Freie Universität Berlin

Polymer Supported Organocatalysts for Regio- and Stereoselective Synthesis

DISSERTATION

zur Erlangung des akademischen Grades des
Doktors der Naturwissenschaften (Dr. rer. nat)

eingereicht im Fachbereich Biologie, Chemie und Pharmazie
der Freien Universität Berlin

vorgelegt von

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Juli 2012

Diese Arbeit wurde unter der Anleitung von Prof. Dr. Rainer Haag im Zeitraum von Juni 2007 bis Juni 2012 am Institut für Chemie und Biochemie der Freien Universität Berlin angefertigt.

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Datum der Einreichung: 19.07.2012

Datum der Promotion: 31.08.2012

Acknowledgement

First of all I would like to thank Prof. Dr. Rainer Haag for offering me the opportunity to work on these interesting research projects in his group.

I would like to thank Prof. Dr. Christian Hackenberger for being the co-referee of my PhD thesis.

Further I would like to acknowledge the Tel Aviv University and Prof. Dr. Moshe Portnoy for valuable discussions and supervision while doing research in his group.

I am grateful to my cooperation partners, Dipl.-Chem. Jan Krämer of the research group of Prof. Dr. Berkessel (University of Cologne); Dr. Kerem Goren and Prof. Dr. Moshe Portnoy, Tel Aviv University, and also to Dr. Christian Eidamshaus and André Niermann of the research group of Prof. Dr. Reissig (FU Berlin).

I would like to acknowledge my research students, Karol Nowosinski, Thomas Heinrich, and Sebastian Hackelbusch.

My special thanks go to Cathleen Schlesener for her synthetic support in the lab.

Thanks also go to Jutta Hass for the handling of all the requests and invoices.

I am grateful to Jun.-Prof. Dr. Carl Christoph Tzschucke, Dr. Juliane Keilitz and Dr. Pamela Winchester for proof-reading.

Former and present colleagues from the lab and office, Dr. Ilona Papp, Dr. Wiebke Fischer, Christian Kördel, Haixia Zhou, Min Shan, Dr. Chris Popeney, Markus Hellmund, Emanuel Fleige, Maike Lukowiak, Pradip Dey, Dr. Sumati Bhatia, Dr. Juliane Keilitz, Dr. Venkatakrishnan Thengarai, Dr. Chakib Hajji, Cathleen Schlesener, and Sabrina Nowag are also thanked for a nice working atmosphere and for discussions.

For numerous small and also big discussions I thank Jun.-Prof. Dr. Carl Christoph Tzschucke.

I would like to acknowledge the analytical department of the Institute of Chemistry and Biochemistry for hundreds of NMRs and my frequent request for prolonged ^{31}P measurements for my polymeric catalysts. I am also grateful to Mr. Keller and Ms. Leo for their outstanding cooperativeness.

Last but not least I thank all former and present group members of the group of Prof. Dr. Rainer Haag and special thanks go to the “coffee group” on the first floor.

Finally I would like to thank my beloved parents, my friends, and especially Jens Langner for their never-ending support.

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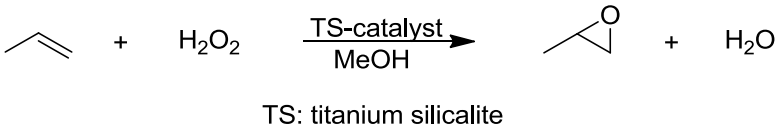
1. Introduction

1.1 General Aspects

The demand for new, sustainable, and "green" methods in organic chemistry has stimulated the scientific community quite significantly. Catalysis is a good tool to achieve this goal, since catalyzed reactions can be performed more efficiently, for instance by reducing the energy consumption, by using less toxic or hazardous (and usually expensive) noble metal catalyst, or by reducing the waste production. An example for the successful application of this concept in industry is the HPPO (hydrogen peroxide to propylene oxide) process, which was recently launched by BASF in Antwerp/Belgium.[1]



Scheme 1. Oxidation of propylene using a powerful "green" catalyst.

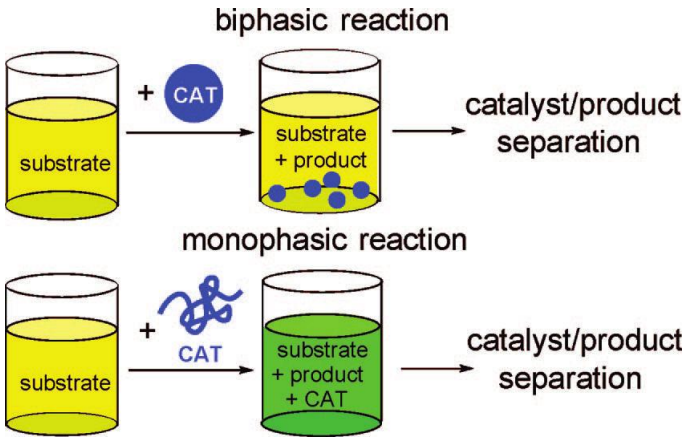
BASF claims that the new noble metal free process operates with up to 35 % less energy consumption and 70-80 % less waste production compared to the previously applied chlorohydrine process.[1]

Besides the achiral products mentioned above, the enantioselective synthesis of fine chemicals is also a growing field. The catalytic synthesis of chiral molecules is relevant because about 40 % of all existing pharmaceutically active compounds are chiral[2] and 56 % of the drugs, which were launched between 2000 and 2004, are single enantiomers.[3] This trend can be attributed to the fact that one enantiomer of a pharmaceutically active compound is usually superior to its antipode regarding biological activity and/or toxicity, and due to economical and environmental reasons this value will increase in the future.[4]

The field of catalysis in industry as well as in academia is mainly dominated by heterogeneous and (noble) metal catalysts[5] with the newly launched area of organocatalysis.[6] The latter term describes a system which increases the rate of a reaction with the help of an organic catalyst that in principle just consists of carbon and hydrogen but may also include sulfur, phosphor and other non-metallic elements found

in organic compounds. Organocatalysts are mostly well-defined small molecules which can be simply modified. In most cases, chirality can be easily introduced. Most organocatalysts are nontoxic, not air and water sensitive, they do not require inert conditions, and metal leaching is not a problem. A disadvantage is that some organocatalysts are needed in stoichiometric amounts. Furthermore, the workup procedure for the separation of the organocatalyst from the product is often tedious. A possible solution for these problems is the immobilization of an organocatalyst on a soluble support, which allows simple separation, recovery and recycling of the catalyst, and better reactivity of the catalyst due to both the high local concentration of the catalyst on the support and cooperative catalytic effects.[7] All these features can help to reduce the amount of catalyst needed.

There are just a few examples for the immobilization of organocatalysts in literature, and in most cases the catalyst has been immobilized on a heterogeneous support, with drawbacks such as lower activity and enantioselectivity. These effects derive from the heterogeneous reaction conditions, which lead to mass transfer problems, unfavorable reaction kinetics, and undefined catalytic sites.[8] In addition, the catalyst loading is usually low (< 1 mmol/g), the insoluble support is sensitive towards mechanical stress, and the catalytically active site can often not be analyzed sufficiently.[5]



Scheme 2. Two different strategies for the use of a catalyst supported on a solid and soluble support, respectively.[9]

The use of a soluble support combines the advantages of homogeneous catalysis and heterogeneous immobilization (Scheme 2). The immobilization on a soluble support allows reaction under homogeneous conditions, which usually gives results comparable to the non-supported analog.[10] A further application of such systems is possible in continuous flow reactors.[11]

1.2 Immobilization Approaches

The immobilization of homogeneous catalysts can be achieved by numerous approaches including covalent attachment, adsorption or ion-pair formation, encapsulation or entrapment.[12] A schematic representation is shown in Figure 1.

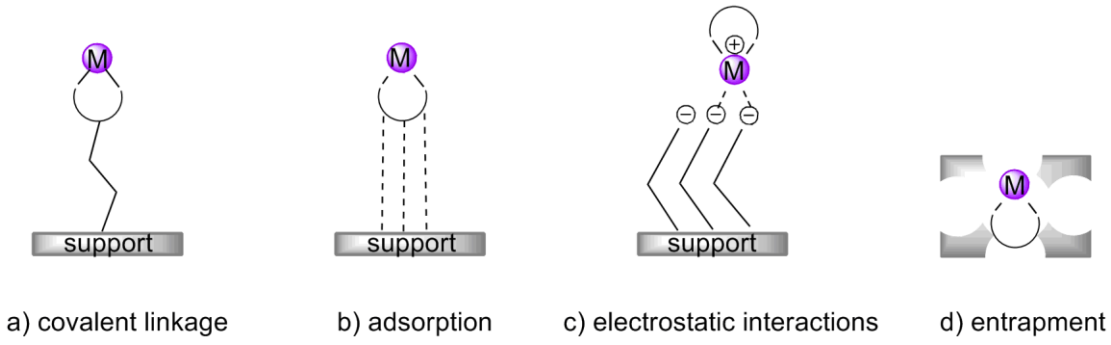


Figure 1. Schematic representation of some strategies for the immobilization of homogeneous catalysts.

In principle, all approaches are suitable for the immobilization of organocatalysts onto a support. However, up to now it is a rarely explored field and just a few examples are known for the immobilization of the organocatalyst proline.

The covalent approach is the most popular and versatile one. It can be achieved by copolymerization of the modified catalyst with an appropriate monomer or more commonly by grafting the catalyst onto a polymeric support that was synthesized in advance. The major drawback for the covalent approach is that the (chiral) catalyst has to be modified to insert an attachable unit. This also leads to higher costs for the catalyst, usually entails several synthetic steps, and it might have negative effects, due to a new conformational preference of the modified catalyst attached to the polymer. This may also have a negative influence on the catalytic performance.[13] To avoid the above-mentioned problems, the point of attachment and the catalytically active center should be as far away as possible, in order not to disturb the chiral induction. Other parameters also have to be considered, such as the type of the polymeric backbone of the support, spacer and spacer length, flexibility, and degree of catalyst loading to obtain a high catalytic performance of the supported catalyst, which is at least comparable to the non-supported analog.[14] Due to the stable covalent bond, the problem of catalyst leaching is generally low. In addition, leaching of an organocatalyst usually does not lead to toxic contaminations.

The adsorption by *van der Waals* interactions and hydrogen bonding, as well as ion-formation by electrostatic interaction are also useful approaches for catalyst immobilization, because it avoids the chemical modification of the (chiral) catalysts.[13b] However, the stability of the adsorbed or electrostatically bound catalyst strongly depends on several factors such as ionic strength of the medium and the solvent.

The encapsulation and entrapment of catalysts is the last example for the immobilization approach, which is shown in Figure 1. It requires a porous support with pore sizes that are small enough to prevent catalyst leaching. There are two methods for this approach: The catalyst is build-up inside the preformed support like a "ship-in-a-bottle",[15] or the support is synthesized around the catalysts.[16] The advantage in this approach is that the catalyst does not have to be modified, but the resulting catalysts often suffer from diffusion problems.

1.3 Separation Techniques for Supported Catalysts

The major benefit of supported (organo-) catalysts is that they can be recovered from the reaction mixture and subsequently reused. While catalysts on insoluble supports can be easily separated by filtration, there is no general concept for separation of soluble supports from small weight compounds in the reaction mixture. Several concepts for the separation have been published,[9,17] which make use of the solubility effects of the polymer or of the size of the support.

Separation by solubility effects is most frequently used to separate soluble a support from small molecules. There, the precipitation of the polymer is caused by the addition of a non-solvent, by changing the temperature, or by addition of a small amount of an additive, for instance, to change the pH. The most practical application is the solvent induced precipitation. It is widely applied for poly(ethylene glycol) (PEG), which is soluble in water and most organic solvents, but insoluble in alkanes and diethyl ether and the linear polystyrene, which is soluble in non-polar solvents, but insoluble in methanol.[18] Thermal precipitation is less frequently used,[19] as well as precipitation by pH change that can only be used when the polymer contains basic or acidic groups.[20]

In all cases, entrapment of reagents and products in the precipitated polymer usually occurs, which requires several repeated precipitation and filtration cycles. However, the major drawback is that the recovery rates are variable.

Macromolecules and small molecules in solution can also be separated by size using ultrafiltration or dialysis. Since both techniques separate molecules based on their hydrodynamic volume, their application is feasible, if the molecular weight of the polymer is roughly about 2 kDa or higher and shows a narrow weight distribution (PDI < 2). Membrane technology has been used to separate small molecules from the soluble polymer, e.g. excess reagents, salts from synthesis, or to separate the desired product after catalysis.[17c,21]

The membrane filtration technology can be divided into micro-, ultra-, nanofiltration, and reversed osmosis depending on the size of the molecules, which are retained from the membrane (Figure 2). For the separation of a soluble polymeric catalyst ultrafiltration is usually used.

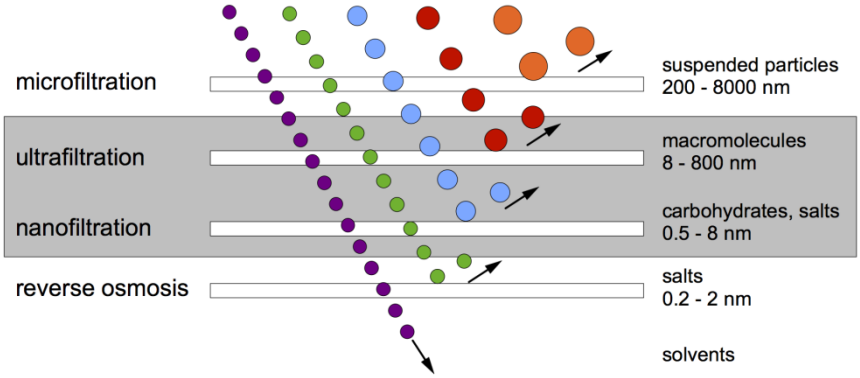


Figure 2. Classification of membrane filtration types by size.[22]

The filtration membranes, which are commercially available are characterized by their molecular weight cut-off (MWCO), which is a term to describe the pore size of the membrane. The smaller the MWCO is, the smaller the membrane pore size. A membrane with a MWCO of 1000 will reject about 90% of the molecules with the molecular weight of 1000 g mol^{-1}. As membrane material, organic (polymeric) membranes[23] are used, as well as inorganic (ceramic) membranes.[24] For the separation purpose it should be mentioned that the actual pore size of a polymeric membrane is strongly influenced by the solvent that is used.[25]

In dialysis, the reaction mixture is poured into the dialysis tubing, which consists of the membrane material. The tube is then put into a beaker filled with the same solvent used for the polymer solution. Small molecules (< MWCO) can now diffuse out of the tubing, while the big macromolecules (> MWCO) remain inside. The driving force for the diffusion phenomenon is the concentration gradient. Therefore the surrounding solvent has to be changed several times to obtain a sufficiently pure polymer.[17a,21]

Since a higher purity is achieved with ultrafiltration and applications in continuous flow systems are feasible,[17c,26] those were the preferred methods for polymer purification in the experimental part. For the purification of polymers which are dissolved in organic solvents, solvent-resistant stirred cells are commercially available, which have the polymeric membrane in the bottom part of the apparatus (Figure 3).

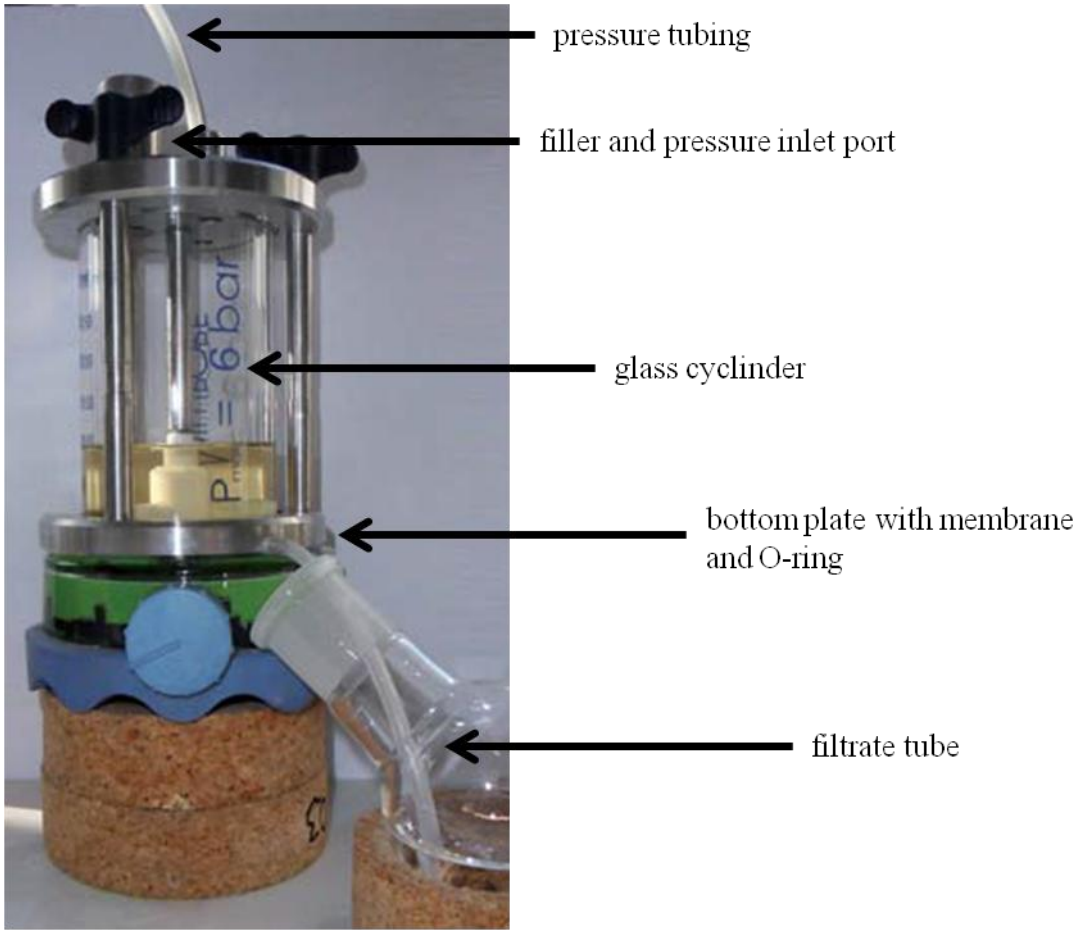


Figure 3. Ultrafiltration setup.[27]

A constant argon or nitrogen pressure of up to 6 bar operates from the top and the low molecular weight compounds accompanied by the solvent molecules are pushed though the membrane. The macromolecules (e.g. the polymeric catalyst) remain inside the cell. The low molecular weight compounds can be collected in fractions as shown in Figure 3.

Another application for the membrane technique is the use of so-called continuous flow membrane reactors (CFMR).[11,22,28] There the membrane is used to retain a soluble polymer-supported catalyst in the reactor, where a chemical transformation continuously occurs. The product is separated by the membrane and new substrate and reagent are permanently added to the reactor. The advantage is the easy set up with simple product purification, and the total turnover number of the catalyst can be increased.[17c,29] However, this concept requires highly stable supported catalysts and a high catalyst retention must also be guaranteed. In addition, the process is demanding for the support itself.

Another way to separate molecules by size is to use size exclusion chromatography (SEC) or preparative gel permeation chromatography (GPC).[17a] Both methods make use of the tunable pore sizes, which are present in the stationary solid phase. Macromolecules with a large hydrodynamic volume do not interact with the pores due to their bigger size and therefore have shorter retention times than small molecules, which diffuse into the pores and show higher retention times. This method can be applied for analytical and preparative samples, but it is a rather costly means to purify polymers.

1.3.1 Catalyst Leaching

The leaching of catalytically active sites is a major problem in supported catalysis.[30] Until now, it is mainly discussed in literature for metal catalysts, but it is - at least partially - also valid for supported organocatalysts. In principle, two forms of catalyst leaching can be discerned: The supported catalyst is leaching through the membrane during filtration or the catalyst itself dissociates from the support into the solution and is subsequently filtered off through.[22] The latter phenomenon can be caused by decomposition of the catalytic site or linker. Overall, this causes two problems: the loss of catalytically active sites, which reduces the activity and the life-time of the whole support, and the contamination of the product. In addition, when the catalyst is applied in industrial continuous flow membrane reactors, catalyst retentions of at least 99.99% per reactor are required to obtain an efficient process. Therefore, high rates are usually not achieved and the reported values are about 99.8%.[31]

1.3.2 Linear Soluble Polymers as Support

The most widely used soluble support is monomethylated polyethylene glycol (typically mPEG 5 kDa) (Figure 4), which is compatible with most common organic solvents and can be easily purified and recovered by precipitation in nonpolar solvents[9]. In addition, PEG is commercially available with a broad range of molecular weights.[32] However, it suffers from its low loading capacity (e.g. 0.2 mmol g^{-1} $mPEG_{5000}$), which is caused by the linear structure of this polyether, with just one functional group per macromolecule.[17b,33]

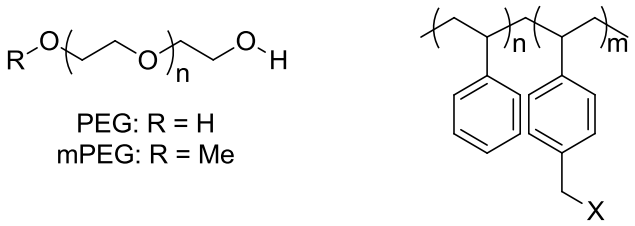


Figure 4. Chemical structure of poly(ethylene glycol) (PEG), its monomethylated form (mPEG) and polystyrene copolymers (PS).

Linear polymers (Figure 5) with higher loading capacity usually bear a functional group on every repeating unit. For example, polyvinyl alcohols, polyacrylic acid, polyacrylamide have been applied as supports with significantly higher loading.

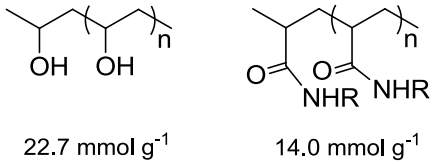


Figure 5. High-loading linear polymers with one functional group per monomeric unit. The given loading capacities correspond to the respective functional group (R = H).

For instance, the commercially available polyvinyl alcohol (PVA) (Figure 5) has been used as support in the polynucleotide synthesis and a loading of up to 10 mmol g^{-1} with nucleotide was achieved. However, other supports with better solubility in polar organic solvents have been mostly recommended.[34]

Another type of linear polymeric supports is polyacrylamide, which potentially offers high loading capacity. Until now, it has been used in two modifications: the first one is as soluble support in the oligonucleotide synthesis and the second one is as cross-linked microbeads for the synthesis of glycopeptides. The reduced chemical stability of polyacrylamide compared to polystyrene and polyethers limits its broad application as support.

Besides the challenge of the catalyst loading, there are several parameters that play a role in catalysis, where these supported catalysts have to prove their efficiency. Benaglia et al. reported the application of a PEG-supported phase-transfer catalyst, which was compared to different insoluble and soluble supports.[35] In general, insoluble polystyrene based catalysts need higher reaction temperatures and/or longer reaction times, which indicates kinetic and diffusion problems. Other disadvantages that have

been observed are the need for a conditioning time for bead swelling and mechanical degradation by stirring, which results in recovery problems.

Overall linear polymeric support have potentially high loading capacities, but their solubility and chemical stability as well as their material properties can limit their use as catalyst supports in some cases.

1.4 Catalysts on Soluble Support

The use of a soluble polymeric support was first reported by Bayer and co-workers, who used poly(ethylene glycol) (PEG) as support for peptide synthesis.[36] While the use of PEG as a support for peptide synthesis is no longer common, the polystyrene-PEG composite material he introduced is widely used today and is known as Tentagel. In 1975 a homogeneous hydroformylation using a rhodium-complex which was immobilized on a soluble support was described.[37] After the first achiral example of a soluble polymer supported catalyst, it took about 20 years before Janda and co-workers reported an catalyzed asymmetric reaction, that used MeO-PEG-dihydroquinidine as a catalyst for the dihydroxylation of alkenes.[38] In the meantime, a wide range of polymeric supports has been used for chiral ligands and transition metal catalysts, for instance, dendrimers,[39] hyperbranched polymers[40] (like polyglycerol), poly(ethylene glycol)s,[9,41] and functionalized soluble polystyrenes.[42]

The soluble supports can be divided into two main groups: linear and branched polymeric supports. Linear polymeric supports can only be decorated with catalysts at the functional end-groups or at functional groups along the polymer backbone, whereas branched polymers are subdivided into star shaped polymers, dendrimers and dendrons, and hyperbranched polymers (Figure 6). Also structural mixtures are known, for example linear polymers with dendritic site groups.[43]

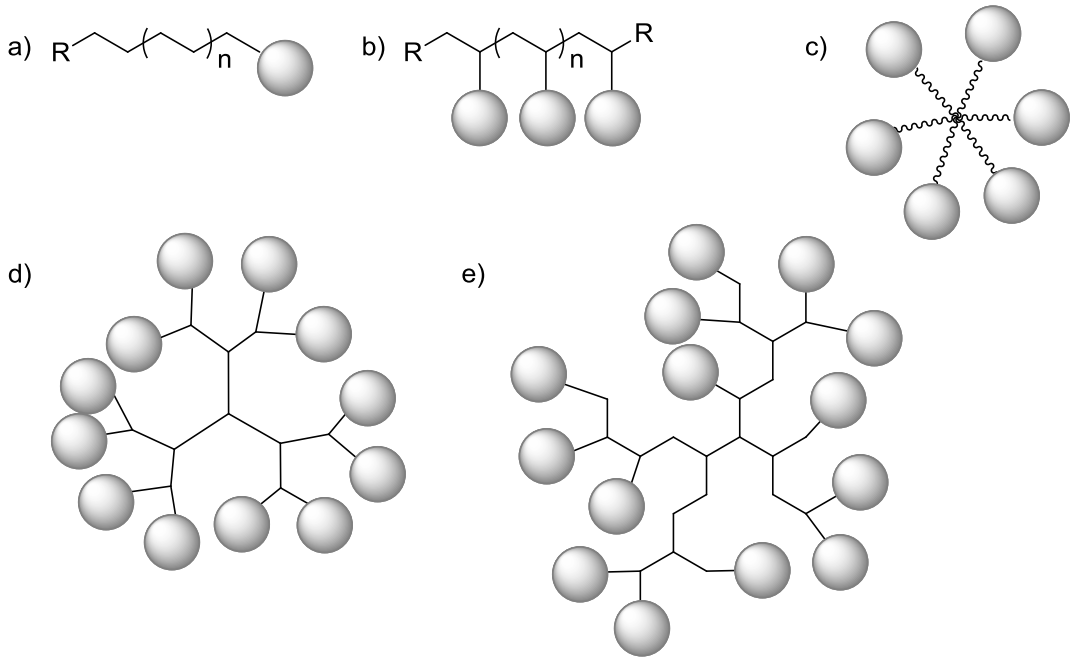


Figure 6. Classification of soluble polymers into linear (a-c) and branched polymers (c-e). (a) A linear polymer with functional end-groups, (b) with functional group throughout the chain, (c) a branched star-shaped polymer, (d) a dendrimer, and (e) a hyperbranched polymer.

1.4.1 Branched Polymers as Catalyst Support

Some disadvantages of linear polymers, like their limited solubility in organic media, can be resolved by using branched polymer architectures.[17b,44] One type is the star-like branched polymer shown in Figure 6. These systems consist of several polymeric arms, which are linked to a central core. This type of branched structure can be easily synthesized in a one-pot, single reaction.[45] Catalysts can either be linked to the core,[46] to the terminal position at the arms,[47] or randomly throughout the arms.[48]

A special class of branched architectures are perfectly branched polymers, which are defined as dendrimers. A dendrimer is typically symmetric around the core, and often adopts a spherical three-dimensional morphology. The first dendrimers were made via a divergent synthesis by Fritz Vögtle[49] in 1978, by Donald Tomalia[50] at Dow Chemical in 1983, and by George Newkome[51] in 1985. In 1990, a convergent synthetic approach was introduced by Jean Fréchet.[52] Dendrimers have been also applied as soluble support in catalysis.[26,39h,44,53]

Dendrimers are characterized by their structural perfection, high symmetry is predicted, and they are mostly spherical. The properties of dendrimers are dominated by

the functional groups on the surface, although there are also examples of dendrimers with internal functionality.[54] The high loading with functional groups and their high solubility in a wide range of organic solvents make dendrimers a good catalyst support. Upon immobilization they usually show kinetics, activity, and selectivities which are comparable to the conventional homogeneous analogs. The high local concentration of functional groups in dendrimers and the attachment of catalysts can lead to enhanced or reduced catalytic activity and selectivity, also called "dendritic effect."[55] This includes enhanced stability by the shielding of the catalytic sides and cooperative effects of the catalysts which are caused by the close proximity of the reactive groups. The catalysts can be attached in the core, at the branching units, or at the periphery of the dendrimer (Figure 7).

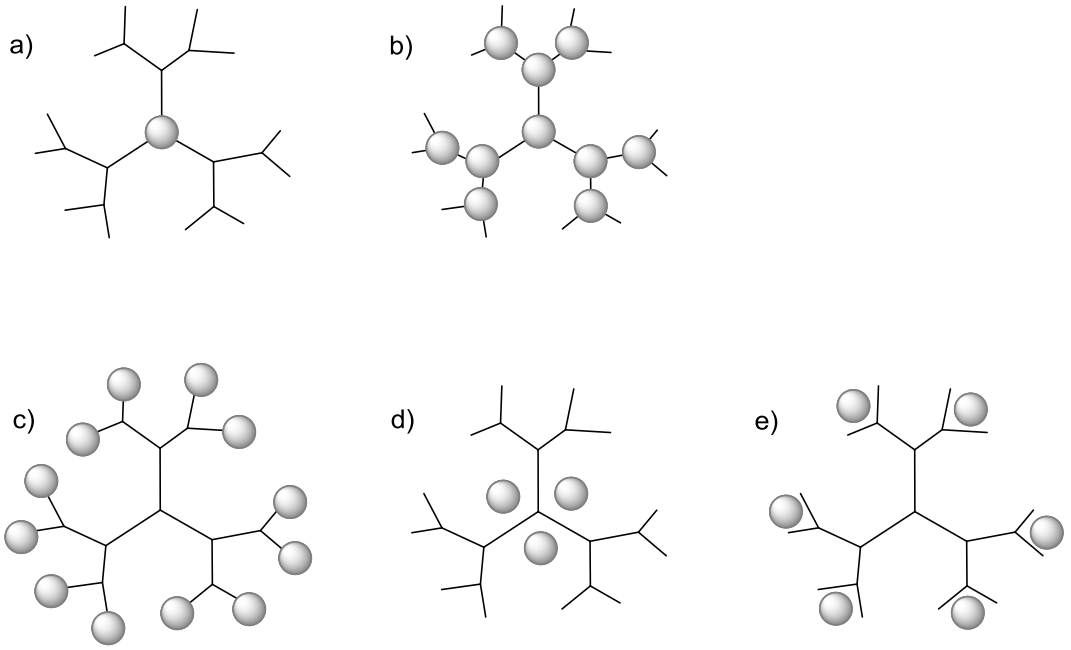


Figure 7. Possible locations for catalytically active units in perfectly branched structures: covalently linked (a) in the core, (b) at the branching units, (c) at the periphery, or non-covalently, (d) entrapped in the dendrimer cavities, or (e) located at the periphery.[56]

Positioning of the catalyst at the core results in a very low loading capacity and slow reaction rates, but the catalyst is well shielded.[57] Higher catalyst loading is achieved when the catalyst is attached at the periphery[56] of the dendrimer or at each branching unit. However, the latter case is less common and has been rarely reported.[58]

The functionalization of the periphery is the most common approach in dendrimer immobilized catalysis and has been reviewed several times.[26,44,53a,59] The high local

concentration of the catalytic sites at the dendrimer surface make them highly accessible for substrates, and the catalyst interaction can either increase (positive dendritic effect) or decrease (negative dendritic effect) the catalytic performance.[55] A wide range of catalyzed reactions has been published in the field of dendrimer catalysis, which includes hydroformylation, hydrogenation, epoxidation, metathesis, and oxidations.[26]

In principle, dendrimeric catalysts can also be recycled by membrane filtration techniques,[22,40c,44] but the tedious and expensive synthesis of higher generation dendrimers, which are needed for membrane separation techniques (> 1.5 kDa), makes the application of those techniques far less attractive.

Hyperbranched polymers are a highly attractive alternative to expensive dendrimers,[14a,40c,40d] because they are easily available in an one-pot reaction, allowing the synthesis of large amounts[40d,60] in a polymerization reactor. Within the polymeric backbone, there are linear, branched, and terminal repeating units. Hyperbranched polymers can therefore be classified as an intermediate between linear polymers (degree of branching, DB=0) and perfectly branched dendrimers (DB of 100%) with a DB of 50 to 60%.[17b] Such polymers are polydisperse and their reactive sites are distributed over the entire macromolecule, but it has been shown that the catalytic results are mostly comparable with those obtained with a catalyst on a perfect dendrimer support.[40d,53c] It seems obvious that structural perfection is not always required. A wide range of hyperbranched polymers are known[61] and some of them are even commercially available, e.g., poly(ethylene imine), polyesters, and polyglycerol.[17b]

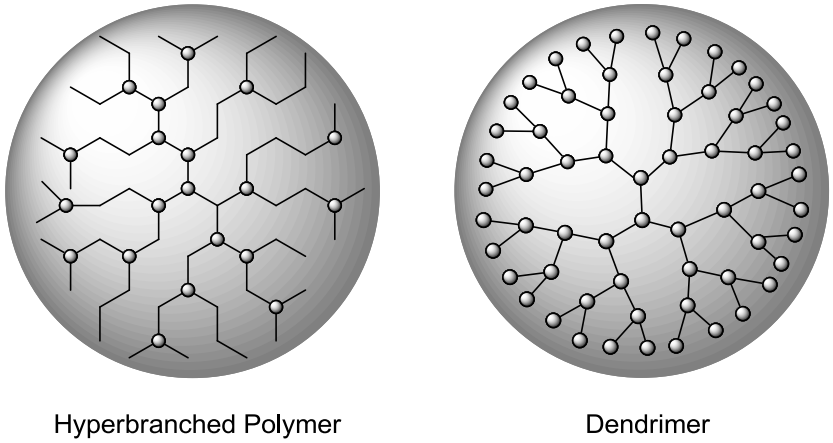


Figure 8. Structural features of a hyperbranched polymer in comparison to a dendrimer.

Hyperbranched polyglycerol (hPG) is of special interest due to its chemical stability compared to branched polymers, such as polyesters and polyamines. The hPG can be

obtained in a one-step polymerization reaction, which allows the synthesis of different molecular weights. Additionally, it can be easily functionalized and has versatile properties, such as high loading capacity (up to 14 mmol g^{-1}), which is in the range observed for dendrimers.[17b] Its non-coordinating properties make it an ideal support for catalysts. Due to its biocompatibility, it has found many applications for biomedical purposes.

1.4.2 Choice of the Soluble Polymeric Support

Since the support can have a significant impact on the catalytic performance of a supported catalyst, the choice of the support has to be well-considered. For homogeneous systems it is restricted to soluble polymers, such as poly(ethylene glycol). Linear mono- or difunctionalized polymers, such as mPEG suffer from the low loading capacity, which displays the mass ratio of supported catalyst to mass of the support. Here, dendritic architectures can open the way for a high loading of almost a 1:1 ratio of catalyst per repeating unit of the polymer and those catalysts can be applied in so-called continuous flow membrane reactors. In contrast to dendrimers, hyperbranched polymers can be synthesized on a large scale in a one-step process in a comparatively short time.[62] In addition, it is readily available from the cheap commercial starting material glycidol by anionic ring opening polymerization. It also has the beneficial feature that it is stable in a wide range of temperatures and is inert at both, low and high pH values. With the hydroxy functionality of polyglycerol it can undergo simple organic transformations,[63] which simplifies the covalent attachment of catalysts and makes polyglycerol a promising candidate for catalyst immobilization.

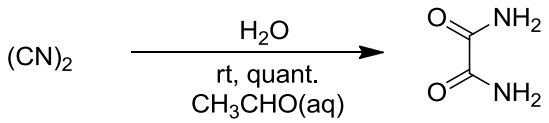
1.4.3 Choice of catalysts for immobilization

As already discussed in the introduction, there is a huge diversity of organocatalytically active compounds available, which could be immobilized on a support. In order to choose the “right” one, some aspects have to be taken into consideration. The attachment to the support as well as the modification of the catalyst precursor should involve as few steps as possible. In addition, chemical transformation on the polymer should also be reduced to a minimum. Further requirements are: The

supported catalyst should be stable towards moisture and temperature to ensure easy handling and preferentially the polymer should also be bench-stable in order to achieve a long lifetime of the resulting immobilized catalysts.

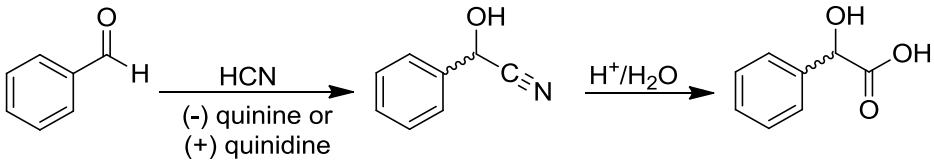
1.5 Organocatalysis – Historical Background

The first discovery of an organocatalytic reaction can be attributed to Justus von Liebig, who accidentally found in 1859 that water which is saturated with cyanide gas formed upon addition of small amounts of an aldehyde the crystalline oxalamide (Scheme 3). Rather surprised by the new reaction, von Liebig wrote in his lab journal: "*ich habe die nämliche Flüssigkeit… dreimal hintereinander mit Cyanidgas gesättigt, ohne daß die Wirkung des Aldehyds im mindesten geschwächt zu sein schien. Mit jeder neuen Portion Cyan … bildete sich eine entsprechende Menge Oxamid.*"[64] The acetaldehyde was the first discovered pure "organocatalyst" that acted similarly to "enzymes."



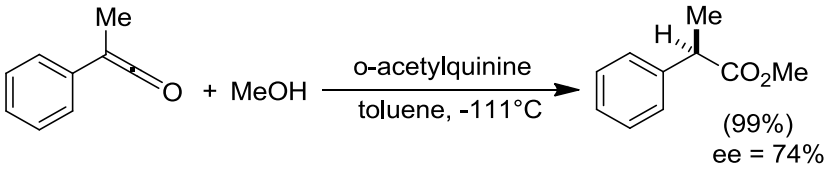
Scheme 3. Justus von Liebig's oxamide synthesis.

Almost five decades later, the German physical chemist Georg Bredig published the first asymmetric C-C-bond forming reaction[65] where the chiral *d*-mandelic acid is formed from benzaldehyde and hydrogen cyanide in the presence of an alkaloid like quinine (Scheme 4). The enantiomeric excess obtained was only 10%.



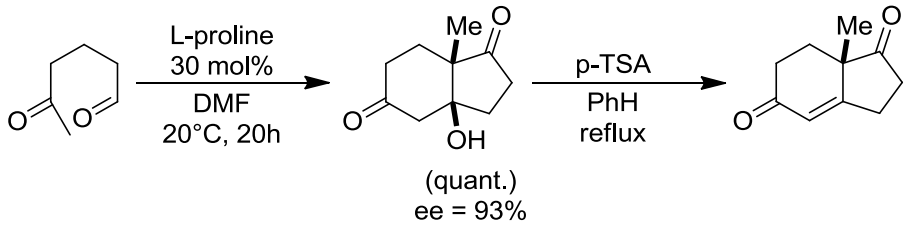
Scheme 4. Bredig's enantioselective mandelonitrile synthesis.

A synthetically useful level of enantioselectivity was achieved in the 1960s, when Parcejus reported an *ee*-value of 74% in the *O*-acetylquinine catalyzed methyl ester synthesis (Scheme 5).[66]



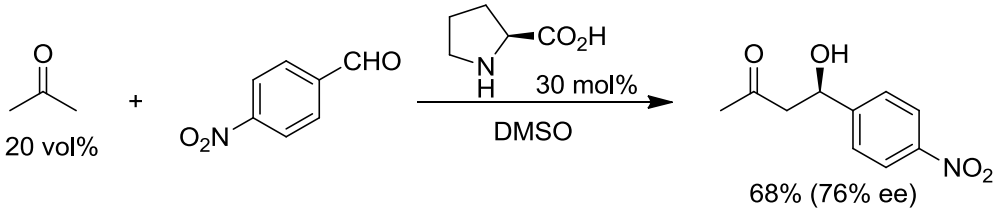
Scheme 5. Pracejus's enantioselective ester synthesis from phenyl methyl ketene.

Almost two decades later organocatalysis became synthetically useful with the discovery of the asymmetric Robinson annulation (Scheme 6) as a key step in steroid synthesis. The second step in the Robinson annulation is an asymmetric intramolecular aldol reaction which is catalyzed by the organocatalyst L-proline, whose supported version will be investigated in this thesis.



Scheme 6. The L-proline-mediated Robinson annulations.

Reinvestigation of the asymmetric intramolecular aldol reaction by List and Barbas[67] (Scheme 7) in the late 1990s opened the door for related reactions, like the enantioselective Mannich, Michael and Diels-Alder[68] reactions, and initiated the idea of domino (multi-step) reactions.[69]



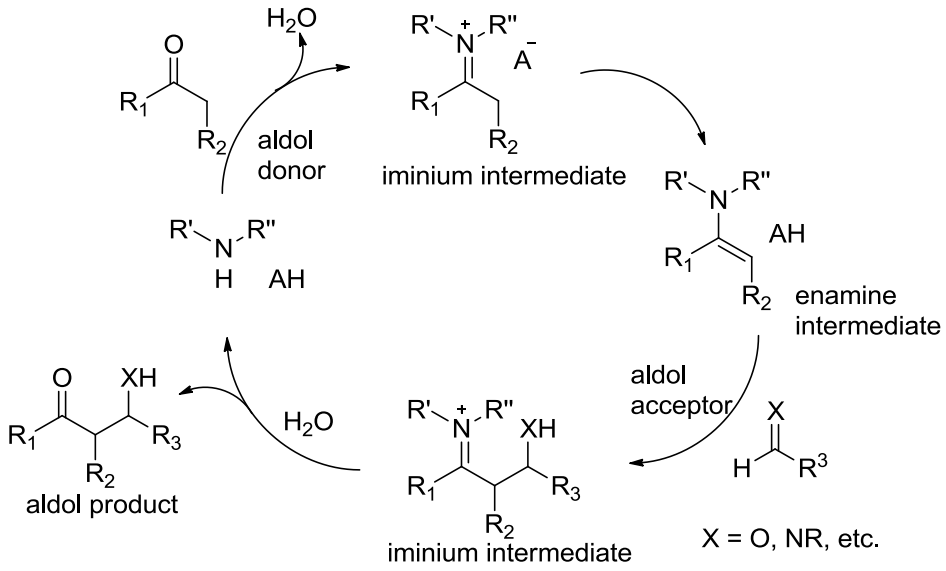
Scheme 7. The proline catalyzed direct asymmetric aldol reaction.

