a dramatic decrease in the third round for with ee values going from 60 to 40 % ee over a prolonged reaction time.

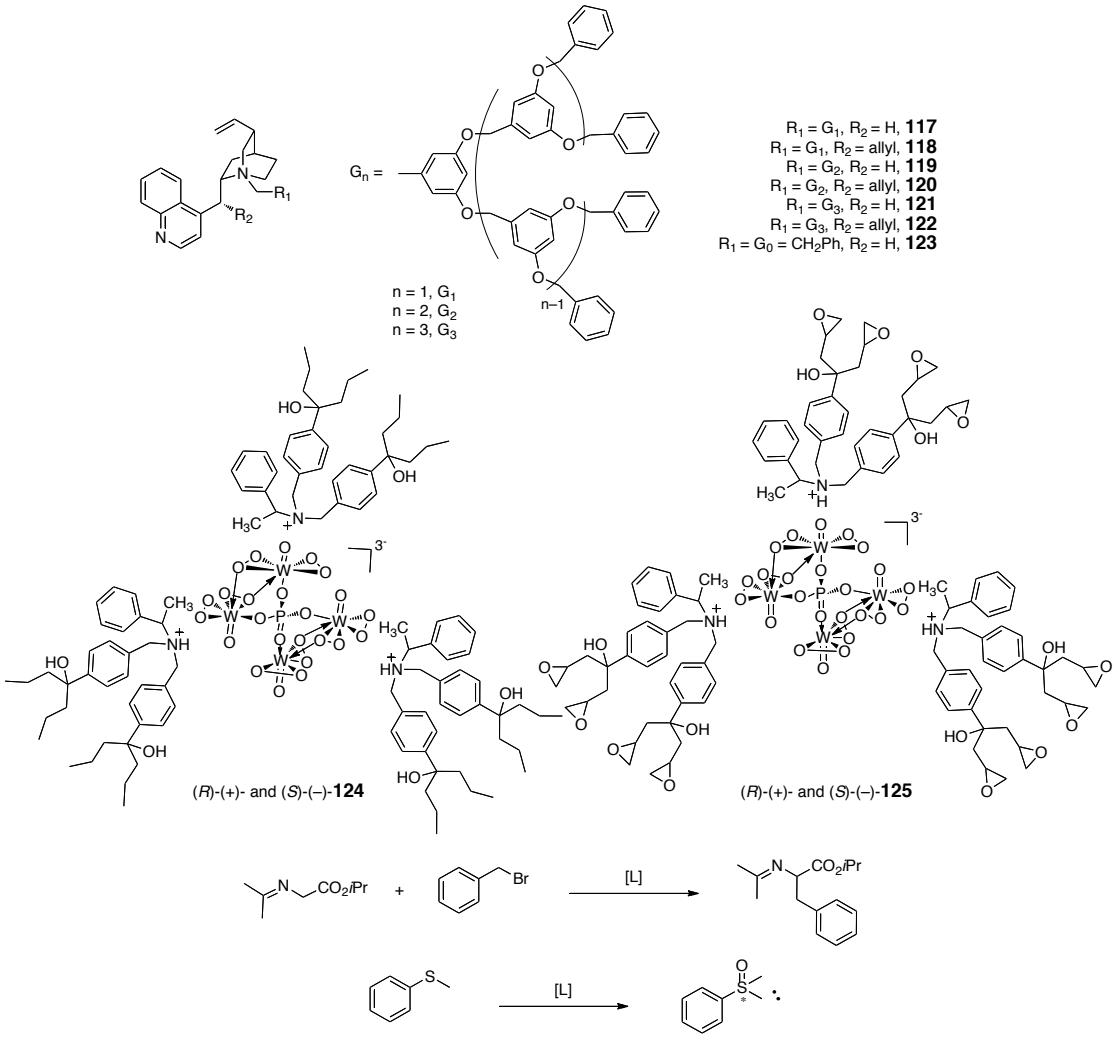

Figure 15. Dendritic cinchonidines and dendritic POM-salts.

Recently, Nlate and coworkers reported on the synthesis of enantiopure polyoxometalates (POM) and their use as catalyst in the asymmetric sulfide oxidation (Figure 15).[51] Their original approach created chiral dendritic POMs through the interaction of three enantiopure ammonium ions with the achiral trianionic POM. The activity of compounds (*R*)-(+)-**125** and (S)-(+)-**125** was tested in the oxidation of

thioanisole with H_2O_2, which resulted in the full oxidation to the corresponding sulfoxide with 14 % ee. The POM-catalysts could be recovered by precicpitation with ether and were reuse up to three times without any noticeable deactivation. Despite the low enantioselectivity of these catalysts, this work showed an unprecedented example of chirality transfer from an organic dendritic counterion to the activity of a non-chiral catalyst.

1.3 Dendrimer functionalisation at the periphery

1.3.1 Phosphorus-based ligands

1.3.1.1 Diphosphines ligands

In a number of papers, Togni and coworkers reported the immobilisation of the chiral ferrocenyl-based diphosphine ligand Josiphos on the periphery of dendrimers (Figure 16).[52] This study represents one of the earlier studies on enantioselective catalysis used peripherally functionalized dendrimers. Up to eight Josiphos ligands were immobilised on different core molecules via linkers that ensured sufficient flexibility of the bisphosphine moieties. These dendritic 'multi-ligands' were tested in the rhodium-catalysed asymmetric hydrogenation of dimethyl itaconate (reaction shown in Figure 6). The parent Josiphos ligand is known to catalyse this reaction with good activity and enantioselectivity. The performances of compounds **126-129** were very similar to the monomeric Josiphos (98.7-98.0 vs. 99 % ee, respectively); the slight decrease in enantioselectivity was correlated to the increasing size of the dendrimer. The recyclability of these catalysts was not investigated, although the authors demonstrated that a commercially available nano-filtration membrane was able to retain the dendrimers.