1.6 Proline as Catalyst

The amino acid proline has the extraordinary capacity to promote not only one but rather a variety of chemical reactions. This feature attracted our attention, because it can be expected that upon immobilization the resulting supported catalyst can be tested for several reactions. Although L-proline is a well-known and extensively investigated organocatalyst, only a few attempts have been made for its immobilization. In principle, both enantiomeric forms of proline are available; the natural L-isomer is a magnitude cheaper than the D-isomer and is therefore more frequently investigated in the labs. Proline is unique among all natural amino acids because it has a secondary amino group that has a higher pK_a than any other amino acids and therefore features an enhanced nucleophilicity. In chemical reactions proline can react with carbonyl compounds or Michael acceptors as a nucleophile and forms iminium ions or enamines upon reaction. In these reactions, the carboxylic group of the amino acid acts as a Brønsted acid and activates the carbonyl group, which renders the bifunctional character of this catalyst.

1.6.1 Proline in Aldol-type Reactions – Enamine Catalysis

Proline has been used as catalyst for aldol reactions, Mannich-type reactions, and other reactions that proceed via the enamine catalytic cycle (Scheme 8).



Scheme 8. The enamine catalytic cycle.

In the catalytic cycle, the first step is the formation of the iminium intermediate by the amine catalyst and the aldol donor. The iminium ion is deprotonated to a neutral enamine intermediate which then acts as a nucleophile with an electrophile, like an aldehyde. After hydrolysis the aldol product is released and the amine-based catalyst is regenerated.

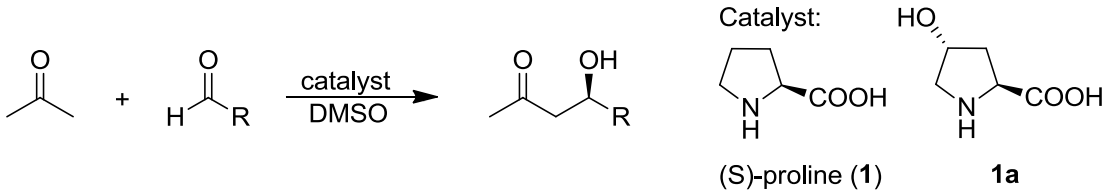
Since the early 1960s, the natural amino acid proline has been used stoichiometrically in asymmetric enamine-type reactions.[70] In those reactions, the enamine intermediate was isolated and then reacted with the aldol acceptor. In the early 1970s, the first asymmetric intramolecular aldol-type reaction was developed which was catalyzed by proline and other primary and secondary amino acids (phenylalanine and alanine).[71] In 1997, Barbas and co-workers compared proline catalysis and the aldolase antibody catalyst in the intermolecular aldol reaction. Both promoters act like enzymes via the enamine catalytic cycle.[72] They found that proline and aldolase are analogous in many ways and that they are able to catalyze many of the same reactions, both using enamine catalysis. They successfully conducted further studies with proline and other amino acids in the intermolecular aldol[73] and in the Michael-aldol[74] reactions which had been previously performed with aldolase antibodies.[72c-e] In 2000, Barbas and co-workers extended the substrate scope to a wide variety of electrophiles, without the limitations connected to sterically demanding enzymes. With this starting point, the field of direct asymmetric catalyzed intermolecular reactions has grown and many developments have been made by proceeding via in situ-generated enamine intermediates.[73a,75]

The benefit of these proline catalyzed reactions is that high enantiomerically enriched products can be obtained under mild conditions without the need of pre-formation or isolation of enamines or pre-activation of carbonyl compounds; this is in contrast to Mukaiyama aldol chemistry which requires preformed enolates. The proline catalyzed aldol reaction can be easily performed by mixing the reactants and the catalyst in an appropriate solvent under air and at room temperature. The procedure is simpler than for reactions which use lithium amides to form enolate intermediates and the control of the stereochemistry is possible by addition of stoichiometric amounts of a chiral auxiliary. In addition, a low temperature, absolute solvents, and an inert atmosphere are usually required.

1.6.2 Proline in Aldol Reactions with Ketone Donors

(*S*)-Proline (**1**) and its derivatives, such as (2*S*,4*R*)-4-hydroxyproline (**1a**), which can be used for immobilization approaches, catalyze aldol reactions of ketone donors (Table 1).[73b]

Table 1. Aldol reactions of acetone and aldehydes.[73b]



Entry	R	Catalyst	Yield [%][a]	*ee* [%][b]
1	4-$NO_2C_6H_4$ (**10**)	1	68	76
2	4-$NO_2C_6H_4$ (**10**)	1a	85	78
3	*i*-Pr	1	97	96
4	*c*-C_6H_{11}	1	60	85

Reagents and conditions: [a] isolated yields after column chromatography. [b] The *ee* was determined by chiral-phase HPLC analysis.

These reactions were performed by mixing a large excess of acetone (20 Vol%) with the aldehyde and L-proline (**1**) or proline derivative (20 mol%) in DMSO at room temperature. The typical enantioselectivity that was typically observed were between 60 and 90% enantiomeric excess (*ee*) for arylaldehydes acceptors, and up to 96% *ee* for α,α-disubstituted aldehyde acceptors. Although the enantioselectivities were not perfect in these reactions, it is shown that a simple amino acid can substitute a much more complex enzyme in the intermolecular direct aldol reaction. Although the reaction conditions using (*S*)-proline (**1**) can be optimized, L-proline **1** is not always the best catalyst for many reactions. Indeed, it is a good starting point for the immobilization of organocatalysts and if the synthetic immobilization protocol is successful, it can be extended to more complex and potentially more efficient L-proline derivatives.

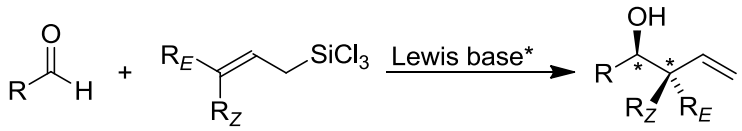
1.7 Phosphoramides as Catalysts

The addition of nucleophiles to carbonyl compounds is an important transformation in organic synthesis, with classical examples such as the Grignard reaction, aldol condensation, and $LiAlH_4$ reduction. However, less reactive nucleophiles such as allylsilanes[76] and allylstannanes[76-77] have to be activated beforehand. Phosphoramides are able to act as Lewis base and coordinate to the nucleophile, which increases its nucleophilicity and facilitates for example aldol reactions.[78] Since only the coordinated species is reactive enough, the phosphoramide may be applied in catalytic amounts, is only needed in the C-C bond forming step, and can be released when the reaction cycle is completed. If the phosphoramide is chiral, a preference for one enantiomer of the product can be expected.

Since there are numerous examples where phosphoramides promote reactions, this work is focused on the activation of silicon reagents, namely, the aldol reaction of allylsilanes and the Mukaiyama aldol reaction.

1.7.1 Phosphoramides in Allylation Reactions

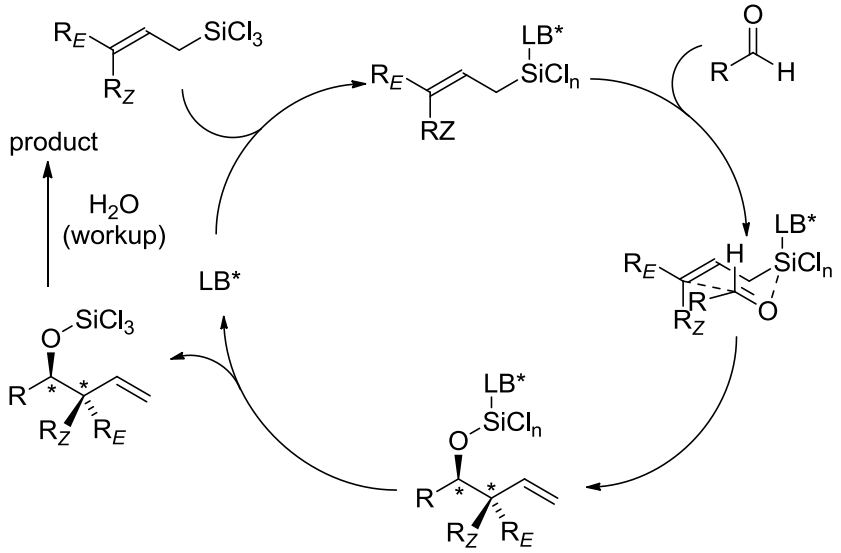
Phosphoramides as Lewis bases can promote allylation reactions by activating the donor component, but they do need $AllylSiCl_3$ (Scheme 9), since the methyl analog is not acidic enough to coordinate to the Lewis base.



Scheme 9. Asymmetric allylation of aldehydes.

When chiral phosphoramides like in Scheme 9 are used, enantioenriched products can be expected. If the reaction proceeds through a closed transition state, as shown in Scheme 10, then a good diastereocontrol can be expected. Consequently, *trans*-crotyl allyl derivatives should yield the *anti*-product; if the starting material has a *cis* configuration, then the *syn*-isomer of the hydroxyl allyl product should be formed. The aim is to apply the supported phosphoramides in catalytic amounts with the requirement that the phosphoramide catalyst dissociates from the silicon in the late state of the

reaction cycle with a sufficient rate. Since it is known that polar aprotic solvents like dimethylformamide, dimethyl sulfoxide, and hexamethylphosphoramide can promote the allylation reaction, it is likely that a supported (chiral) phosphoramide in catalytic amounts could be used to substitute the promoters that have been used so far.



Scheme 10. Lewis base-catalyzed allylation of aldehydes with allyl trichlorosilanes.

The early monomeric phosphoramide catalysts (Figure 9a and b) developed by Denmark,[79] only showed modest enantioselectivities in the allylation reaction, but they were helpful in order to better understand the reaction mechanism.

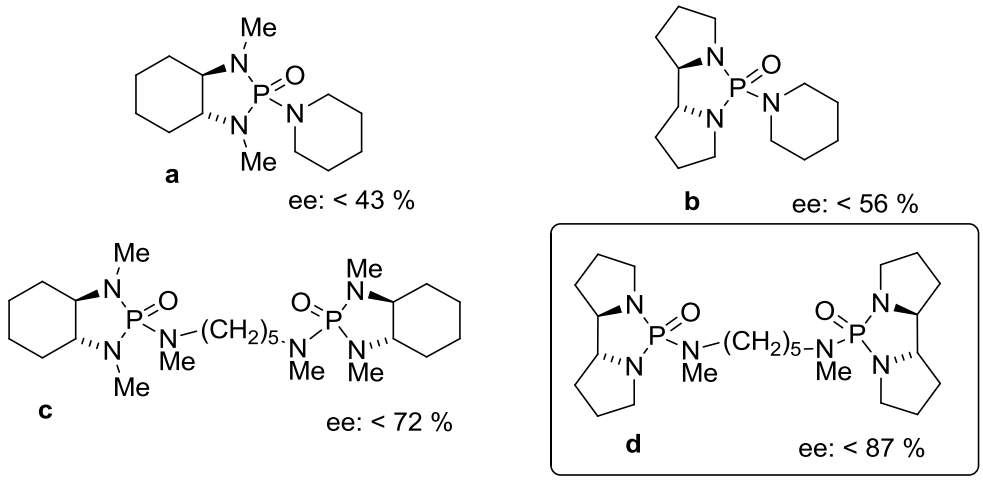
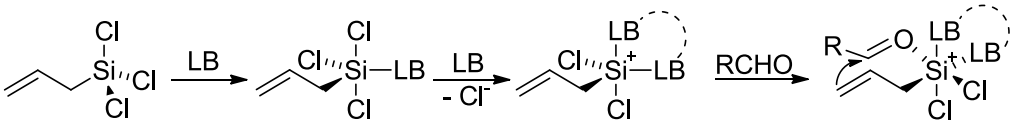


Figure 9. Selected phosphoramide catalysts for the allylation of aldehydes with allyl trichlorosilane.[79-80]

Kinetic measurements and a non-linear relationship between the enantiopurity of the catalyst and the allyl-product led Denmark et al. to the conclusion that more than one phosphoramide molecule is coordinated to the silicon, as it is shown in Scheme 11.



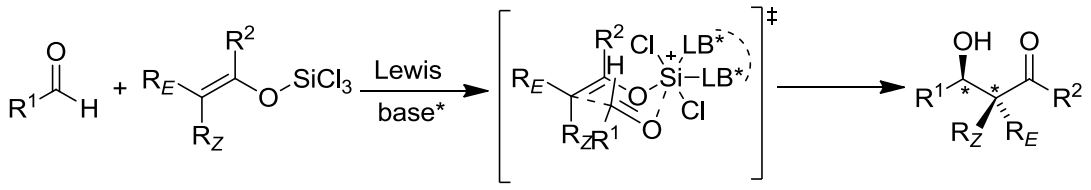
Scheme 11. Coordination of a Lewis base (LB) to allyl trichlorosilane.

As a result, the second generation of phosphoramide catalysts was developed, where a linker connects two phosphoramide moieties, forming a bidentate catalyst that permits the coordination of two phosphoramides to the silicon center. It was observed that the stereocontrol strongly depends on the length of the tether (with an optimum of five methylene units, see Figure 9d).

Since two phosphoramides in close proximity to one another are required to obtain high stereocontrol and usually solvent-like quantities of the promoter are necessary to obtain a sufficient reaction rate, we developed the concept of supported chiral phosphoramides, where the chiral backbone of Denmark's catalysts is supported on a highly branched architecture, such as polyglycerol.

1.7.2 Phosphoramides in Aldol Reactions

In contrast to allylsilanes, which do not react with a carbonyl in the absence of a catalyst (section 1.7.1), silyl enol ethers are already reactive enough to form aldol products at room temperature without a catalyst. Using phosphoramides in the Mukaiyama aldol reaction can substantially accelerate the reaction and provide a starting point for the development of an asymmetric variant. The required trichlorosilyl enol ethers (Scheme 12) can be synthesized in various ways, for instance, starting from the (often) commercially available trimethylsilyl enol ether by subsequent substitution reaction with $SiCl_4$, catalyzed by $Hg(OAc)_2$.[81]



Scheme 12. Asymmetric aldol addition of trichlorosilyl enol ethers to aldehydes.

Denmark et al. introduced several chiral phosphoramides (Figure 10) for the enantioselective C-C bond formation and also investigated the mechanistic details of the reaction.[78a,82] He proposed that small monodentate and bidentate phosphoramides react in a cyclic chair-like transition state (Scheme 9), where *Z*-enol ethers gave *syn*-products and (*E*)-derivatives furnished *anti*-diastereomers. With a more bulky phosphoramide (Figure 10b), where only one molecule can coordinate, the opposite diastereoselectivity is observed.[82]

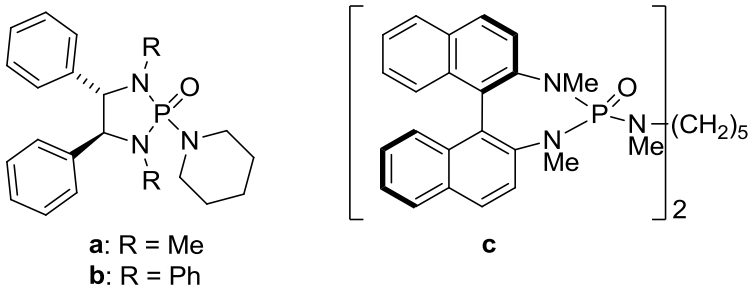
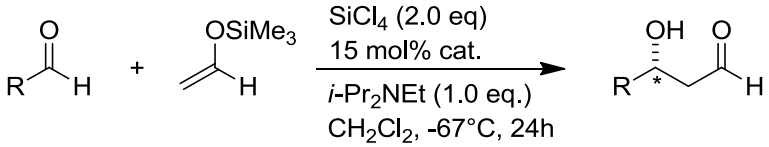


Figure 10. Catalysts for aldol addition.

The range of substrates which can be used in the aldol reaction (and allylation, see Section 1.7.1) of trichlorosilyl enol ethers is generally restricted to aldehydes; the less reactive ketones do not react under these conditions.

The aldol reaction with trichlorosilyl enol ethers would be more attractive if the required ether could be generated in situ. The starting material would be the trimethyl silyl ether, which is alone not acidic enough to react with the aldehyde, but in combination with a phosphoramide as Lewis base and $SiCL_4$, the trichlorosilyl enol ether is formed in situ and subsequently reacts with the aldehyde. The best catalyst for the reaction between the aromatic aldehyde (Scheme 13) and acetal aldehyde-derived silyl enol ether turned out to be a bidentate phosphoramide with a BINOL backbone (Figure 10c), which gave the desired product in good yield and high *ee* (> 94%).

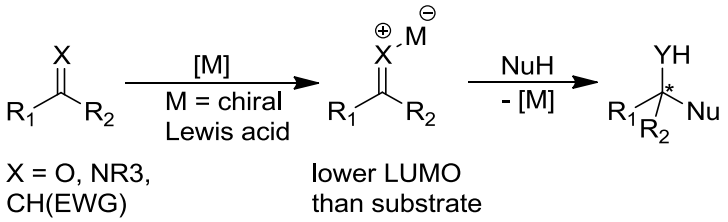


Scheme 13. Aldol reaction of TMS silyl enol ether.

Our supported phosphoramide catalysts will be applied in situ experiments as shown in Scheme 13 in the allylation- and the Mukaiyama aldol reaction.

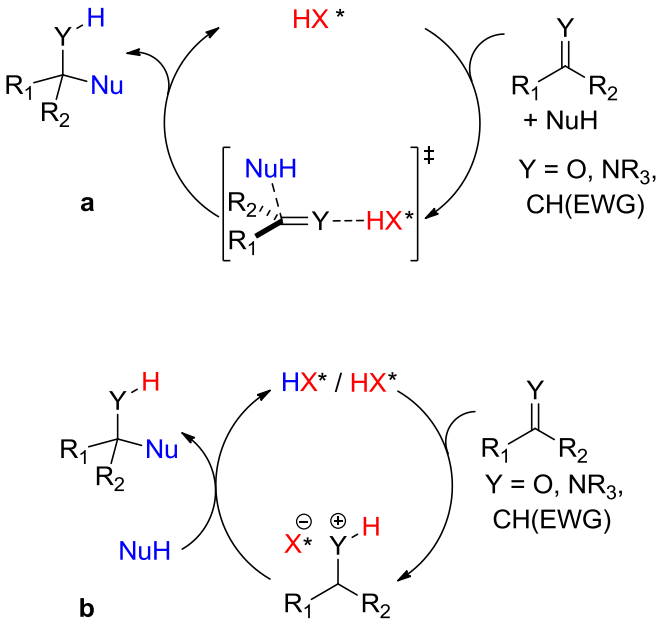
1.8 Chiral Phosphoric Acids as Brønsted Acid Catalysts

The activation of electrophilic substrates is a very useful tool in asymmetric synthesis and is mainly dominated by chiral Lewis acids, which consist of a metal center and a chiral ligand (Scheme 14).[83]



Scheme 14. Lewis acid catalysis.

Just recently, chiral Brønsted acids have been developed as a new class of organocatalysts which are able to activate carbonyl compounds.[84] So far, the field of chiral Brønsted acid catalysis can be divided into two areas and this thesis will discuss both areas. In the first field, the substrates are activated by hydrogen bonding to the catalyst (Scheme 15a), for example, fluorinated alcohols, which typically form aggregates with the substrate. This type of catalyst will be investigated in the last part of the thesis (Chapter 3.5). The second field deals with catalysts, which activate the substrate by protonation (Scheme 15b).



Scheme 15. Asymmetric Brønsted acid catalysis.[85]

Examples for the latter case are *N*-triflyl phosphoramides, dicarboxylic acids, and phosphoric acids (Figure 11). The chiral phosphoric acids with a BINOL backbone were chosen as the immobilization and are discussed in Chapter 3.4.

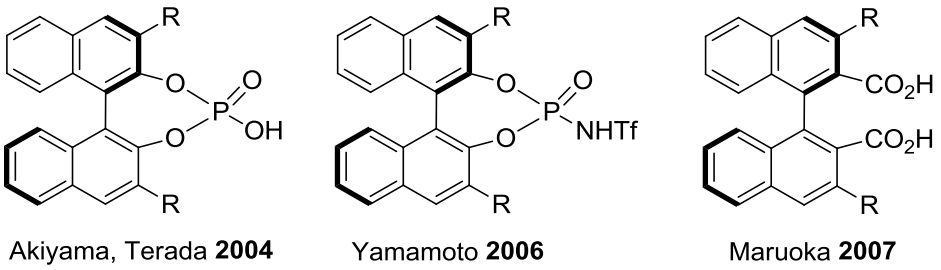


Figure 11. Chiral Brønsted acids.[85]

1.8.1 Chiral Phosphoric Acids with a BINOL Backbone

The field of chiral phosphoric acids with a BINOL backbone was launched in 2004 by the groups of Akiyama and Terada. This new class of chiral organocatalysts can be used to transfer a proton which is surrounded by a chiral environment to perform stereoselective transformations. The backbone which makes the molecule chiral is based on 1,1-binaphthol (BINOL), which exhibits axial chirality and other special characteristics (Figure 12).[83a]

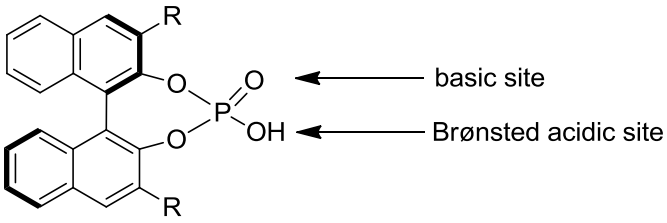
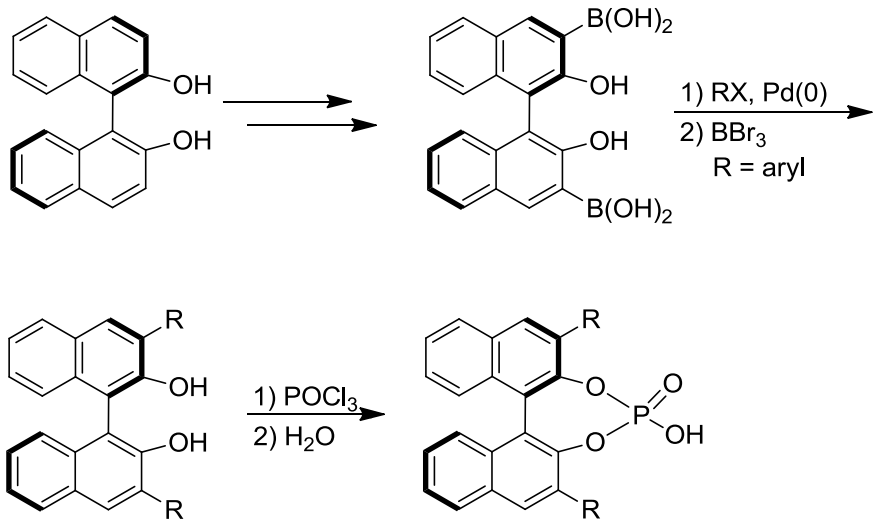


Figure 12. Brønsted acidic and basic sites of BINOL phosphates.

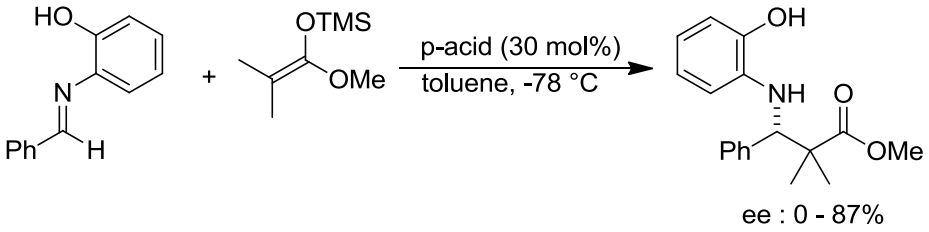
The characteristics are: (1) The phosphorus atom in the final catalyst forms a seven-membered ring with the chiral BINOL ligand, which cannot freely rotate around the P-O bond, which results in a conformational fixation of the final catalyst. This feature is unique and cannot be found for other acids like sulfuric acid. (2) The chiral phosphoric acid is strong enough to protonate substrates, such as imines, and thereby enhances their electrophilicity, which means that a nucleophile can now easily attack the substrate. As a result an enantioenriched product can be formed. (3) Since the phosphoric acid also has a basic site at the phosphoryl oxygen, it may act as a bifunctional catalyst.

So far, chiral phosphoric acids with various substituents in positions 3 and 3' have been published which were obtained from commercial BINOL (Scheme 16). The substituents in position 3 and 3' are crucial for the subsequent stereochemical induction, since the electronic and steric properties of the final catalyst can be easily tuned by choosing the right substituents there.



Scheme 16. Synthesis of BINOL phosphates according to Akiyama and Terada.

Akiyama et al. investigated chiral phosphoric acids with mono-substituted phenyl derivatives as substituents in the 3- and 3'-position (Figure 13), which are sterically not so demanding in the indirect Mannich reaction (Scheme 17).



Scheme 17. Mannich reaction with various phosphoric acids.

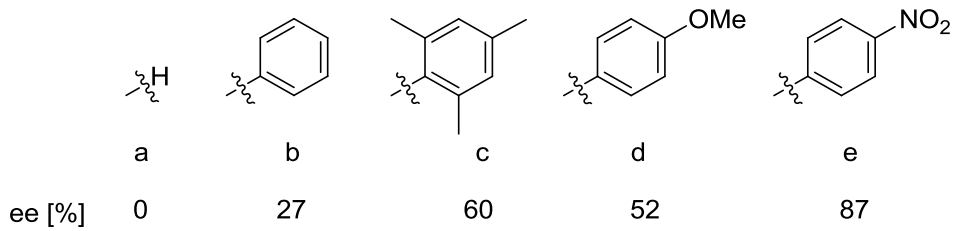


Figure 13. Screened catalyst in the indirect Mannich reaction.

The modified and non-modified phosphoric acid catalysts gave an almost quantitative yield, but the stereochemical induction was strongly dependent on the substituents in the 3,3'-positions. The best catalyst (Figure 13e) provided the desired product with good yield (96 %) and enantioselectivity (87 %).[86]

Terada and co-workers focused on more sterically demanding aromatic substituents like biphenyl or 4-(2-naphthyl)-phenyl (Figure 14) for the formation of chiral phosphoric acids, which were investigated in the direct Mannich reaction.

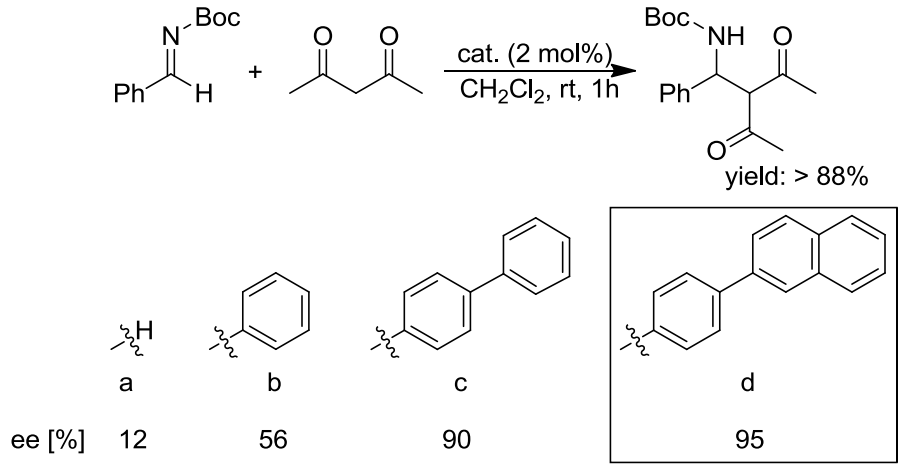


Figure 14. Screening of catalysts in the Mannich reaction.

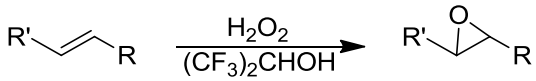
Depending on the substituent on the phosphoric acid, slightly different yields were obtained (always > 88%), the range for the obtained enantioselectivities was much bigger, and the unmodified acid (Figure 14a) gave just 12%, whereas the binaphthol derivative gave excellent enantioselectivity (95%).

Terada and Akiyama et al. have shown that BINOL phosphates can be an outstanding organocatalyst in several asymmetric transformations, but choosing the right substituents is important to obtain high enantiomeric excess in the desired reaction. A remaining problem is the accessability of substituents on the BINOL in the positions 3 and 3'. This thesis will contribute to this field with the concept of easy "click" coupling of various substituents. In addition, since the synthesis of complex chiral phosphoric acids is costly and requires several synthetic steps, a concept for catalyst recycling will be developed.

1.9 Fluorinated Alcohols as Catalysts

Fluorinated alcohols are a group of compounds which operate as promoters in (enantioselective) organic reactions. These compounds activate the reactants by their hydrogen bond donation. An early example of for this type of catalyst are the urea-based compounds reported by Jacobsen and co-workers.[87] Further developments towards the thiourea functionality found application in conjugate addition reactions of α,β-unsaturated carbonyl compounds, as well as in the Strecker and Mannich reactions. Fluorinated alcohols, however, were generally applied in oxidation reactions. The oxidant in such reactions is usually hydrogen peroxide, which is activated by hydrogen bond formation upon addition of the alcohols, such as hexafluoroisopropanol. Model studies emphasized that there is not just one individual hydrogen bond, which would be too weak, but rather a multiple hydrogen bond network that is strong enough to activate the oxidant. This multivalent effect is typically known from water and other biological systems,[88] such as the organization and base pairing of DNA and RNA protein structures,[89] recognition of small compounds,[90] and enzyme catalysis,[91] just to mention a few examples.

The hydrogen donor ability of various fluorinated alcohols has been intensively investigated by Neumann and co-workers in reactions like the epoxidation of alkenes and the Baeyer-Villiger oxidation. In the former reaction, cyclic and acyclic alkenes have been epoxidized with hydrogen peroxide in various fluorinated solvents (Scheme 18).

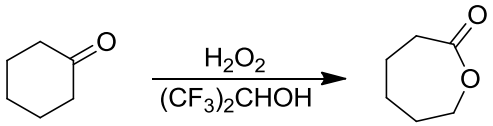


Scheme 18. Epoxidation of alkenes promoted by fluorinated alcohols.

Difficult epoxidations of terminal, aliphatic and 1-octene have shown that the activity in HFIP was greater than in TFE. Non-fluorinated alcohols as solvents such as ethanol and 2-propanol showed no activity. Increasing the temperature and/or using more concentrated hydrogen peroxide simply increased the conversion without changing the selectivity. For cyclic alkenes the reactivity was cyclopentene ~ cyclooctene > cyclododecene ~ cyclohexene.

The activation of hydrogen peroxide in HFIP also found application in the Baeyer-Villiger oxidation of ketones. Neumann and co-workers observed that cyclic ketones were cleanly converted into the corresponding lactones in good yields without the observation of by-products.[92] The substrate scope is rather limited, as acyclic ketones can only be converted with a small reaction rate.

Table 2. Baeyer-Villiger Oxidation of Ketones.[92][a]



Substrate	Conversion [%]	Substrate	Conversion [%]
cyclopentanone	88[b]	cyclooctanone	60[b]
cyclohexanone	82[b]	2-octanone	6.5[c]
cycloheptanone	68[b]	acetophenone	0

[a] Reaction conditions: 1.2 mmol of substrate, 2 mmol of 60% H_2O_2, 1 mL of HFIP, 60 °C, 20h. [b] Only lactones were obtained. [c] hexyl acetate was the only product.

2. Scientific Goals

The aim of this work is (1) the application of dendritic polyglycerol as support for various organocatalysts using a covalent approach; (2) to study the effects of immobilization and to compare them with non-immobilized analogs; (3) to investigate the effect of the high local catalyst concentration on the polymer; (4) to identify cooperative and dendritic effects; (5) to perform reusability studies.

The initial project will focus on the immobilization of L-proline **1** as our model organocatalyst onto hyperbranched polyglycerol (**5**). As described in the introduction, L- proline **1** is a frequently used organocatalyst, which enables important enantioselective transformations. Since high catalyst loadings are typically needed in such reactions, an immobilization approach will be used that makes use of the high degree of functional groups on hyperbranched polyglycerol (hPG). The catalyst will be attached via a partially flexible triazole linker, using the alcohol functionality of 4-hydroxyproline **1a**. The application of the proline catalyst **9** in the aldol reaction should be used to investigate potential dendritic effects and the influence of the surface loading on the outcome of the test reaction.

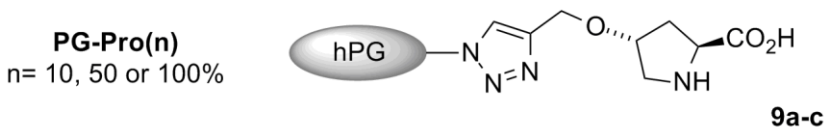


Figure 15. **L**-Proline **1** supported on hPG with a degree of functionalization of 10, 50 and 100%.

In the second project an efficient strategy for the immobilization of hexamethylphosphoramide (HMPA) should be developed and extended to various chiral phosphoramides, which can be applied in asymmetric transformations. The hPG supported HMPA analog is expected to be non-toxic and non-carcinogenic, in contrast to HMPA itself, because exposure by inhalation is prevented and also the skin penetration will at least be decelerated by the macromolecular size of over 10 kDa. Furthermore, it is expected that the amounts of HMPA that are usually required for reactions can be reduced to catalytic amounts. The mimic of a high total concentration may also facilitate transition states which involve two HMPA molecules.

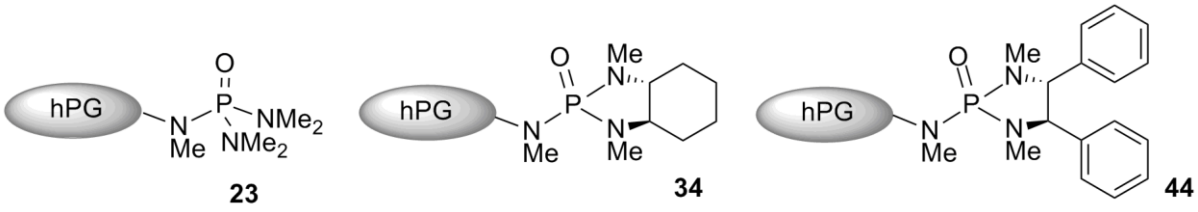


Figure 16. Supported HMPA analog **23** and two examples for chiral supported phosphoramides **34** and **44**.

Another goal of this thesis is the design of a new dendritic acid-based organocatalyt. For this project a chiral phosphoric acid should be designed, which is based on 1,1'-binaphthol, and should have dendritic polyglycerol substituents in the 3,3-position. The efficiency should be evaluated in the catalytic transfer-hydrogenation of ketimines.

Finally, catalytic reactions which are promoted by multiple hydrogen bond networks should be investigated. Promoter compounds are usually applied as solvents in order to sufficiently enhance the reaction rate, which is not only cost-intensive, but also requires the handling of corrosive compounds (e.g. fluorinated alcohols). Therefore, the immobilization of hexafluoroisopropanol (HFIP) onto hPG will be achieved. In collaboration with the group of Prof. Berkessel the promoting mechanism by cooperative effects should be investigated.

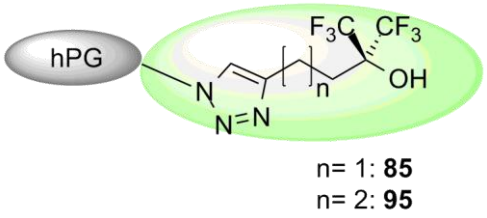


Figure 17. hPG **7** loaded with hexafluoroisopropanol analogs **84** and **94**.

3. Results and Discussion

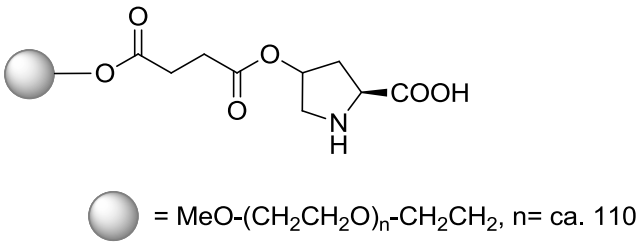
3.1 Proline

Although L-proline **1** has shown its efficiency in the aldol reaction, affording the corresponding products with high regio-, diastereo-, and enantioselectivity, there are some aspects of such transformations that could be improved. Among these are the large excess of the ketone donor that has to be used in the intermolecular reaction between a ketone and an aldehyde, long reaction times, and the rather high catalyst loading of 20-30 mol%. These problems are sometimes attributed to the low solubility of L –proline **1** in organic media.

Since, L-proline **1** is inexpensive and readily available in both enantiomeric forms, its immobilization could be considered useless. It should also be noted that immobilization is cost-intensive, because a more expensive proline derivative is used as starting material, and several synthetic steps are necessary for its immobilization. In order to counterbalance this point, three main reasons for proline immobilization may be considered: The first one is that usually up to 30 mol% of proline are used, which can be a large amount of catalyst, especially if the reaction is performed in multigram scale. Moreover, immobilization of proline may enhance its reactivity and stereoselectivity. The second reason is that an improved immobilization strategy can be applied to more expensive proline derivatives or other organocatalysts, and hence its recovery and reuse would be of higher impact from an economical point of view. In addition, immobilization allows the use of supported proline derivatives in different solvents which are normally not applicable for L-proline itself. Most important is that immobilization on a soluble support enables us to investigate and analyze properties of the supported catalyst, which would not be accessible e.g. with insoluble supports.

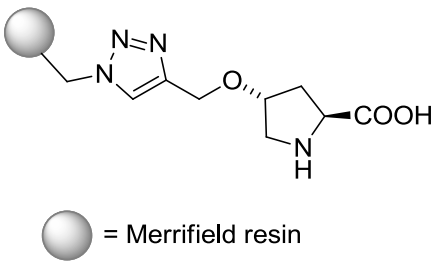
Three different general approaches for the immobilization of proline have been established so far: L-proline or a derivative is (a) covalently linked to a soluble (e.g. PEG, dendrimer), (b) an insoluble (e.g. polystyrene) support, or (c) the organocatalyst is non-covalently linked for instance by absorption (e.g. onto modified SiO_2) or electrostatic interaction (e.g. PS/SO_3H), or the catalyst is dissolved in ionic liquids and the product is extracted with an immiscible solvent (biphasic catalysis).

A soluble polymer-supported version of proline has been prepared by anchoring (2*S*,4*R*)-4-hydroxyproline **1a** to the monomethyl ether of PEG_{500} by means of a succinate spacer (Scheme 19).[93] Benaglia and co-workers reported that in the presence of 0.3 eq. of this catalyst, acetone reacted with several aldehydes in DMF at room temperature (40-60 h) to afford β-ketols in good yield (up to 80%) and high *ee* (up to >98%),[93a] comparable to those obtained with non-supported proline derivatives as the catalysts (those gave faster reactions).[73a] Their catalyst was recovered and recycled 3-4 times in the aldol reaction. However, the reaction occurred in slowly diminishing yields and virtually unchanged *ee*'s.



Scheme 19. Structure of proline immobilized on soluble support.

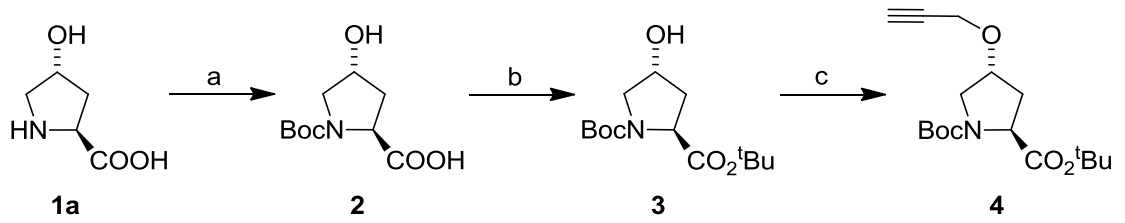
In 2006 new developments in the field were reported by Pericas and co-workers. A polystyrene-supported proline was prepared by 1,3-dipolar cycloaddition of an azide-substituted Merrifield resin with *O*-propargyl hydroxyproline (Scheme 20).[94] The resulting resin was used in the aldol reaction of several ketones (e.g. acetone) with arylaldehydes. Solvent screening showed that the reaction also worked when water was added. Both diastereo- and enantioselectivity were good, whereas pure DMF and DMSO gave lower stereoselectivity. However, by increasing the amount of water in these solvents, a higher stereoselectivity was observed, while the yield was lower. No decline of the performance was observed after three uses of the same catalyst sample.



Scheme 20. Structure of proline immobilized on an insoluble support.

3.1.1 Synthesis of Proline Immobilized on Hyperbranched Polyglycerol

For the development of a proline-based polymeric catalyst, it was decided to retain the amine and carboxylate function since both functional groups are essential for the asymmetric transformation. A covalent linkage should connect proline through a short spacer to polyglyceryl azide (**7**), which can be easily synthesized from polyglycerol (**5**) itself. L-hydroxyproline (**1a**), which has already been successfully applied as catalyst in the aldol reaction,[75a] was the building block of choice, since its immobilization via the hydroxy group leaves the amine and the carboxyl group available. The amine functionality of commercially available (2*S*,4*R*)-4-hydroxy-pyrrolidine-2-carboxylic acid (**1a**, Scheme 21) was protected using Boc anhydride,[95] and then **2** was converted into the *tert*-butyl ester **3** by treatment with potassium carbonate and *tert*-butyl bromide using benzyltriethylammonium chloride as phase transfer catalyst.[96] The "clickable" linker was introduced by reacting the protected hydroxyproline derivative **3** with sodium hydride and propargyl bromide[97] (Scheme 21).