Next, the same group reported the synthesis of dendrimers **130-131** with different core molecules that could bear up to 16 Josiphos moieties.[53, 54] These dendrimers were also tested in the rhodium catalysed asymmetric hydrogenation of dimethyl itaconate and showed a very similar performance as ligands **126-129** (the product was obtained with 98 % ee), with no significant influence of the dendrimer generation on the performance of the catalyst. When the same dendrimers were used in the palladium-catalysed substitution of allylic acetate with dimethyl malonate (85-92 % yield, 85-91 % ee) or

the rhodium-catalysed hydroboration of styrene (63-97 % yield, 60-68 % ee), no remarkable effect of the nature or generation of the dendrimer could be observed.

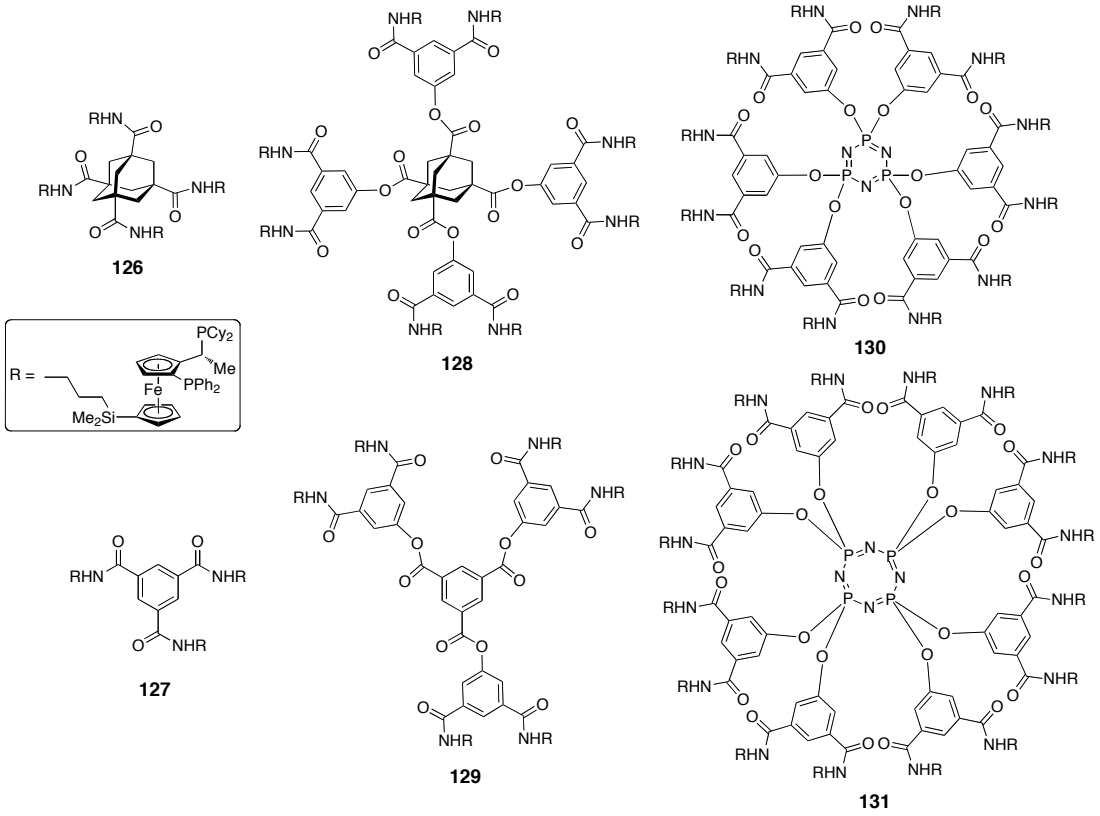

Figure 16. Josiphos dendrimers.

In a report from 2002, Gade *et al.* reported the synthesis of dendrimers bearing chiral diphosphine ligands on their peripheries (Figure 17).[55] Pyrphos-derived ligands were linked to the outer shell of different generations of poly(propyleneimine) (PPI) dendrimers to form dendrimers **132-136** with up to 32 immobilised ligands. The different dendrimers were employed in the rhodium-catalysed asymmetric hydrogenation of Z-methyl-α-acetomidocinammate and dimethyl itaconate (reaction shown in Figure 2 and 6, respectively) for which a clear relationship between the activity and the dendrimer size could be established. The stereoselectivity as well as the activity of the catalysts indeed showed a decrease with increasing dendrimer generation that was explained by the authors as the result of a potentially reduced accessibility of all metal centres. In an extension of this work, Gade *et al.* reported the synthesis of pyrphos ligands immobilised on the periphery of poly(amidoamine) dendrimers (PAMAM) (ligands **137-141**) and their use in the palladium-catalysed allylic amination of 1,3-diphenyl-1-acetoxypropene

with morpholine.[56] The performance of these dendritic catalysts was compared to the monomeric pyrphos ligand and showed a dramatic improvement in the stereoselectivity, with up to 69 % ee for the most selective catalyst vs. 9 % ee for the parent pyrphos. It was shown that the increasing stereoselectivity of the catalysts correlated with the higher dendrimer generation. Interestingly, this positive dendritic effect was also observed when PPI dendrimers **132-136** were used for this reaction, albeit that a lower extent was reached with **136** than with the higher generation **141** (40 vs. 69 % ee).

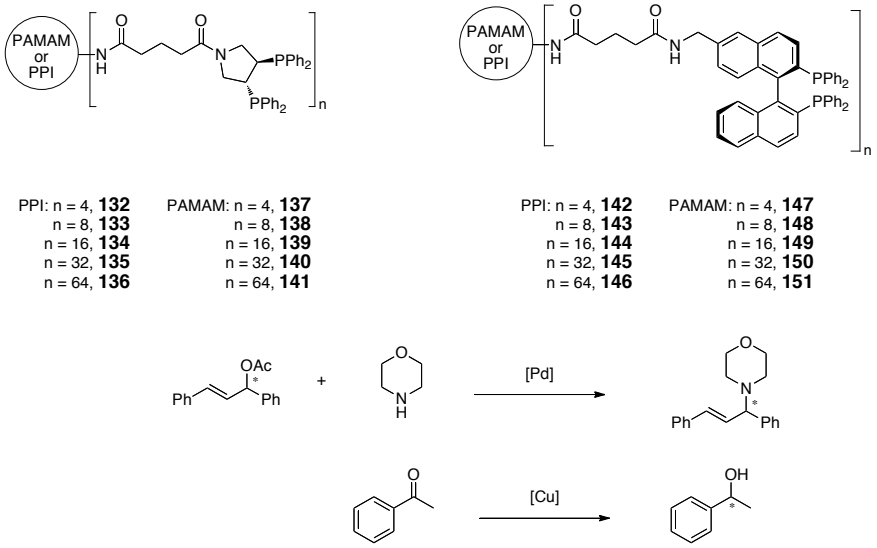

Figure 17. PPI and PAMAM dendrimer immobilised pyrphos (left) and BINAP (right) ligands.

Despite their widespread application in homogeneous asymmetric catalysis, the first example of BINAP ligands immobilised at the periphery of a dendrimer was reported in 2008 by Gade *et al.*[57] The authors immobilised BINAP derivatives on PPI and PAMAM dendrimers of different generations in order to study the influence of the dendritic support on the catalytic performances of the compounds (Figure 17). The latter was studied in the copper-catalysed hydrosilylation of acetophenone, where it was found that the compounds **142-151** performed similarly as the non-immobilised ligand with a slightly better enantioselectivity (90 % ee for BINAP and 93-94 % ee for ligands **142-151**). No evidence for an influence of the type of support or the dendrimer generation was observed for this reaction, indicating that the conversion is controlled by the first coordination sphere around copper and that there is no mutual interaction between individual BINAP moieties that imparts the enantioselectivity.

1.3.1.2 Monophosphines

In a similar approach to the one developed by Togni,[53] Majoral and coworkers reported the synthesis of chiral ferrocenyl P, S ligands immobilised on dendrimers and their use as ligands in asymmetric catalysis (Figure 18).[58] The dendrimers **151-154** were used in the palladium-catalysed allylic substitution reaction with dimethyl malonate (see reaction in Figure 12), where they showed high activities (87-95 % yield) and enantioselectivities (81-93 % ee), similar to the parent catalyst (96 % yield and 93 % ee) and independent of the dendrimer generation. A preliminary study on the recyclability of the dendrimer **154** by means of precipitation revealed a decrease in activity and stereoselectivity.

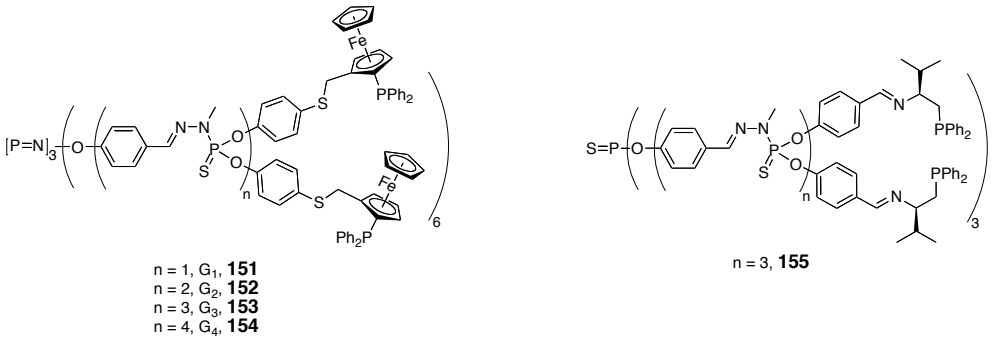

Figure 18. Chiral monophosphine dendrimers.

In 2005, the same group synthesised a new dendrimer functionalised with a P, N-iminophosphine ligand and investigated its use in the palladium catalysed allylic substitution, for which this ligand had previously been applied in a successful manner.[59] Dendrimer **155** showed a good activity and selectivity (87-97 % yield and 84-95 % ee, depending on the reaction conditions), however the recycled catalyst showed a slight decrease in reactivity and enantioselectivity upon reuse.

In 2006, Rossell and coworkers reported the immobilisation of chiral P-stereogenic monophosphine ligands at the periphery of different generations of carbosilane dendrimers (Figure 19).[60] The reaction of compounds **156-161** with $[Pd(\mu\text{-}Cl)(\eta^3\text{-}2\text{-}MeC_3H_4)]_2$ afforded the corresponding palladodendrimers which were employed as catalysts in the hydrovinylation of styrene. The catalysts were found to have a good activity (54-95 % conversion) and good enantioselectivity (up to 79 % ee), which did not seem to depend on the structure of the dendrimer. The nature of the halide

scavenger, and in particular its corresponding counter ion was found to have a large influence on the performances of the catalysts, in particular the use of NaBARF instead of AgBF4 increased the chemoselectivity and enantioselectivity. The same reaction was also performed in supercritical carbon dioxide and the catalytic results were very similar to those obtained in organic solvents.[61]