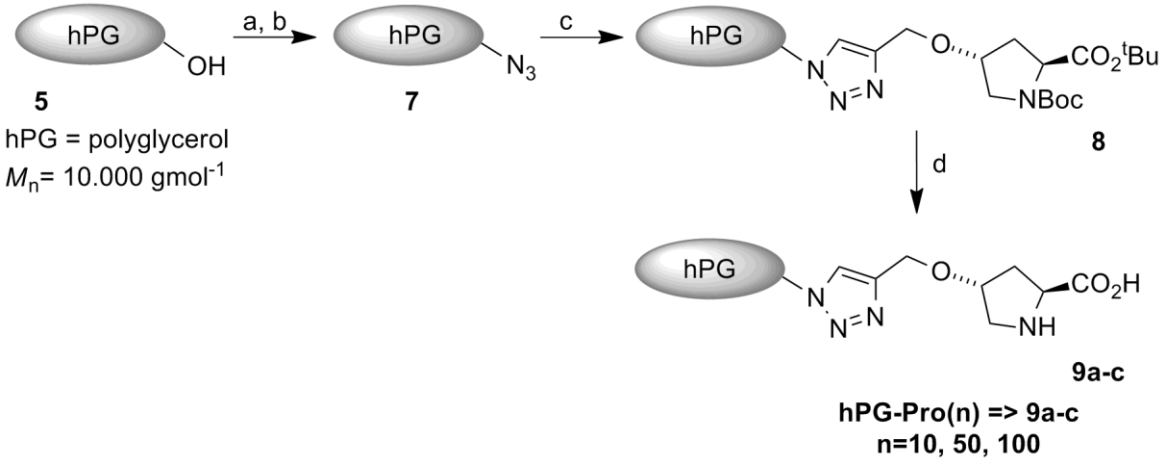


1a **2** **3** **4**

Scheme 21. Synthesis of proline derivative **4**. Reagents and conditions: (a) Boc_2O, 10% aq. NaOH, THF:H_2O (2:1), 0 °C, 95%; (b) ^tBuBr, $Et_3NBn^+Cl^-$, K_2CO_3, DMA, 55 °C; (c) NaH, propargyl bromide, DMF, -20 °C to rt.

The hydroxyl groups of polyglycerol **5** (M_w=10 kDa) (Scheme 22) were converted into good leaving groups by mesylation, and subsequently displaced by azide using sodium azide in dimethylformamide. Thereafter, the click reaction between azide-terminated polyglycerol **7** and the propargyl modified proline **4** was performed according to a modified procedure described in literature[98] to form the cycloaddition product hPG-Pro **8a-c** (Scheme 22). Optimal results were obtained with 10 mol% of $CuSO_4$, 10 mol% of sodium ascorbate and 10 mol% of *N*,*N*-diisopropylethylamine (DIPEA) to generate the desired structures in very good yields for all three degrees of functionalization (10, 50, and 100%). Traces of copper salts in the products were easily removed by washing with a saturated solution of ethylenediaminetetraacetic acid (EDTA). The boc-group and the *tert*-butyl ester of **8** were removed by treatment with

trifluoroacetic acid (TFA) in DMSO (1:1), releasing the protonated amine and the carboxy functionality (Scheme 22).

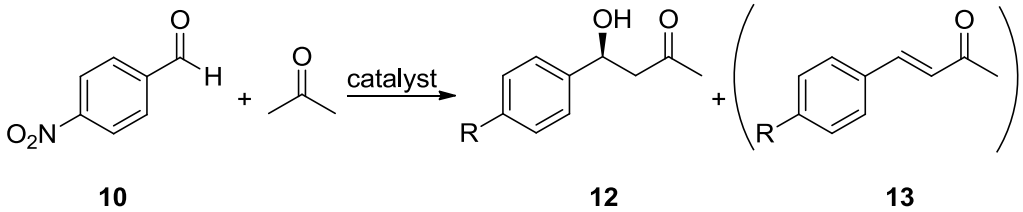


Scheme 22. Synthesis of hPG-supported proline derivatives **9a-c**. Reagents and conditions: (a) MsCl, pyridine, 0 °C to rt, 16 h; (b) NaN_3, DMF, 80°C, 16 h; (c) protected proline, DIPEA, sodium ascorbate, $CuSO_4$, THF/H_2O, rt, 16h; (d) TFA in DMSO (1:1), rt, 16h.

The low molecular weight impurities were removed from the polymeric catalysts **9a-c** by ultrafiltration and the pH was adjusted to neutral (pH 7). Complete deprotection was confirmed by ^{1}H NMR and ^{13}C NMR. The proline loading in mmol per gram polymer was determined using sodium acetate as an internal standard and D_2O as NMR solvent. The CH_2 signal of the five-membered proline ring was integrated in the ^{1}H NMR spectra against the CH_3 signal of the acetate.

3.1.2 Experiments with Immobilized Proline in the Asymmetric Aldol Reaction

Among a variety of aldol reactions, we choose the one using 4-nitrobenzaldeyhde (**10**) with acetone as a model (Scheme 23).



Scheme 23. The model aldol reaction of aldehyde **10** with acetone.

For that purpose, the catalysts hPG-Pro(10%), hPG-Pro(50%) and hPG-Pro(100%) and commercially available L-proline **14** were applied and the results were compared with those obtained with the non-supported counterpart **19** (Figure 18).

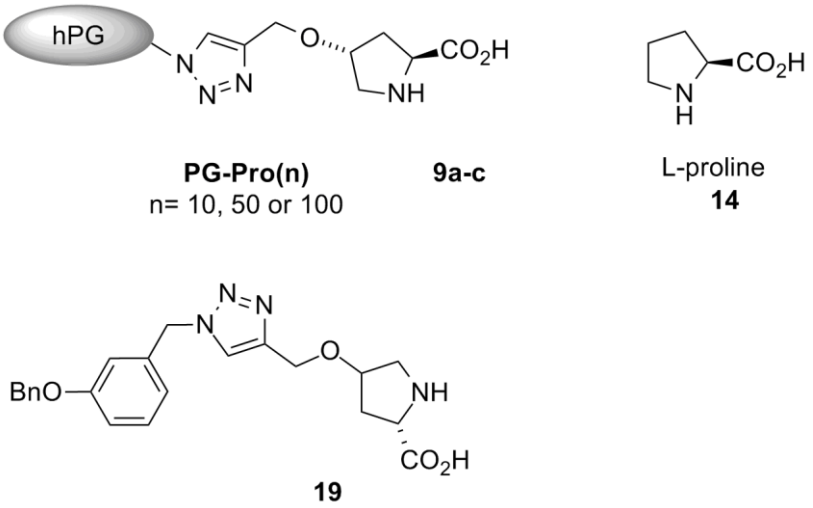


Figure 18. Structures of L-proline, non-supported proline catalyst **19**,[99] and polymeric proline catalysts **9a-c.**

In the aldol reaction (Scheme 23) the polymeric catalyst **9a** gave almost quantitative conversion and a satisfying yield of 71 % (aldol product **12**) in already 24 hours (Table 3, Entry 5). Moreover, the enantiomeric excess, induced by the dendritic catalyst **9b**, is 63%, which is similar to results obtained with L-proline **14** under the same conditions, where a value of 65% *ee* was observed. The non-supported analog **19**, which is much closer to the structure of **9** than non-supported L-proline **14** and therefore better comparable to the supported proline, just gave the aldol product in considerably lower enantiomeric excess of 51% (Table 3, Entry 5). This result is remarkable, since enantioselectivities obtained with hPG-supported catalysts are sometimes very low which has been explained with a "negative dendritic effect."[100] In contrast to these results a higher stereoselectivity was observed with immobilized proline **9b.**

Table 3. The model aldol reaction with hPG-supported proline **9a-c**.[a]

Entry	Catalyst	Conversion[b] (%)	Yield[b] (%)	*ee*[c] (%)
1	None	0	-	-
2	non-supported proline **19**	> 99[e]	> 99[e]	51
3	hPG-Pro (100%) (**9c**)	0	-	-
4	hPG-Pro (50%) (**9b**)	57	44	62
5	hPG-Pro (10%) (**9a**)	97	71	53

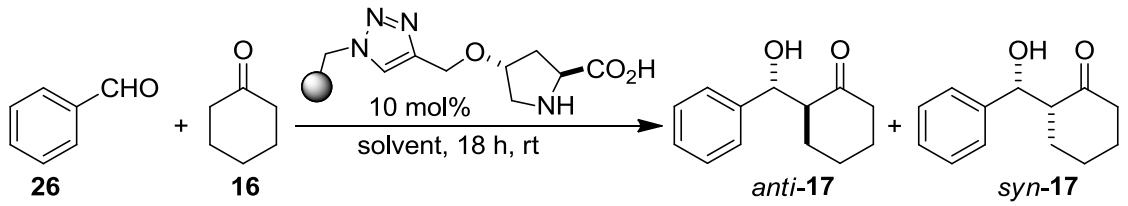
[a] Reaction conditions: 0.5 mmol of aldehyde **10**, 1 ml acetone, 4 ml DMSO, 0.3 equiv. of polymer supported proline **9a-c**, 24 h, rt. [b] Conversions and yields determined by ^{1}H NMR. [c] *ee* determined by HPLC, using Chiralcel OJ column. [d] nd = not determined. [e] Determined by ^{1}H-NMR; reaction time: 30 h.

Besides yield and stereoselectivity the experiments revealed two general issues for the polymeric catalyst **9**. The reaction product **12** is always accompanied by the elimination byproduct **13** and the catalytic experiment, performed in DMSO at room temperature with 30 mol% of the polymeric catalyst showed a remarkable influence of the dendritic support on the conversion, yield and enantioselectivity (Table 3). In terms of stereoselectivity, the supported catalysts **9a** and **9b** led to higher enantiomeric excess of product 1**2** than the click proline analog **19.**

Optimization Experiments – Water Addition

The addition of water to the proline catalyzed aldol reaction has been reported by Pericas et. al as a key to ensure high stereoselectivity. They used a polystyrene based hydroxyproline derivative, which was immobilized using click chemistry (Table 4).[97] Very interestingly, the aldol reaction between benzaldehyde **26** and cyclohexanone **16** worked nicely in water, yielding the aldol product **17** in high diastereoselectivity and high *ee* for the major *anti* diastereomer (Entry 1). On the other hand, the diastereoselectivity was lost and the *ee* for the *anti* diastereomers deteriorated when good resin-swelling solvents such as DMSO (Entries 2) were used in the reaction. Increasing the water content in DMSO improved the diastereo- and enantioselectivity, but at the expense of high yields (Entry 3-5). Without solvent the reaction proceeded very slowly (Entry 6).

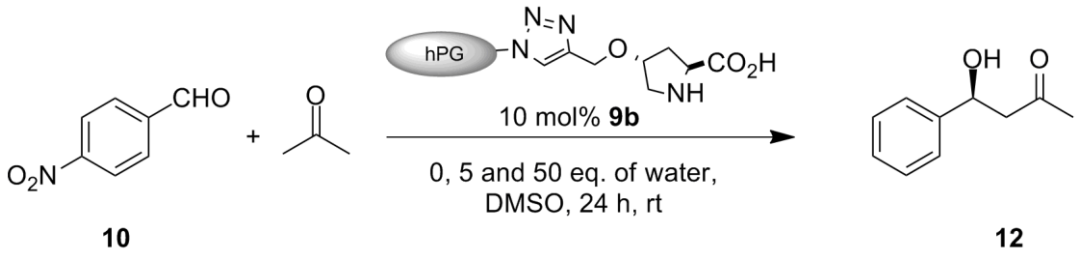
Table 4. Solvent effects on the aldol reaction of cyclohexanone (**16**) with benzaldehyde **26** .



Entry	Solvent	Yield[a] (%)	*anti*/*syn*[b]	*ee anti*[c] (%)	*ee syn*[c] (%)
1	water	26	95:5	96	61
2	DMSO[d]	95	50:50	84	89
3	DMSO/water 94:6	90	82:18	91	90
4	DMSO/water 71:29	73	91:9	95	95
5	DMSO/water 50:50	55	93:7	96	87
6	neat	<5	nd	nd	nd

[a] Isolated yield. [b] Determined by ^{1}H NMR of the crude product. [c] Determined by HPLC using a chiral stationary phase. [d] Synthesis grade.

Prompted by the results of Pericas et al., the influence of water (5 and 50 eq.) in the aldol reaction of nitrobenzaldehyde **10** and acetone (Scheme 24) was investigated using hPG-proline catalyst **9b** which showed the best enantiomeric excess in the initial experiment (Table 3).



Scheme 24. Investigation of hPG-Pro **9a-c** in the aldol reaction.

The results for catalyst hPG-Pro(50) (**9b**) are summarized in Figure 19. It is evident that the reaction rate increasesdue to the addition of water, but at the expense of the enatioselectivity, which dropped from 62% *ee* to 16% *ee*, when 50 eq. of water were added. The ratio of aldol product **12** to the elimination product **13** remained constant with a value of 80:20 and was apparently not influenced by the water addition. Overall, the results showed two opposing trends for conversion/yield and *ee*. Both conversion

and yield increased with the amount of water. A maximum of 46% conversion was obtained by the addition of 50 eq. of water. However, a higher amount of water led to a dramatic decrease of the enantiomeric excess.

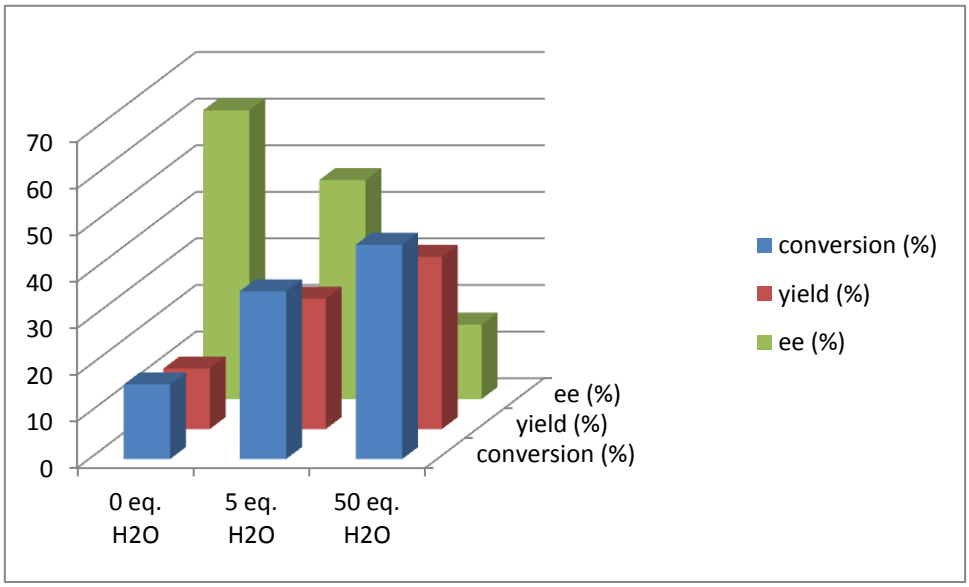


Figure 19. Results for the aldol reaction of nitrobenzaldehyde **10** with acetone catalyzed by hPG-Pro(50) (**9b**) when varying the water content. Reaction conditions: 0.5 mmol of aldehyde **10**, 13.5 mmol of acetone in 4 mL DMSO, 0.05 mmol of polymer-bound proline **9b**, 24 hours, rt.

Experiments with the hPG catalyst **9c** with a higher proline-loading showed the same opposing trend: higher conversion when more water was added accompanied by diminished enantiomeric excess, but without water added, the hPG-Pro(100) (**9c**) did not lead to any conversion. Possibly, the high loading with catalytically active sites on the polymeric surface requires the addition of water to solubilize the surface charged polymer.

Solvent and Concentration Effects

The effect of different solvents for the supported proline-catalysts has been investigated by many groups.[99] Depending on the support, pure DMSO and DMSO:acetone mixtures have been mostly applied. Since the solubility of the polymeric catalyst **9b** in acetone was very poor, a 4:1 DMSO/acetone mixture was used to ensure homogeneous reaction conditions. In order to find the ideal amount of DMSO the concentration was varied and studied (Figure 20). The substrate to catalyst ratio was adjusted to 10 mol% to avoid full conversion in all samples.

It was observed that with increasing the concentration the conversion/yield and enantiomeric excess slightly decreased (Figure 20). However, the trend was stronger for the enantiomeric excess (61% vs. 54%) than for the conversion (47% vs. 43%). It was assumed that the 1:2 ratio of DMSO to acetone caused partial inhomogeneity of the reaction solution, which led to diminished results in the aldol reaction. Further experiments were performed with a 4:1 ratio DMSO/acetone to avoid this problem.

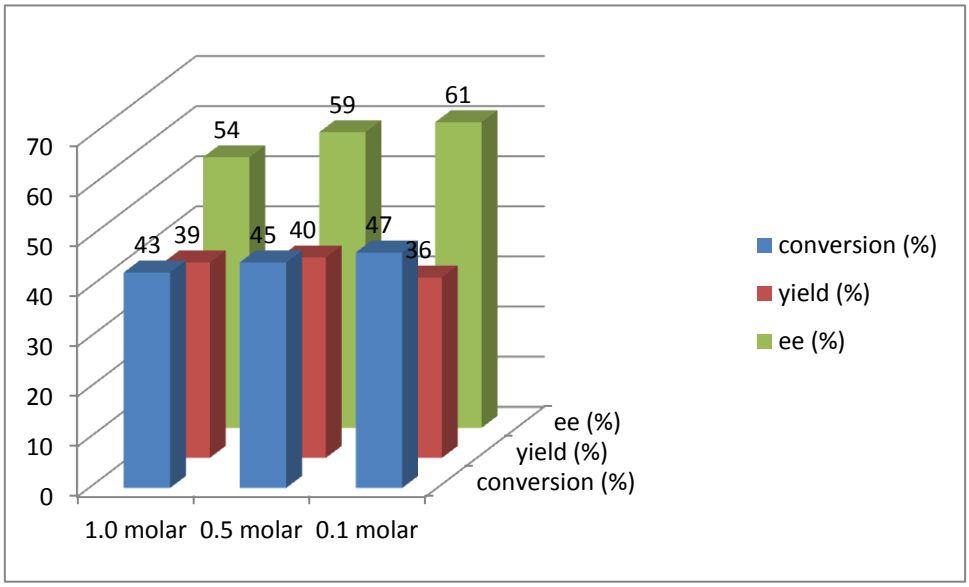


Figure 20. Results for the aldol reaction of aldehyde **10** with acetone catalyzed by **9b** using different concentrations. Reagents and conditions: 0.5 mmol of aldehyde **10**, 13.5 mmol of acetone in 0.5, 1.0 or 4.0 mL of DMSO, 0.05 mmol of polymer-bound proline **9b**, 48 hours, rt.

Influence of the Reaction Time

The influence of the reaction time with respect to the parameters conversion, yield, and *ee* has been investigated. In the initial experiments the aldol reaction was stopped before it was completed to clearly show the trends. Now the interest was whether full conversion could be obtained within a reasonable amount of time. Secondly, the focus was on the evolution of the enantiomeric excess and yield over the reaction time.

Interestingly, full conversion of **10** was already achieved after 48 hours (Figure 21) with polymeric catalyst **9b** and a loading of 30 mol%. Whereas the aldol reaction with proline on other supports required reaction times of 4 to 9 days to obtain full conversion.[99] With catalyst **9b** conversion and yield increased with time, in contrast to other proline catalysts on insoluble support, where a deterioration of the product over time had been reported.[99] It should be mentioned that the amount of elimination

product **13** slightly increased with the reaction time. After 24 hours a ratio of 80:20 was obtained, which increased after 48 hours to 75:25. The enantiomeric excess remained constant at 61% (±2%) over time independent of the substrate to catalyst ratio (Figure 21). The best results in terms of yield and enantiomeric excess were obtained after 48 hours with a loading of 30 mol% using hPG-Pro **9b**. In comparison with other proline supported polymers, aldol reactions with hPG-Pro **9b** were at least two to four times faster than other systems previously reported.[101]

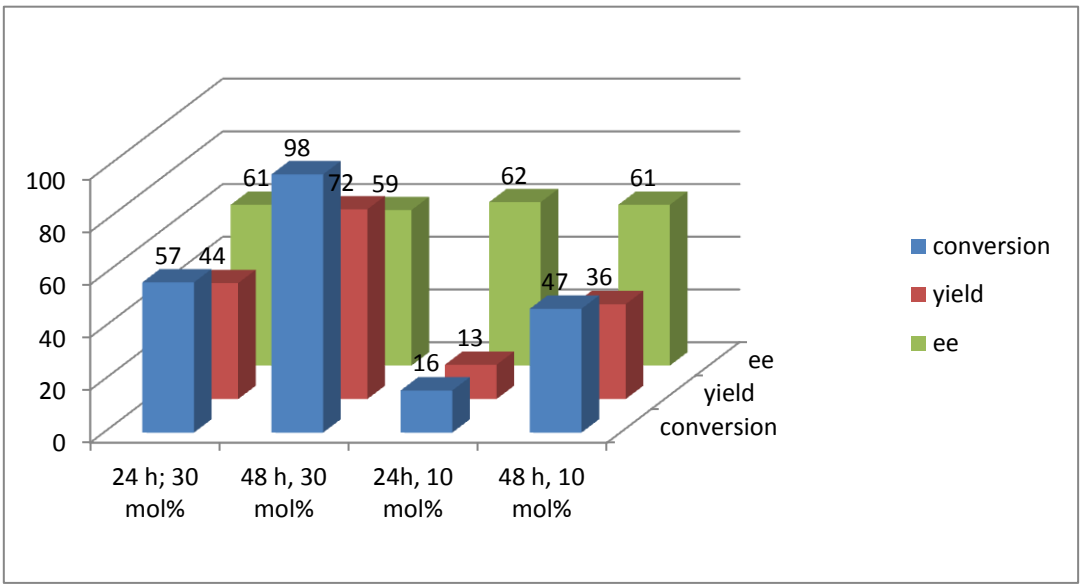


Figure 21. Results of the aldol reaction of nitrobenzaldehyde **10** with acetone with variations for the reaction time. Reagents and conditions: 0.5 mmol of aldehyde **10**, 13.5 mmol of acetone in 4.0 mL of DMSO, 10/30 mol% of hPG-Pro(50) **9b**, 24/48 hours, rt.

Influence of the Substrate/Catalyst Ratio

The amount of catalyst which is needed for proline catalyzed aldol reaction has mostly been reported to be 30 mol% no matter if it is a supported or non-supported catalyst.[73a] The aim was to investigate whether the substrate to catalyst ratio could be reduced, e.g., to 10 mol%. In the aldol reaction with hPG-Pro(50) **9b**, 10 mol% loading was compared to 30 mol%. For the immobilized proline a remarkable catalyst activity was observed even when only 10 mol% were used (Figure 22). However, the reaction time had to be extended to 48 hours to obtain as high yield as with 30 mol% of **9b**.

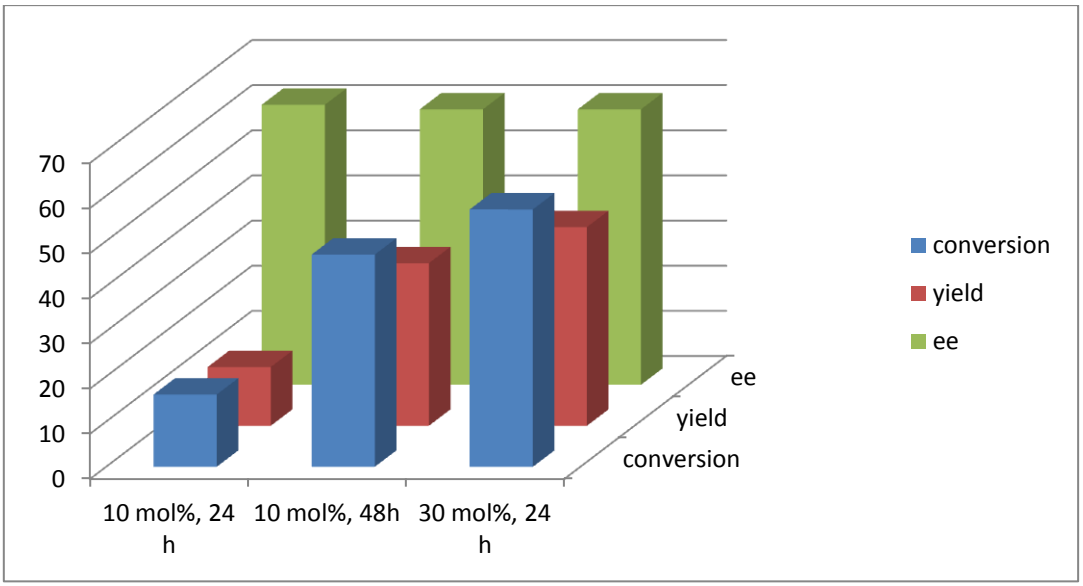


Figure 22. Results of the aldol reaction catalyzed by hPG-Pro(50) **9b** with variations of the substrate to catalyst ratio. Reagents and conditions: 0.5 mmol of aldehyde **10**, 13.5 mmol of acetone in 4.0 mL of DMSO, 10/30 mol% of hPG-Pro(50) **9b**, 24/48 hours, rt.

A Dendritic Effect with hPG-Pro?

Dendritic effects have been observed in the past for a number of metal-based catalysts, but only rarely for organocatalysts, in particular chiral organocatalysts.[7b,7d,31a,55,100,102] In order to investigate a potential dendritic effect we compared hPG-Pro(10) **9a**, hPG-Pro(50) **9b**, and hPG-Pro(100) **9c** in the aldol reaction under identical conditions. The overall catalyst to substrate ratio remained constant in all samples. Upon increasing the surface loading with proline from 10% to 50%, the enantiomeric excess significantly improved from 53% to 62% and the ratio of aldol product **12** to elimination product **13** increased from 73% to 77% (Figure 23). Overall, it can be assumed that the close proximity between two proline units is critical for the catalytic performance of the catalyst in the aldol reaction.

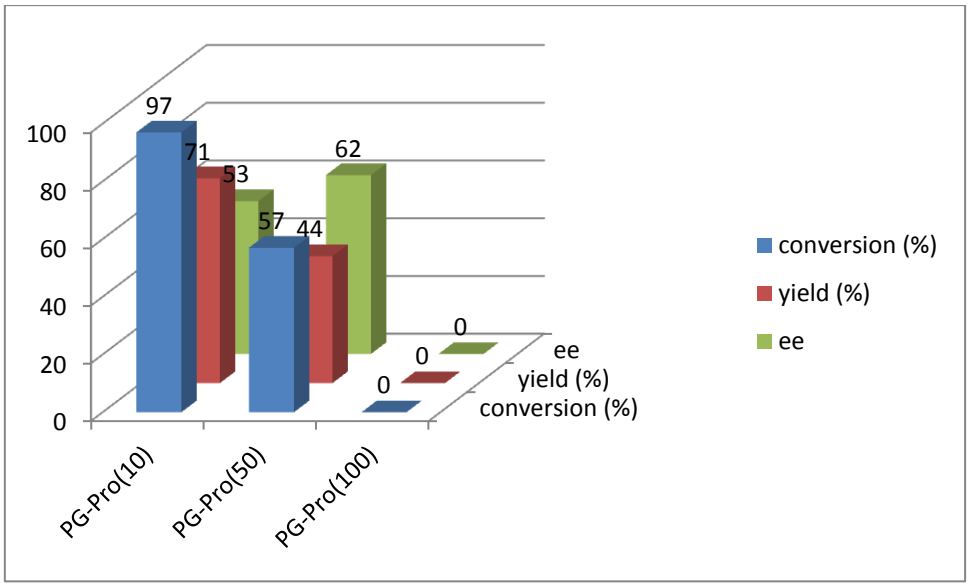


Figure 23. Results of the aldol reaction of nitrobenzaldehyde **10** with acetone, catalyzed by hPG-Pro(10-100) **9a-c**. Reagents and conditions: 0.5 mmol of aldehyde **10**, 13.5 mmol of acetone in 4.0 mL of DMSO, 30 mol% of hPG-Pro(10/50/100) **9a-c**, 24 hours, rt.

Unfortunately, the catalyst with the highest loading, hPG-Pro(100) **9c**, did not show any conversion, which is most likely due to its insolubility in the DMSO/acetone solvent mixture (Figure 23). However, small amounts of water could prove the activity of hPG-Pro(100) **9c**. As expected, the enantiomeric excess was low due to the water addition (Figure 24).

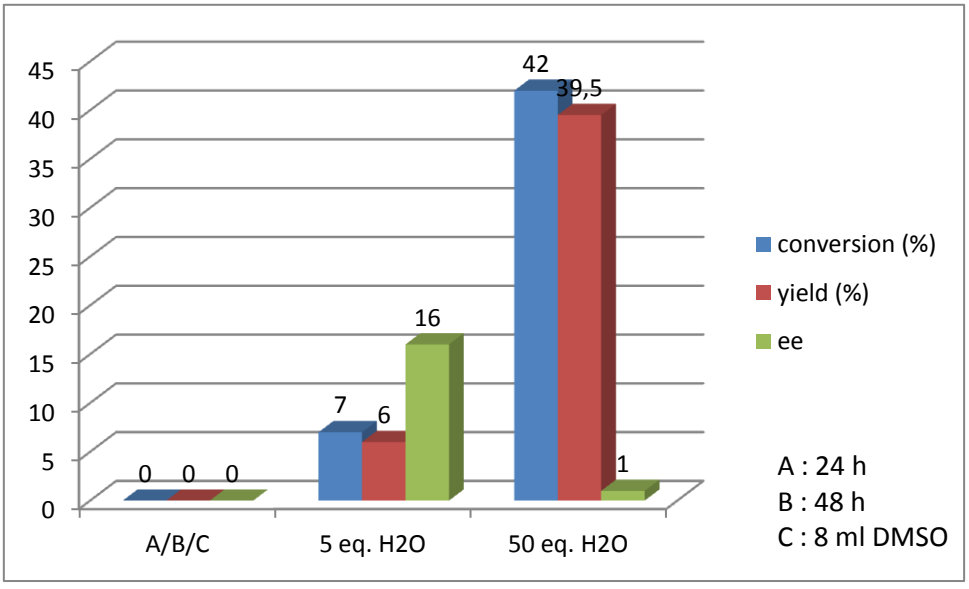


Figure 24. Results of the aldol reaction catalyzed by hPG-Pro(100) **9c**. Reagents and conditions: 0.5 mmol of aldehyde **10**, 13.5 mmol of acetone in 4 mL of DMSO, 30 mol% of hPG-Pro(100) **9c**, 24 hours, rt.

Conclusion

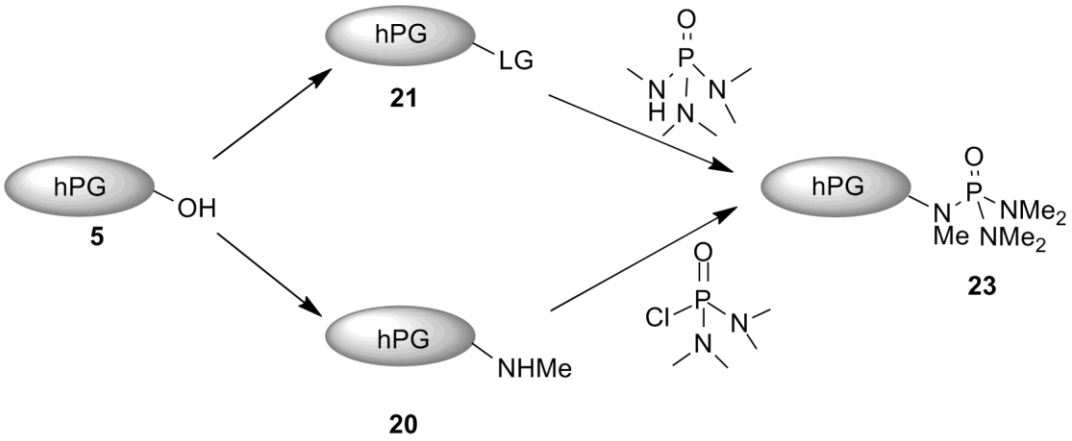
Over the last ten years, the immobilization of proline and proline derivatives has attracted much interest.[97,103] Many concepts for the immobilization of proline **14** have been developed, but the perfect support material has not yet been discovered. With hPG as support the advantages of homogeneous materials were combined with the easy recovery that is known for heterogeneous supports. With a covalent linkage of proline, leaching of the catalyst could be avoided. So far, the homogeneous PEG supported proline benefits from a high loaded support, but recovery requires precipitation which is often not quantitative. The polyglycerol with high molecular weight is a support that can be easily recovered by membrane ultrafiltration. In the aldol reactions catalyzed by proline **14** supported on polyglycerol **9** high conversion and enantioselectivity could be observed and it was possible to carry out reactions in highly polar solvents, which has many applications. The reaction rate of the hPG-Pro **9a-c** in the aldol reaction is much higher than with proline on insoluble support (e.g. polystyrene) under the same conditions.[7c] But the covalent immobilization requires several synthetic steps, which also makes a supported catalyst, such as catalyst **9**, expensive. As a consequence, the number of steps was reduced to five. A subsequent dendronization of the support could be omitted, because this feature is already included in the hyperbranched polymer hPG.

3.2 Hexamethylphosphoramide (HMPA)

Due to its superior solvation and coordination properties, hexamethylphosphoramide (HMPA) is still widely used in research.[104] It facilitates a number of reactions in organic synthesis, such as typical C-C bond forming reactions (aldol-, and allylation reaction, etc.), as well as various transition metal mediated reactions. However, HMPA induces nasal cancer in rats upon inhalation and has been identified as a potential carcinogenic reagent for humans. These characteristics in addition to its difficult removal from product mixtures and its costs limit the broad use of HMPA, and it is actually forbidden in industry. The superior solvent and coordination properties of HMPA in combination with its practical limitations make the development of a supported HMPA analog most desirable.[105] It seemed likely that the polymeric support might show new and potentially useful catalytic properties. We have recently reported several catalysts that were supported on a soluble polymeric backbone and have shown that dendronized catalysts often benefit from better reaction kinetics in solution and that the catalyst loading can often be decreased by using dendritic architectures.[7a,7b,100,106] Outstanding examples for a positive dendritic effect were also reported.[100,106a] Immobilization onto a polymeric support also decreases the threat of HMPA inhalation. Potential contamination by skin penetration can at least be reduced by immobilization on the polymeric support,[107] whereas non-supported HMPA easily penetrates the skin due to its high swelling properties.[108] The multivalent presentation of HMPA on a dendritic polymer also generates a high local concentration, which is required in many reactions, where HMPA is currently being employed.

3.2.1 Synthesis of an HMPA Analog Supported on Polyglycerol

Two strategies for the covalent immobilization of HMPA analogs on polyglycerol **5** were envisioned. For the first strategy, polyglycerol **5** is functionalized with good leaving groups to give **21**, which upon treatment with an appropriate phosphoramide precursor forms the corresponding polymeric HMPA analog **23**. In the second approach, the hydroxy groups of hPG **5** are converted to monomethylamine functionalities (hPG-NHMe, **20**), which subsequently react with tetramethylphosphorodiamidic chloride to give the desired product **23** (Scheme 25).



Scheme 25. Two synthetic concepts for the immobilization of HMPA on hPG **5**.

The goal for the immobilization of HMPA on the polymeric support was to be as close as possible to the structure of non-supported HMPA. That means that we did not want to use a linker system, which would have made the approach less general and would have required more synthetic steps. The synthetic aim was to have only one coupling step of the phosphoramide precursor to the polymer and no more synthetic steps with the hPG-supported HMPA.

For the first approach, two modifications of polyglycerol with good leaving groups (**21**) were synthesized, first by mesylation of hPG **5** to give hPG-OMs (**6**) and second by replacing the hydroxyl group with a chlorine using thionyl chloride. Although both functional groups (mesylate and chloride) can be considered to be good leaving groups, they could not be replaced by the phosphoramide precursor.

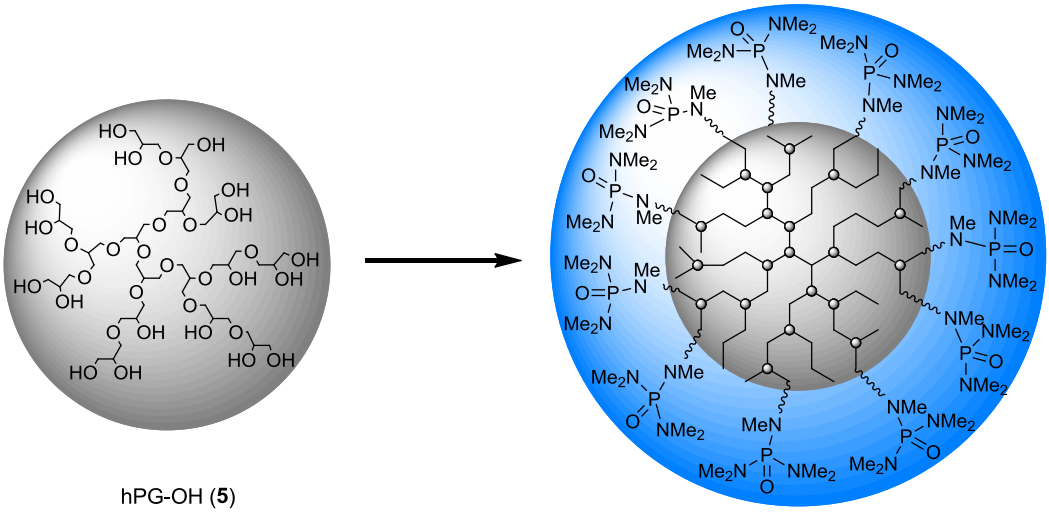
In the second approach, polyglyceryl-methylamine (**20**) was prepared starting from hPG**5** by converting the OH groups of **5** into monomethylamino groups. This replacement was achieved by first converting the alcohol into the mesylate[63d] and subsequently displacing the mesylate with methylamine. Therefore, an autoclave was filled with hPG-OMs (**6**) dissolved in a small quantity of dimethylformamide and monomethylamine, which was condensed before for easy handling. The autoclave was sealed, stirred with a magnetic stir bar and an external stirrer plate and heated to 60 °C for 24 hours. Small molecular weight compounds were separated from **20** by membrane ultrafiltration and the anionic mesylate, which was still present due to ionic interactions, was removed by addition of a small portion of triethylamine to the filtration cell. All mesylate groups were replaced by amine which was proven by the disappearance of the mesylate signal at 3.2 ppm in the ^{1}H-NMR and by elemental analysis. In the initial

experiments commercial methylamine 2.0 M in tetrahydrofurane was applied in a glass pressure tube at 120 °C, which led to incomplete conversion of the mesylate groups of **6** and partially insoluble product **20**. Best results were obtained by using pure methylamine (~ 10 eq. per mesylate) with a higher final concentration in the reaction mixture, and using a metal autoclave, which could hold the pressure more reliably. The solubility problem was prevented by decreasing the reaction temperature from 120 °C to 60 °C (Table 5)

Table 5. Screening of reaction conditions for the synthesis of hPG-methylamine **20**.

Entry	Amine	Time [h]	Solvent	Conditions	Temp. [°C]	Yield [%]
1	methylamine solution, 2.0 M in THF	48	DMF	pressure tube	120 °C	partially insoluble product
2	methylamine solution, 2.0 M in THF	48	DMF	autoclave	120 °C	partially insoluble product
3	methylamine as condensed gas, ~ 10 eq.	24	DMF	autoclave	60 °C	95 %

The amine modified hPG **20** was then directly coupled to commercially available bis(dimethylamido)phosphoric chloride (**22**) using *n*-BuLi as a base in anhydrous tetrahydrofuran at -78 °C (Scheme 25). The polymeric HMPA analog **23** (Scheme 26) was separated from small molecular weight compounds by ultrafiltration. The degree of functionalization with HMPA was determined by ^{31}P-NMR using triphenylphosphine oxide as an internal standard and was found to be up to 2 mmol g^{-1}. Two different loadings were synthesized, whereby 1 mmol HMPA per gram refers to compound **23a** and 2 mmol HMPA loading refers to compound **23b**.



Scheme 26. Structure of hPG (**5**) and the functionalized HMPA-analogs **23a** and **23b**.

Since the solubility of polymeric catalysts sometimes limits its broad application, the polymeric compounds **23a/b** were investigated in terms of solubility. As shown in Table 6 the polymeric HMPA analogs **23a/b** are soluble in a variety of organic solvents ranging from halogenated to non-halogenated ones, as well as in water. The only exception are alkyl ethers.

Table 6. Solubility of hPG-supported HMPA-analogs **23a/b** in different solvents.

Entry	Solvent	Solubility[a]
1	chloroform	+
2	dimethylformamide	+
3	methanol	+
4	acetonitrile	+
5	water	+
6	dichloromethane	+
7	tetrahydrofuran	-

[a] 5 mg hPG-HMPA **23a/b** in 1 mL of solvent.

The catalytic performance of hPG-HMPA **23a** was compared to commercially available HMPA (**24**) as the non-supported analog of our polymeric catalyst **23**.

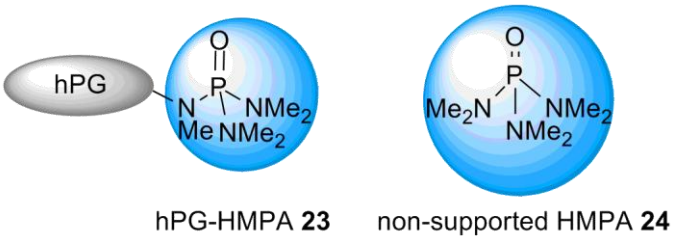
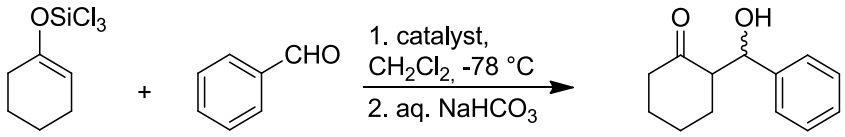


Figure 25. Schematic structure of supported HMPA analog **23** and non-supported HMPA **24**.