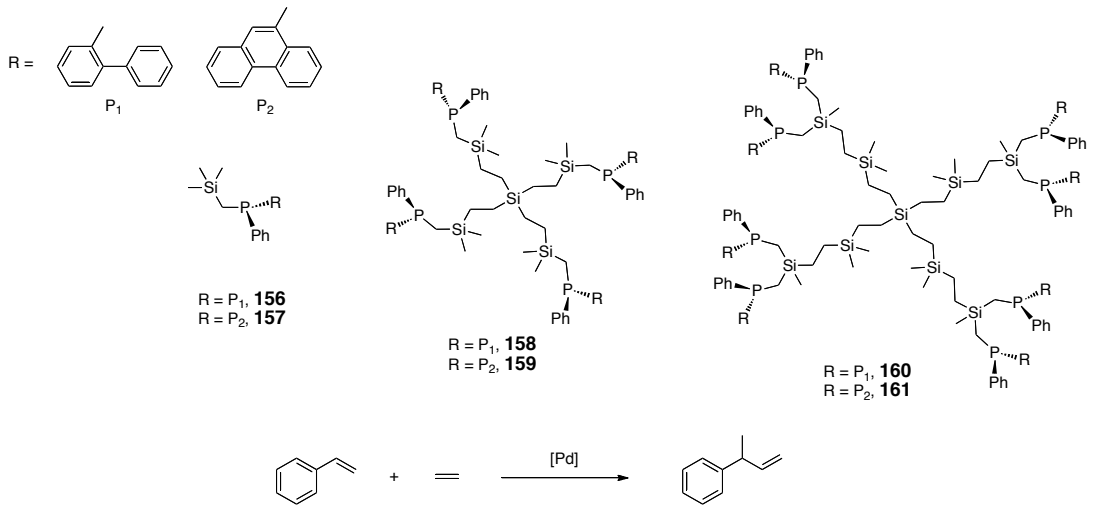

Figure 19. P-stereogenic ligands immobilised on carbosilane dendrimers.

Compounds **156-161** were also applied in the rhodium-catalysed asymmetric hydrogenation of dimethyl itaconate and their activity was found to decrease when increasing the dendrimer generation from **158** to **160** from 94.4 % to 68.6 % conversion, respectively. Furthermore, the catalysts failed to induce any chirality. The ruthenium-catalysed ATH of acetophenone was also tested with the immobilised phosphines. For this reaction, a positive effect of the dendrimer generation on the catalytic activity was observed, albeit without any enantioselectivity.[62, 63]

1.3.2 Nitrogen-based ligands

1.3.2.1 Proline-derived ligand

Kokotos *et al.* reported in 2005 on the immobilisation of trans-4-hydroxyproline on the periphery of different generations of PPI dendrimers (Figure 20).[64] The catalytic performance of dendrimers **162-166** was evaluated in the asymmetric aldol reaction of 4-nitrobenzaldehyde and acetone and compared to the activity of non-immobilised L-proline. The activity of the second generation dendrimer **163** was found to be the most

efficient with a yield and ee value comparable to the parent compound (63 % yield and 69 % ee vs. 61 % yield and 65 % ee). The authors found that with this catalyst the reaction ran faster than with proline itself, however with an actual catalyst loading of 52 mol% of proline (compared to 20 mol% for the free proline). A negative dendritic effect was observed when the higher dendrimers generations **164**-**166** were used, with both the activity and the enantioselectivity decreasing.

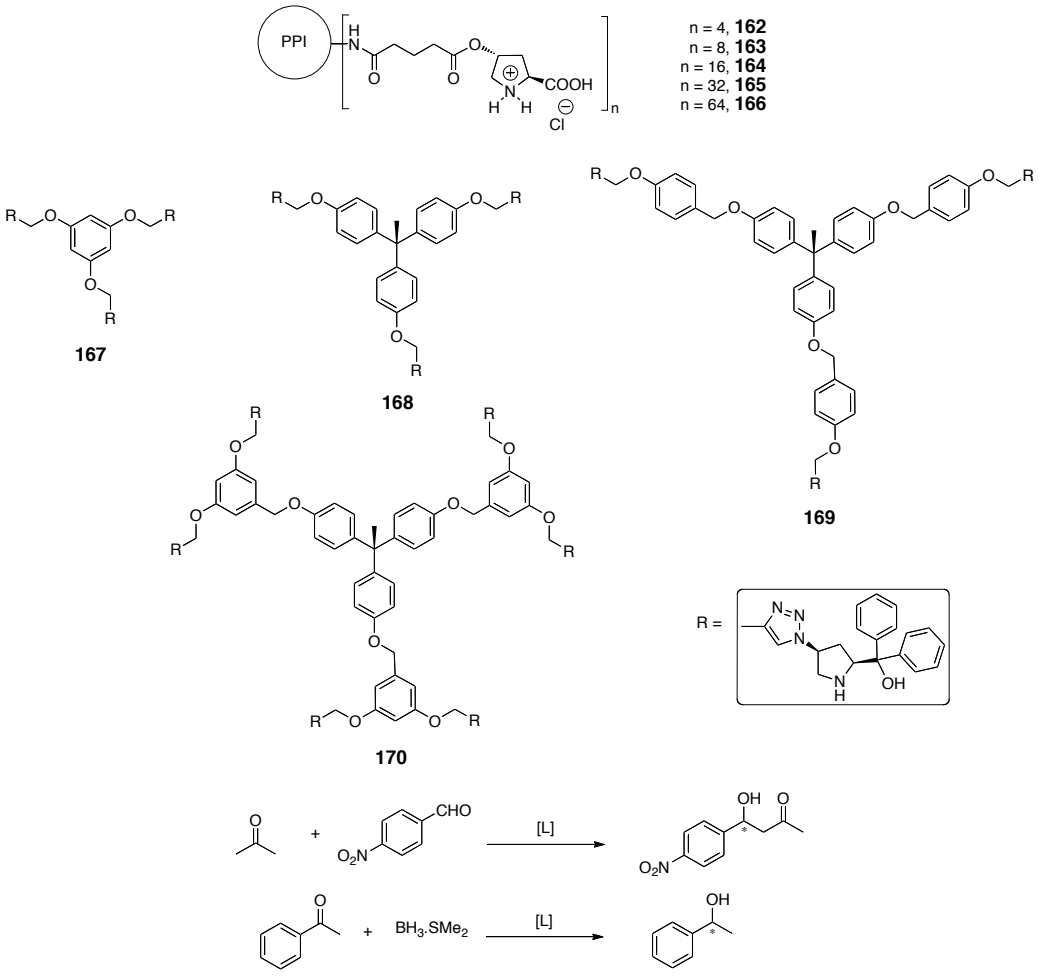

Figure 20. Dendrimer-immobilised proline derivatives.