3.2.2 Experiments with hPG-Supported HMPA-Analogs 23a/b

The supported HMPA analog **23a** and the non-supported species **24** were investigated in the Mukaiyama aldol reaction of trichlorosiloxy cyclohexene (**25**) with benzaldehyde **26**.[109] The first goal was to show that the immobilization of HMPA on a dendritic support leads to an active catalyst. Initial experiments were performed as described in the literature without the use of any additives.[82c]It was shown, that hPG **23a** was highly reactive in the test reactions and gave even slightly better yields than the non-supported analog **24** (Table 7, Entry 2 and 3). As a control experiment, the test reaction was also performed in the absence of a catalyst, which gave very low yields (Table 7, Entry 1). Since the polymer **23a** promoted the test reaction quite nicely, the question appeared whether compound **23a** might be able to gernerate (diastereo-) selectivity in the product. For that purpose the ratio of the *syn*-to the *anti*-aldol product was compared by ^{1}H-NMR. It was found that polymer **23a** gave almost a 1:1 mixture of *syn*- and *anti*-product in the test reaction. The same result was observed for the non-supported analog **24**, which could lead to the conclusion that they both promoted the Mukaiyama aldol reaction along the same reaction pathway. In comparison, the test reaction without catalyst led to a *syn*/*anti*-ratio of 20:1.[82d] The equal *syn*/*anti* ratio in the aldol reaction with **23a** and **24**, respectively, was alsosurprising because it has been often observed in the past that selectivities of a certain catalyst changed upon immobilization.[100]

Table 7. Mukaiyama aldol reaction catalyzed by hPG-HMPA **23a**, non-supported HMPA **24**, and without a promoter.



25 **26** **27**

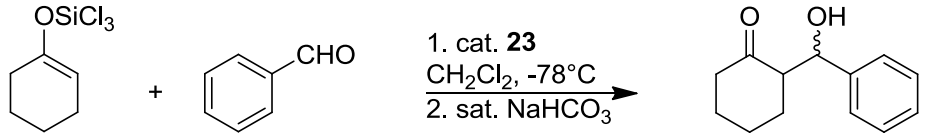
Entry	Catalyst	Amount of catalyst [mol%]	*syn*/*anti*[a]	Yield[b] [%]
1	None	0	> 20:1	< 5
2	hPG-HMPA (**23a**)	10	1 : 1	63
3	HMPA (**24**)	10	1 : 1	60

[a] Determined by ^{1}H-NMR analysis. [b] Isolated yield after column chromatography.

It was surprising that both catalyzed reactions (with **23a** and **24**, respectively) did not show any selectivity towards the *anti*-product. When HMPA **24** is used as co-solvent in the aldol reaction it clearly favored the *anti* product.[82c] Usually a *syn*/*anti* ratio of 1 to 5 was observed in such experiments. To investigate whether the mentioned selectivity can also be observed with catalytic amounts, the reaction parameters have been optimized under catalytic reaction conditions in accordance to examples in literature.[82c] As a variation the benzaldehyde **26** is now slowly added to the reaction and diluted beforehand. Diisopropylethylamine is used as an additive as suggested by Denmark et al.[82c] to enhance the *anti*-selectivity and at least, the reaction mixture was slightly more concentrated. In effect, under these optimized reaction conditions for polymer **23a** the yield increased from 63% in the initial experiment to 93% and the diastereoselectivity was improved from a 1:1 to a 1:4 ratio (Table 8, Entry 2), which is a moderate *anti*-selectivity. The non-supported HMPA **24** led to comparable results, such as 98% yield and a *syn*/*anti*-ratio of 1:5 (Table 8, Entry 1). In conclusion, the performance of supported HMPA **23a** could be improved remarkably by optimization, so that almost quantitative yield is observed in the aldol reaction and a moderate *anti*-selectivity in the product. Even with HMPA **24** in solvent-like quantities, no better yields or selectivities are observed. These findings clearly show that hPG-HMPA **23** is a feasible substitute for HMPA, and that it is as catalytically as effective as the non-supported analog **24**, but at

the same time avoids the threat of inhalation of toxic HMPA. In addition, hPG-HMPA **23** can be recycled as it will be shown for the allylation reaction.

Table 8. Aldol reaction catalyzed by **23a** and **24** under optimized conditions.



25 **26** **27**

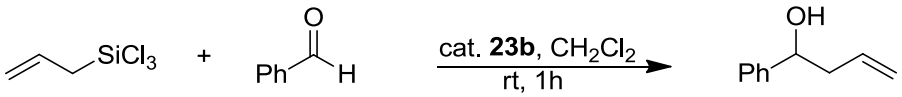
Entry	Catalyst	Amount of catalyst [mol%]	*syn*/*anti*[a]	Yield[a] [%]
1	non-supported HMPA **24**	10	1:5.3	98
2	hPG-HMPA **23a**	10	1:4.2	93

Conditions: 1.0 equiv. benzaldehyde **26**, 1.1 equiv. silyl enol ether **26**, 5.0 equiv. DIPEA, 10 mol% catalyst. Slow addition of diluted benzaldehyde **26** over 1 h; final concentration: 0.8 M. [a] Determined by ^{1}H-NMR analysis.

Although the dendritic HMPA showed an excellent catalytic performance, the overall aim was to investigate if a positive dendritic effect takes place. In this case the catalyst loading could be lowered to truly catalytic amounts which are most favorable in a region where the non-supported catalyst is not active at all, while at the same time the selectivity and activity could be retained. To achieve this goal, the amount of HMPA on the polymer surface was doubled from 1 to 2 mmol, thereby increasing the local concentration of HMPA. With this catalyst in hand, another C-C coupling reaction was investigated, the allylation reaction of benzaldehyde **26** with allyl trichlorosilane **28**.[80d] This reaction was chosen because HMPA is essential for this type of coupling, and, since no product is formed without its presence, its effect is more easily comparable to the aldol reaction, where the competing background reaction has to be taken into account. In the initial experiment of the allylation between allyl trichlorosilane **28** and benzaldehyde **26** with 10 mol% catalyst loading, the dendritic catalyst **23b** performed best (97% yield), followed by catalyst **24** with 40% yield (Table 9). The allylation reaction without catalyst gave no conversion after 1 hour (by ^{1}H-NMR), while the catalyzed reactions were almost finished after less than 10 min (observed by TLC). The next goal was to reduce the catalyst loading. Surprisingly, a nearly quantitative yield

was obtained with only 0.5 mol% of dendritic catalyst **23b,** while the allylation reaction catalyzed by non-supported HMPA (**24**) was very slow and gave less than 2% yield after 1 hour. With those experiments it could be demonstrated that the high local concentration of the catalyst on the polymer surface makes reactions feasible that usually need higher catalyst concentrations. The higher loaded polymer **23b** showed the predicted positive dendritic effect.

Table 9. Results of the allylation reaction of allyl trichlorosilane **28** and benzaldehyde **26** catalyzed by polymer **23b** and HMPA **24**.



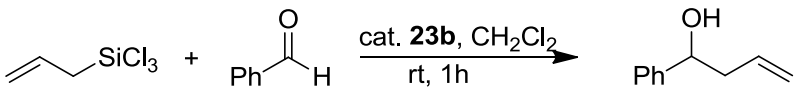
28 **26** **29**

Entry	Catalyst	Loading [mol%]	Yield[a] [%]
1	none	0	0
2	non-supported HMPA (**24**)	10	40
3	non-supported HMPA (**24**)	0.5	< 2
4	hPG-HMPA (**23b**)	10	97
5	hPG-HMPA (**23b**)	0.5	99

[a] Determined by ^{1}H-NMR analysis.

The reusability and recyclability of the dendritic catalyst **23** was investigated by reusing catalyst **23b** in three consecutive allylation reactions. After each catalytic run the catalyst **23b** was successfully separated from the product by ultrafiltration. Due to the small reaction scale and the large size of the ultrafiltration cell, small amounts of catalyst per run could not be recovered, which was rather a technical problem. Here the application of a continuously operating stirred cell could improve the recovery of the catalyst. With the help of ^{31}P-NMR, it was proven that the product was not contaminated with the catalyst. As shown in Table 10, no loss of activity could be observed in the experiments.

Table 10. Recovery of hPG-HMPA **23b** in the allylation reaction.



28 **26** **29**

Run	Catalyst leaching[a]	Conversion[b]
1st	not detectable	quant.
2nd	not detectable	quant.
3rd	not detectable	quant.

[a] Determined by ^{31}P-NMR. [b] Determined by ^{1}H-NMR.

Summary and Conclusion

With the first successful synthesis of HMPA covalently supported on a soluble polymer, it has been shown that dendritic polyglycerol **5** is suitable for the immobilization of organocatalysts. The high local concentration of HMPA at the surface of the polymer was used to mimic a high total concentration of HMPA in the reaction, which is necessary since the investigated aldol and allylation proceeds via a cooperative mechanism, which means that two or more HMPA molecules are involved in the transition state. Therfore, the goal was to mimic this cooperative effect with our polymeric HMPA derivative. The supported catalyst has been investigated in the Mukaiyama aldol reaction (test reaction) and showed a high activity comparable to the using HMPA as a solvent, e.g. rate enhancement and *anti*-selectivity. By increasing the HMPA loading on the polymer a positive dendritic effect has been shown in the allylation. In detail, the catalyst ratio could be reduced to 0.5 mol%, yielding almost quantitative yield, while the non-supported catalyst **24** did not show significant conversion (< 2%) at this concentration level. Recycling of the catalyst was successfully achieved by membrane filtration for three times without loss catalytic activity.

As a result, we were able to show that toxic reagents can be safely immobilized on a dendritic support and at the same time the catalyst loading could be reduced from stoichiometric to (sub)-catalytic amounts, which is the result of the high local concentration on the dendritic polymer.

3.3 Chiral Phosphoramides

Since the achiral phosphoramide **23** on support (Scheme 25) has been successfully employed (see Chapter 3.2), the concept was extended to chiral phosphoramides. This chiral modification enabled asymmetric transformation, such as the asymmetric aldol- and allylation reactions. For these reactions, 1,2-diaminocyclohexane (**30**), 2,2'-bipyrrolidine, 1,1'-binaphthyl-2,2'diamine, and 1,2-diphenylethylenediamine (**40**) as chiral phosphorus ligands were successfully employed by Denmark et al. (Figure 26).[79,81e,110] They observed that high phosphoramide loadings are needed for the aldol and allylation reaction to achieve high yields and stereoselectivities. Therefore, a special bidentate phosphoramide with a defined tether linker was designed, which improved the stereocontrol of the reaction and enabled a reduction of the phosphoramide loading.

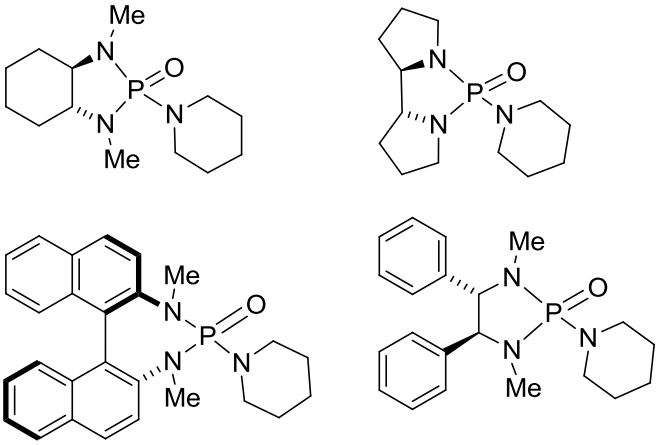


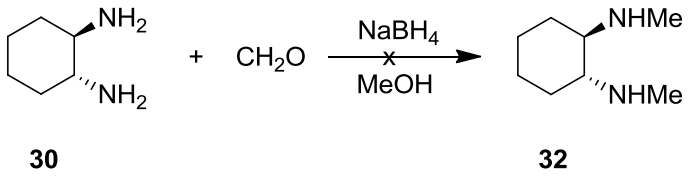
Figure 26. Chiral phosphoramides as catalysts.

Two chiral phosphoramides were immobilized on hPG **20** and chirality has been introduced by using two outstanding chiral 1,2-diamino compounds (diphenylethylenediamine (**40)** and diaminocyclohexane (**30**)) which serve as phosphorous ligands. It is expected that the catalyst amount can be reduced due to the high local concentration of the catalyst on the polymer surface.

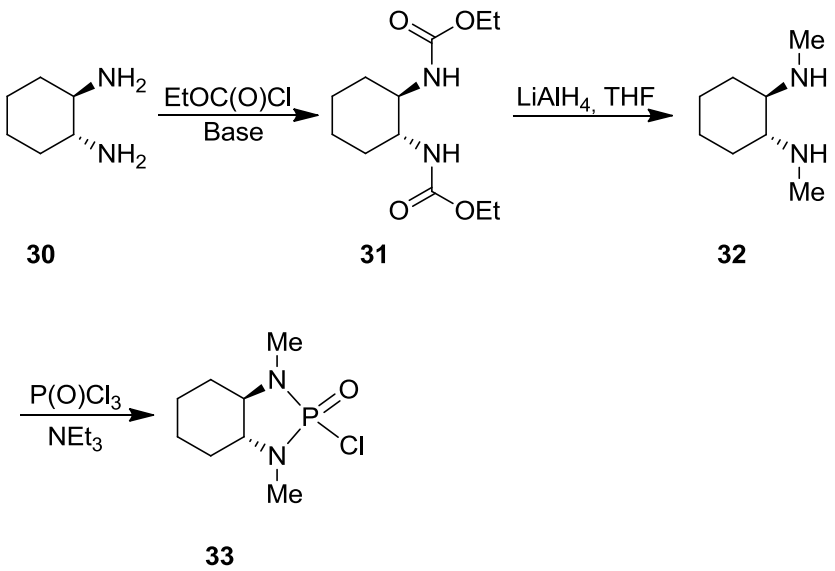
3.3.1 Synthesis of a DACH-Type Chiral Phosphoramide Supported on hPG 20

The synthesis started with commercially available (1*R*, 2*R*)-diaminocyclohexane (**30**), and also its tartrate salt can be used accordingly. The first synthetic step was the *N*,*N*'-

dimethylation of the aminocyclohexane **30**. Since the *N*,*N*'-dimethylation by reductive amination with formaldehyde (Scheme 27) is reported to result in a polyalkylation process,[111] the dimethylation of **30** described by Alexakis[112] was attempted, which included the formation of biscarbamate **31** followed by reduction with lithium hydride to yield compound **32** (Scheme 28).



Scheme 27. *N*,*N*'-dimethylation of diaminocyclohexane **30** via reductive amination using formaldehyde.



Scheme 28. Synthetic route for the preparation of the chiral phosphoramide precursor **33**.

The carbamate formation was achieved by addition of 2.4 eq. of ethylchloroformate to the starting material **30** in toluene at 0 °C. Almost quantitative conversion could be obtained in this step (95% after flash column chromatography). The formation of the biscarbamate **31** was proven by ^{1}H-NMR spectroscopy. The biscarbamate **31** was reduced with the help of 5 eq. of lithium aluminium hydride in refluxing tetrahydrofuran vernight. The consumption of **31** was monitored by TLC, but the work up proposed by Alexakis failed.[112] It turned out that product **32** heavily stuck to the inorganic aluminate salt and was too slimy to be easily filtratable. Other groups have also failed to obtain reproducible results, which they accounted to be due to incomplete reduction, which leads to the formation of highly insoluble complexes.[111] Since

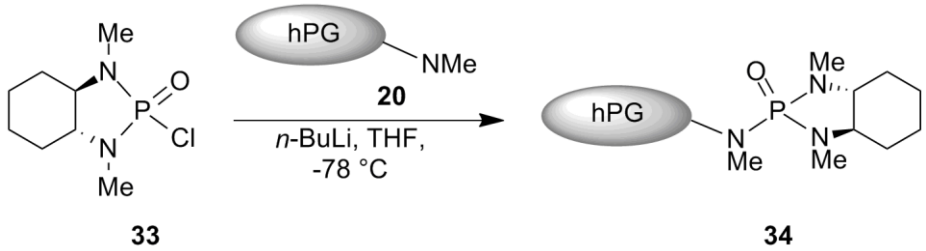
product **32** was detected by TLC, but could not be isolated, the aqueous work up was modified to obtain a more crystalline precipitation (Table 1). Finally, a yield of 56% was obtained after 12 hours, using potassium hydroxide in the aqueous work up step (Table 11). Since the *N*,*N*'-dimethylated raw product **32** could not be purified by column chromatography on silica gel, Kugelrohr distillation was successfully applied.

Table 11. Screening of work-up conditions after the reduction of carbamate **31** to the dimethylated product **32**.

Entry	$LiAlH_4$ (eq.)	Work up reagents	Time [h]	Yield [%]
1	4	ethylenediamine, 15% NaOH, EtO_2	36	0
2	10	15% NaOH, H_2O, CH_2Cl_2	14	36
3	5	10% KOH, reflux, CH_2Cl_2	12	56

Subsequently, the dimethylated diamine **32** was phosphorylated using phosphoryl trichloride in triethylamine as base and solvent (Scheme 28). The raw product **33** could be easily purified by Kugelrohr distillation (125 °C, 10^{-2} mbar) or flash column chromatography (hexane/ethyl acetate, 1:1), which gave pure phosphoramide precursor **33** in 79 % yield. In contrast to biscarbamate **31** and compound **33**, the dimethylated compound **32** cannot be subjected to high vacuum (10^{-2} mbar) due to its volatility.

The final coupling of the chiral phosphoramide precursor **33** to the polymer template **20** was performed under anhydrous conditions using *n*-BuLi in anhydrous THF at -78 °C, which yielded the chiral phosphoramide functionalized hPG **34** (Scheme 29). Small molecular weight compounds were separated from hPG **34** using ultrafiltration as described before.

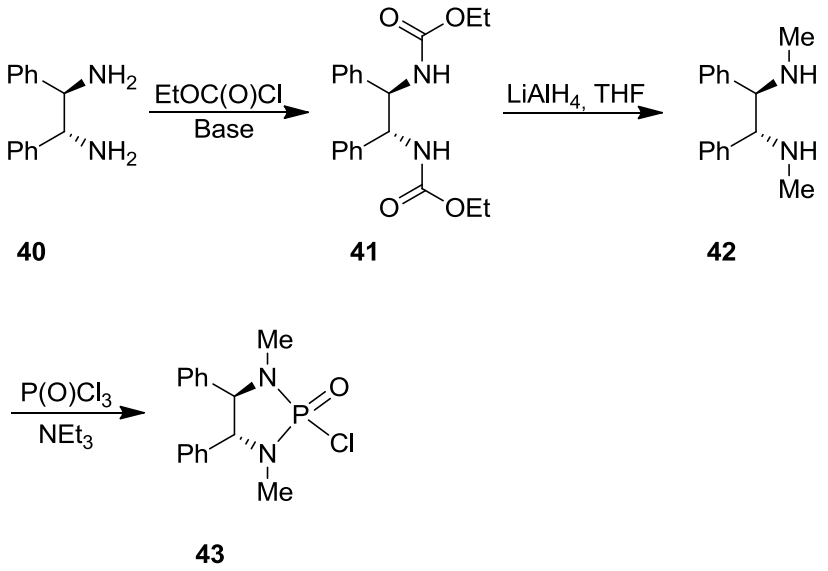


33 **34**

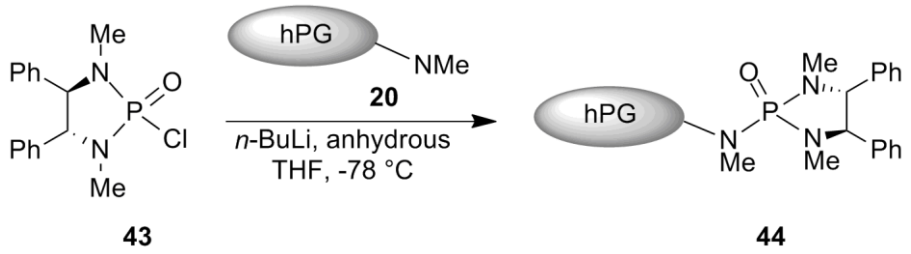
Scheme 29. Coupling step of the chiral phosphoramide precursor **33** to polyglycerylmethylamine **20**.

3.3.2 Synthesis of DPEN-Type Chiral Phosphoramide Supported on hPG

The synthetic procedure from the diphenylethylene diamine **40** to the supported analog **44** was identical with the one for diaminocyclohexane **30.** For synthetic details see Section 3.8 and the Experimental part.



Scheme 30. Synthetic route for the preparation of the chiral phosphoramide precursor **43**.

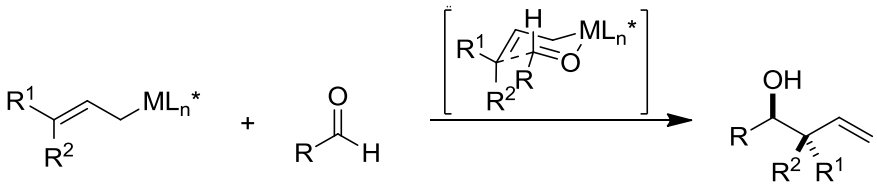


Scheme 31. Coupling of the chiral phosphoramide precursor **43** to hPG **20**.

3.3.3 Experiments with hPG-Supported Chiral Phosphoramides

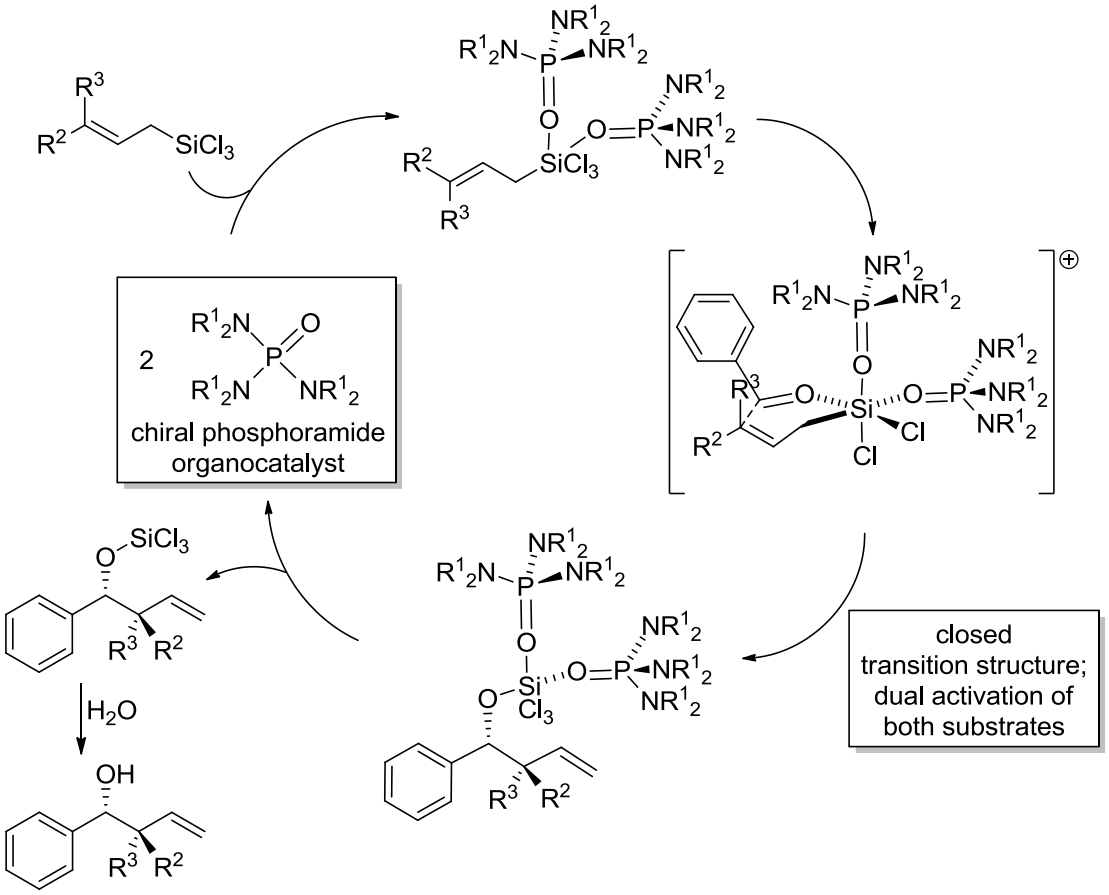
The enantioselective allylation of aldehyde is one of the most important carbon-carbon bond forming reactions and has attracted many research groups.[113] The α,β-unsaturated products are versatile building blocks and have been successfully employed in the synthesis of natural products. The outstanding features of allylic alcohols are the

numerous potential modifications, especially useful in the natural product synthesis. The "classic" approach[114] in the enantioselective allylation is based on the use of allyl metal reagents in which the chiral modifier is covalently linked to the metal such as boron,[115] titanium,[116] silicon,[117] and tin.[118] Despite the excellent selectivity, this approach (Type I allylation) needs a stoichiometric amount of chiral ligand for the modification of the organometallic starting material.



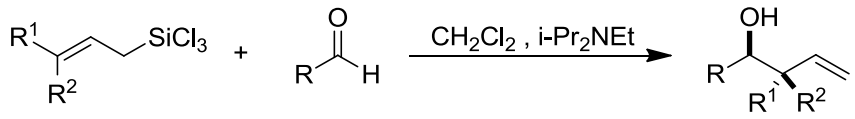
Scheme 32. Type I allylation reaction.

An alternative approach involves the use of chiral organocatalysts that are able to promote and also stereocontrol the asymmetric allylation.[78c,114] This approach is attractive because the desired chiral allylic alcohol can be synthesized in larger amounts, starting from achiral starting material and only catalytic amounts of chiral catalyst. Organocatalysts, which catalyze the allylation reaction with high enantioselectivity and tolerate a wide range of substrates, are phosphoramides, formamides and *N*-oxides. Among these catalysts, chiral phosphoramides are the best known ones. In terms of mechanistical studies, the Denmark group has been investigating the phosphoramide-catalyzed allylation reaction in detail.[78b,80a,80c] The key step is the binding of an allylsilane to the Lewis-base (catalyst) to form a reactive hypercoordinated silicon species. This intermediate subsequently reacts with the aldehyde to give the desired allylic alcohol product. Recently, the Denmark group reported NMR-studies and X-ray crystallographic data which supported this mechanism and also gave some insight into the transition state structure.[80c]



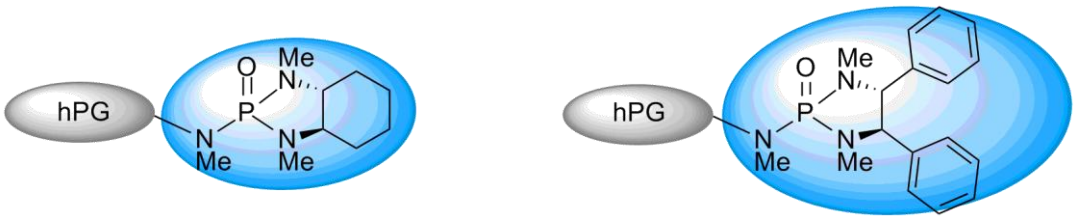
Scheme 33. Dual activation mechanism proposed by Denmark.[80a]

The supported phosphoramides **34** and **44** were investigated in the catalyzed enantioselective allylation reaction (Scheme 34) to see whether our chiral phosphoramides supported on hPG are able to improve the stereoselectivity in the allylation reaction by offering chiral catalytic sites in close proximity to each another.



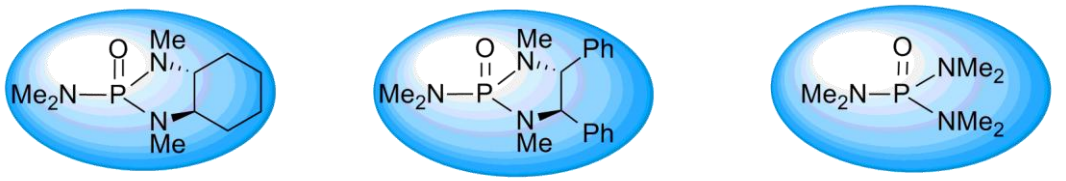
Scheme 34. Enantioselective allylation reaction.

The catalytic activity of supported chiral phosphoramides **34** and **44** has been compared with the activity of their non-supported analogs **35** and **45** and with (achiral) HMPA **24** as a control (Figure 27 and Figure 28).



chiral phosphoramide **34** chiral phosphoramide **44**

Figure 27. Chiral supported phosphoramides **34** and **44**.

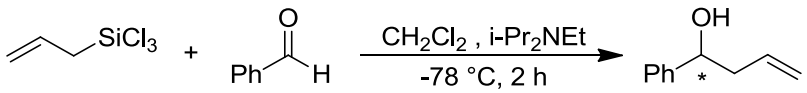


monomeric chiral phosphoramide **35** monomeric chiral phosphoramide **45** monomeric HMPA **24**

Figure 28. Chiral non-supported phosphoramide analogs **35** and **45** and HMPA **24** for comparison.

The results of the test reactions are summarized in Table 12. Both of the supported chiral phosphoramides (**34** and **44**) showed significant catalytic activity in the allylation reaction of allylic trichlorosilane **28** with benzaldehyde **26**. In terms of stereoselectivity two observations were made: the supported diphenylethylenediamine analog **44** (Table 12, Entry 2) showed a much higher selectivity than the monomer **45** (42 % vs. 26 %); in contrast, the supported diaminocylohexane derivative **34** gave lower *ee*-values than the non-supported analog **35** (Table 12, Entry 1 and 3). As result, the stereoselectivity in the phosphoramide catalyzed allylation reaction was enhanced (for **44**) upon immobilization, which can be attributed to the presence of multiple catalytic sites on the polymer. In case of polymer **34** the stereoselectivity was diminished in comparison to its monomeric analog **35.**

Table 12. Results for the allylation reaction catalyzed by various phosphoramides.



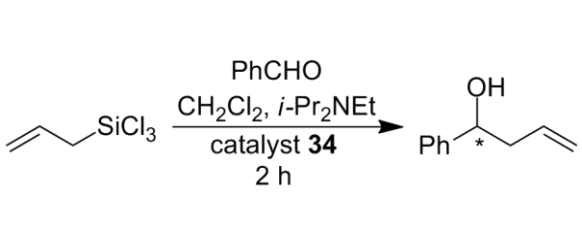
Entry[a]	Catalyst	Yield[b] [%]	*ee*[c] [%]
1	hPG-PA **34**	27	30
2	hPG-PA **44**	13.5	42
3	PA-Dach **35**	78	55
4	PA-DPEN **45**	68	26
5	HMPA (**24**)	n.d.	<1

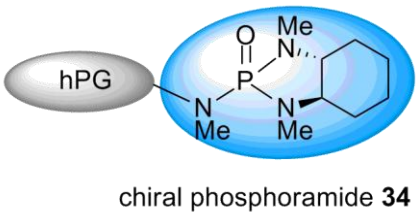
[a] Reaction conditions: 10 mol% catalyst, -78 °C. [b] Isolated yields. [c] Determined by chiral HPLC-analysis.

As shown by Denmark et al., usually stoichiometric amounts of phosphoramide (1.0 to 0.1 eq.) are needed in the allylation reaction. Therefore, the interest is focussed on the reducation of the catalyst loading while the stereoselective outcome of the reaction should be retained. In order to investigate this, the catalyst to substrate ratio as well as the reaction temperature have been varied.

To sum up the results in Table 13, the catalyst to substrate ratio can be reduced to 1.5 mol% without a significant change of the enantioselectivity, which is another proof for the validation of the catalyst concept. The reaction temperature can be increased to -25 °C without deterioration of the enantiomeric excess (Table 13, Entry 1 and 4).

Table 13. Optimization experiments for catalyst **34.**





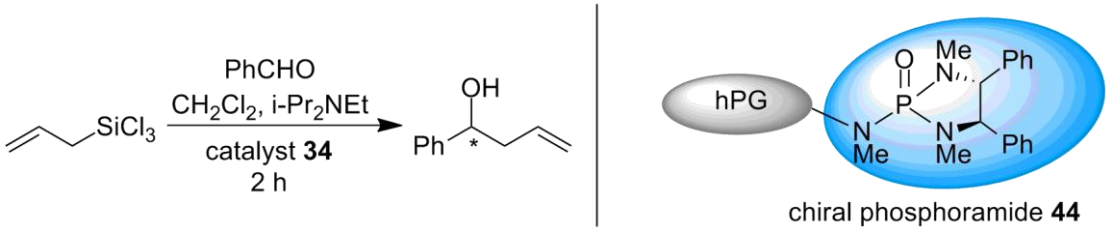
chiral phosphoramide **34**

Entry[a]	Catalyst [mol%]	Temperature [°C]	Yield[b] [%]	*ee*[c] [%]
1	1.5	-78 °C	16	28
2	10	-78 °C	27	30
3	20	-78 °C	11	32
4	1.5	-25 °C	n.d.	28

[a] Reaction conditions: Conditions: 1.0 equiv. benzaldehyde **26**, 1.1 equiv. silyl enol ether **28**, 5.0 equiv. DIPEA, 1.5-20 mol% catalyst. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

With the trends for the DACH-based supported catalyst **34** in mind, the DPEN catalyst **44** was tested under the same conditions. As summarized in Table 14, the best results in terms of stereoselectivity were obtained at -78 °C. The enantiomeric excess was not diminished when as little as 1.5 mol% of the DPEN-modified chiral phosphoramides were used. Since the loading of 1.5 mol% refers to the amount of phosphoramide units, our aim to reduce the catalyst loading from stoichiometric to catalytic amounts by using a soluble support with multiple catalytic sites has been reached.

Table 14. Allylation reaction with DPEN-based supported catalyst **44**.

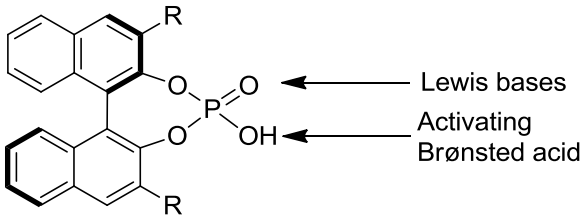


Entry[a]	Catalyst [mol%]	Temperature [°C]	Yield[b] [%]	*ee*[c] [%]
1	1.5	rt	n.d.	8
2	1.5	-25	n.d.	26
3	1.5	-78	19	43
4	10	-78	13.5	42
5	20	-78	28	46

[a] Reaction temperature: rt to -78 °C, 2 h. [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC-analysis.

3.4 Chiral Phosphoric Acids with a BINOL-Backbone

To date, several efficient and selective Brønsted acid analogs (including bifunctional Brønsted acid/base systems) which catalyze a wide range of chemical transformations, including symmetric Strecker,[87,119] Mannich,[119c,120] aza-Henry (nitro-Mannich),[121] aza-Baylis–Hillman,[122] Pictet–Spengler,[123] and hydrophosphonylation[124] reactions have been reported. In 2004, the groups of Akiyama[86] and Terada[125] independently reported a new class of chiral phosphoric Brønsted acid catalyst (Figure 29).



R = 4-NO_2-C_6H_4
R = 4-(2-naphthyl)-C_6H_4

Figure 29. Prototype chiral phosphoric acid catalysts.

These catalyst prototypes are conformationally rigid and their catalytic activity is based on a single proton of remarkable acidity (pK_a ~ 1).[126] They possess axially chiral substituents for the transfer of the stereochemical information to the substrate, while the presence of the Lewis basic phosphoryl moiety in proximity to the Lewis acidic site potentially allows bifunctional catalysis to take place (meaning, simultaneous activation of both electrophile and nucleophile).

Even though many research groups contributed to this field of chiral phosphoric Brønsted acid catalysis for instance with the first organocatalytic reductive amination,[127] the number of catalysts is still small. In addition, these catalysts have to be prepared in a multi-step reaction sequence. In order to make the catalyzed reaction more simple and practical, it would be desirable to reuse and to recover them.

For the initial study, chiral phosphoric acids of the BINOL-type with polyglycerol dendrons in the 3,3'-positions (Figure 30) were synthesized and investigated as the model catalyst for catalytic asymmetric transfer hydrogenation reactions (Scheme 35).[127a-c,128] The incorporated dendrons would allow for a straightforward solution of the recovery issue, by increasing the molecular weight by a factor of 3, which enables the use of membrane filtration techniques. The phosphoric acid was

synthesized using a modular covalent approach, in which different dendritic substituents can be easily coupled to a BINOL derivative with "clickable" groups in the 3,3'-positions.

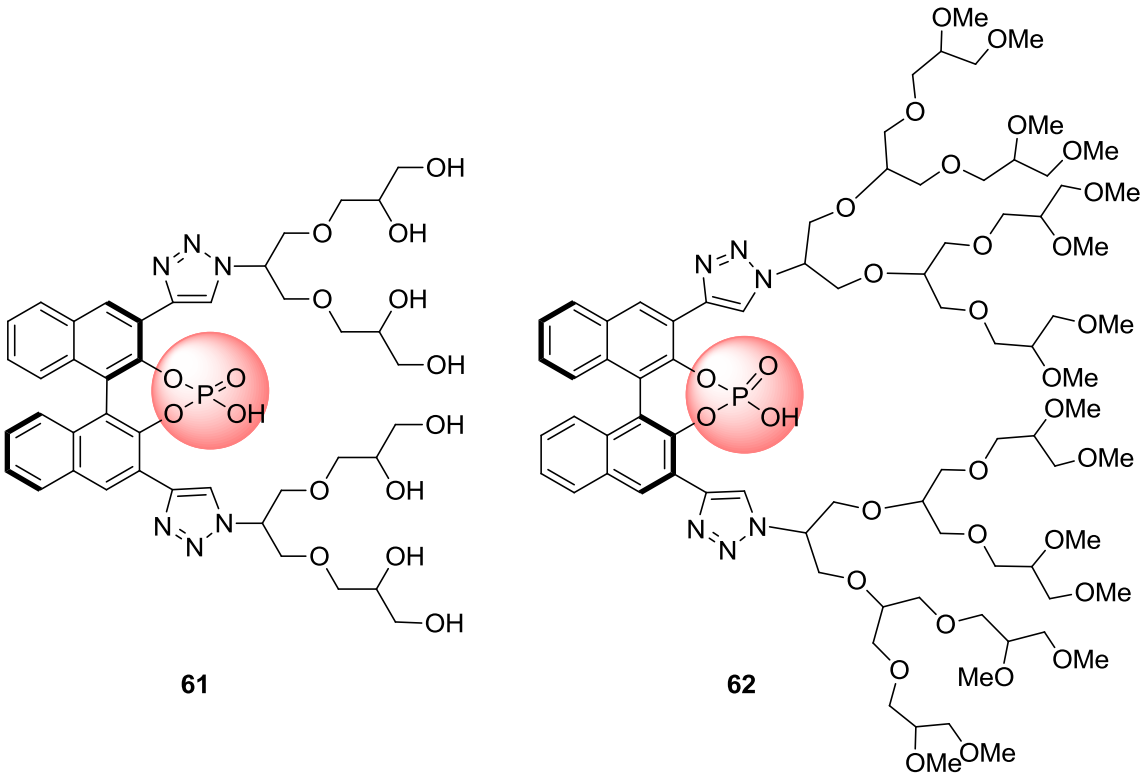
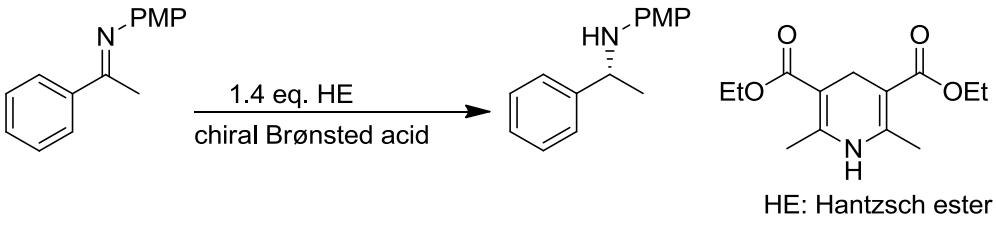
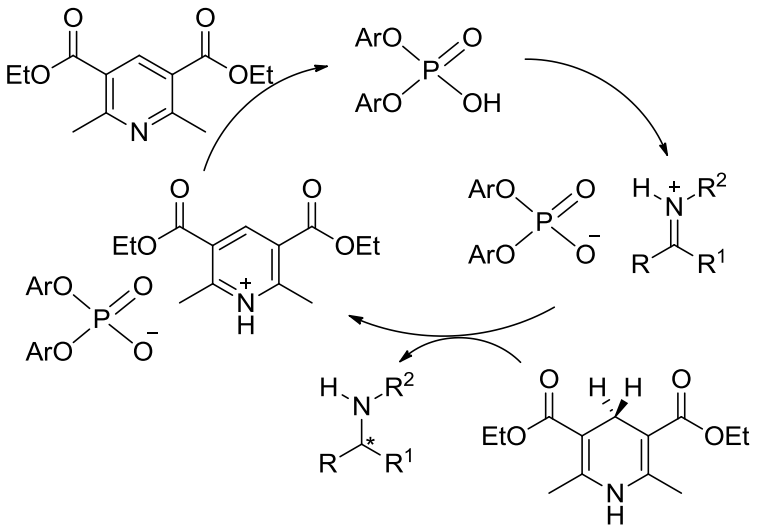


Figure 30. Structures of two types of chiral phosphoric acids with a polyglycerol dendron of generation 1 (acid **61**) and with PG-dendrons of generation 2 (acid **62**).



Scheme 35. Transfer hydrogenation of imines catalyzed by chiral phosphoric acids.