Diphenylprolinol ligands were used by Liang *et al.* to decorate the periphery of different types of dendrimers with varying core moeities through triazole linkers (Figure 20).[65] Dendrimers **167**-**170** were used as catalysts in the enantioselective borane reduction of ketones where they proved to be excellent catalysts. Dendrimer **170** even showed a higher reactivity than the parent, monomeric diphenylprolinol catalyst

(95 % ee vs. 89 % ee). This hexa-prolinol dendrimer could be recycled by precipitation up to four times without appreciable loss of reactivity or enantioselectivity.

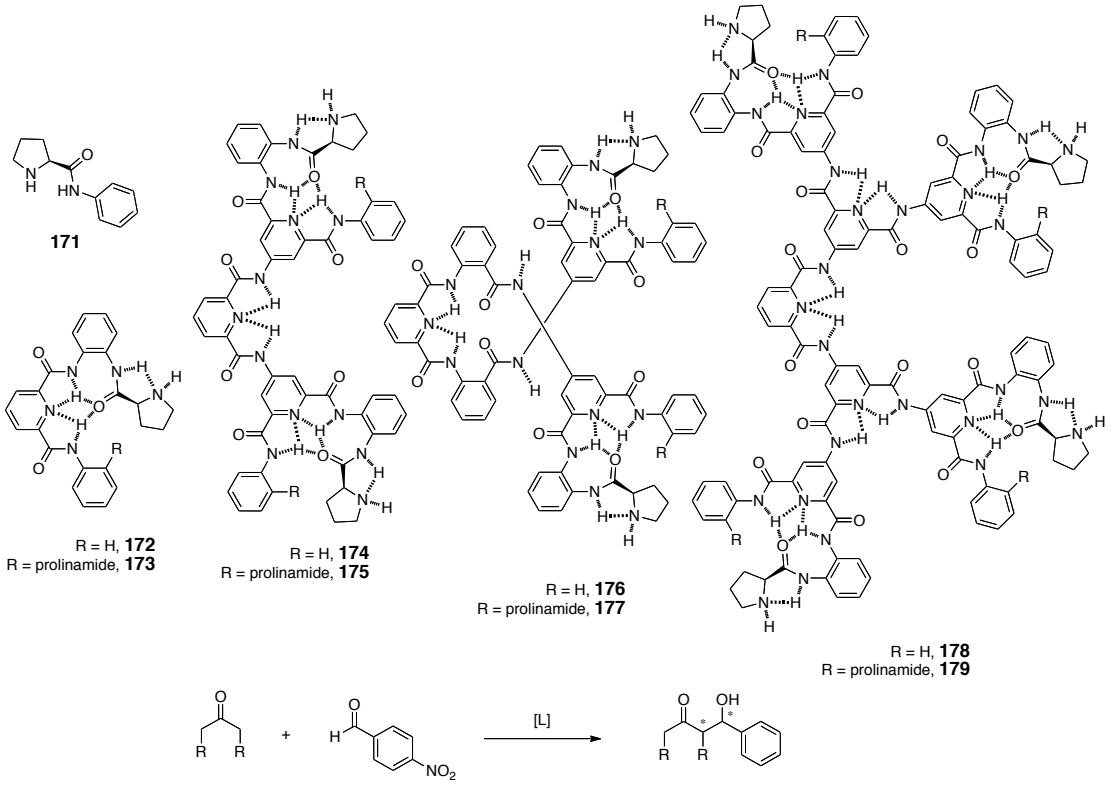

Figure 21. Parquette's proline derived dendrimers.

Parquette *et al.* prepared folded dendritic organocatalysts by attaching proline derivatives to pyridine-2,6-dicarboxyamide branching units and used dendrimers **172-179** in the asymmetric aldol reaction of 4-nitrobenzaldehyde with acyclic and cyclic ketones (Figure 21).[66] A significant increase in selectivity was observed when cyclic or substituted ketones were employed in these reactions (ee: 36-59 % to 63-92 %). Interestingly, the stereoselectivity turned out to be independent of the prolinamide density at the dendrimer periphery, i.e. no significant difference in ee was opbserved between compounds bearing all prolinamides or alternately (compounds with R = H or prolinamide).

1.3.2.2 Amino alcohol derivatives

Another early example in this field comes from Soai and coworkers, who reported the immobilisation of chiral ephedrine ligands on the periphery of different dendritic supports. The so-formed dendrimers were applied in the enantioselective catalytic

addition of dialkylzincs to aldehydes (Figure 22).[67, 68] After some investigations on the addition of dialkylzincs to *N*-diphenylphosphinylimines, the authors concluded on a negative interaction of the PAMAM support and restricted their study to the catalytic activity of dendrimers **182**-**185** with an inert backbone. These catalysts all exhibited a good activity for this reaction with excellent enantioselectivities (32-70 % yield and 77-86 % ee).