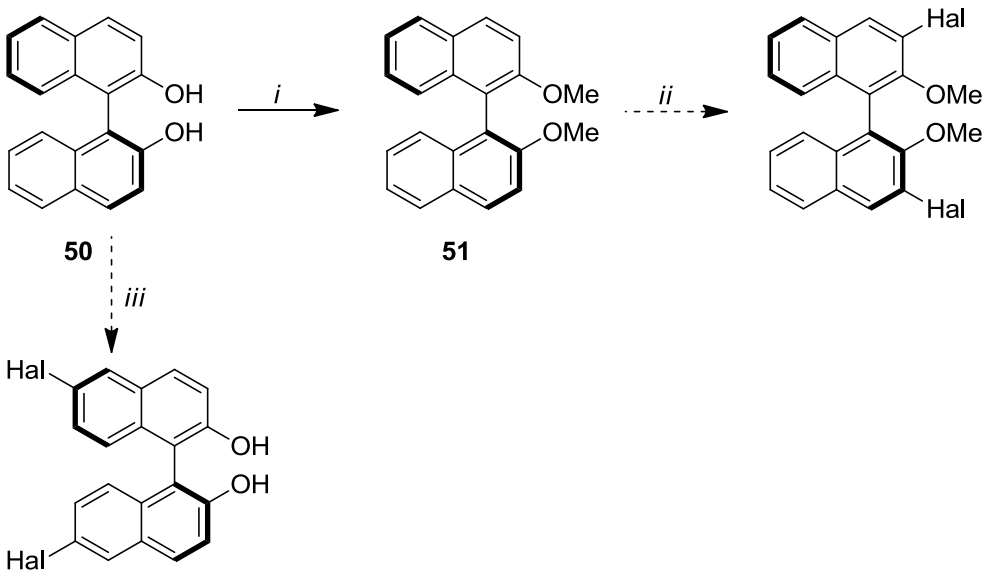
Mechanistically, it is most likely that the activation of the ketimine substrate occurs by protonation through the Brønsted acid, which generates an iminium cation. Subsequent hydrogen transfer from the Hantzsch ester results in a chiral amine product and protonated pyridinium salt, which transfers the proton back and regenerates the Brønsted acid catalyst (Scheme 36).



Scheme 36. Proposed mechanism for the transfer hydrogenation.[127b]

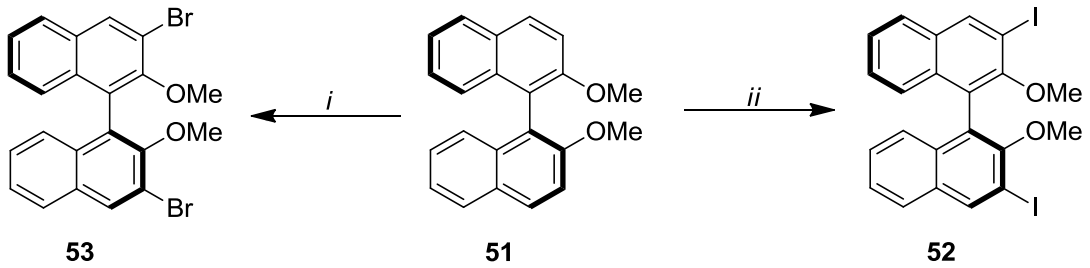
3.4.1 Synthesis of a BINOL-Type Chiral Phosphoric Acid with Polyglycerol Dendrons as Substituents

The synthetic approach for the construction of chiral acids **61** and **62** (Figure 30) is outlined in Scheme 37 to Scheme 45 and two different strategies concerning for the halogenations in the position 3 and 3' of BINOL are presented. The protection of the free hydroxyl groups of (*S*)-1,1'-binaphthalene-2,2'-diol (*S*-BINOL, **50**) as methoxy was the first step. Methoxy derivative **51** was synthesized according to a procedure by Cram et al. in 86% yield after column chromatography.[129] The protection is necessary for the further functionalization of the BINOL backbone in the 3,3'-position, since unprotected BINOL would lead to the 6,6-functionalized BINOL derivative (Scheme 37).



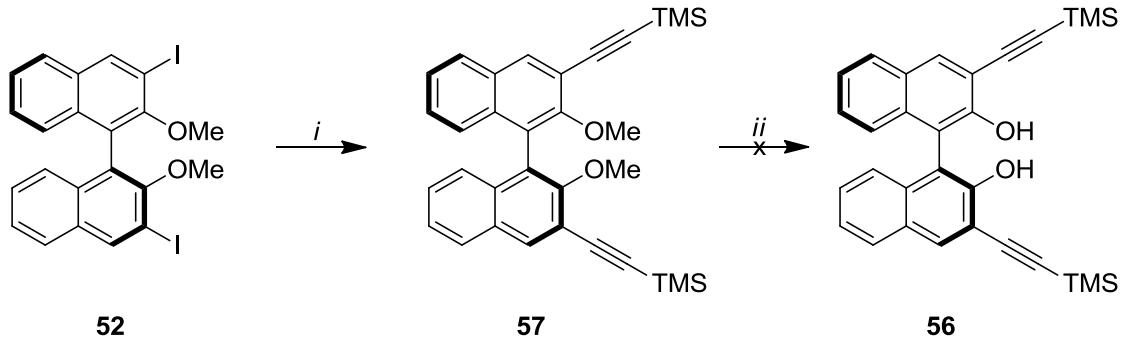
Scheme 37. Halogenation of BINOL **50** and of the protected analog **51**. Reagents and conditions: (i) K_2CO_3, MeI, acetone, reflux, 24 h, 86%; (ii) *n*-BuLi, TMEDA, Et_2O, 6h, rt, Hal, -78 °C.[130] (iii) Br_2, CH_2Cl_2, 0°C to rt;

Solid iodine proved to be the best electrophile to react with the in situ generated *ortho*-lithiated species **51**, since the use of bromine afforded a nearly 1:1 mixture of bis- and monobrominated species (**53**). Bisiodide **52** was synthesized in 96% yield by lithiation of **51** **w**ith *n*-BuLi in the presence of TMEDA in Et_2O at room temperature and subsequent reaction with I_2 (Scheme 38).



Scheme 38. Bromination and iodination of protected BINOL **51**. (i) *n*-BuLi, TMEDA, Et_2O, 6h, rt, Br_2, -78°C to rt, 36%. (ii) *n*-BuLi, TMEDA, Et_2O, 6h, rt, I_2, -78 °C to rt, 96%.

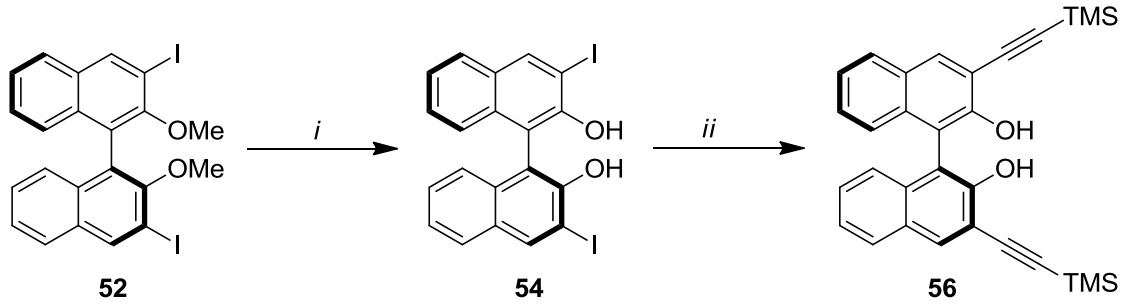
A "clickable" group was introduced by Sonogashira coupling of **52** with trimethylsilyl acetylene **64** in position 3,3' at room temperature in triethylamine as solvent. Compound **57** was obtained in 64% yield. Several deprotection agents were tested for the cleavage of the methoxy groups of compound **57**. The use of the common Lewis acids BBr_3 and $AlCl_3$ were not successful, since only the starting material was reisolated with $AlCl_3$. With BBr_3 quantitative conversion was observed, but only small amounts of the deprotected compound **56** were isolated after column chromatography.



Scheme 39. Introduction of a "clickable" group in **52** and attempts for the methoxy deprotection of **57**. Reagents and conditions: (i) TMSC≡CH, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, 16 h, rt, 64%, (ii) BBr_3, CH_2Cl_2, 1h, -78°C.

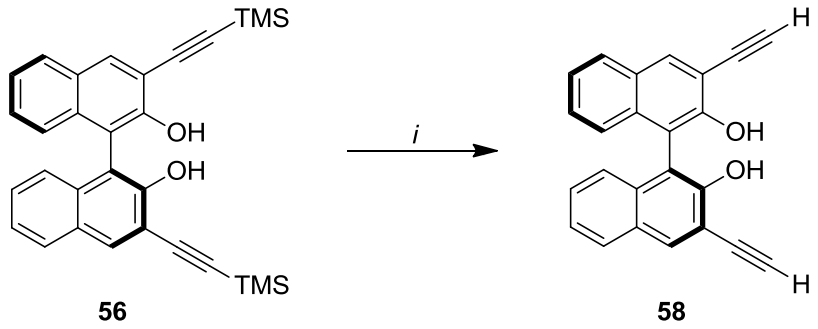
The option of other synthetic strategies was studied to avoid a late deprotection. Finally, the methoxy-groups were removed right after the iodination in positions 3,3' with BBr_3 in anhydrous CH_2Cl_2 at -78 °C to give compound **54** in 89% yield (Scheme 40).

The Sonogashira-coupling with trimethylsilyl acetylene **64** in trimethylamine at 40 °C gave alkylated species **56** in 60% yield. The yields in the C-C coupling reaction are slightly lower in the absence of the electron donating methoxy group (64% versus 60%).



Scheme 40. Ether cleavage in bisiodide **52** and introduction of acetylene groups in position 3,3' of compound **54.** Reagents and conditions: (i) BBr_3, CH_2Cl_2, 16 h, -78 °C to rt, 89%; (ii) TMSC≡CH, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, 16 h, 40 °C, 60%.

Subsequent cleavage of the TMS-groups under basic conditions led to bisalkyne **58** in quantitative yield.

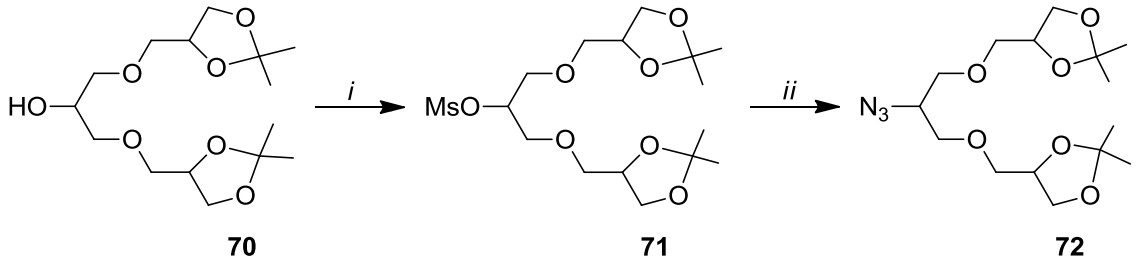


56 **58**

Scheme 41. Cleavage of the TMS-groups of compound **56.**
Reagents and conditions: (i) KOH, MeOH/H_2O, 1h, quant.

The [2+3] Huisgen cycloaddition,[131] rediscovered and improved by Sharpless et al.,[132] was used to attach the polyglycerol dendrons **59** (PG-dendron generation 1) and **60** (PG-dendron generation 2) to the BINOL backbone. The methodology of click coupling was introduced in the field of macromolecular chemistry[133] only a couple of years ago, but is already being widely applied.[131,134] This reaction impresses with its simplicity, reliability, and perfect atom economy. Many functional groups are tolerated, such as alcohol groups, which is interesting for us, since the BINOL backbone has to be unprotected at this stage. The formed triazole tolerates a wide range of pH values, which is important, because the phosphoric acid will be introduced under harsh conditions.[84g]

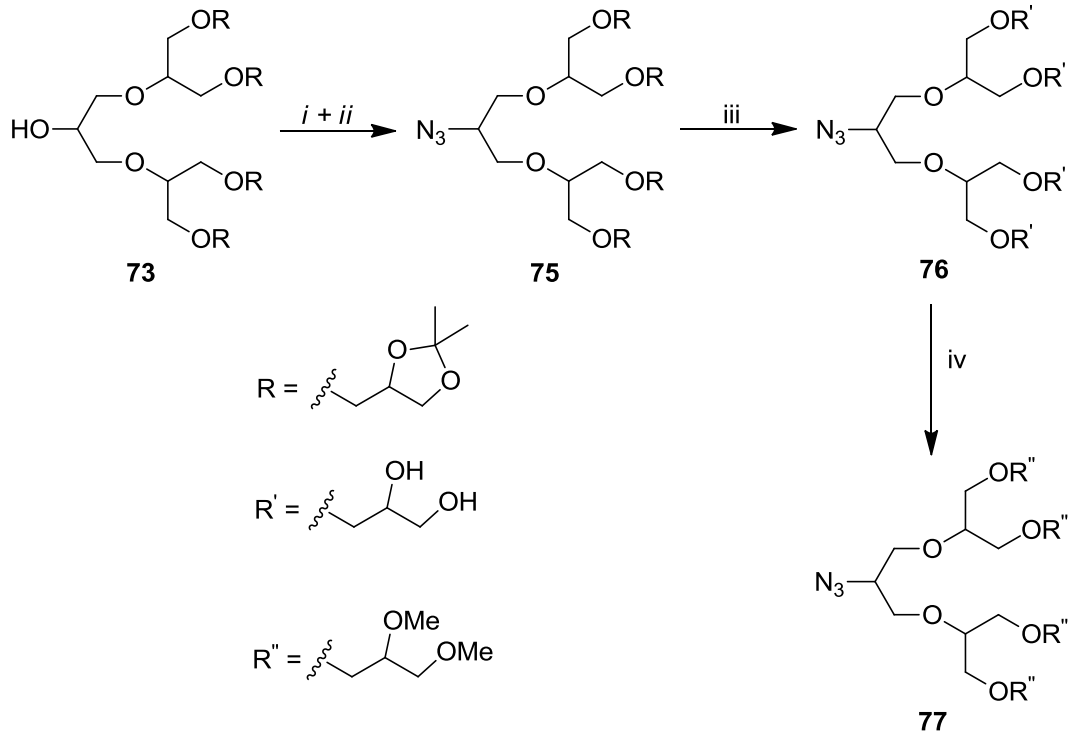
The synthesis and modification of polyglycerol dendrons with an azide functionality in the core were first introduced by our group.[98,135] This methodology was used to synthesize two types of dendrons, hPG-dendron **72** of generation 1 (Scheme 42) and hPG-dendron **77** of generation 2. The focal point of the dendron was first mesylated to give the corresponding dendrons **71** and **74** in quantitative yield and 94% yield (for **71** and **74**, respectively).[136] Subsequent treatment of **71** and **74** with sodium azide gave the azide modified dendrons **72** and **75**, both in quantitative yields (Scheme 42 and Scheme 43).



Scheme 42. Mesylation and azidation of hPG-dendron of generation 1 (**70**)**.** Reagents and conditions: (i) MsCl, NEt_3, toluene, 0 °C to rt, 16h; (ii) NaN_3, DMF, 120 °C, 3h.

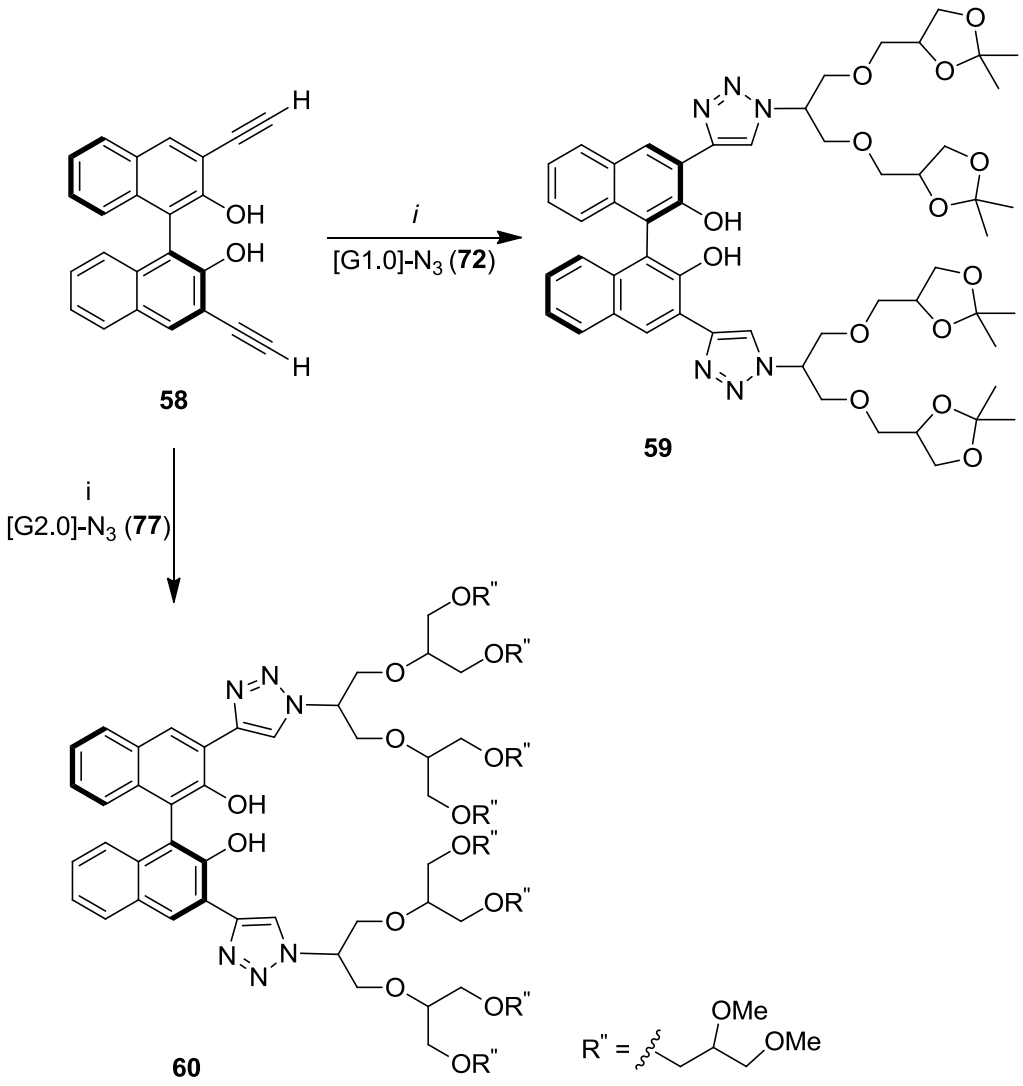
The hPG-[G2.0]-N_3 (**75**) was further modified to the methylated dendron **77**. This was necessary because the acetal protected hydroxyl groups of **76** are cleaved during the introduction of the phosphoric acid and the free hydroxyl groups render the final catalyst insoluble in non-protic solvents. Additionally they may form hydrogen bronds and therefore disturb the catalytic reaction.

The dendron **75** was first deprotected with trifluoroacetic acid in a 3:1 DMSO/ water mixture to give compound **76** in quantitative yield. Then the deprotected dendron **76** was methylated using sodium hydride and methyliodide as methylating agent to give only 23% yield of **77**.



Scheme 43. Mesylation, azidation, deprotection and methylation of hPG-[G2.0]-OH (**73**). Reagents and conditions: (i) MsCl, NEt_3, toluene, 0 °C to rt, 16h; (ii) NaN_3, DMF, 120 °C, 3h. (iii) trifluoroacetic acid (99%), DMSO/H_2O, rt, 16h; (iv) NaH, anh. THF, reflux (2h), then MeI, rt, 16 h, 23%.

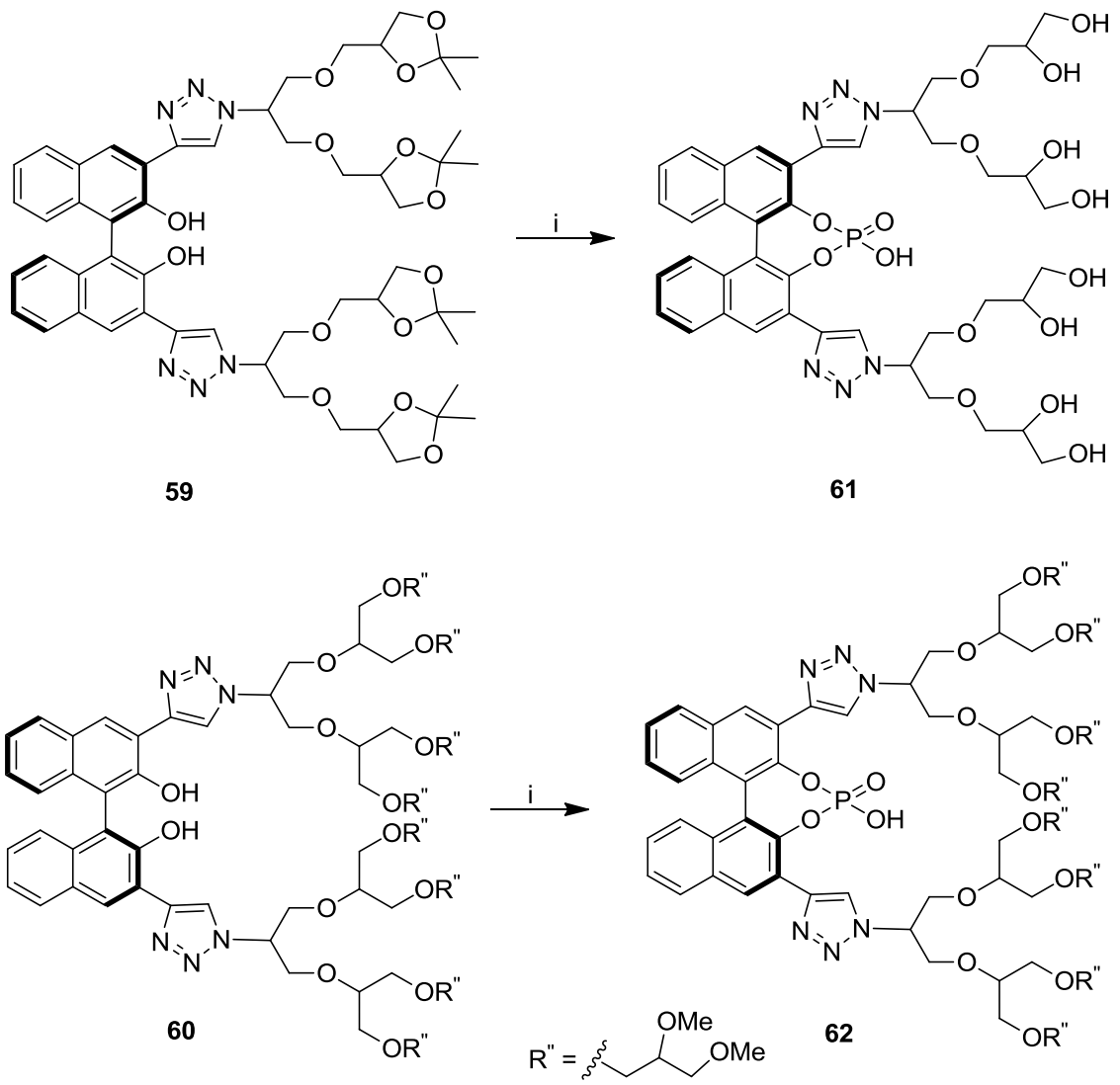
The click reaction between hPG-[G1.0]-N_3 (**72**), hPG-[G1.0]-N_3-OMe (**77**) and the alkyne derivative **58** was performed using catalytic amounts (10 mol%) of $CuSO_4$, sodium ascorbate and diisopropylethylamine (DIPEA), which were dissolved in small quantities of Millipore water (the salts) or tetrahydrofuran (the coupling partner **58**, **72** and **77**). Catalytic quantities of the copper catalyst were sufficient to give the "click" product in 54% and 46% yield, of **59** and **60**, respectively (Scheme 44).



Scheme 44. [2+3] Huisgen cycloaddition between BINOL derivative **58** and two types of dendrons (**72** and **77**). Reagents and conditions: (i) 10 mol% $CuSO_4$, 10 mol% sodium ascorbate, and 10 mol% DIPEA, THF/H_2O (1/1).

The copper salt impurities were removed by extraction with a saturated aqueous solution of ethylenediaminetetraacetic acid (EDTA). Purification of click products **59** and **60** was performed by column chromatography.

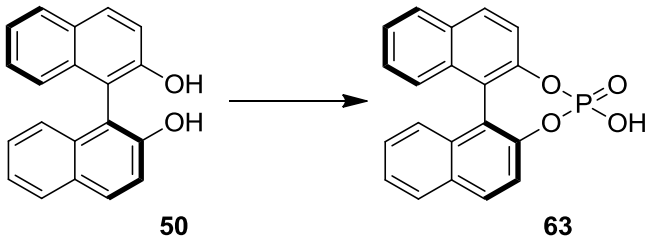
The final phosphoric acid catalysts **61** and **62** (Scheme 45) were obtained by treatment of **59** and **60** with phosphoryl chloride in pyridine, followed by hydrolysis under acidic conditions with 6N hydrochloric acid (Scheme 45). As a side reaction the acetal groups of **59** were cleaved. The phosphoric acid bearing the "smaller" dendron (**61**) was obtained in 53% yield, whereas the BINOL derivative **60** could not be phosphorylated successfully.



Scheme 45. Phosphorylation of the BINOL-derivatives **59** and **60**.
Reagents and conditions: (i) $POCl_3$, pyridine, H_2O, and 6N HCl.

Characterization of the phosphoric acid **61** was performed using ^{1}H-, ^{13}C- and ^{31}P-NMR spectroscopy as well as two-dimensional NMR techniques.

In order to design a comparable non-supported phosphoric acid we decided to synthesize the phosphorylated BINOL derivative **63**. The non-supported species **63** was obtained from commercial (*S*)-BINOL **50** with a yield of 65% (Scheme 46).

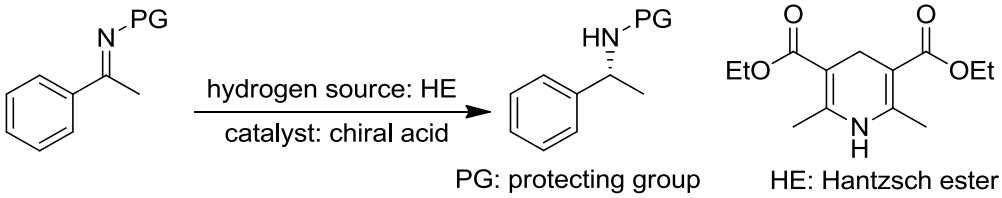


Scheme 46. Synthesis of chiral phosphoric acid **63** starting from simple (S)-BINOL (**50**).

In summary, the synthetic route gives facile access to chiral Brønsted acids, which are modified in the 3,3'-position. These acid-base catalysts can be easily modified by using other clickable groups as well as other acid motifs, which can be introduced in the last step of the protocol.

3.4.2 Catalytic Experiments with BINOL-derived Chiral Phosphoric Acid

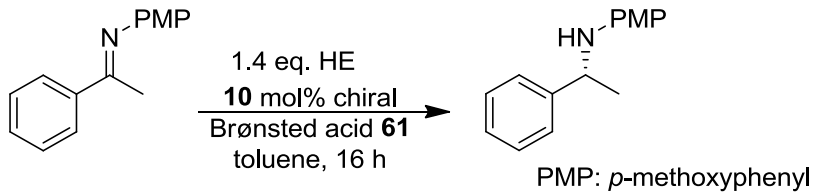
The chiral phosphoric acid **61** was investigated in the reduction of imines under hydrogen-transfer conditions with Hantzsch dihydropyridine as the hydrogen source (Scheme 47).[128a,137]



Scheme 47. Stereoselective reduction of imines with Hantzsch ester as hydrogen source.

The initial experiments were performed in order to answer the question whether the dendritic phosphoric acid **61** shows catalytic activity and selectivity and second if the reaction temperature could be reduced to ambient conditions.

Table 15. Initial experiments in the imine transfer hydrogenation catalyzed by dendritic chiral phosphoric acid **61**.



Entry	Temperature [°C]	Yield[a] [%]	*ee* [%]
1	35	99.9	rac.
2	60	99.9	rac.

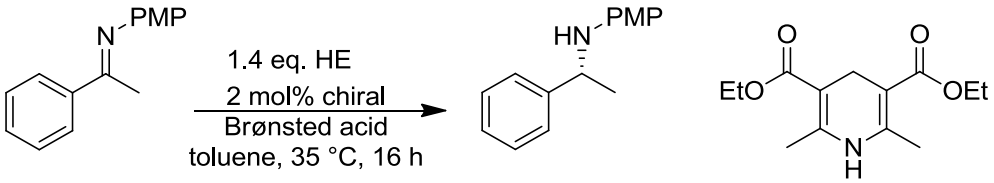
[a] Determined by ^{1}H-NMR spectroscopy.

The polymeric catalyst **61** showed high activity in the benchmark reaction, even when the reaction temperature was lowered. Other groups had to apply higher temperature (60 °C) and longer reaction times (3 days) to achieve good yields.[127b]

To our disappointment the catalyst did not induced any stereoselectivity, which is important and one of the aims.

Further examination of catalyst **61** concentrated on the solvent employed in the imine reduction reaction (Table 16). Since it is known that polar protic media such as methanol did not result in any conversion in this reaction,[127b] the study focused on nonpolar solvents.

Table 16. Solvent screening in the imine reduction catalyzed by the dendritic phosphoric acid **60.**



HE: Hantzsch ester

Entry	Solvent	Yield[a] [%]
1	dichloromethane	97
2	chloroform	91
3	2-butanone	6.5
4	acetonitrile	99.9
5	dimethylformamide	94

[a] Determined by ^{1}H-NMR spectroscopy.

Almost all tested solvents gave yields higher than 90%, with the single exception of methyl ether ketone. However, a quantitative yield was only obtained with acetonitrile (Table 16) and toluene (Table 15).

After optimizing the reaction conditions by varying the temperature and solvent, the enantiomeric excess was investigated in the imine reduction reaction (Scheme 47). In this series of experiments, the catalyst loading was varied from 0.5 mol% to 5 mol% and the results were compared to the uncatalyzed reaction and with the reaction catalyzed by the naked phosphorylated BINOL.

It was found that the amount of catalyst **61** could be lowered to 0.5 mol% without diminishing the yield. The control experiment without catalyst showed no conversion. A disappointing result was that the amine products (Scheme 47) were always obtained as racemic mixtures of the *R*- and *S*-products. The enantiomeric excess was determined by chiral HPLC in cooperation with Dr. C. Czekelius group.

3.5 Fluorinated Alcohols (HFIP-Derivative)

Fluorinated alcohols such as 2,2,2-trifluoro-ethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) are known to enhance the rate and selectivity of various reactions involving positively or partially positively charged transition states.[138]

88

Figure 31. Structures of selected fluorinated alcohols.

The high ionizing power, strong H-bond donor ability, and, in particular, low nucleophilicity of fluorinated alcohols account for the observed effects.[139]

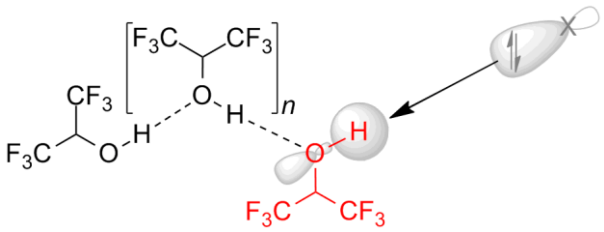
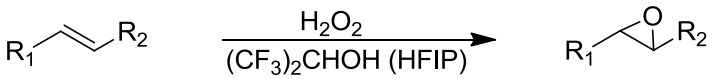


Figure 32. Aggregation-induced hydrogen bonding enhancement of HFIP.

In the epoxidation of olefins with aqueous hydrogen peroxide as terminal oxidant, a quite remarkable acceleration (up to ca. 10^5) has been achieved by using TFE and especially HFIP (**88**) as solvents.[140]



Scheme 48. Epoxidation of alkenes with hydrogen peroxide in HFIP as solvent.

The same holds for the Baeyer-Villiger oxidation of ketones with aq. H_2O_2 which proceeds via the cationic rearrangement of peroxidic ketone-H_2O_2 adducts.[141] In the oxidation of thioethers with aq. H_2O_2, fluoroalcohol solvents generate remarkable selectivities for sulfoxide formation, with basically no overoxidation to the sulfone derivative.[142] Overall, the preparative scope of aqueous hydrogen peroxide – probably the most "clean" and readily available oxidant available to date – is largely enhanced when applied in fluoroalcohols as solvents.

The latter, i.e. the necessity of applying fluoroalcohols such as HFIP as solvent, poses limitations, because these materials are, for example, prohibitively expensive for large scale applications. The obvious solution to the problem is to switch from fluoroalcohol solvents to a fluoroalcohol catalyst, which is applicable in conventional solvent systems. Previous studies by Berkessel et al. on the mechanism of the HFIP-catalyzed epoxidation of alkenes by H_2O_2, that were ultimately aiming at the development of such catalysts, identified multiple H-bonding interactions between the solvent and the oxidant as the crucial factor.[3] Figure 33 illustrates how the oxidant is electrophilically activated by multiple hydrogen bonds from a total of two or even three HFIP molecules. Most importantly, cyclic H-bond networks are established which allow for the (almost) barrier-free, cascade proton transfer from the transition state towards the formation of the epoxide and water.

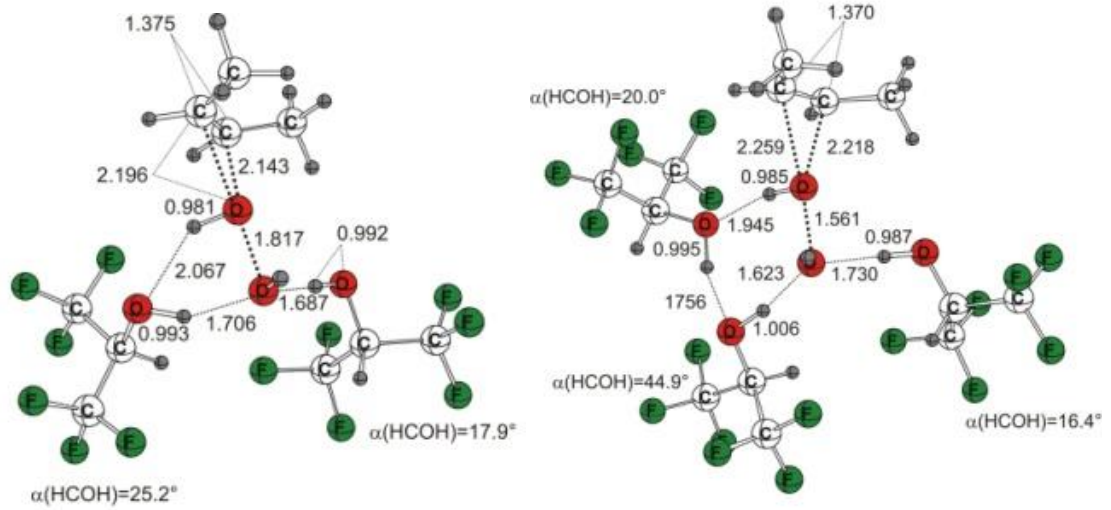


Figure 33. Epoxidation of 2-butene, effected by two (left) and three (right) molecules of HFIP, based on hydrogen bonding networks.[140a]

Clearly, a high local concentration of the fluoroalcohol, like it is present in a solvent, is the prerequisite for an effective formation of such multiple hydrogen bonded supramolecular aggregates. For the catalyst design, the attachment of fluoroalcohol head groups to relatively polar dendritic polymers was envisioned. By doing so, a high local fluoroalcohol concentration is assured, together with compatibility of the catalyst with both the highly polar aqueous H_2O_2 and olefin/solvent mixtures. Hyperbranched polyglycerol (hPG, **5**) was chosen as the dendritic scaffold. HFIP analogs supported on hPG (**85**/**95**) have been synthesized (Figure 34) and have been applied for the metal-free epoxidation of alkenes with hydrogen peroxide.

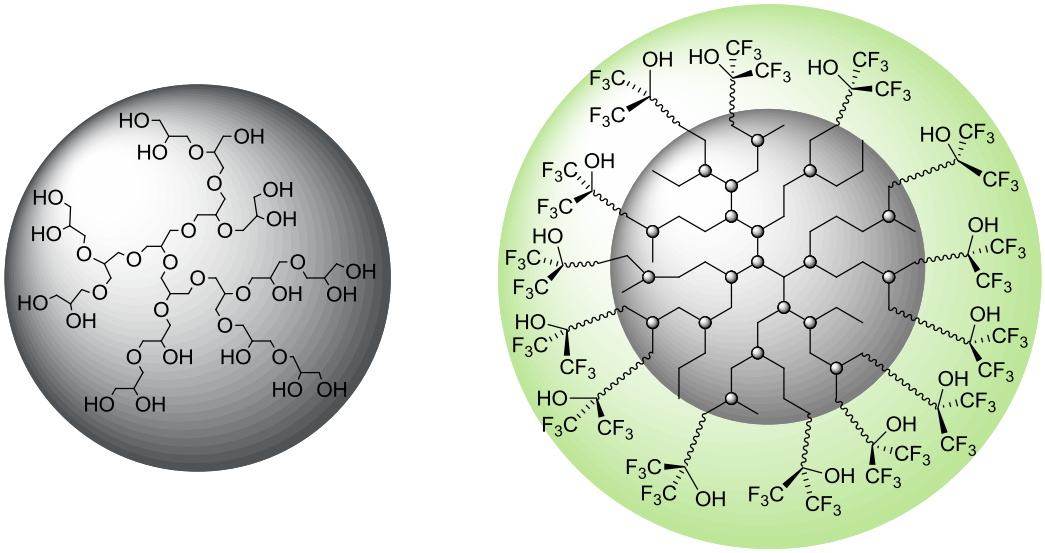
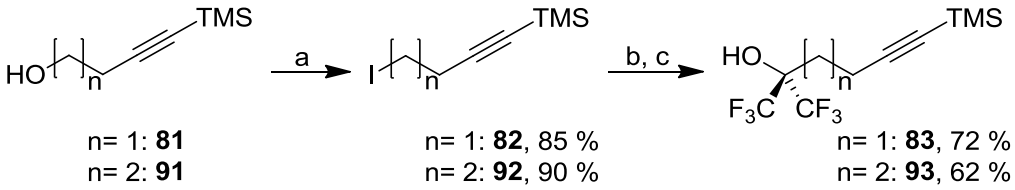


Figure 34. HFIP analogs immobilized on hyperbranched polyglycerol **7** for catalytic applications.

3.5.1 Synthesis of Hexafluoroisopropanol Supported on hPG 7

For the synthesis of the polymeric epoxidation catalysts **85** and **95** (Figure 34), the alkynyl fluoroalcohols **83** and **93** were used as HFIP analogs (Scheme 49). Compounds **83** and **93** were synthesized from commercially available 3-butynol and 4-pentynol, to yield **83** and **93**, respectively, in three steps (Scheme 49). In the first step, the alkyne function was quantitatively silylated, using *n*-butyllithium and trimethlysilyl chloride (not shown in Scheme 49).[143] The resulting TMS-protected alkynols **81** and **91** were converted to the corresponding iodo compounds **82** and **92** by treatment with triphenylphosphine, imidazole, and iodine.[143-144] In the last step, the iodides **82** and **92** were first transformed to the organozinc compounds by treatment with zinc, 1,2-dibromoethane, and trimethylsilyl chloride. The zinc organyl was then added to hexafluoroacetone (HFA, **88**) under copper(I) catalysis, affording the corresponding fluoroalcohols **83** and **93** in good yields (Scheme 49).[145]



n= 1: **81**
n= 2: **91**

n= 1: **82**, 85 %
n= 2: **92**, 90 %

n= 1: **83**, 72 %
n= 2: **93**, 62 %

Scheme 49. Preparation of HFIP analogs **83** and **93**. Reagents and conditions: (a) imidazole, PPh_3, I_2, Et_2O / CH_3CN, 0 °C; (b) Zn, $C_2H_4Br_2$, TMS-Cl, DMF, rt; (c) HFA, $CuBr \cdot Me_2S$, DMF, -40 °C.

As expected, the fluoroalcohols **83** and **93** show strong hydrogen bond donor abilities, which are comparable to their mother compound HFIP. Figure 35 shows the X-ray crystal structures of their 2:1-adducts with triethylendiamin (DABCO). The salient feature of both structures are the relatively short (ca. 2.65 Å) and almost linear H-bonds between the fluoroalcohols and the tertiary amine acceptor.