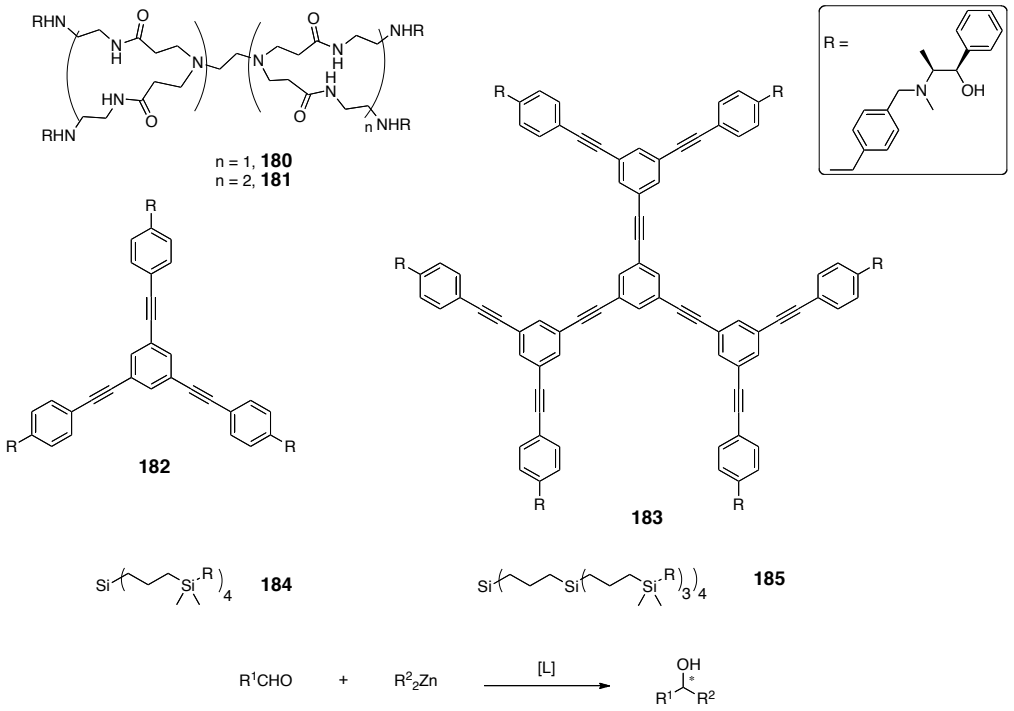

Figure 22. Ephedrine-derived ligand immobilised on different dendritic supports.

Later, Eilbracht and coworkers developed a new synthetic protocol for the preparation of polyamino alcohol dendrimers (not shown).[69] These polyamine-based dendrimers were employed in the ruthenium catalysed ATH reaction of acetophenone. The authors observed in general good to excellent conversions (71-86 %) and moderate to good ee's (22-69 % ee). Upon increase of the dendrimer generation, a negative dendritic effect on the enantioselectivity of the catalysts was observed.

1.3.2.3 Oxazoline derivatives

Recently, Gade et al. immobilised bis and tris(oxazoline)ligands on carbosilane dendrimers and investigated their efficiency as ligand in the copper(II) catalysed α-hydrazination of a β-keto ester as well as in the Henry reaction of 2-nitrobenzaldehyde

with nitromethane (Figure 23).[70] In the first reaction, the performances of ligands **186-194** proved to be excellent with good activities and enantioselectivities (90-99 % ee) obtained with a minimal catalyst loading of 1 mol%.

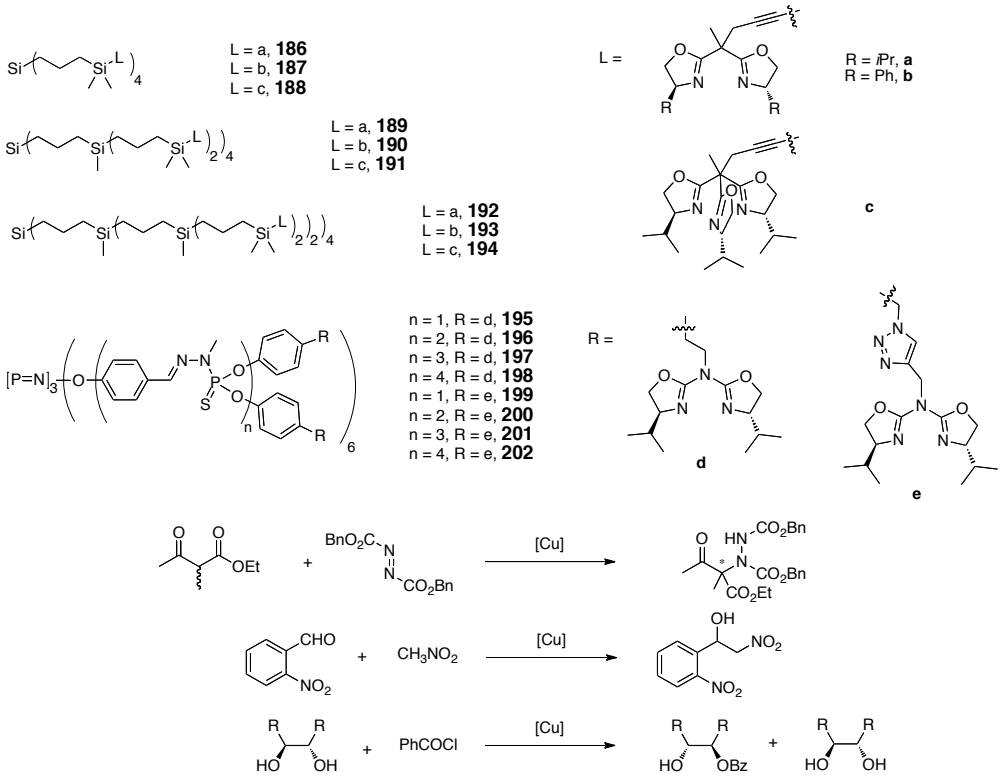

Figure 23. Dendrimer-immobilised bis and tris(oxazoline) ligands.