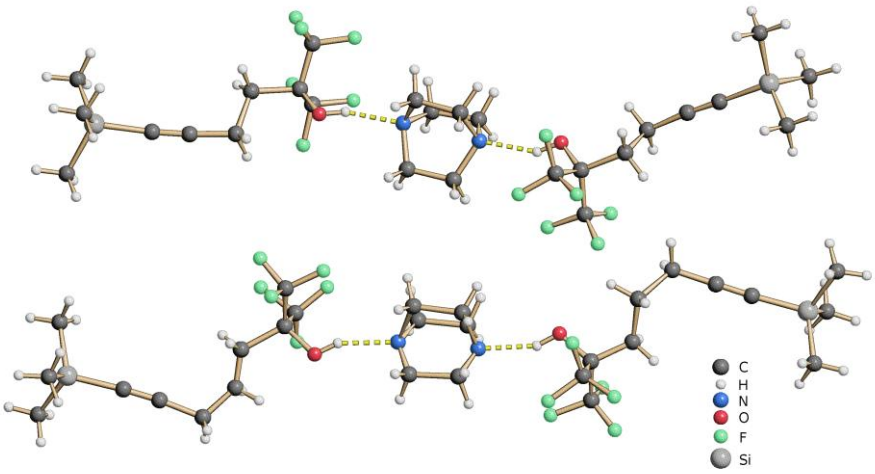
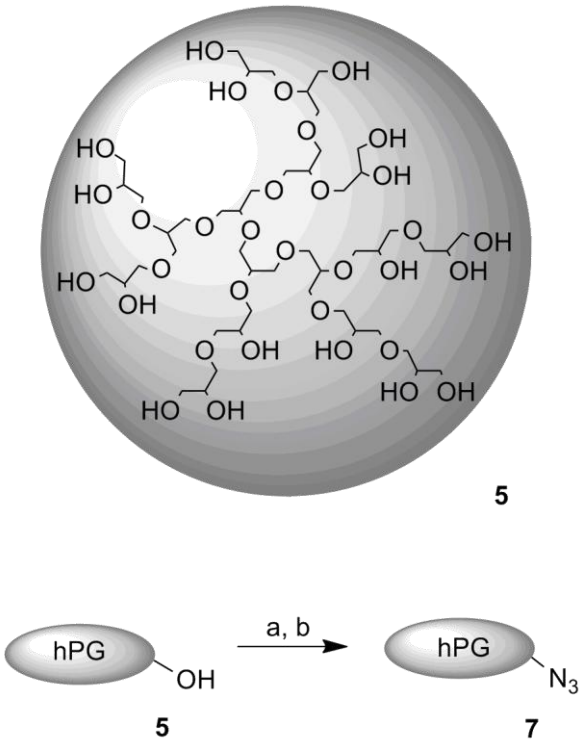


Figure 35. X-ray crystal structures of the DABCO adduct of the fluorinated alkynol **83** (top) and **93** (bottom).[146]

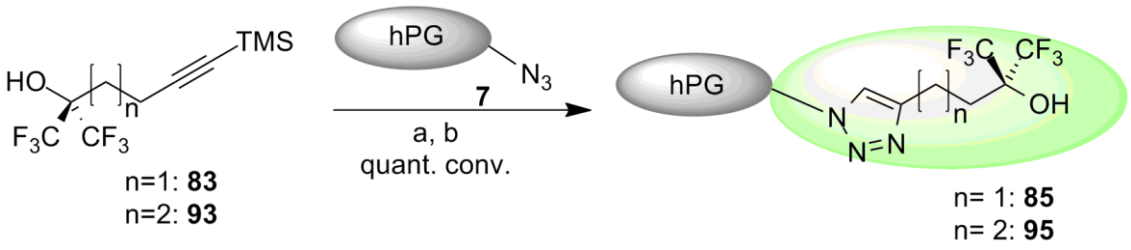
Similarly, ^{1}H-NMR titration of alcohols **83** and **93** with THF as H-bond acceptor provided an association constant of 260 $L \cdot mol^{-1}$ for **83**, and 70 $L \cdot mol^{-1}$ for **93**. These numbers are within the same range as those determined earlier for HFIP itself (65 $L \cdot mol^{-1}$)[140] and for perfluoro-*tert*-butanol (796 $L \cdot mol^{-1}$),[147] respectively.

For the polymeric support, azide-modified hPG (hPG-N_3, **7**) was chosen, which has been prepared from hPG (**5**) (M_n= 10kDa) in two steps, which are mesylation and subsequent nucleophilic substitution of the mesylate with sodium azide (Scheme 50).



Scheme 50. Modification of the functional groups of polyglycerol **5**. Reagents and conditions: (a) MsCl, pyridine, 0°C, 16h; (b) NaN_3, DMF, 100 °C, 16h.

The two alkynols **83** and **93** were coupled to hPG-N_3 (**7**) using "click-chemistry"[132] (Scheme 51) with high yields. The final polymeric catalysts (**85** and **95**) were purified by membrane ultrafiltration using a Millipore stirred cell and analyzed by ^{1}H-, ^{13}C-, ^{19}F-NMR, and IR spectroscopy.



Scheme 51. Syntheses of the hPG-HFIP catalysts **85** and **95**. Reagents and conditions: (a) TBAF, THF, r.t., 20 min; (b) Na-ascorbate, $CuSO_4$, THF/H_2O, r.t., 24 h.

The surface loading (amount of fluoroalcohol-groups on the polymer) was determined by ^{19}F-NMR with 4-trifluoroaniline as internal standard to be 3.0 mmol "HFIP"·g^{-1} for catalyst **85** and 2.9 mmol "HFIP"·g^{-1} for catalyst **95**.

For comparison, the non-supported catalysts **86** and **96** were prepared starting from benzyl azide **97** instead of hPG-azide (**7**).

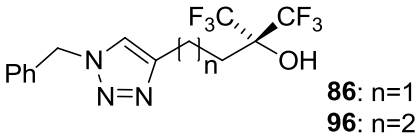


Figure 36. Structures of the non-supported HFIP analogs **86** and **96**.

The polymeric HFIP derivatives **85** and **95** were soluble in a variety of organic solvents (Table 17), but insoluble in halogenated solvents, such as dichloromethane.

Table 17. Solubility of the hPG-HFIP analogs **85** and **95** in various solvents.[a]

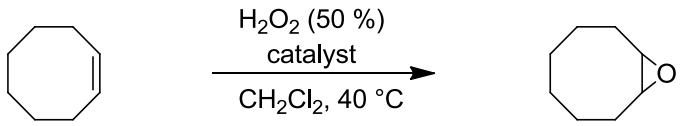
Entry	Solvent	Solubility[a]
1	Dichloromethane	-
2	Methanol, Ethanol	+
3	Acetonitrile	+
4	Chloroform	-
5	Tetrahydrofuran	+
6	*n*-Hexan	-
7	Toluene	-
8	Diethyl ether	-
9	Aceton	+
10	Ethyl acetate	+
11	DMSO	+
12	Dimethylformamide	+
13	Water	-

[a] 5 mg polymer in 1 mL of solvent.

3.5.2 Catalytic Results with HFIP Supported on hPG (85/95) in the Epoxidation of Alkenes

As the next step, the catalytic activity of the dendronized fluoroalcohols **85** and **95** was evaluated and compared with the results obtained with their non-supported analogs **86** and **96** and with HFIP. The epoxidation of *cis*-cyclooctene (**87**) with aqueous hydrogen peroxide was chosen as the test reaction, and the results are summarized in Table 18. Both dendronized HFIP analogs **85** and **95** showed a significantly higher catalytical activity than the non-supported analogs **86** and **96** or HFIP itself (applied at the same concentration as the other fluoroalcohols, i.e. 20 mol% rel. to olefin). This positive dendritic effect not only validates the initial catalyst design concept, but in retrospect supports the multiple-HFIP transition state model for olefin epoxidation catalyzed by HFIP (Figure 33).[138,140b,148]

Table 18. Epoxidation of alkene **87** with hydrogen peroxide and catalyzed by **85**, **86**, **88**, **95** and **96**.[a]



87 **89**

Entry	Catalyst	Time [h]	Conversion[b] [%]	Yield[b] [%]
1	hPG-HFIP (**85**)	24	quant.	quant.
2	hPG-HFIP (**95**)	24	quant.	quant.
3	Bn-HFIP (**86**)	24	13	11
4	Bn-HFIP (**96**)	24	11	< 10
5	HFIP (**88**)	24	16	14

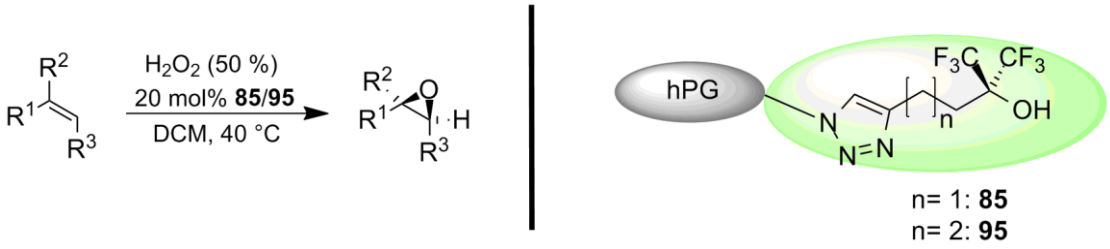
[a] Reaction conditions: general epoxidation method (see Experimental Section), 20 mol% of "HFIP-euquivalents". [b] Determined by GC.

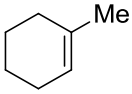
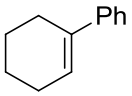
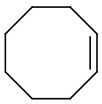
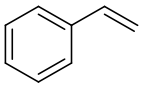
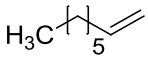
In the next step, the reaction conditions were optimized by screening a wide range of solvents, reaction temperatures, hydrogen peroxide solutions (with respect to pH and c[H_2O_2]), and alkene/catalyst concentrations. In non-polar solvents (such as *n*-hexane or toluene), the catalysts **85** and **95** were completely insoluble and the yields of epoxide **89**

were typically very low, identical to those of the background reaction. In polar, H-bonding acceptor solvents, such as ethanol, 1,4-dioxane, or ethyl acetate, the epoxide yields again did not differ significantly from the background reaction, although the catalysts were completely soluble in most of those solvents. As in the case of HFIP itself, catalyst inhibition resulted in the presence of H-bond acceptor molecules.[149] The best results were obtained at concentrations of 0.125 M for the alkene and 0.025 M for the catalyst (20 mol% with respect to fluoroalcohol monomers attached to the polymer), in a biphasic system with halogenated solvents such as dichloromethane and unbuffered hydrogen peroxide (50 wt. %) at 40 °C.

With these optimized conditions, the substrate scope was investigated by submitting various alkenes to the new reaction conditions. As summarized in Table 19, excellent olefin conversions and epoxide yields were achieved with as little as 20 mol% of the dendronized fluoroalcohols **85** and **95**. Since the loading of 20 mol% refers to the amount of fluoroalcohol present, our goal of providing a substoichiometric catalytic system as opposed to using fluoroalcohols as solvent, was clearly reached. Similar to the epoxidations in fluoroalcohol solvents,[92,150] the dendrimeric catalysts **85** and **95** perform particularly well with cycloalkenes as substrates, as exemplified by cyclohexene, 1-methyl- and 1-phenylcyclohexene, or cyclooctene (Table 19, Entries 1-4). As shown in control experiments, the poor epoxide yield in the case of 1-methyl-cyclohexene (Table 19, Entry 2) is due to product instability under the reaction conditions, which again is in accord with earlier studies done with this substrate in fluoroalcohol solvents.[92,150] Similarly, open-chain alkenes such as styrene (Table 19, Entry 5) and 1-octene (Table 19, Entry 6) were epoxidized with moderate efficiency. As an example for a thioether oxidation, thioanisol was subjected to the reaction conditions (not shown in Table 19). As a result, the very high sulfoxide selectivity typical for sulfoxidations in fluoroalcohol solvents is maintained by the dendrimeric catalysts **85** and **95** since only the sulfoxide PhS(O)Me was formed in quantitative yield. No sulfone was observed.

Table 19. Scope of the hPG-HFIP (**85** and **95**)-catalyzed epoxidation of alkenes.[a]



Entry	Substrate	Catalyst	Time [h]	Conversion[b] [%]	Yield[b] [%]
1		**85** **95**	15 16	98 97	95 93
2		**85**	15	98	10-26[c]
3		**85** **95**	19 19	97 95	94 90
4		**85** **95**	24 23	quant. quant.	quant. quant.
5		**85** **95**	72 72	48 98	35 28
6		**85** **95**	72 70	37 42	28 32

[a] Reaction conditions: general epoxidation method (see Experimental section). [b] Determined by GC. [c] Product not stable under reaction conditions.

An additional advantage of the dendrimeric catalyst systems is the ease of their recovery which allows for multiple usage. In the current case, recovery of the catalysts **85** and **95** was successfully achieved by ultrafiltration using a Millipore stirred cell. The polymeric catalyst **85** and **95** could be recovered and reused twice in the epoxidation reaction of cyclooctene with hydrogen peroxide without decrease in the epoxide yield or loss of catalyst.

In conclusion, it was proven that the immobilization of fluoroalcohol monomers on a soluble dendritic support is a suitable method for the generation of organocatalysts that promote transformations by multiple H-bond networks. In the current case, the high local concentration of fluoroalcohol groups on the polymer was exploited for the

electrophilic activation of hydrogen peroxide. Epoxidations with hydrogen peroxide, hitherto attainable only in fluoroalcohol solvents, were for the first time achieved with catalytic amounts of fluoroalcohol units. This positive dendritic effect not only validates the multifunctional catalyst design concept, but also supports the multiple-HFIP transition state model for catalytic olefin epoxidation. Similarly, the typical sulfoxide selectivity in thioether oxidation could be achieved by our catalytic dendrimers. This novel catalytic principle will certainly find further use, e.g., in other electrophilic oxidations using peroxide as terminal O-donor, or in other transformations requiring substrate activation/transition state stabilization by multiple H-bonding.

4. Summary

In this thesis, the successful immobilization of several chiral and non-chiral organocatalysts on hyperbranched polyglycerol **5** has been shown, which resulted in highly active catalytic systems.

For the immobilization, a new type of amine modified polyglycerol **20** was introduced using a modular approach for the catalyst synthesis and triazole moieties were used to efficiently link different organocatalysts to the polyglycerol polymer. Both methods gave air stable und storable supported organocatalysts in high yield, which can be handled more easily than their non-supported analogs. For example the highly toxic co-solvent hexamethylphosphoramide (HMPA), which is also called "liquid cancer" was immobilized and successfully tested in fundamental C-C bond forming reactions, such as aldol and allylation reactions. Furthermore, a positive dendritic effect was observed which demonstrated that the catalytically active sites on the polymer surface were well accessible and not blocked by the polymer. The origin of the positive dendritic effect is certainly due to the high local concentration of catalytically active sites on the polyglycerol surface. Due to the high loading on the polymer surface the overall catalyst loading could be reduced in several cases to catalytic amounts, where before stoichiometric amounts of the non-supported analog were needed.

In the first part, it was shown that polyglycerol **7** is a suitable support to immobilize zwitterionic compounds such as amino acids. This was demonstrated by the successful synthesis of the proline catalyst **9a-c**, where polyglycerol was decorated to a degree of 10, 50 and 100%.

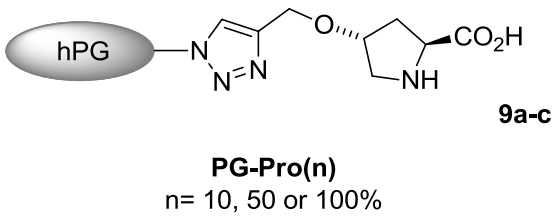


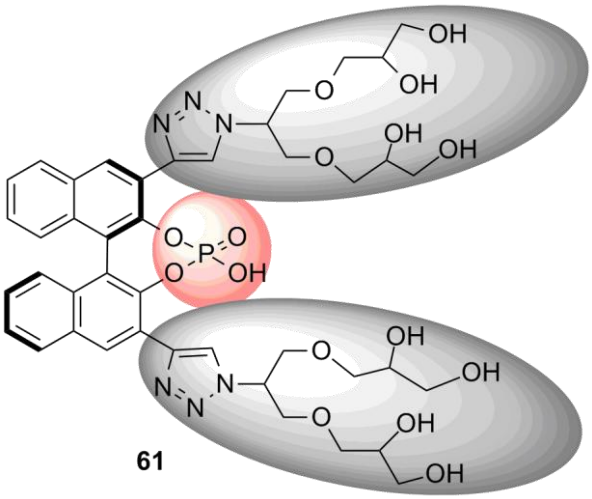
Figure 37. Structure of hPG-proline **9a-c** with three different levels of proline loading.

For the proline catalyst **9**, a positive dendritic effect in terms of enantioselectivity was observed in the catalyzed aldol reaction. With the higher loaded polyglycerol the *ee* increased to up to 10%, while the overall substrate to catalyst ratio remained constant. A second positive dendritic effect was observed with regard to the substrate to catalyst

ratio. By dendronization of the catalyst the ratio could be reduced from 30 mol% to 10 mol% by still getting full conversion. Another positive dendritic effect was the shortened reaction times; other groups reported reaction times of 4 to 9 days with proline on a dendronized insoluble support.[7c] In contrast, full conversion is achieved with catalyst **9** in 24 hours, which proves the good accessibility of the catalytic sites on the polymer surface. The enantioselective outcome of catalyzed aldol reaction is reported to be strongly dependent on the degree and type of dendronization.[151] The enantiomeric excess achieved with the dendritic proline catalyst **9** was in the same range of what is observed with "free" proline and stands in contrast to the fact that several groups reported diminished *ee*-values upon immobilization.[100,151] Additionally, there is no change in the *ee*-value over reaction time. Finally, the addition of small amounts of water (50 eq.) clearly enhances the reaction rate, but leads to a diminished stereoselectivity.

In the second part, a supported hexamethylphosphoramide (HMPA) on hyperbranched polyglycerol has been successfully synthesized. Here three interesting effect can be highlighted: (A) HMPA is an extremely useful organic reagent, which is widely used in organic synthesis, but is highly toxic. Upon immobilization on hPG, the molecular weight of the reagent increases and inhalation is not possible anymore. (B) HMPA, which is mostly used as a (co-)solvent, can now be used in catalytic amounts without diminishing the catalytic outcome, and (C) the multiple catalytic sites promote the same reaction pathways as the non-supported analog, which could be proven with the stereoselective outcome of the reaction. The benefits of supported HMPA can be mostly attributed to the high local concentration of HMPA groups at the polymeric surface. This concept was developed to mimic a high total concentration of HMPA under the reaction conditions. The polymeric catalyst was investigated in two important C-C bond forming reactions, the aldol- and allylation reaction. In the latter reaction, a positive dendritic effect was clearly observed. Finally, the catalyst loading could be lowered to 0.5 mol% and still a quantitative yield was obtained, which is in contrast to the non-supported analog where no significant conversion (<2 %) was observed at this low level of catalyst concentration. In addition, it was possible to demonstrate the efficient recovery and reuse of the dendritic HMPA for three times, which was achieved by ultrafiltration using a Millipore ultrafiltration stirred cell. No catalyst leaching could be detected.

In the third part, a chirally active Brønsted acid derived from BINOL bearing dendritic polyglycerol dendrons in the 3,3'-position has been developed. Best results in the synthetic protocol were obtained by first iodinating at the 3,3'-position, followed by early deprotection of the BINOL alcohol functionality. The alternative bromination gave product mixtures of unreacted substrate, mono- and difunctionalized product. The late deprotection of the alcohol functionality resulted in decomposition of the compound. With the [2+3]-Huisgen-cycloaddition an efficient protocol for the connection of different polyglycerol dendrons to the BINOL backbone (Scheme 52) was found.



61

Scheme 52. Chiral phosphoric acid **61** bearing polyglycerol dendrons.

The dendronized phosphoric acid was investigated as catalyst in the transfer hydrogenation of ketimines with regard to activity and enantioselectivity. It catalyzed the hydrogenation of imines to the corresponding protected amines with quantitative yield after 16 hours. Other groups reported reaction times of 3 days in the same reaction. To our surprise there was no stereoinduction detectable, which may have several reasons: (A) the polyglycerol dendrons in the 3- and 3'-position might be too flexible, (B) the substrate might coordinate to the oxygens of the polyether backbone and thereby may form a hydrogen network that did not lead to the preferred product and (C) the polyhydroxy functionalities of the dendron might disturb or interfere with the formation of the acid/base adduct in the transition state. An evidence for (C) could be that no enantioselectivity was observed when alcohols such as methanol were used as solvent.

In the fourth part, hexafluoroisopropanol (HFIP) was covalently immobilized on polyglycerol by using two different linker-length. It was demonstrated, that the

polymer-supported fluoroalcohols (**85**/**95**) catalyze the epoxidation of alkenes with hydrogen peroxide and were significantly more active than their non-supported analogs (**86**/**96**) or HFIP itself (applied at the same concentration of 20 mol% relative to olefin).

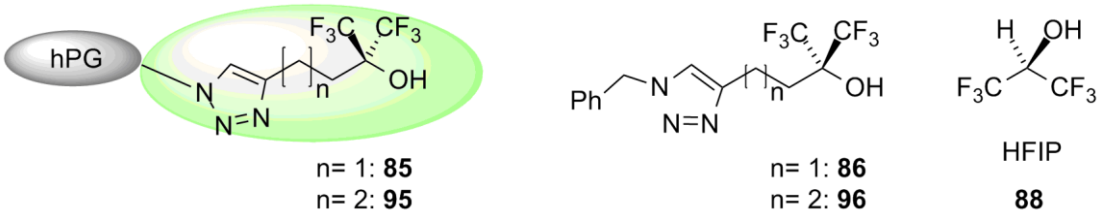


Figure 38. Structure of hPG-HFIPs, (**85**/**95**) non-supported HFIP analogs (**86**/**96**) and commercial HFIP (**88**).

This positive dendritic effect clearly supports the concept of the initial catalyst design, but also supports the multiple HFIP-transition state model by Berkessel et al. for the HFIP-catalyzed olefin epoxidation.[138,140b,148] The best solvent with regard to the outcome of the reaction was found to be dichloromethane. Catalyst **85** and **95** performed well with cycloalkenes, such as cyclohexene, methylcyclohexene or cycloctene, as substrates. Open-chain alkenes were only converted with moderate efficiency.

Overall, it could be shown that the immobilization of fluoroalcohol monomers on our soluble dendritic support is a suitable method for the development of organocatalysts that promote reactions via multiple hydrogen bond networks. In the current example the high local concentration of HFIP groups was used for the electrophilic activation of hydrogen peroxide. Up to now, the epoxidation of alkenes by hydrogen peroxide was only doable when HFIP was applied in solvent-like quantities. The results presented here, demonstrate the activation of hydrogen peroxide for the first time with catalytic amounts of HFIP. This positive dendritic effect nicely shows the benefit of the multiple catalyst design and at the same time supports the multiple transition state model. In the same way, the typical sulfoxide selectivity in thioether oxidation could be achieved with dendritic HFIP. It seems likely that this catalytic concept will find further use, for instance in other electrophilic oxidations using peroxide or in other transformations that are promoted by multiple hydrogen bonding.

5. Conclusion and Outlook

Recently, the field of "green" organocatalysis, has been critized because (sometimes) large amounts (20 to 30 mol%) of catalyst is required in order to achieve results comparable to metal-based reactions. It was considered that a "green" reaction has not only has to be highly selective, but more importantly, has to show a high efficiency. Therefore, the recovery of organocatalysts has been investigated by using techniques of extractive acid-base work-up, simple filtration or centrifugation, which is mostly accompanied by a decrease in yield and/or stereoselectivity. In order to make organocatalysts more "green" their immobilization on a support is the goal, which facilitates catalyst recovery and reuse by simple work-up protocols and is the only solution for the above-mentioned dilemma.

We were able to show with four examples that our strategy to use hyperbranched polyglycerol for the immobilization of organocatalysts is a suitable concept. It was demonstrated that low amounts of catalyst can be used because the catalytically active sites are well distributed and the local concentration is higher relative to a non-supported catalyst. In conclusion the soluble supports were superior to solid analogs in the investigated reactions, especially since solid supports often show diminished chemical yields after a few runs in a recycling experiments, which is usually caused by the deterioration of the polymer backbone due to mechanical stress.

Our concept has been initially proven by the immobilization of proline, which is one of the simplest organocatalysts. The linkage using the [2+3]Huisgen cycloaddition is a versatile tool, which also enables the binding of more complex organocatalysts which is of great interest.

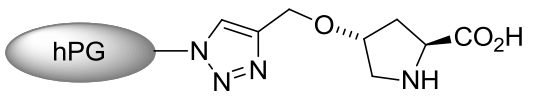
Another benefit of the polymeric catalysts is that their possible application in a continuous flow reactor. Since no catalyst leaching was observed, this opportunity should be investigated in the future. Another important feature of an immobilized catalyst is the stereochemical outcome of the investigated reactions. In this thesis, it has been shown that it is almost impossible to predict the stereochemical outcome of a reaction after immobilization of the catalyst, even though the performance of the monomeric catalyst is known. From our experimental results it can be concluded that the *ee*'s obtained upon immobilization are rarely better than these obtained for the monomers.

6. Zusammenfassung

In der vorliegenden Arbeit wurden das Konzept, die Synthese und die Anwendung von Organokatalysatoren dargestellt, die auf hochverzweigtem Polyglycerol immobilisiert sind. Thematisch handelt es sich um die kovalente Anbindung von chiralen und nicht-chiralen metallfreien Katalysatoren, die auf einem löslichen Träger immobilisiert wurden.

Die Gültigkeit des Ansatzes konnte anhand von vier Beispielen belegt werden:

Im ersten Teil der Arbeit wurde gezeigt, dass hochverzweigtes Polyglycerol ein geeigneter Träger für die kovalente Anbindung des Organokatalysators Prolin ist. Es wurden drei verschiedene polymere Katalysatoren dargestellt, die sich im Beladungsgrad unterscheiden, und ihre Verwendung in der asymmetrischen Aldolreaktion untersucht.



9a-c

PG-Pro(n)
n= 10, 50 or 100%

Abbildung 1. Der Organokatalysator Prolin immobilisiert auf hochverzweigtem Polyglycerol.

Der polymere Prolin-Katalysator **9a** zeigt in der Aldolreaktion hohe Aktivität, so dass die beobachteten Reaktionszeiten bis zum kompletten Umsatz deutlich unter denen von anderen geträgerten Prolin-Katalysatoren liegen. Die hohe Reaktionsrate ist unser Ansicht auf die hohe Lokalkonzentration an Prolin Einheiten auf der Polymeroberfläche zurückzuführen. Die in der Testreaktion beobachteten Enantiomerenüberschüsse lagen für den polymeren Katalysator **9b**, deutlich über denen des ungeträgerten Prolin-Derivats **19** (62% vs. 51%) und zeigen damit einen positiven dendritischen Effekt. Im Vergleich zu anderen Trägern, wie unlöslichen dendritischen System oder perfekten Dendrimeren, die jeweils eines hohen synthetischen Aufwands bedürfen, erlaubt hPG den einfacheren und leichteren Zugang zu polymeren Prolin-Katalysator, ohne dass auf Vorzüge wie hohe lokale Konzentration (Dendrimer) oder einfaches Recycling unlöslicher Träger verzichtet werden muss.

Im zweiten Teil der Arbeit wurde ein Derivat von Hexamethylphosphoramid (HMPA) auf hochverzweigtem Polyglycerol immobilisiert. Diese Verbindung HMPA wird häufig

als Lösungsmittel zur Reaktionsbeschleunigung eingesetzt, hat sich jedoch in Tierversuchen als krebserzeugend erwiesen. Neben der Inhalation, die durch die Immobilisierung komplett verhindert werden kann, ist die Aufnahme über die Haut der zweite wichtige Aufnahmeweg in den Körper. Auf Grund der Größe unseres Konjugats wird dies deutlich erschwert bzw. verlangsamt. Daneben gibt es über die Anbindung des achiralen HMPA hinaus die Möglichkeit andere z.B. chirale Phosphoramid-Voräufer an den Träger zu binden. Dies funktioniert aufgrund des gewählten modularen Ansates relativ einfach, was auch zu einer deutlichen Erweiterung in der Anwendbarkeit führt.

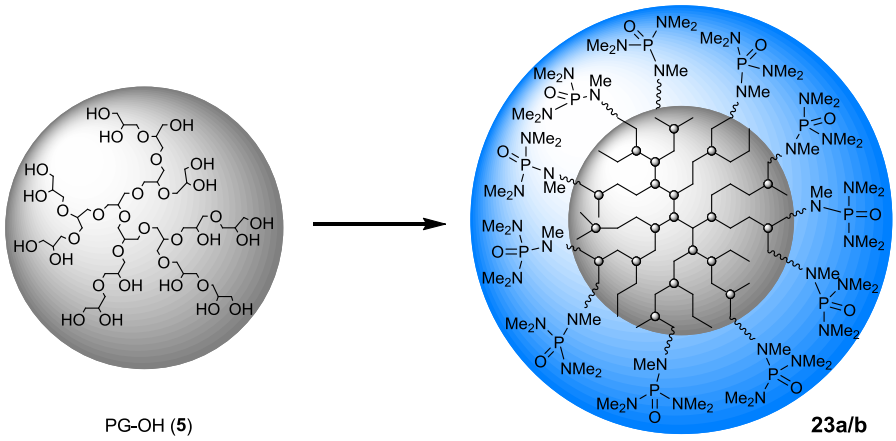


Abbildung 2. HMPA immobilisert auf dem löslichen Träger hPG.

Der erhaltene Katalysator (kurz: hPG-HMPA) wurde sowohl in der Mukaiyama-Aldol-, als auch in der Allylierungsreaktion erfolgreich eingesetzt. In der katalysierten Allylierung konnte zudem ein positiver dendritischer Effekt mit dem Konjugat nachgewiesen werden, so dass das sonst in überstöchiometrischen Mengen verwendete HMPA nun in katalytischen Mengen quantitativen Umsatz lieferte. Die hohen Reaktionsgeschwindigkeiten mit dem polymeren Katalysator sind unserer Ansicht nach auf die hohe lokale Konzentration des HMPA auf der Polymeroberfläche zurückzuführen. Zum anderen konnte der von Denmark et al. vorgeschlagene Reaktionsmechanismus für das *anti*-Produkt gestützt werden, bei dem zwei Moleküle HMPA im Übergangszustand postuliert werden. Die kann sonst nur durch eine hohe Konzentration von HMPA in der Reaktionslösung erreicht werden. Damit passt Denmark's These hervorragend zu unseren Ergebnissen in der Katalyse und zu unserem Katalysator-Konzept der hohen lokalen Konzentration auf der polymeren Oberfläche. Der HMPA-Katalysator konnte zudem leicht durch Ultrafiltration abgetrennt und merhfach wiederverwendet werden, wobei keine Aktivitätsverluste beobachtet wurden.

Eine Modifizierung des oben beschriebenen Konzepts mit chiralen Phosphoramiden wurde mit Hilfe von chiralen 1,2-Diamin-Derivaten erreicht und in den oben genannten C-C-Bindungsknüpfungsreaktionen eingesetzt. Ausgehend von chiralem Diaminocyclohexan bzw. Diphenylethylendiamin wurden in einer mehrstufigen Synthese die Verbindungen am Stickstoff jeweils monomethyliert und zum entsprechenden Phosphoramid-Vorläufer phosphoryliert. In einer Kupplungsreaktion konnten die unterschiedlichen Vorläufer an das modifizierte Polyglycerol gebunden werden. Dieser modulare Syntheseweg erlaubt die einfache Modifikation des polymeren Katalysators ohne eine „neue“ Chemie am Polyglycerol zu etablieren. Die darstellten chiralen Phosphoramide auf polymeren Träger katalysierten die Testreaktionen nicht nur mit guten Reaktionsgeschwindigkeiten, sondern generierten auch in allen Fällen Enantiomerenüberschüsse. Eine Voraussage über die Selektivität des geträgerten Katalysators bei bekannten *ee*-Werten des monomeren Katalysators war in den von uns bearbeiteten Fällen nicht möglich. Es wurden sowohl höhere, als auch niedrige *ee*'s beobachtet, wenn ein geträgerter Katalysator verwendet wurde.

Der dritte Teil dieser Arbeit beschäftigte sich mit einem neuartigen Säure-Base-Katalysator, der aus chiralem Binaphthol und Polyglycerol-Dendronen als Substituenten aufgebaut ist.

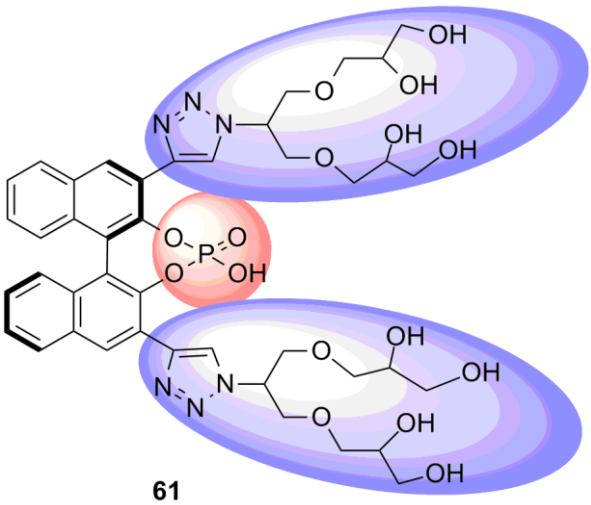


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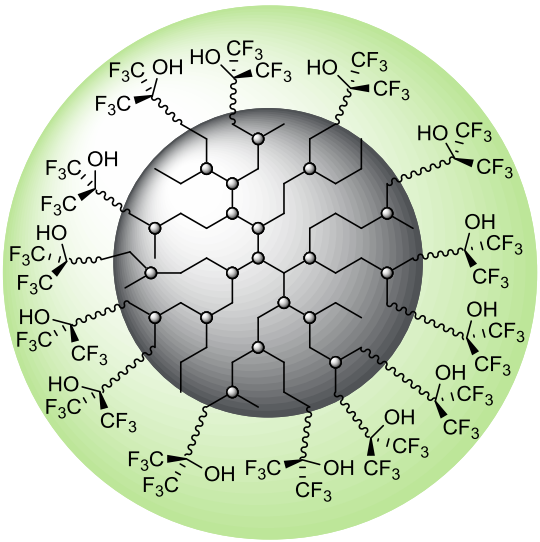
Abbildung 3. Binaphthol als Rückgrat für eine neuartige Brønsted-Säure mit dendritischen Substituenten (**61**).

Dieser Katalysator wurde nach erfolgreicher Synthese in der Transferhydrierung von Ketiminen mittels eines NADH-Analogon eingesetzt. Hierbei wurde eine hohe Katalysatoraktivität festgestellt, die in der Testreaktion zu quantitativen Umsätzen in

Verbindung mit kurzen Reaktionszeiten führte. Diese lagen zum Teil deutlich unter denen, die von anderen Gruppen unter gleichen Reaktionsbedingungen beobachtet wurden.[127b,127c] Das zeigt, dass trotz der dendritischen Substituenten am BINOL in Position 3 und 3‘ die Phosphorsäure weiterhin für das Substrate zugänglich ist. Jedoch wurden „nur“ racemische Gemische erhalten und damit die Stereoinformation des Katalysators nicht übertragen. Eine Diskussion zu den möglichen Ursachen und Schlußfolgerungen befindet sich im Abschnitt „Conclusion and Outlook“.

Im vierten Teil wurde gezeigt, dass hochverzweigtes Polyglycerol auch ein ausgezeichneter Träger für Organokatalysatoren ist, die einzig über die Ausbildung von multiplen Wasserstoffbrücken Substrate bzw. Reagenzien aktivieren können. Fluorierte Alkohole wie das Hexafluoroisopropanol (HFIP), gehören zu einer Gruppe von Verbindungen, die über den oben genannten Mechanismus Wasserstoffperoxid aktivieren, mit dem dann zum Beispiel Alkene bzw. Thioether oxidiert werden können. Die Verwendung von Wasserstoffperoxid als Oxidationsmittel kann als „grüne“ bzw. saubere Methode angesehen werden, da neben dem gewünschten Produkt nur Wasser als Nebenprodukt gebildet wird. Für die Anwendung im großen Maßstab entsteht das Problem der sicheren Handhabung und der Kosten von großen Mengen HFIP als Lösungsmittel. Hier wäre es hilfreich, wenn man statt der üblichen Lösungsmittelmengen zu katalytischen Mengen wechseln könnte. Dies motivierte uns einen Katalysator zu entwickeln, bei dem fluorierte Alkohole als Kopf- bzw. Endgruppen an die multiplen Bindungsstellen von Polyglycerylazid gebunden werden. Dies garantiert eine hohe lokale Konzentration an fluorierten Gruppen, was für die oben genannten Reaktionen essentiell ist.



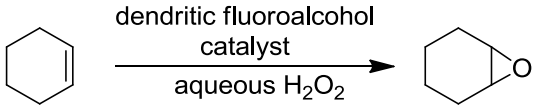


Abbildung 4. Schematische Darstellung des auf hPG immobilisierten Hexafluoroisopropanols.

Ausgehend von Alkynolen wurde das Hexafluroaceton (HFA) mittles einer Organozink-Verbindung nucleophil angegriffen. Erhalten wurden zwei HFIP-Analoga mit unterschiedlich langen CH_2-Linkern und terminalen C-C Dreifachbindungen. Mit Hilfe von Huisgen‘s 1,3-dipolare Cycloadditionreaktion wurden verschiedene polymere HFIP-Analoga synthetisiert, bei denen die Linkerlänge und der Beladungsgrad variiert wurden. Die jeweilige Oberflächenbeladung wurde mittels ^{19}F NMR und internem Standard zu 3 mmol „HFIP“ pro Gramm Katalysator bestimmt, was einer Beladung von über 95% entpricht.

Die Epoxidierungsreaktion von Cycloocten mit 50% wässrigem Wasserstoffperoxid wurde als Testreaktion verwendet. Dabei wurden die polymeren HFIP-Analoga mit den auf Phenylazid geklickten Monomeren verglichen. Es zeigte sich, dass bei jeweils gleichem Katalysator zu Substrat Verhältnis die polymeren HFIP’s deutlich reaktiver sind als die jeweiligen Monomere oder das kommerzielle HFIP. Mit den Ergebnissen konnte nicht nur ein positiver dendritischer Effekt nachgewiesen, sondern auch das Konzept des Katalysatordesigns bestätigt werden. Daneben unterstützt es auch den von Berkessel et al. vorgeschlagenen Reaktionsmechanismus der Aktivierung von Wasserstoffperoxid in der HFIP-vermittelten Epoxidierung mittels multipler Wasserstoffbrücken im Übergangszustand.[140b,148] Nach der Optimierung der Reaktionsbedingungen wurden verschiedene Cycloalkene und offenkettige Alkene in sehr guten (für cyclische Substrate) bis guten Ausbeuten (für offenkettige Substraten) unter katalytischen Reaktionsbedingungen erhalten. Ebenso konnte Methylphenylsulfid (Thionanisol) als ein Vertreter der Thioether unter milden Bedingungen selektiv zum entsprechenden Sulfoxid oxidiert werden, wobei kein Sulfon beobachtet wurde. Zusätzlich konnte unter Recyclingbedingungen die mehrfache Wiedergewinnung und –verwendung gezeigt werden.

Zusammenfassend lässt sich festhalten, dass hochverzweigtes Polyglycerol ein vielseitiger löslicher Träger für verschiedenste Organokatalysatoren darstellt, der mittels Ultrafiltrationstechniken wiedergewonnen werden kann. Außerdem bietet er die Möglichkeit des Einsatzes in kontinuierlich arbeitenden Membranreaktoren. Mit Hilfe

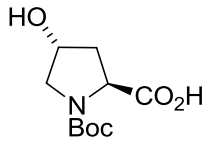
der beobachteten dendritischen Effekte durch die hohe lokale Katalysatorkonzentration lässt sich die Gesamtkatalysatormenge verringern, sowie Reaktionswege und Selektivitäten (teilweise) positiv beeinflussen. Desweiteren können die Lösungseigenschaften den Reaktionsbedingungen angepasst werden, so dass zum Beispiel der hydrophobe Katalysatorcharakter maskiert werden kann.

7. Experimental Part

All experiments were carried out under an argon atmosphere using dried glassware. Chemicals were purchased from commercial suppliers and used as received unless otherwise noted. Benzaldehyde was freshly distilled prior to use. Dry CH_2Cl_2 was purchased from Sigma-Aldrich and dried via *Solvent Purification System MB-SPS 800* from *MBraun*. Column chromatography was performed on *Merck Silica Gel 60* (230-400 mesh). Reactions were monitored by thin layer chromatography (TLC) using *Merck TLC Silica gel 60 F_{254}*. Products were detected using a UV/Vis lamp (254 nm). Ultrafiltration was performed with a 300 mL solvent-resistant stirred cell with regenerated cellulose membranes (molecular weight cutoff 5000 g mol-1), both from Millipore. ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded at room temperature using a *Jeol ECX 400* and *Bruker AV 700*. 2D spectra were recorded on a *Jeol Eclipse 500*. Chemical shifts (δ) were reported in parts per million (ppm) relative to tetramethylsilane and coupling constants (*J*) in Hertz (Hz). The spectra were referenced against the internal solvent ($CDCl_3$, δ ^{1}H = 7.26 ppm, ^{13}C = 77.0 ppm; DMSO-d_6, δ ^{1}H = 2.50 ppm, ^{13}C = 40.0 ppm). Data is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. IR spectra were recorded on a *Nicolet Avatar 320 FT-IR* with a ZnSe optical window. The absorption bands are given in wave numbers (cm^{-1}), intensities are reported as follows: s = strong, m = medium, w = weak. For chiral HPLC a Hitachi LaChrom® HPLC equipped with a Chiralpak® IA column has been used. The signal was detected by UV- and diffraction detector.

7.1 Synthesis of Proline Suppported on Hyperbranched Polyglycerol

(2S, 4R)-1-(tert-butoxycarbonyl)-4-hydroxy-2-pyrrolidinecarboxylic acid (2)[95]



$C_{10}H_{17}NO_5$
Mol. Wt.: 231.25

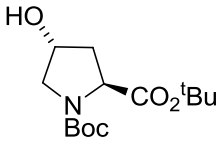
A mixture of commercial (2S,4R)-4-Hydroxyproline (**1a**) (15.5 g, 118 mmol) and 10% aqueous sodium hydroxide (80 mL) was dissolved in 300 mL of a 2:1 mixture of

THF/H2O. Then di-tert-butyldicarbonate (38.7 g, 177 mmol, 1.5 eq.) was added. The reaction mixture was stirred overnight at room temperature and then the THF was removed in vacuo. The residue was adjusted to pH 1 by addition of aqueous NaHSO4. The aqueous solution was extracted several times with ethyl acetate. The combined organic phases were washed with brine, dried over NaSO4, filtered, and evaporation of the solvent in vacuo gave the product 2 as syrup. The crude product was further purified by flash column chromatography (hexane/ethyl acetate 2:1) to yield 20.74 g (89.7 mmol, 76 %).

1H-NMR (400 MHz, CD3OD): δ (ppm) = 4.40-4.35 (m, 1H, α-CH), 4.34-4.25 (m, 1H, γ-CH), 3.54-3.39 (m, 2H, δ-CH2), 2.30-1.99 (m, 2H, β-CH2), 1.44 and 1.41 (s, 9H, C(CH3)3).

13C-NMR (100 MHz, CD3OD): δ (ppm) = 175.4, 175.0, 155.1, 154.7, 80.4, 80.1, 69.4, 68.8, 58.1, 57.6, 54.6, 54.2, 38.8, 38.1, 27.4, 27.2.

tert-butyl (2S, 4R)-N-Boc-4-hydroxyprolinate (3)[96]



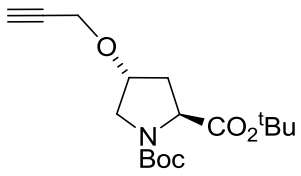
$C_{14}H_{25}NO_5$
Mol. Wt.: 287.35

(2S,4R)-N-Boc-4-Hydroxyproline (**2**) (8.6 g, 37 mmol, 1 eq.), benzyltriethylammonium chloride (8.5 g, 37 mmol, 1 eq.), K_2CO_3 (134 g, 0.97 mmol, 26 eq.) and *tert*-butyl bromide (204 mL, 1.49 mol, 40 eq.) were suspended in N,N-dimethylacetamid (188 mL) and vigorously stirred at 55 °C for 21 h using a KhPG-stirrer. The reaction mixture was cooled to room temperature and water was added until all the potassium carbonate completely dissolved. The reaction mixture was extracted with diethyl ether (3 times). The combined organic extracts were washed with brine, dried with $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane / *EE* = 9:1 to 4:1) gave the product **3** as a foamy white solid (8.8 g, 30.6 mmol, 83 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.44-4.36 (m, 1H, H-2), 4.28-4.18 (m, 1H, H-4), 3.58-3.33 (m, 2H, H-5), 2.29-2.14 (m, 1H, H-3), 2.04-1.92 (m, 1H, H-3), 1.42 and 1.39 [s, 18H, $C(CH_3)_3$].

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ (ppm) = 172.3, 172.2 (C-1), 154.6, 154.4 (NCO_2), 81.3, 81.2, 80.3, 79.9 [$C(CH_3)_3$], 70.1, 69.2 (C-2), 58.65, 58.6 (C-4), 54.7, 54.6 (C-5), 39.1, 38.4 (C-3), 28.5, 28.4, 28.1, 28.0 [$C(CH_3)_3$] .

tert-butyl (2S, 4R)-N-Boc-4-propargyloxyprolinate (4)[97]



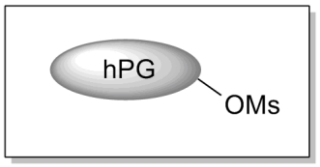
$C_{17}H_{27}NO_5$
Mol. Wt.: 325.40

In a flame-dried flask, tert-butyl (2S,4R)-N-Boc-4-hydroxyprolinate (3) (4.9 g, 17.0 mmol) dissolved in THF (20 mL), was added dropwise to a suspension of sodium hydride (1.36 g, 60% on mineral oil, 34 mmol, 2 eq.) in THF (20 mL) at -20 °C, and was stirred for 30 min at this temperature. Then propargyl bromide (3.8 ml, 34 mmol, 80% in toluene, 2 eq.) was syringed dropwise into the reaction mixture. After stirred for 30 min at -20 °C, the mixture was allowed to reach room temperature overnight. MeOH (5 mL) was added to eliminate excess of NaH. The reaction mixture was extracted with ethyl acetate (3x 50 mL). The combined organic extracts were washed with brine, dried with MgSO4, and concentrated in vacuo. The residue was purified by column chromatography (Hex/EE 4:1) and gave 4 (4.9 g, 15.1 mmol, 89 %) as colorless oil.

1H-NMR (400 MHz, CDCl3): δ (ppm) = 1.39-1.46 (s, 18H), 1.98-2.09 (m, 1H), 2.21-2.40 (m, 1H), 2.42 (t, 1H, J = 2.37 Hz), 3.43-3.67 (m, 2H), 4.06-4.33 (m, 4H).

13C-NMR (100 MHz, CDCl3): δ (ppm) = 28.0, 28.1 (CH3), 28.4, 28.5 (CH3), 36.6 (CH2), 51.1 (CH2), 56.5 (CH), 58.5 (CH2), 74.8 (≡CH), 75.7 (≡C), 79.4 (CH), 80.1 (C), 81.2 (C), 154.0 (C=O), 172.1 (C=O).

O-Mesylpolyglycerol (6)[63d]



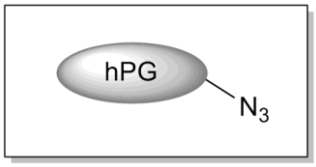
Polyglycerol (**5**) (11.0 g, 149 mmol OH-groups) in a two-necked 1 L flask equipped with a septum, thermometer, and magnetic stirrer was dissolved in abs. pyridine (200 mL). The solution was cooled to 0 °C using an ice/NaCl bath. Mesyl chloride (12.7 mL, 18.8 g, 164 mmol, 1.1 eq.) was added dropwise by syringe at such a rate that the temperature did not exceed 5 °C. The resulting dark-brown solution was stirred overnight at room temperature. The solution was cooled to 0 °C and 500 ml ice-cold water was added which resulted in a light brown solid precipitation. The liquid phase was decanted and the remaining solid was washed with H_2O, dissolved in acetone and purified by dialysis in the same solvent to give 18 g of the yellow honey-like product **6**. Conversion: 98 %; yield: 80 %.

^{1}H-NMR (700 MHz, $(CD_3)_2CO$): δ (ppm) = 5.11 − 4.85 (functionalized secondary hPG-groups), 4.62−4.32 (functionalized primary hPG-groups), 4.06-3.51 (hPG), 3.22 (Me), 0.96 (hPG-starter).

^{13}C-NMR (175 MHz, $(CD_3)_2CO$): δ = 81.4-76.7 (hPG), 72.2-68.0 (hPG), 38.0 (Me), 36.8 (Me).

IR (bulk): ν = 3027, 2940, 1459, 1331, 1168, 1108, 969, 919, 800, 731 cm^{-1}.

Polyglycerylazide (7)[63d]



In a 500 mL one-necked flask with reflux condenser and magnetic stirrer *O*-mesylpolyglycerol (**6**) (18 g, 117 mmol OMs-groups) in dry DMF (250 mL) was dissolved, upon ultrasonication. Sodium azide (38 g, 585 mmol, 5 eq.) was added and the resulting suspension was heated at 80 °C overnight behind a safety screen. After

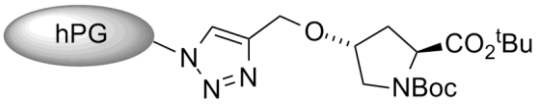
cooling, a white residue of excess NaN_3 was removed by filtration. The reddish filtrate was concentrated under vacuum at temperatures below 40 °C. The residue was dissolved in $CHCl_3$ and washed 3 times with water. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. Traces of DMF were removed from the raw product by membrane-ultrafiltration in chloroform/methanol mixture, which resulted in 11.7 g of a light-brown honey-like product **7**. Conversion: quant.; yield: 99 %.

^{1}H-NMR (700 MHz, $CDCl_3$): δ (ppm) = 3.83-3.17 (hPG), 1.93 (hPG-starter), 0.87 (hPG-starter).

^{13}C-NMR (175 MHz, $CDCl_3$): δ (ppm) = 79.6-78.1 (hPG), 72.6-69.3 (hPG), 61.4-60.2 (functionalized secondary hPG-groups), 52.4-51.2 (functionalized primary hPG-groups).

IR (bulk): ν = 2871, 2089 (N_3), 1446, 1266, 1101, 834 cm^{-1}.

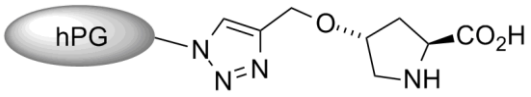
Cycloaddition of *tert*-Butyl (2S,4R)-N-Boc-4-propargyloxyprolinate (4) with polycerylazide (7)



Diisopropylethylamine (95 µL, 0.56 mmol, 0.1 eq.) and polyglyceryl azide (**7**) (1.1 g, 11.1 mmol azide group) dissolved in THF (1 mL) was added to the *tert*-butyl (2S,4R)-N-Boc-4-propargyloxyprolinate (**4**) (1.82 g, 5.58 mmol, 1 eq.) in THF (1 mL). After the mixture had been stirred for 5 min, sodium ascorbate (110 mg, 0.56 mmol, 0.1 eq.) dissolved in 1.5 mL Millipore water was added, followed by copper(II)-sulfate pentahydrate (139 mg, 0.56 mmol, 0.1 eq.) in 1.5 mL Millipore water. The reaction mixture was stirred overnight at r.t. TLC analysis indicated complete consumption of the prolinate. The solution was concentrated and the residue was diluted in water and extracted with dichloromethane. The combined organic layers were washed several times with small portions of saturated EDTA solution until the blue color of the aqueous phase disappeared. The crude product was further purified by ultrafiltration (solvent: methanol; membrane material: regenerated cellulose, NWCO (molecular weight cut-off): 5 kDa). The product **8** was obtained as crystalline compound (2.52 g, 86 % yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.25-1.43 (m, 18H), 1.82-2.09 (m, 1H), 2.11-2.34 (m, 1H), 3.04-5.31 (hPG-backbone), 3.99-4.29 (m, 2H), 4.29-4.61 (m, 2H), 7.22-7.97 (m, 1H).

Deprotection



1 g of the cycloaddition adduct **8** from the previous step was dissolved in DCM (3 mL) and heated up to 40 °C. After 10 min, 8 mL of trifluoroacetic acid (99 %) were added and the deprotection reaction was followed by FTIR. The reaction was quenched after 16 hours, when the IR-band of ^{t}Bu and carbonyl had disappeared. The pH of the reaction mixture was then adjusted to neutral with the help of aqueous potassium hydroxide. The supported proline **9** (hPG-Pro) was obtained in quanitative yield after purification by ultrafiltration using distilled water.

^{1}H-NMR (500 MHz, D_2O): δ (ppm) = 1.92-2.08 (m, 1H), 2.29-2.48 (m, 1H), 3.18-5.40 (m, 2xCH_2, hPG-backbone), 7.68-8.27 (m, 1H, triazol).

^{13}C-NMR (125 MHz, D_2O): δ (ppm) = 35.5 (CH_2), 50.2-51.1 (CH_2, functionalized primary hPG-groups), 59.9-61.5 (CH_2, functionalized secondary hPG-groups), 68.9-71.3 (hPG), 77.5-78.9 (hPG, CH), 125.5, 144.3.

7.2 Catalysis with the Proline-based Catalyst

General procedure for the aldol reaction:

The polymeric catalyst hPG-Pro(50) was dissolved (75 mg, 0.15 mmol, 0.3 eq.) in 4 mL DMSO and then acetone was added (1 mL, 13.5 mmol, 27 eq.). The mixture was stirred for 10 min at room temperature and then the nitrobenzaldehyde (**10**) (76 mg, 0.5 mmol, 1 equiv) was added. The reaction mixture was stirred at room temperature for 24 hours. Progress of the reaction was followed by TLC analysis. After 24 hours, the reaction mixture was diluted in ethyl acetate and washed with water (10 mL) and saturated

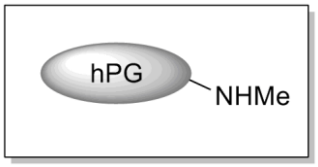
aqueous NH4Cl solution (10 mL). The organic extracts were combined, dried on MgSO4, filtered and the solvent was evaporated. The crude product was analyzed by 1H NMR to determine conversion and yield. Further purification by column chromatography on a silica gel (1:9 EE: hexane up to 3:7 EE:hexane) yielded the pure product 12 as yellow oil. The ee of the product was determined by HPLC, using Chiralpak AD (benzaldehyde product) or OJ (4-nitrobenzaldehyde product) columns.

7.3 Synthesis of HMPA Supported on hPG

O-Mesylpolyglycerol (6)[63d]

see Section 4.1

Polyglycerylmethylamine (20)[63d]



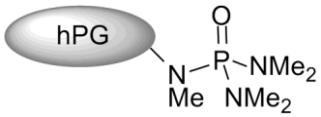
O-mesylpolyglycerol **6** (4.4 g, 28.6 mmol mesyl groups) was dissolved in p.a. DMF (20 mL) in a glass tube using ultrasonication. In the next step, 15 mL methylamine gas was condensed into the tube and fixed in an autoclave and sealed afterwards. The mixture was stirred and heated up to 60 °C for 24 h. For workup the mixture was diluted with methanol and filtered using a glass frit. The crude product was further purified by ultrafiltration with methanol as solvent and 2 mL triethylamine as an additive in the first run. After the third run the filtrate became colorless. The solvent was evaporated and a brown honey-like product **20** was obtained. Yield: 95 %, 8 mmol methylamine-groups per gram polymer.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.87–3.16 (br m, hPG-backbone), 2.77−2.62 (m, functionalized hPG groups), 2.42-2.17 (br m, NCH_3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 78.6–68.7 (hPG), 62.0–46.0 (functionalized hPG groups), 43.0-34.0 (NHMe).

IR (neat) ν = 3395 (N-H), 2931, 2857, 2797 (C-H), 1146, 1043 (N-C) cm^{-1}.

hPG-Hexamethylphosphoramide Analog (23)



Polyglycerylmethylamine **20** (1 g, 8 mmol) was dissolved in dry THF (20 ml) in a 50 mL Schlenk tube. The clear yellow solution was cooled to -78 °C and after 30 min, N,N,N',N'-tetramethylphosphorodiamidic chloride (**22**) (8 mmol, 1.2 mL) was added dropwise via syringe. The reaction was warmed to room temperature overnight and then quenched by addition of methanol. The crude product was purified by ultrafiltration (membrane: 5kDa, solvent: methanol).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.85–3.28 (br m, hPG-backbone), 2.65−2.16 (br m, NCH3);

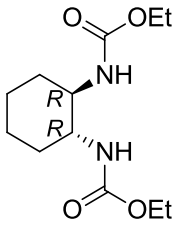
^{31}P-NMR (121.5 MHz, $CDCl_3$): δ = 26.0, 27.4 ppm.

Loading: 1 mmol HMPA per gram polymer; determined by addition of triphenylphosphine oxide as internal standard, followed by integration in the ^{31}P spectra.

Synthesis of hPG-supported chiral Phosphoramides:

7.4 Synthesis DACH-Type Chiral Phosphoramide on hPG

Diethyl (1R,2R)-cyclohexane-1,2-diyldicarbamate (31)[152]



$C_{12}H_{22}N_2O_4$
Mol. Wt.: 258.31

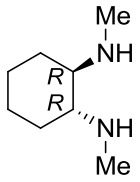
A solution of commercial (1R,2R)-1,2-diaminocyclohexane (**30**) (5.0 g, 43.8 mmol, 1 eq.) in toluene (150 mL) was stirred and cooled at 0 °C. Afterwards ethyl chloroformate (11.4 g, 105 mmol, 2.4 eq.) and sodium hydroxide (4.2 g, 105 mmol, 2.4 eq.) dissolved

in water (50 mL) were added simultaneously. The addition rate has been adjusted so that the reaction temperature did not exceed 5 °C. After the addition was complete, the reaction mixture was stirred at r.t. for 3 h, before the heavy precipitate was filtered off and rinsed once with CH_2Cl_2 (80 mL). The filtrate was dried on $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography using ethyl acetate. The dicarbamate **31** was obtained as white crystals in 10.74 g (41.6 mmol, 95%) yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.19-1.35 (m, 6+4 H, C*H*$_3$CH$_2$, C*H*$_2$-Cy), 1.71-2.07 (m, 4H, C*H*$_2$-Cy), 3.29-3.38 (m, 2H, NC*H*-Cy), 4.04-4.14 (m, 4H, CH$_3$C*H*$_2$), 4.94 (d, 2H, *NH*, J = 3.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 14.6 (s, *C*H$_3$CH$_2$), 24.9 (s, *C*H$_2$-Cy), 32.8 (s, *C*H$_2$-Cy), 55.4 (s, N*C*H-Cy), 60.8 (s, CH$_3$*C*H$_2$), 157.0 (s, N*C*O$_2$).

(1R,2R)-N,N'-Dimethylcyclohexane-1,2-diamine (32)[152]



$C_8H_{18}N_2$
Mol. Wt.: 142.24

The dicarbamate **31** (10.7 g, 41.4 mmol) in THF (75 mL) was slowly added at room temperature to a solution of lithium aluminium hydride (8.2 g, 216 mmol, 5.2 eq.) in THF (75 mL). After the addition, the mixture was heated at reflux overnight. Afterwards the mixture is cooled to 0 °C and a 10% solution of potassium hydroxide in water carefully added (100mL) and shortly heated to reflux. The precipitate was removed by a glass frit and washed 2 times with CH_2Cl_2. The filtrate was two times extracted with CH_2Cl_2. The combined organic phases were further washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. After vacuum distillation, using a Kugelrohr oven, the colorless diamine **32** was obtained in 3.24 g (22.8 mmol, 84%) yield. bp 100-110 °C (15 mbar).

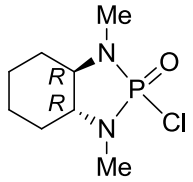
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.82-1.13 (m, 2H, C*H*$_2$-Cy), 1.14-1.27 (m, 2H, C*H*$_2$-Cy), 1.45-1.59 (s, 2H, N*H*), 1.66-1.71 (m, 2H, C*H*$_2$-Cy), 1.95-2.04 (m, 2H, C*H*$_2$-Cy), 2.04-2.15 (m, 2H, NC*H*-Cy), 2.38 (s, 6H, C*H*$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 23.9 (s, NH*C*H$_3$), 29.7 (s, *C*H$_2$-Cy), 31.9 (s, *C*H$_2$-Cy), 61.0 (s, N*C*H-Cy).

IR (KBr) ν = 3395 (N-H), 2931, 2857, 2797 (C-H), 1146, 1043 (N-C) cm^{-1}.

(+)ESI-TOF: calcd for $C_8H_{18}N_2H^+$: 143.1543, found: 143.1530.

(3R,7R) -1,3-dimethyl-2-chlorooctahydrobenzo[1,3,2]diazaphosphole 2-oxide (33)[112]



$C_8H_{16}ClN_2OP$
Mol. Wt.: 222.65

(R,R)-N,N'-Dimethyl-1,2-diaminocyclohexane (**32**) (560 mg, 3.9 mmol, 1 eq.) was dissolved in toluene (15 mL) and triethylamine (1.1 mL, 790 mg, 7.8 mmol, 2 eq.) was added with stirring. The mixture was cooled to 0 °C and $P(O)Cl_3$ (0.4 ml, 600 mg, 3.9 mmol) was carefully and slowly added dropwise. The mixture was stirred for 4 hours and allowed to warm to room temperature. The reaction mixture was filtered through a glass frit to remove the precipitated salts. The filtrate was dried over $MgSO_4$, filtered and solvent evaporated. Purification by Kugelrohr distillation (10^{-2} mbar, 125 °C) gave product **33** as colorless solid (683 mg, 3.1 mmol, 79%).

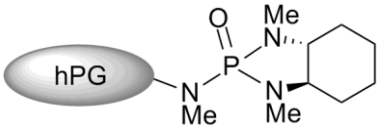
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.11-1.40 (m, 4H, CH_2-Cy), 1.77-1.98 (m, 2H, CH_2-Cy), 1.94-2.04 (m, 2H, CH_2-Cy), 2.53 (d, $^{3}J_{P-H}$ = 15.9 Hz, 3H, NCH_3), 2.56-2.60 (m, 1H, NC*H*), 2.65 (d, 3H, NC*H*$_3$, $^{3}J_{P-H}$ = 11.9 Hz), 2.76-2.88 (m, 1H, NC*H*).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.2 (m, CH_2-Cy), 24.1 (m, CH_2-Cy), 27.5 (d, $^{3}J_{P-C}$ = 12.9 Hz, NCH*C*H$_2$), 28.2 (d, $^{3}J_{P-C}$ = 8.5 Hz, NCH*C*H$_2$), 28.4 (d, $^{2}J_{P-C}$ = 3.7 Hz, PN*C*H$_3$), 28.7 (d, $^{2}J_{P-C}$ = 1.1 Hz, PN*C*H$_3$), 62.7 (d, $^{2}J_{P-C}$ = 9.7 Hz, PN*C*H), 64.3 (d, $^{2}J_{P-C}$ = 10.0 Hz, PN*C*H),

^{31}P-NMR (162 MHz, $CDCl_3$): δ (ppm) = 36.3 (s).

IR (KBr) ν = 2942, 2865 (C-H), 1464 (P=O), 1274 (C-N), 1226, 1176 (P-N), 988 (P-Cl) cm^{-1}.

Coupling of the Chiral Phosphoramide Precursor (33) with Polyglycerylmethylamine (20)



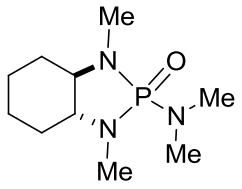
Polyglycerylmethylamine **20** (1g, 4.5 mmol, 1 eq.) was dissolved in dry THF (25 mL) and cooled to -78 °C with the help of a cryostat. After 30 min of stirring, *n*-BuLi (1.8 mL, 2.5 M in hexane, 4.5 mmol, 1 eq.) was added dropwise, followed by the addition of phosphoramide **33** (1.0 g, 4.5 mmol, 1 eq.) in dry THF (15 mL). The reaction mixture was kept at this temperature for 30 min and stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was purified using membrane-ultrafiltration (solvent: methanol; membrane cut off: 5KDa, material: regenerated cellulose). A honey-like clear brown compound **34** was obtained.

The loading was determined to be 1.1 mmol g^{-1} using ^{31}P spectroscopy and $POPh_3$ as internal standard.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.03-1.38 (m, 4H, 2x CH_2), 1.68-1.86 (m, 2H, CH_2), 1.89-2.04 (m, 2H, CH_2), 2.25-3.13 (m, 2x NCH, NCH_3, functionalized hPG-groups), 3.13-4.01 (hPG backbone).

^{31}P-NMR (162 MHz, $CDCl_3$): δ (ppm) = 30.3-30.7 (m), 31.6-32.6 (m).

(3R,7R)-2-Aminooctahydro-*N*,*N*,1,3-tetramethyl-2H-1,3,2-benzodiazaphosphole-oxide (35)[80d]



$C_{10}H_{22}N_3OP$
Mol. Wt.: 231,27

In a 100 mL Schlenk-tube was placed a solution of N,N'-dimethylamine (1.5 ml, 2.0 M, 3 mmol, 1 eq.) in 15.0 mL of dry THF and the solution was cooled to -78 °C in a dry ice acetone bath. To this solution was added dropwise *n*-BuLi (1.2 mL, 2.5 M, 3.0 mmol, 1 eq.). The solution was warmed up to 0 °C and was stirred at 0 °C in an ice bath for 60 min. To this solution was added a solution of DACH-derivate **33** (668 mg, 3.0 mmol, 1 eq.) in 15 mL of THF. The solution was stirred at 0 °C in an ice bath for 1 h and was then was allowed to warm to room temperature and stirred over night. The white suspension was filtered and the clear filtrate evaporated. The residue was purified by chromatography (silica gel, $CHCl_3$/MeOH, 99/1) to give 520 mg (2.3 mmol, 75 %) of **35** as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.04-1.38 (m, 4H, 2x CH_2), 1.73-1.83 (m, 2H, CH_2), 1.89-2.00 (m, 2H, CH_2), 2.41 (d, $^3J_{P-H}$ = 11.5 Hz, 3H, NCH_3), 2.46 (d, $^3J_{P-H}$ = 10.5 Hz, 3H, NCH_3), 2.49-2.57 (m, 1H, CH), 2.60-2.69 (d, overlapping m, $^3J_{P-H}$ = 9.5 Hz, 7H, 2x NCH_3, CH).

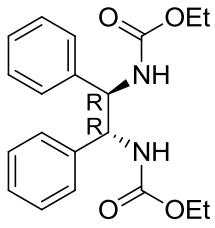
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 65.4 (d, $^2J_{C-P}$ = 9.2 Hz, N*C*H), 63.1 (d, $^2J_{C-P}$ = 9.0 Hz, N*C*H), 36.8 (d, $^2J_{C-P}$ = 4.1 Hz, N*C*H_3), 28.9 (d, $^2J_{C-P}$ = 1.6 Hz, N*C*H_3), 28.7 (d, *J* = 8.2 Hz), 28.4 (d, *J* = 10.6 Hz), 28.2 (d, $^2J_{C-P}$ = 1.6 Hz, N*C*H_3), 24.3 (m).

^{31}P-NMR (162 MHz, $CDCl_3$): δ (ppm) = 31.2 ppm.

TLC: R_f = 0.22 (EtOAc/MeOH, 10/1) [$KMnO_4$].

7.5 Synthesis of a DPEN-Type Chiral Phosphoramide supported on hPG

Biscarbamate of diphenylethylenediame (41)



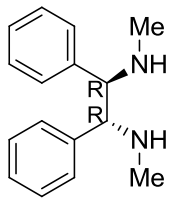
$C_{20}H_{24}N_2O_4$
Mol. Wt.: 356.42

The tartaric salt of (1R,2R)-(+)-1,2-Diphenylethylenediamine (40) (8.9 g, 24.6 mmol, 1 eq.) in toluene (70 mL) was cooled to -10 °C. Then, ethyl chloroformate (6.15 g, 56.6 mmol, 2.3 eq) and sodium hydroxide (9.44 g, 236 mmol, 9.6 eq.) in 11 ml water were added simultaneous to the reaction mixture. After 30 h stirring the mixture was diluted with chloroform (50 mL) and two times extracted with water. The organic layer was dried of K2CO3 and the solvent was evaporated under reduced pressure. Product 41 was obtained after flash chromatography as white powder (6. 51 g, 18.26 mmol, 74 %).

1H-NMR (500 MHz, CDCl3): δ (ppm) = 7.24-7.11 (m, 6H, Ar-H), 7.10-7.03 (m, 4H, Ar-H), 6.15-5.97 (bs, 2H, NH), 5.02-4.91 (m, 2H, CH), 4.19-4.02 (m, 4H, OCH2), 1.27-1.10 (m, 6H, CH2CH3).

13C-NMR (125 MHz, CDCl3): δ (ppm) = 14.7, 60.9, 61.2, 127.6, 127.8, 128.5, 157.0.

(1R,2R)-N,N'-dimethyl-1,2-diphenylethylene-1,2-diamine (42)[153]

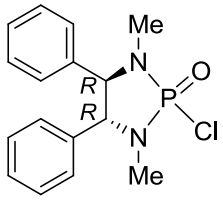


$C_{16}H_{20}N_2$
Mol. Wt.: 240.34

Procedure see section 7.4 precursor type A. The product **42** was obtained after kugelrohr distillation as white solid (3.72 g, 15.5 mmol, 76 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.13–7.02 (m, 10H, Ar-*H*), 3.52 (s, 2H, PhC*H*), 2.24 (s, 6H, NCH_3).

(1R,2R)-2-Chloro-1,3-dimethyl-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (43)[112]



$C_{16}H_{18}ClN_2OP$
Mol. Wt.: 320.75

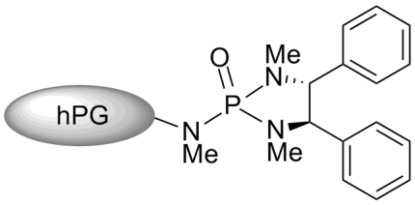
A solution of (1R,2R)-N,N'-Dimethyl-1,2-diphenylethylenediamine (**42**) (4.85 g, 20.2 mmol, 1 eq.) and triethylamine (6.1 g, 60.6 mmol, 3 eq.) in dry dichloromethane (250 mL) was cooled to 0 °C and stirred. To this solution was slowly added $POCl_3$ (3.1 g, 20.2 mmol, 1 eq.). After stirring at room temperature overnight, the reaction mixture was extracted with water (150 mL), followed by brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate 9:1) gave a waxy white solid product **43** in quantitative yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.34–7.28 (m, 6H, Ar-*H*), 7.14–7.09 (m, 2H, Ar-*H*), 7.07–7.03 (m, 2H, Ar-*H*), 4.13 (dd, 1H, $^{3}J_{H\text{-}H}$ = 8.6 Hz, $^{3}J_{P\text{-}H}$ = 4.3 Hz, PNC*H*), 3.83 (d, 1H, $^{3}J_{H\text{-}H}$ = 8.6 Hz, PNC*H*), 2.58 (d, 3H, $^{3}J_{P\text{-}H}$= 10.4 Hz, PNCH_3), 2.44 (d, 3H, $^{3}J_{P\text{-}H}$= 14.4 Hz, PNCH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 29.3 (d, $^{2}J_{C\text{-}P}$ = 5.3 Hz, $PNCH_3$) , 30.1 (d, $^{2}J_{C\text{-}P}$ = 2.7 Hz, $PNCH_3$) , 70.4 (d, $^{2}J_{C\text{-}P}$ = 12.0 Hz, PNCH), 71.0 (d, $^{2}J_{C\text{-}P}$ = 12.1 Hz, PNCH), 127.8, 128.0, 128.7, 128.9, 129.0 (C-Ar), 136.0 (d, $^{3}J_{C\text{-}P}$ = 12.9 Hz, C quat), 137.0 (d, $^{3}J_{C\text{-}P}$ = 5.6 Hz, C quat).

^{31}P-NMR (162 MHz, $CDCl_3$): δ (ppm) = 30.0 (s).

Coupling of the Chiral Phosphoramide Precursor (43) with Polyglycerylmethylamine (20) to polymeric catalyst 44



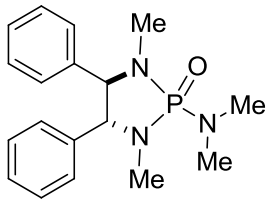
Polyglycerylmethylamine **20** (1g, 4.5 mmol, 1 eq.) was dissolved in dry THF (25 mL) and cooled to -78 °C with the help of a cryostat. After 30 min of stirring, *n*-BuLi (1.8 mL, 2.5 M in hexane, 4.5 mmol, 1 eq.) was added dropwise, followed by the addition of DPEN-based phosphoramide **43** (1.4 g, 4.5 mmol, 1 eq.) in dry THF (15 mL). The reaction mixture was kept at this temperature for 30 min and stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was purified using membrane-ultrafiltration (solvent: methanol; membrane cut off: 5KDa, material: regenerated cellulose). A honey-like clear brown compound **44** was obtained.

The loading was determined to be 0.7 mmol g^{-1} using ^{31}P spectroscopy and $POPh_3$ as internal standard.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.13-2.95 (m, 2x NCH, NCH_3, functionalized hPG-groups), 3.18-3.96 (hPG backbone), 3.98-4.13 (m, 2H, 2x, PhCH), 7.03-7.14 (m, 4H, CH(Ar)), 7.20-7.33 (m, 6H, CH(Ar)).

^{31}P-NMR (162 MHz, $CDCl_3$): δ (ppm) = 30.3-30.7 (m), 31.6-32.6 (m).

(4R,5R)-1,3-Dimethyl-4,5-diphenyl-2-dimethylamino-1,3,2-diazaphospholidine 2-oxide (45)[80d]



$C_{18}H_{24}N_3OP$
Mol. Wt.: 329,38

In a 100 mL Schlenk-tube was placed a solution of N,N'-dimethylamine (1.5 ml, 2.0 M, 3 mmol, 1 eq.) in 15.0 mL of dry THF and the solution was cooled to -78 °C in a dry ice acetone bath. To this solution was added dropwise *n*-BuLi (1.2 mL, 2.5 M, 3.0 mmol, 1 eq.). The solution was warmed up to 0 °C and was stirred at 0 °C in an ice bath for 60 min. To this solution was added a solution of DPEN-derivate **43** (962 mg, 3.0 mmol, 1 eq.) in 15 mL of THF. The solution was stirred at 0 °C in an ice bath for 1 h and was then was allowed to warm to room temperature and stirred over night. The white suspension was filtered and the clear filtrate evaporated. The residue was purified by chromatography (silica gel, $CHCl_3$/MeOH, 99/1) to give 730 mg (2.2 mmol, 74 %) of **45** as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.34 (d, $^3J_{P-H}$ = 7.5 Hz, 3H, NCH_3), 2.37 (d, $^3J_{P-H}$ = 6.4 Hz, 3H, NCH_3), 2.87 (d, $^3J_{P-H}$ = 9.7 Hz, 6H, $N(CH_3)_2$), 3.87-3.96 (m, 2H, 2x PhCH), 7.02-7.09 (m, 2H, CH(Ar)), 7.09-7.15 (m, 2H, CH(Ar)), 7.21-7.31 (m, 6H, CH(Ar)).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 138.5 (d, $^2J_{C-P}$ = 10.5 Hz, ipso-Ph), 138.3 (d, $^2J_{C-P}$ = 6.7 Hz, ipso-Ph), 128.5 (CH(Ar)), 128.1 (CH(Ar)), 128.0 (CH(Ar)), 127.8 (CH(Ar)), 72.4 (d, $^2J_{C-P}$ = 11.1 Hz, *C*H), 70.8 (d, $^2J_{C-P}$ = 10.9 Hz, *C*H), 37.1 (d, $^2J_{C-P}$ = 4.3 Hz, $N(CH_3)_2$), 30.2 (d, $^2J_{C-P}$ = 2.6 Hz, NCH_3), 29.3 (d, $^2J_{C-P}$ = 4.7 Hz, NCH_3).

^{31}P-NMR (162 MHz, $CDCl_3$): δ (ppm) = 29.0 (s).

TLC: R_f = 0.2 (EtOAc/MeOH, 10/1)

7.6 Catalysis with the phosphoramide-based Catalysts

General procedure for the catalyzed aldol reaction with slow addition of aldehyde[80d,154]

The polymeric catalyst hPG-Phosphoramide (50 mg, 0.05 mmol, 0.1 equiv.) was dissolved in dry CH_2Cl_2 (0.5 mL), and the solution was cooled to -78 °C with the help of a cryostat and stirred for 30 min. Then, 1-cyclohexenyloxytrichlorosilane (**25**) (100 µL, 0.55 mmol, 1.1 equiv.) was syringed to the reaction mixture. After 5 minutes, a solution of benzaldehyde (**26**) (50 µL, 0.5 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 mL) was dropwise added using a syringe pump (speed: 0.3 mL/1 h). The temperature remained constant at -78 °C for additional 60 min. Afterwards the reaction mixture was quickly poured into a cold (2 °C) saturated aqueous solution of sodium bicarbonate (2 mL). The mixture was allowed to warm to rt. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, $CHCl_3$). The pure product **27** was obtained as a colorless solid, as a mixture of *syn*/*anti* isomers. The *syn*/*anti* ratio was determined by 1H NMR (400 MHz).

Analytical data for *syn*/*anti* ratio 1:1: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.22 (m, 10 H, 2 Ph), 5.38 (d, J = 2.5 Hz, 1 H, *syn*-PhCHOH), 4.78 (d, J = 8.8 Hz, 1 H, *anti*-PhCHOH), 3.97 (s, 1 H, *anti*-OH), 3.06 (s, 1 H, *syn*-OH), 2.64-1.25 (m, 18 H, CHax+ CHeq).

General procedure for the allylation reaction of benzaldehyde (**26**) with allyl trichlorosilane (**28**):

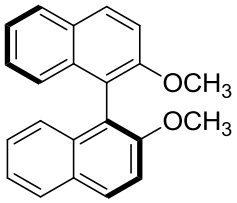
To a solution of hPG-HMPA (2 mmol HMPA / g^{-1}) (50 mg, 0.1 mmol, 10 mol%) in 0.2 mL of CH_2Cl_2 under N_2 at r.t. was added dipea (0.5 mL), benzaldehyde (102 µL, 1.0 mmol, 1.0 equiv.), and allyl trichlorosilane (**28)** (290 µL, 2.0 mmol, 2.0 equiv.). The resulting mixture was stirred for 1 h, before it was quenched with 2.0 mL NH_4Cl solution and 2.0 mL CH_2C1_2 were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x10mL). The combined organic layers were washed with brine and dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product **29** was analyzed by ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.36-7.28 (m, 5 H, HC(aryl)), 5.86-5.76 (m, 1 H, HC-3), 5.18-5.13 (m, 2 H, H_2C-4), 4.78 (dd, J = 7.3, 5.5, 1 H, HC-1), 2.57-2.45 (m, 1 H, HC-2), 2.05 (br s, 1 H, OH).

HPLC (column: Daicel Chiralpak® IA, 254 nm): *n*-hexane/*i*PrOH 99:1, flow rate: 0.8 mL/min; t_R 20.0 min (major, (*R*)-isomer), 20.9 min (minor, (*S*)-isomer).

7.7 Synthesis of BINOL-Type Chiral Phosphoric Acid with Polyglycerol Dendrons as Substituents

(S)-2,2'-Dimethoxy-1,1'-binaphthyl (51)[155]



$C_{22}H_{18}O_2$
Mol. Wt.: 314.38

To a suspension of commercial (S)-1,1'-binaphthalene-2,2'-diol (**50**) (25.0 g, 87.3 mmol, 1 eq.) in acetone (1.0 L) was added potassium carbonate (40.6 g, 294.2 mmol, 3.4 eq) and methyl iodide (21.4 mL, 48.8 g, 343.7 mmol, 3.9 eq.). The reaction mixture was heated at reflux for 22 h to give a homogeneous solution. Then methyl iodide (5 mL, 11.4 g, 80 mmol, 0.9 eq.) was added and heated for additional 2 h to complete the reaction (checked by TLC). The solvent was evaporated in vacuo to a volume of 200 mL, which was treated with 800 mL of water and stirred for 30 min. The resulting precipitation was filtered, dissolved in dichloromethane, and washed with brine. The organic phase was dried over $MgSO_4$ and the solvent was evaporated in vacuo to give the raw product, which was further purified by flash chromatography with silica gel (eluent: dichloromethane) to give the light yellow product **51** (23.7 g, 75.4 mmol, 86 %).

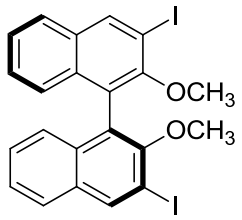
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.76 (s, 6H), 7.10 (d, 2H, J = 8.4 Hz), 7.21-7.25 (m, 2H), 7.31 (m, 2H, J = 6.8 Hz), 7.45 (d, 2H, J = 9.2 Hz), 7.86 (d, 2H, J = 8.1 Hz), 7.97 (d, 2H, J = 9.0 Hz).

^{13}C-NMR (100 MHz, CDCl3): δ (ppm) = 56.6 (CH_3), 113.9 (CH), 119.3 (C_q), 123.2 (CH), 125.0 (CH), 126.0 (CH), 127.6 (CH), 128.9 (C_q), 129.1 (CH), 133.7 (C_q), 154.7 (C_q).

MS (ESI, 250 V): m/z = 337.1 (660, $[M+Na]^+$), 315.1 (280, $[M+H]^+$).

IR (KBr) ν = 3043, 2920, 1457 cm^{-1}.

(S)-3,3'-Diiodo-2,2'-dimethoxy-1,1'-binaphthyl (52)



$C_{22}H_{16}I_2O_2$
Mol. Wt. 566.17

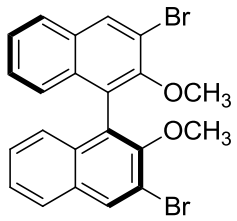
(S)-2,2'-Dimethoxy-1,1'-binaphthyl **51** (10 g, 31.8 mmol, 1 eq.) and tetramethylethylenediamine (TMEDA, 18.9 ml, 14.7 g, 126.8 mmol, 4 eq.) were dissolved in diethyl ether (750 mL) in a flame dried flask. Afterwards *n*-BuLi (51 mL, 2.5 M in hexane, 127.5 mmol, 4 eq.) dropwise added. After 6 hours, the reaction mixture was cooled down to -78 °C and iodine (32.32 g, 127.3 mmol, 4 eq) was added and stirred at room temperature overnight. The reaction was quenched by the addition of a 1 M sodium disulfite aqueous solution. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography on Celite with diethyl ether afforded a light brown solid product **52** (17.37 g, 30.7 mmol, 96 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.40 (s, 6H, OCH3), 7.06 (d, 2H, H(8), J = 8,5 Hz), 7.25 (m, 2H, H(7)), 7.39 (m, 2H, H(6)), 7.78 (d, 2H, H(5), J = 8.2 Hz), 8.52 (s, 2H, H(4)).

MS (ESI, 300 V): m/z = 588.9 (100, $[M+Na]^+$)

DC: R_f = 0.45 (hexane / ethyl acetate 9:1)

(S)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-binaphthyl (53)[156]



$C_{22}H_{16}Br_2O_2$
Mol. Wt.: 472.17

To a solution of (S)-2,2'-Dimethoxy-1,1'-binaphthyl **51** (8 g, 25.4 mmol, 1 eq.) and tetramethylethylenediamine (TMEDA, 15.2 ml, 11.8 g, 101 mmol, 4 eq.) in diethyl ether (600 mL) was dropwise added *n*-BuLi (61 mL, 2.5 M in hexane, 152.5 mmol, 6 eq.). After 6 hours, the reaction mixture was cooled down to -78 °C and bromine (10.4 mL, 32.4 g, 203 mmol, 8 eq.) was added and stirred at room temperature overnight. The reaction was quenched by the addition of a 1 M sodium disulfite aqueous solution. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. After column chromatography on silica gel (hexane / ethyl acetate 19:1) a solid product **53** was obtained (4.35 g, 9.2 mmol, 36 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.51 (s, 6H, OCH3), 7.09 (d, 2H, ^3J = 8.0 Hz), 7.27 (m, 2H), 7.43 (m, 2H), 7.82 (d, 2H, ^3J = 8.0 Hz), 8.27 (s, 2H).

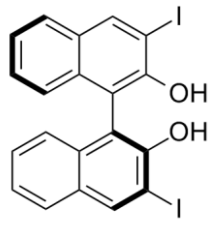
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 61.3 (OCH_3), 117.7 (C_q), 125.9 (CH), 126.0 (CH), 126.7 (C_q), 127.0 (CH), 127.3 (CH), 131.6 (C_q), 133.1 (CH), 133.2 (C_q), 152.7 (C_q).

MS (ESI, 280 V): m/z = 494.9 ($[M+Na]^+$).

IR: ν = 3047 (sb), 2932 (m), 1457 (s), 1387 (s),1349 (s), 1230 (s), 750 (s) cm^{-1}.

DC: R_f = 0.57 (hexane / ethyl acetate 19:1) [Cer].