The activity of ligands **188**, **191** and **194** of the tris(oxazoline) series (type c) displayed a decreased reactivity in the Henry reaction compared to the bis(oxazoline) series (type b, Figure 22), albeit that the enantioseelctivitiy was higher for the tris(oxazolines) (81-84 % ee vs. 52-53 % ee). The latter series exhibited an improved reactivity and enantioselectivity compared to the parent compound, however without correlation with the dendrimer generation. In order to investigate the recyclability of dendrimers **190** and **191**, the catalysts were placed in a "tea-bag", a membrane bag made of dialysis tubing, and this "tea-bag" was placed in a fresh batch of substrates after a certain reaction time. The catalyst activity slightly decreased as well as the enantioselectivity; still displaying 77 % ee after the seventh run for **190** (compared to 82 % ee in the first run), but only 14 % ee for **191** (69 % ee in the first run).

The group of Majoral reported on the synthesis azabis(oxazoline) ligands immobilised on phosphorus-based dendrimers via click chemistry (Figure 23).[71] The

performance of ligands **199-202** was evaluated in the copper-catalysed asymmetric benzoylation of diols and compared with the performance of ligands **195-198**, in order to determine the influence of the backbone on the catalysis, in particular the influence of the triazole ring, which is known to coordinate to copper. The catalytic results indicated a moderate yield (34-41 %) but a good selectivity (73-80 % ee) for **195-198** and did not show any interference of the backbone on the catalytic activity, which suggested a strong affinity of the azabis(oxazoline) ligand for copper. Ligands **199-202** appeared to be less reactive (28-31 % yield) than **195-198,** however with similar enantioselectivities except for the higher generation dendrimer **202** (33 % ee). The recyclability of these catalysts by means of precipitation was also investigated with **200** and did not show any deterioration of the catalytic performances after three successive runs.

1.3.2.4 Other types of ligand

In a report from 2000, Jacobsen *et al.* reported the immobilisation of [Co^{III}(salen)] complexes on the periphery of PAMAM dendrimers (Figure 24).[72] By doing so, the authors were expecting the proximity of the metal centres, induced by the geometry of the dendrimer, to have a positive effect on the reactivity, as it was shown earlier that the mechanism of the asymmetric ring opening (ARO) of epoxides involves a cooperative bimetallic catalysis (i.e. a second order kinetic dependence on [Co^{III}(salen)]). Dendrimers **203-205** were then employed in the hydrolytic kinetic resolution (HKR) of terminal epoxides and showed a dramatic improvement of the reactivity relative to the monomer: at a catalyst loading of 0.025 mol% no conversion was detected for the monomer whereas with 0.027 mol% of **204** 98 % ee was obtained with 50 % conversion. A further increase of the dendrimer generation, and accordingly the number of [Co^{III}(salen)] units per dendrimer, resulted in a decrease in activity/selectivity (relative rate going from 24 to 11 and ee from 42.8 to 39.8 %). According to the authors, this positive dendritic effect may be attributed to higher order productive cooperative interactions between the [Co^{III}(salen)] units, that apparently were most optimal in **204**.

In a continuation of their work on the influence of the dendritic backbone on the ruthenium-catalysed ATH reaction of pro-chiral ketones with chiral diamine ligands (see Figure 9), Deng and coworkers reported the synthesis of dendrimers functionalised at the periphery with TsDPEN-derived ligands (Figure 24).[73] The performance of dendrimers **206-208** was investigated in the ATH of acetophenone and showed good activities

(97 % conversion) and enantioselectivities (97.6 % ee), which were comparable to the monomeric TsDPEN catalyst (>99 % conversion and 97.7 % ee). The scope of the reaction was extended to other ketones and imines and showed in general good activities and enantioselectivities.

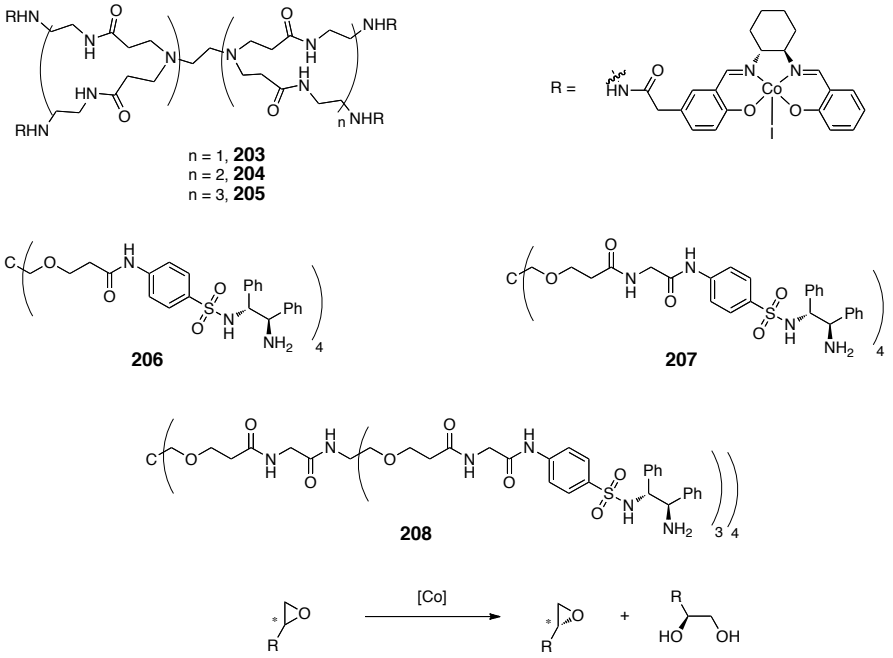

Figure 24. Other types of peripherally immobilised ligands.

1.3.3 Oxygen-based ligands

In 2002, Sasai and coworkers synthesised polyether dendrimers **209**-**210** functionalised with BINOL ligands at their periphery and the corresponding hetero bimetallic catalysts, synthesised by coordination of the BINOL ligands with the complex AlLibis(binaphtoxide) containing aluminium and lithium metals (Figure 25).[74] These dendrimers were used as catalysts in the Michael addition of dibenzylmalonate to 2-cyclohexanone and exhibited a moderate activity (57-63 % yield) but excellent enantioselectivity (91-94 % ee). No evidence of the influence of the dendrimer size could be observed and the catalyst could be reused without showing a diminished activity.

In a report by Ma *et al.*, the synthesis of BINOL ligands **211**-**212** immobilised on Fréchet type dendrimers is presented.[74] Their use as catalysts in the asymmetric addition of diethyl zinc to benzaldehyde (reaction shown in Figure 22) was evaluated and revealed a good activity (94-96 % yield) and enantioselectivity (87.1-89.2 % ee) with all the catalysts in the presence of Ti(O*i*Pr)$_4$, similar to the reactivity of the non-immobilised

BINOL ligand. Interestingly, without addition of $Ti(OiPr)_4$ the dendrimers showed a good activity (75-78 %) and moderate enantioselectivity (40 % ee), though significantly higher than the BINOL ligand (17 % yield and 5.2 % ee). The dendritic catalyst was precipitated at the end of the reaction and reused in two extra catalytic runs without loss of reactivity.

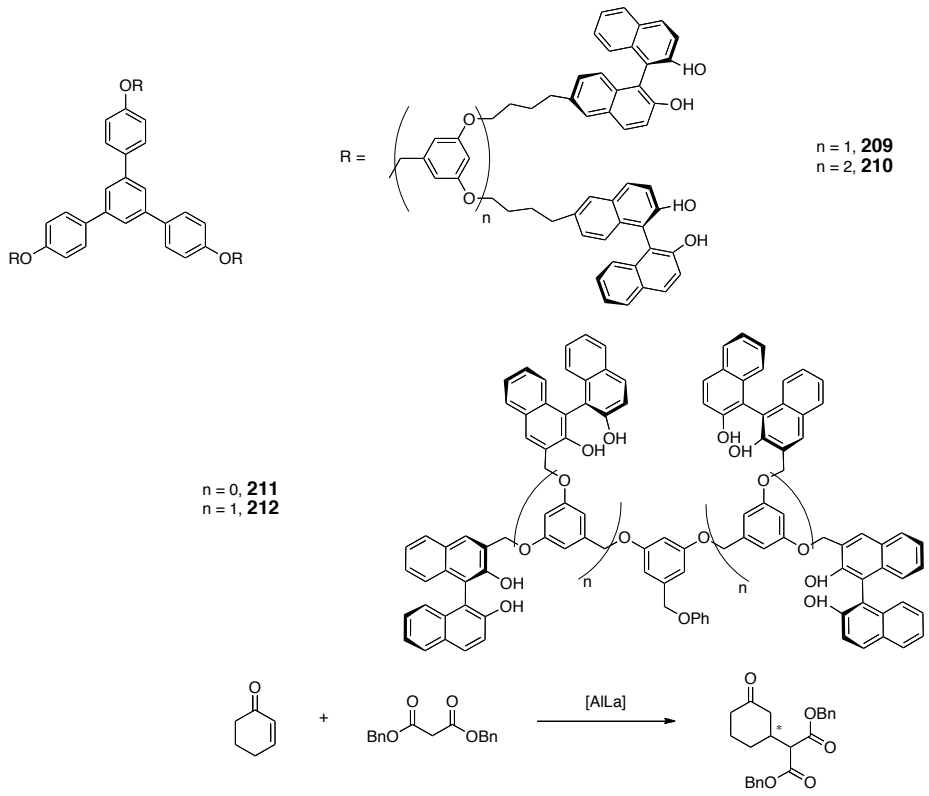

Figure 25. Immobilised BINOL ligands.

1.4 Concluding remarks

After about fifteen years of active research, the field of catalytic metallodendrimers has seen many advances, particularly in enantioselective catalysis. In its early days, the idea of using a chiral dendrimer that would be able to induce chirality to a non-chiral reaction site over a long distance range was a tempting concept. Investigations on this concept were never successful so far and lead to a general consensus that enantioselectivity can only be induced if chirality is present in the close vicinity of the metal centre.

The success of the dendrimer immobilisation approach was validated by the induction of enantiomeric product excesses observed in both types of catalyst attachments, either when the catalyst is shielded by the core of a dendrimer or dendron or when it is more exposed on the surface on a dendrimer. These investigations have also shown that the dendrimer backbone itself can be responsible for an enhancement of the catalytic activity or enantioselectivity through steric congestion induced by increasing dendrimer generation. This dendritic effect is in most cases limited to a size range above which catalytic sites are hardly accessible or where the ever closer proximity of metallic centres interferes with their activity, even though this interference can be constructive in some rare cases. The recyclability of the catalyst via different methods, i.e. precipitation or filtration, gave interesting results, nevertheless little care is taken to really "measure" the activity of the recovered catalyst by for example determining the kinetic profiles upon reuse of the dendritic catalyst, which would be indicative of a truly unaltered catalyst performance.

These findings are now of crucial importance to make progression towards 'the Holy Grail' of homogeneous catalysis: the synthesis of highly (enantio)selective catalysts that are recoverable and reusable without alteration of their performance. In order to reach this goal it is expected that ligand and dendrimer design have to go hand in hand with kinetic studies and advanced separation technology.

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