(S)-3,3'-Diiodo-2,2'-dihydroxy-1,1'-binaphthyl (54)[157]



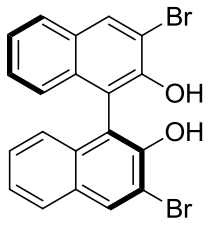
$C_{20}H_{12}I_2O_2$
Mol. Wt.: 538.12

A solution of (S)-3,3'-diiodo-2,2'-dimethoxy-1,1'-dinaphthyl (**52**) (8.7 g, 15.3 mmol, 1.0 eq.) in dry dichloromethane (500 mL) was cooled to -78 °C and a solution of boron tribromide (10 mL, 26.4 g, 105.4 mmol, 10 eq.) in dichloromethane (200 mL) was dropwise added under an inert atmosphere and stirred at room temperature overnight. The reaction was quenched by triethylamine (45 mL) and 200 mL water and stirred 2 hours. The reaction mixture was extracted with CH_2Cl_2 and the organic layer was dried over $MgSO_4$. After removing of the solvent under reduced pressure, the remaining residue was purified by column chromatography (solvent: dichloromethane) to afford a light yellow solid product **54** (7.3 g, 13.6 mmol, 89 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.41 (s, 2H, OH), 7.08 (d, 2H, H(8), *J* = 8,8 Hz), 7.30 (m, 2H, H(7)), 7.37 (m, 2H, H(6)), 7.78 (d, 2H, H(5), *J* = 7,9 Hz), 8.51 (s, 2H, H(4)).

DC: R_f = 0.5 ($CHCl_3$).

(S)-3,3'-Dibromo-2,2'-dihydroxy-1,1'-binaphthyl (55)[156]



$C_{20}H_{12}Br_2O_2$
Mol. Wt.: 444.12

(S)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-dinaphthyl (**53**) (4.15 g, 8.8 mmol, 1.0 eq.) in dry dichloromethane (100 mL) was cooled to -78 °C and boron tribromide (6.5 mL, 67

mmol) in dichloromethane (80 mL) was dropwise added under an inert atmosphere and stirred at room temperature for 2.5 h. The reaction was quenched by the addition of water (200 mL) cooling with ice/NaCl bath. The organic layer was separated, washed with brine, dried over $MgSO_4$. After removing of the solvent, the crude product was purified by column chromatography (solvent: hexane / ethyl acetate 9:1) to afford a light yellow solid product **55** (3.85 g, 8.7 mmol, 99 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.55 (s, 2H, OH), 7.10 (d, 2H, *J* = 8.0 Hz), 7.29-7.33 (m, 2H), 7.37-7.41 (m, 2H), 7.82 (d, 2H, *J* = 8.0 Hz), 8.25 (s, 2H).

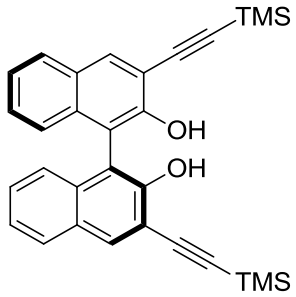
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.2 (C_q), 114.6 (C_q), 124.6 (CH), 124.8 (CH), 127.4 (CH), 127.6 (CH), 128.9 (C_q), 129.7 (C_q), 132.8 (CH), 148.0 (C_q).

MS (ESI, 250 V): m/z = 466.9 ([M+Na]).

IR: ν = 3452 (m), 3048 (sb), 1572 (s), 1420 (s) cm^{-1}.

DC: R_f = 0.40 (hexane / ethyl acetate 9:1) [Cer].

(S)-3,3'-Di[(trimethylsilyl)ethynyl]-2,2'-dihydroxy-1,1'-binaphthyl (56)[158]



$C_{30}H_{30}O_2Si_2$
Mol. Wt.: 478.73

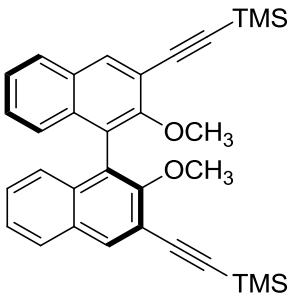
(S)-3,3'-Diiodo-2,2'-dihydroxy-1,1'-binaphthyl (**54**) (7.4 g, 13.7 mmol, 1.0 eq.), Palladium(II)bis(triphenylphosphine) dichloride (965 mg, 1.4 mmol, 0.1 eq.) and copper iodide (262 mg, 1.4 mmol, 0.1 eq.) were dissolved in triethylamine (200 mL, 145 g, 1.4 mol, 105 eq). The mixture was then degassed by ultrasonication and argon flow for 30 min. Freshly distilled trimethylsilyl acetylene (11.7 mL, 8.1 g, 82 mmol, 6 eq.) was added and the reaction mixture was stirred at 40 °C overnight. The solvent was removed under reduced pressure and the residue was redissolved in ethyl acetate and filtered over a pad of Celite. The organic layer was washed with 1 M HCl, and brine. The combined

organic layers were dried over $MgSO_4$. The raw product was purified by column chromatography on silica gel (hexane/chloroform 1:1) to give a light brown solid **56** (3.9 g, 8.2 mmol, 60 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.28 (s, 18H, TMS), 5.93 (s, 2H, OH), 7.12 (d, 2H, H(8), J = 8.3 Hz), 7.27 (m, 2H, H(7)), 7.33 (m, 2H, H(6)), 7.82 (d, 2H, H(5), J = 8.0 Hz), 8.11 (s, 2H, H(4)).

DC: R_f = 0.45 ($CHCl_3$)

(S)-3,3'-Di[(trimethylsilyl)ethynyl]-2,2'-dimethoxy-1,1'-binaphthyl (57)



$C_{32}H_{34}O_2Si_2$
Mol. Wt.: 506.78

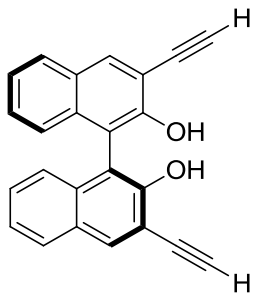
(S)-3,3'-Diiodo-2,2'-dimethoxy-1,1'-binaphthyl (**52**) (17.37 g, 30.6 mmol), Palladium(II)bis-(triphenylphosphine) dichloride (1.29 g, 1.8 mmol) and copper iodide (351 mg, 1.8 mmol) were dissolved in triethylamine (350 mL). The mixture was then degassed by ultrasonication and argon flow for 30 min. To that solution freshly distilled trimethylsilyl acetylene (26.2 mL, 8.1 g, 184 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solution was filtered over a pad of Celite and rinsed with diethyl ether. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/chloroform 2:1) to give a light brown solid **57** (10 g, 19.7 mmol, 64 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.27 (s, 18H, TMS), 3.64 (s, 6H, OCH_3), 7.05 (d, 2H, H(8), *J* = 8.4 Hz), 7.23 (m, 2H, H(7)), 7.37 (m, 2H, H(6)), 7.81 (d, 2H, H(5), *J* = 8,0 Hz), 8.15 (s, 2H, H(4)).

MS (ESI, 200 V): m/z = 529.2 (100, $[M+Na]^+$)

DC: R_f = 0.75 ($CHCl_3$)

(S)-3,3'Diethynyl-2,2'-dihydroxy-1,1'-binaphthyl (58)[159]



$C_{24}H_{14}O_2$
Mol. Wt.: 334.37

(S)-3,3'-Di[(trimethylsilyl)ethynyl]-2,2'-dihydroxy-1,1'-binaphthyl (**56**) (4.8 g, 10 mmol, 1 eq.) in methanol (100 mL) was treated with 1 M potassium hydroxide solution (48 mL). After stirring at room temperature for 1 h, the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 1 M HCl and brine. The organic layer was dried over $MgSO_4$ and the solvent removed to obtain product **58** as brown oil (3.46 g, 10 mmol, quantitative yield).

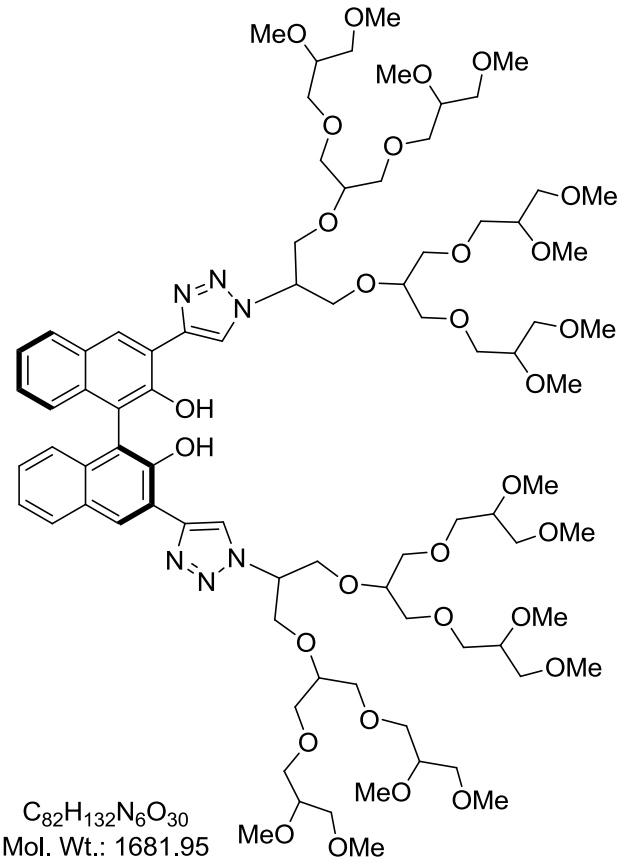
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.50 (s, 2H, alkyne), 5.69 (s, 2H, OH), 7.11 (d, 2H, ^3J = 9.0 Hz), 7.28-7.38 (m, 4H), 7.83 (d, 2H, ^3J = 7.5 Hz), 8.18 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 78.9, 84.0, 103.4, 111.1, 113.3, 124.6, 124.7, 128.3, 128.6, 134.0, 134.5, 151.4.

MS (ESI, 250V): m/z = 357.1 (9.25, $[M+Na]^+$).

DC: R_f = 0.5 ($CHCl_3$).

Cycloaddition of the BINOL-derivative 58 with hPG-Dendron Generation 2.0 (77) to product 60.



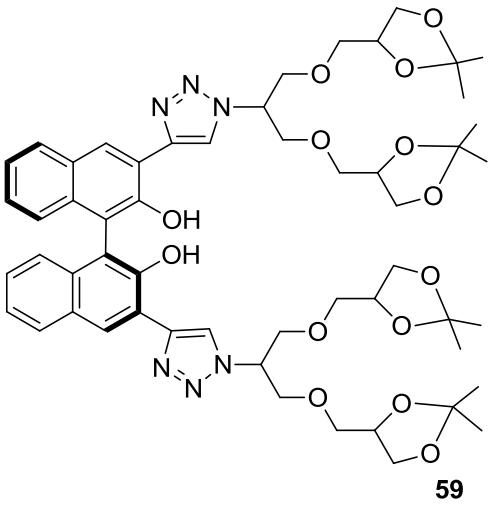
$C_{82}H_{132}N_6O_{30}$
Mol. Wt.: 1681.95

To solution of (S)-3,3'Diethynyl-2,2'-dihydroxy-1,1'-binaphthyl (**58**) (121 mg, 0.36 mmol, 1 eq.), [G2.0]-N_3,-OMe (**77**) (490 mg, 0.72 mmol, 2 eq.) and diisopropylamine (25.4 µL, 19.3 mg, 0.14 mmol) in THF (2 mL) was added a aqueous solution of sodium ascorbat (29 mg, 0.14 mmol) in 1mL water and after 5 min. copper sulfate (36 mg, 0.14 mmol). To complete the reaction, the temperature was increased after one day to 36 °C for 24 h. The reaction mixture was then extracted with dichloromethane and the organic layers were several times washed with sat. EDTA solution until the aqueous solution did not turn blue anymore. The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo. Purification was performed by column chromatography (eluent: $CHCl_3$/MeOH = 97/3) to yield the desired product **60** (279 mg, 0.17 mmol, 46 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.25-3.41 (m, 48H, OCH_3), 3.41-3.74 (m, 70H, hPG), 4.99 (s, 2H, OH), 7.12-7.24 (m, 4H, H(1),H(2)), 7.27-7.33 (m, 2H, H(3)), 7,90 (d, 2H, H(4), *J* = 8.7 Hz), 8.38 (s, 2H, H(5)), 8.50 (s, 2H, triazol).

DC: R*f* = 0.65 ($CHCl_3$ / methanol 9:1).

Cycloaddition of the BINOL-derivative (58) with hPG-Dendron Generation 1.0 (72) to product 59



59

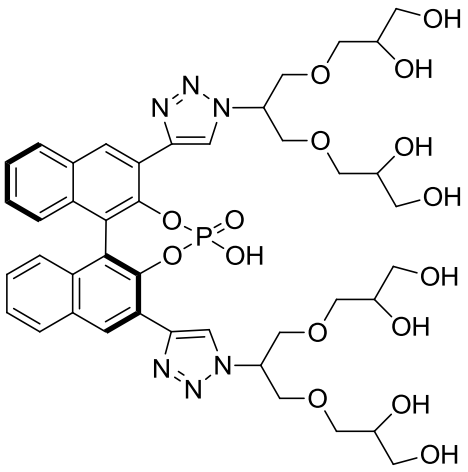
$C_{54}H_{68}N_6O_{14}$
MW: 1025,15

Reaction conditions and workup were as described above, with **58** (300 mg, 0.88 mmol, 1.0 eq.), and [G1.0]-N_3 (670 mg, 1.94 mmol, 2.2 eq) to yield product **59** (490 mg, 0.48 mmol, 54%) as a light yellow, viscous oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.35 (s, 12H, acetal), 1.42 (s, 12H, acetal), 3.51-3.58 (m, 8H), 3.64-3.73 (m, 4H), 3.99-4.07 (m, 12H), 4.21-4.29 (m, 4H), 4.98 (m, 2H), 7.19-7.33 (m, 6H), 7.86 (d, *J* = 8.2 Hz, 2H), 8.32 (s, 2H), 8.38-8.42 (m, 2H),

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 25.4, 26.9, 27.5, 66.4, 70.2, 70.3, 72.4, 72.8, 74.6, 74.7, 109.7, 109.8, 116.9, 117.3, 121.4, 123.7, 125.0, 126.2, 127.0, 128.2, 128.4, 134.0, 146.8, 151.1.

Phosphorylation of Binol derivative 59 to give the acid 61.



$C_{42}H_{51}N_6O_{16}P$
MW: 926,86

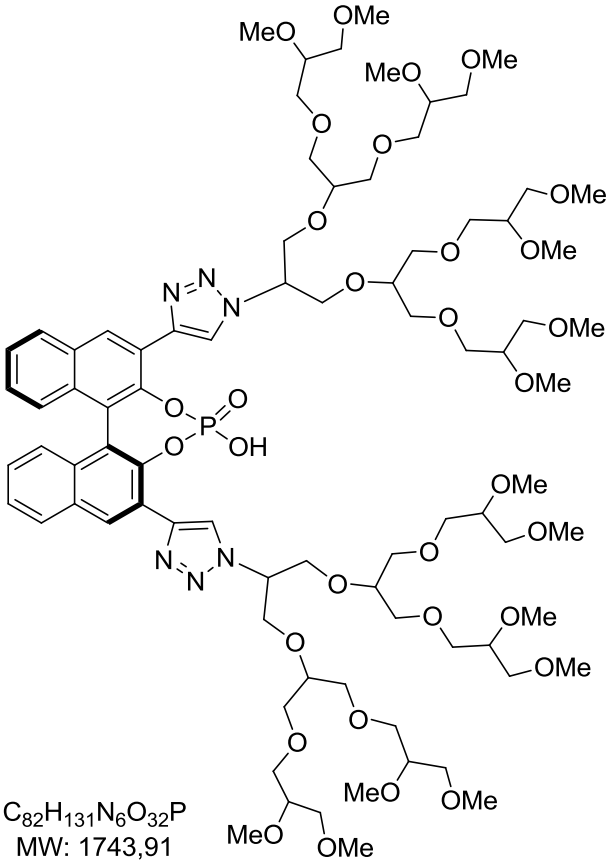
To a solution of **59** (400 mg, 0.39 mmol, 1 eq.) in pyridine (1.6 mL) was added phosphorus oxychloride (50 µL, 0.53 mmol, 1.3 eq.) at room temperature. After stirring at room termperature for 3 hours, the reaction mixture was quenched by addition of H_2O (32 µL) at 0 °C and stirred for 1 h at room temperature. After evaporation of the pyridine under vacuum, 6N HCl (5 mL) was added to the residue at 0 °C. The mixture was one time refluxed (15 min). After cooling to room temperature the resulting solid was collected by filtration, washed with H_2O to give crude material. The crude material was several times washed with ethyl acetate to give **61** as white powder (192 mg, 0.21 mmol) in 53 % yield.

^{1}H-NMR (400 MHz, $CDCl_3$ / CD_3OD 1:1): δ (ppm) = 5.15 (br s, 2H), 7.14 (d, ^3J = 8.5 Hz, 2H), 7.19-7.26 (m, 2H), 7.44 (t, ^3J = 7.3 Hz, 2H), 8.01 (d, ^3J = 8.2 Hz, 2H), 8.64 (s, 2H), 8.98 (s, 2H, triazol).

^{13}C-NMR (100 MHz, $CDCl_3$ / CD_3OD 1:1): δ (ppm) = 120.5, 121.5, 125.6, 126.6, 126.8, 128.4, 131.0, 131.7, 132.2, 147.2, 147.3.

^{31}P-NMR (162 MHz, $CDCl_3$ / CD_3OD 1:1): δ (ppm) = 4.6 (s).

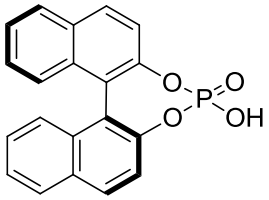
Phosphorylation of Binol derivative 60 to give the acid 62.



$C_{82}H_{131}N_6O_{32}P$
MW: 1743,91

To a solution of **60** (279 mg, 0.16 mmol, 1 eq.) in pyridine (0.5 mL) was added phosphorus oxychloride (30 µL, 0.28 mmol, 1.7 eq.) at room temperature. After stirring at room termperature for 3 hours, the reaction mixture was quenched by addition of H_2O (30 µL) at 0 °C and stirred for 1 h at room temperature. After evaporation of the pyridine under vacuum, 6N HCl (2 mL) was added to the residue at 0 °C. The mixture was one time refluxed (15 min). After cooling to room temperature the resulting solid was collected by filtration, washed with H_2O to give crude material. The crude material could not be purified.

(S)-Binaphthylsphosphoric acid (63).



$C_{20}H_{13}O_4P$
MW: 348,29

To a solution of solution of 1,1-binaphthol (590 mg, 2.0 mmol, 1 eq.) in pyridine (7.8 mL) was added phosphorus oxychloride (250 µL, 2.68 mmol, 1.3 eq.) at room temperature. After stirring at room termperature for 3 hours, the reaction mixture was quenched by addition of H_2O (154 µL) at 0 °C and stirred for 1 h at room temperature. After evaporation of the pyridine under vacuum, 6N HCl (20 mL) was added to the residue at 0 °C. The mixture was one time refluxed (15 min). After cooling to room temperature the resulting solid was collected by filtration, washed with H_2O to give crude material. The crude material was several times washed with ethyl acetate to give **63** as white crystals (453 mg, 1.3 mmol) in 65 % yield.

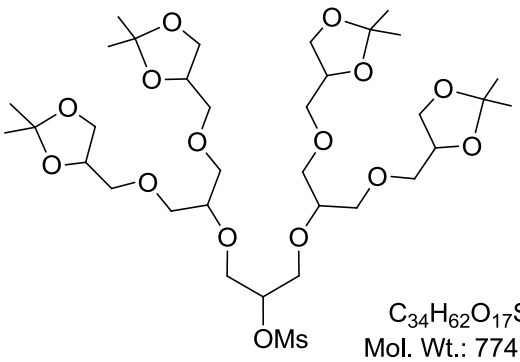
^{1}H-NMR (400 MHz, $CDCl_3$ / CD_3OD 1:1): δ (ppm) = 7.24-7.31 (m, 4H), 7.43-747 (m, 2H), 7.53 (d, ^3J = 7.5 Hz, 2H), 7.95 (d, ^3J = 8.2 Hz, 2H), 8.05 (d, ^3J = 8.9 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$ / CD_3OD 1:1): δ (ppm) = 120.5, 121.5, 125.6, 126.6, 126.8, 128.4, 131.0, 131.7, 132.2, 147.2, 147.3.

^{31}P-NMR (162 MHz, $CDCl_3$ / CD_3OD 1:1): δ (ppm) = 4.6 (s).

7.8 Synthesis of Azide-terminated PG Dendrons in Generation one and two

[G2.0]-OMs (74)[98]



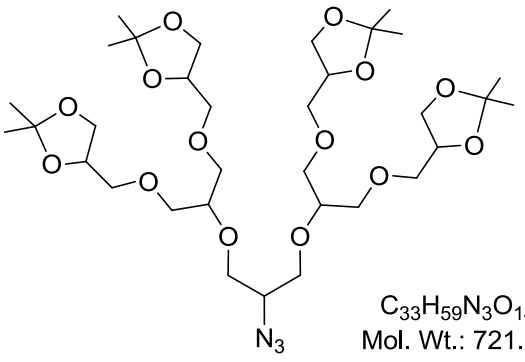
$C_{34}H_{62}O_{17}S$
Mol. Wt.: 774.91

Polyglycerol-dendron generation 2, [G2.0]-OH (2.0 g, 2.87 mmol, 1.0 eq.) and triethylamine (430 µL, 3.1 mmol, 1.1 eq.) were dissolved in dry toluene (12 mL) and cooled to 0 °C in an ice bath. Then, mesyl chloride (MsCl, 250 µL, 3.2 mmol, 1.1 eq.) was added dropwise to the reaction mixture and stirred at room temperature overnight. Progress of the reaction was monitored by TLC. After completion, the precipitation was removed by filtration and the mixture was concentrated under vacuum to give product **74** (2.1 g, 2.7 mmol, 94%), which was used without purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.34 (s, 12H, CH_3), 1.40 (s, 12H, CH_3), 3.08 (s, 3H, mesyl), 3.48 (m, 4H, hPG), 3.51-3.67 (m, 18H, hPG), 3.71 (m, 5H, hPG), 4.02 (dd, 4H, hPG, *J* = 6.4, 8.2 Hz), 4.23 (m, 4H, hPG).

DC: R_f = 0.57 ($CHCl_3$ / methanol 9:1)

[G2.0]-N_3 (protected) (75)[98]



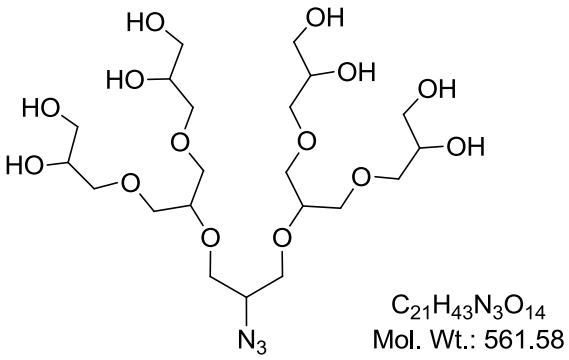
$C_{33}H_{59}N_3O_{14}$
Mol. Wt.: 721.83

The crude product [G2.0]-OMs (2g, 2.6 mmol, 1.0 equiv) was treated with sodium azide (934 mg, 14.4 mmol, 5.5 equiv) in dry DMF (12 mL). After the reaction mixture had been stirred 3 h at 120 °C, excess sodium azide was filtered off using a glass frit and DMF was removed under high vacuum by cryodistillation. Flash chromatography over silica gel (ethyl acetate/n-hexan 6:1) gave a yellow, viscous oil **75** (1.9 g, 2.6 mmol, 100%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.33 (s, 12H, CH_3), 1.39 (s, 12H, CH_3), 3.45-3.71 (m, 27H, hPG), 4.02 (m, 4H, hPG, *J* = 6.5, 8.1 Hz), 4.23 (m, 4H, hPG).

DC: R*f*= 0.7 ($CHCl_3$ / methanol 9:1)

[G2.0]-N_3 (shell: -OH, unprotected) (76)

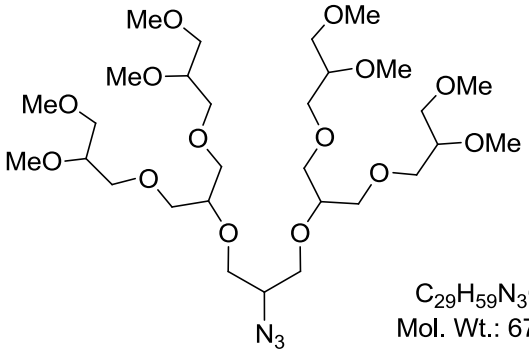


The protected dendron [G2.0]-N_3 (1.9 g, 2.6 mmol, 1.0 eq.) was dissolved in a DMSO/water mixture 3:1 (16 ml), then trifluoroacetic acid (99%, 1 ml) was added and the reaction was stirred overnight at room temperature. The solvent was removed in high vacuum and a yellow oil product **76** could be obtained in quantitative yield with traces of DMSO (2.0 g).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.44-3.80 (m, 35H, hPG).

DC: R_f = 0.17 ($CHCl_3$ / methanol 4:1).

[G2.0]-N_3 (shell: -OMe) (77)



$C_{29}H_{59}N_3O_{14}$
Mol. Wt.: 673.79

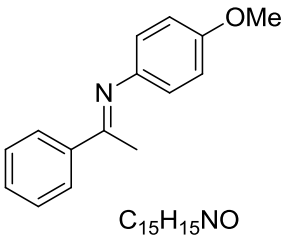
Dendron [G2.0]-N_3, -OH (2 g, 3.5 mmol) in dry THF (60 mL) was treated with sodium hydride (1.9 g, 60% on mineral oil, 48 mmol, 14 eq.). The suspension was heated to reflux and stirred 2 h, before iodomethane (3.6 mL, 8.1 g, 57 mmol, 16 eq.) was added. After stirring overnight, the reaction was quenched with water and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo to give the crude product, which was purified by flash column chromatography on silica gel (hexane to chloroform/methanol 19:1) to yield a yellow oil **77** (520 mg, 0.8 mmol, 23 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.43 (s, 24H, OCH_3), 3.45-3.75 (m, 35H, hPG).

DC: R_f = 0.8 ($CHCl_3$ / methanol 9:1).

7.9 Catalysis with the BINOL-Type Chiral Phosphoric acid

Substrate-Synthesis: N-(1-Phenylethylidene)-4-methoxyaniline.



$C_{15}H_{15}NO$
Mol. Wt.: 225.29

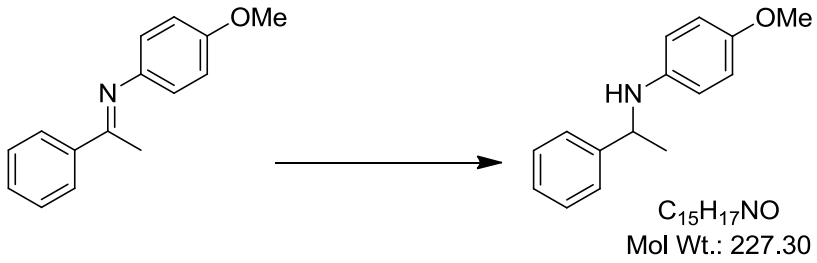
To a solution of acetophenone (6.0 mL, 52.7 mmol, 1.0 eq.) and 4-methoxyaniline (7.4 g, 60.4 mmol, 1.15 eq.) in dry toluene (25 mL) was added 4 Å molecular sieves (25 g)

that had been dried in a vacuum oven. After being heated to reflux overnight, the reaction mixture was filtered through Celite that was washed with toluene. Evaporation of the toluene, followed by kugelrohr distillation of the residue yielded N-(1-phenylethylidene)aniline (8.19 g, 36.4 mmol, 69%) as a pale yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.25 (s, 3H), 3.82 (s, 3H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J*= 8.9 Hz, 2H), 7.39-7.49 (m, 3H), 7.91-8.02 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 17.4 (CH_3), 55.6 (CH_3), 114.3 (CH), 120.8 (CH), 127.2 (CH), 128.4 (CH), 130.4 (CH), 139.9 (C), 144.9 (C), 156.0 (C), 165.8 (C).

Transfer Hydrogenation of imines:



In a typical experiment the ketimine (45 mg, 0.2 mmol, 1 eq.), Binol derived catalyst (9.3 mg, 0.004 mmol, 2 mol%, 0.02 eq.) and Hantzsch ester (71 mg, 0.28 mmol, 1.4 eq.) were dissolved in toluene (1.0 mL) and mixed in an argon atmosphere. The resulting yellow solution was stirred at 35 °C over night. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate 95/5) to give the desired amine as pale yellow solid.

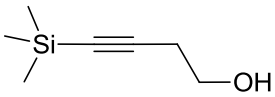
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.50 (d, *J* = 6.7 Hz, 3H), 3.69 (s, 3H), 4.41 (q, *J* = 6.7 Hz, 1H), 6.44-6.50 (m, 2H), 6.66-6.72 (m, 2H), 7.20-7.27 (m, 1H), 7.29-7.37 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 25.2, 54.4, 55.8, 114.7, 114.8, 125.9, 126.9, 128.7, 141.6, 145.5, 152.0.

HPLC conditions: OD-H column, n-hexane/2-propanol = 98/2, flow rate = 0.6 mL min^{-1}, α-enantiomer: t_R = 10.82 min; β-enantiomer: t_R = 11.49 min.

7.10 Synthesis of the Fluorinated Alcohol with Short Linker

4-(Trimethylsilyl)-3-butyn-1-ol (81)[160]



$C_7H_{14}OSi$
Mol. Wt.: 142.27

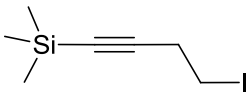
The product was prepared according to the literature.[143] 3-Butyn-1-ol (**80**) (4.2 g, 60 mmol. 1 eq.) was used as starting material to yield the product **81** as colorless oil (8.2 g, 57.6 mmol, 96%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.69 (t, 2H, ^3J = 6.40 Hz), 2.48 (t, 2H, ^3J = 6.40 Hz), 2.08 (brs, 1H, OH), 0.12 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 103.3, 86.7, 60.8, 24.1, 0.0.

FT-IR (ATR) ν [cm^{-1}]: 3324 (m), 2948 (m), 1698 (s), 1506 (s), 1454 (m), 1384 (w), 1303 (m), 1232 (s), 1130 (m), 1025 (s), 908 (m), 772 (m), 728 (s), 694 (s).

1-(Trimethylsilyl)-4-iodo-1-butyne (82)[161]



$C_7H_{13}ISi$
Mol. Wt.: 252.17

The product was prepared according to the literature.[143] With 4-(trimethylsilyl)-3-butyn-1-ol (**81**) (2.85 g, 20.0 mmol, 1 eq.) as starting material a colorless oil **82** was obtained (4.35 g, 17.2 mmol, 86 %).

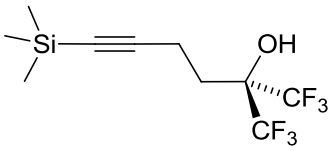
DC: R_f = 0.45 (CH_2Cl_2 / hexane 1:4)

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.21 (t, 2H, ^3J = 7.60 Hz,), 2.78 (t, 2H, ^3J = 7.60 Hz), 0.15 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 105.1, 86.8, 25.1, 1.0, (-0.1).

FT-IR (ATR) ν [cm^{-1}]: 2956 (m), 2894 (w), 2173 (m), 1422 (m), 1323 (m), 1246 (s), 1170 (s), 1062 (w), 1036 (m), 992 (m), 954 (m), 899 (w), 836 (s), 757 (s), 698 (m), 651 (s), 635 (m).

1,1,1-Trifluoro-2-(trifluoromethyl)-6-(trimethylsilyl)hex-5-yn-2-ol (83)



$C_{10}H_{14}F_6OSi$
Mol. Wt.: 292.29

In a schlenk flask, zinc dust (7 g, 111 mmol, 4 eq) was suspended in dry DMF (15 mL) and warmed to 50°C. Subsequently, 1,2-dibromoethane (480 µL, 1.04 g, 5.55 mmol, 0.2 eq) and after 30 min trimethylsilyl chloride (177 µL, 150 mg, 1.39 mmol, 0.05 eq) and 1-(trimethylsilyl)-4-iodo-1-butyne (**82**) (7 g, 27.7 mmol, 1 eq) in dry DMF (15 mL) were added and stirred for 2 h. In a second flask $CuBr{\cdot}SMe_2$ (855 mg, 0.15 g, 4.16 mmol) was heated under vacuum until a light green color appeared (5 min), cooled to room temperature and dissolved in dry DMF (5 ml). The organozinc solution was transferred to the CuBr/DMF mixture, and cooled to −35 °C after 1 h. Then condensed hexafluoroacetone gas (4.60 mL, 6.91 g, 41.60 mmol, 1.50 eq) was slowly transferred into the reaction mixture, which was stirred rapidly at −35 °C for 2 h. Water (50 mL) was added, carefully followed by 1 M HCl (aq) until pH ~4 was reached. The reaction mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/pentane 1:3, R_f = 0.43) to yield a colorless oil **83** (5.83 g, 20 mmol, 72 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.35 (s, 1H, OH), 2.54 (t, 2H, ^3J = 7.2 Hz, H(4)), 2.20 (t, 2H, ^3J = 7.2 Hz, H(3)), 0.16 (s, 9H).

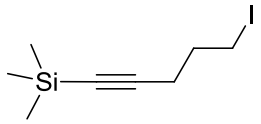
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 122.9 (C1), 104.7 (C6), 88.7 (C5), 28.1 (C3), 14.0 (C4), (-0.3, TMS).

^{19}F-NMR (375 MHz, $CDCl_3$): δ (ppm) = -77.1 (s, 6F).

IR (neat): ν (cm^{-1}) = 3365, 2962, 2486, 2364, 2247, 2225, 2179, 2073, 1450, 1292, 1251, 1236, 1213, 1197, 1166, 1147, 1118, 1037, 974, 918, 842, 759, 721, 680, 638, 601.

7.11 Synthesis of the Fluorinated Alcohol with Long Linker

1-Iodo-5-(trimethylsilyl)-4-pentyne (92)[144]



$C_8H_{15}ISi$
Mol. Wt.: 266.19

The product was synthesized according to the literature.[144] 5-(Trimethylsilyl)-4-pentyn-1-ol (**91**)[162] (3.0 g, 19.2 mmol, 1 eq) was converted into the product **92** (4.57 g, 17.2 mmol, 90 %), which was a colorless oil.

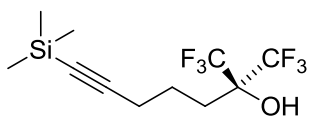
DC: R_f = 0.58 (CH_2Cl_2 / hexane 1:4)

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.21 (t, 2H, ^3J = 6.8 Hz, H-5), 2.38 (t, 2H, ^3J = 6.8 Hz, H-3), 1.95 (m, 2H, H-4), 0.15 [s, 9H, $Si(CH_3)_3$].

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 104.8(C_q), 85.8 (C_q), 32.1 (C-3), 20.9 (C-4), 5.1 (C-5), 0.1 [$Si(CH_3)_3$].

FT-IR (ATR) ν [cm^{-1}]: 2958 (w), 2899 (w), 2360 (m), 2341 (m), 2175 (m), 1425 (w), 1344 (w), 1247 (m), 1219 (m), 1166 (w), 1151 (w), 1029 (w), 1020 (w), 900 (m), 848 (s), 758 (s), 698 (w), 638 (m), 570 (w).

1,1,1-Trifluoro-2-(trifluoromethyl)-7-(trimethylsilyl)-hept-6-yn-2-ol (93)



$C_{11}H_{16}F_6OSi$
Mol. Wt.: 306.32

The fluorinated alcohol **93** was prepared in a similar way to alcohol **80** with a shorter linker.

1-Iodo-5-(trimethylsilyl)-4-pentyne (**92**) (6.4 g, 24 mmol, 1 eq.) gave the fluorinated alcohol **93** as colorless oil (4.8 g, 15.7 mmol, 65 %).

DC: R_f = 0.37 (CH_2Cl_2 / hexane 1:3)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.41 (s, 1H, OH), 2.29 (t, 2H, ^3J = 6.7 Hz, H(5)), 2.12-2.03 (m, 2H, H(3)), 1.84-1.71 (m, 2H, H(4)), 0.14 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 123.2 (C1), 105.8 (C7), 86.7 (C6), 76.1 (C2), 29.1 (C3), 21.0 (C4), 20.0 (C5), (-0.1, TMS).

^{19}F-NMR (375 MHz, $CDCl_3$): δ (ppm) = -76.9 (s, 6F).

FT-IR (ATR) ν [cm^{-1}]: 3365, 2962, 2480, 2245, 2157, 2073, 1462, 1292, 1251, 1234, 1213, 1190, 1165, 1145, 1122, 1062, 975, 844, 759, 717, 696, 669, 638.

7.12 General Procedure for Preparation of the HFIP derived Catalyst

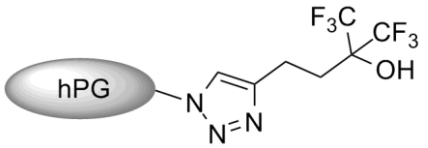
In situ deprotection followed by click-coupling

1,1,1-Trifluoro-2-(trifluoromethyl)-6-(trimethylsilyl)hex-5-yn-2-ol (**83**) (1.52 g, 5.2 mmol) and tetrabutylammonium fluoride trihydrate (1.8 g, 5.72 mmol, 1.1 eq) in THF were stirred until TLC showed complete deprotection to compound **84** (~30 min).

Diisopropylethylamine (88 µL, 0.52 mmol, 0.1 eq.) and polyglycerol azide (**7**) (515 mg, 5.2 mmol azide group, 1 eq.) in THF were added to the deprotected fluorinated alcohol. After the mixture had been stirred for 5 min, sodium ascorbate (103 mg, 0.52 mmol, 0.1 eq.) in 1.5 mL Millipore water was added, followed by copper(II)-sulfate pentahydrate (130 mg, 0.52 mmol, 0.1 eq.) in 1.5 mL Millipore water. The reaction mixture was stirred over night at r.t. TLC analysis indicated complete consumption of the fluorinated alcohol. The solution was concentrated and the residue was diluted in water and extracted with ethyl acetate. The combined organic layers were washed several times with small portions of saturated EDTA solution until the blue colour of the aqueous phase disappeared. The crude product was further purified by ultrafiltration (solvent:

methanol; membrane material: regenerated cellulose, NWCO (molecular weight cut-off): 5 kDa).

The polymeric catalyst **85** with the short alkyl linker was obtained in 1.4 g (84 %) yield with a loading of 3.0 mmol alcohol groups per gramm.



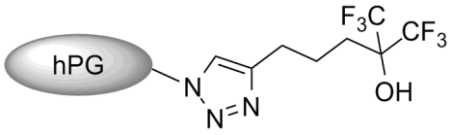
^{1}H-NMR (700 MHz, d_6-DMSO): δ (ppm)= 8.16-7.42 (m, 1H, triazol), 5.30-4.60 (functionalized primary/secondary hPG-groups), 4.09-3.01 (hPG), 2.89-2.66 (m, 2H, H(4)), 2.26-2.03 (m, 2H, H(3)).

^{13}C-NMR (176 MHz, d_6-DMSO): δ (ppm) = 145.6 (s, triazol), 123.9 (s, C-1), 122.1 (s, triazol), 78.5 (br, hPG), 75.7 (m, C-2), 70.1 (br, hPG), 60.2 (br, hPG), 50.3 (br, hPG), 30.3 (s, C-3), 18.6 (s, C-4).

^{19}F-NMR (376 MHz, CD_3OD): δ (ppm) = -77.01 (s).

IR (bulk): ν = 3145, 3079, 2956, 2882, 2736, 1732, 1704, 1556, 1454, 1283, 1199, 1137, 1035, 967, 930 cm^{-1}.

The polymeric catalyst **95** with the long alkyl linker was obtained in 1.4 g (81 %) yield with a loading of 2.9 mmol alcohol groups per gramm.



^{1}H-NMR (700 MHz, d_6-DMSO): δ (ppm) = 7.88-7.30 (m, 1H, triazol), 5.30-4.63 (functionalized primary/secondary hPG-groups), 4.07-3.03 (hPG), 2.68-2.43 (m, 2H, H(5)), 1.97-1.83 (m, 2H, H(3)), 1.83- 1.65 (m, 2H, H(4)).

^{13}C-NMR (176 MHz, d_6-DMSO): δ (ppm) = 146.4 (s, triazol), 123.9 (s,C-1), 122.3 (s, triazol), 78.4 (br, hPG), 75.9 (m, C-2), 70.2 (br, hPG), 60.2 (br, hPG), 50.2 (br, hPG), 30.3 (s, C-3), 25.3 (s, C-5), 22.1 (s, C-4).

^{19}F-NMR (376 MHz, CD_3OD): δ (ppm) = -76.92 (s).

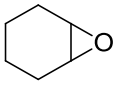
IR (bulk): ν = 3148, 3089, 2952, 2875, 1728, 1704, 1552, 1462, 1444, 1375, 1286, 1273, 1206, 1178, 1137, 1053, 989, 930, 871, 808 cm^{-1}.

7.13 General Procedure for the Catalytic Epoxidation

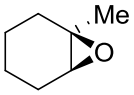
The alkene **87** (50 µmol, 1 eq.), bromobenzene (50 µmol, internal standard) and the catalyst **85** (0.2 eq.) were suspended in CH_2Cl_2 (0.4 ml, c = 0.125 mol/L) in a GC-vial (1.5 mL). Hydrogen peroxide (1 mmol, 50 wt. % in H_2O, 20 eq,) was added and the reaction mixture was stirred at 40 °C for 15-72 h. Frequently 20 µL samples were taken, eluted over Al_2O_3/MnO_2 with CH_2Cl_2 to quench unreacted hydrogen peroxide and analyzed by gas chromatography.

GC-Method for the epoxidation of various alkenes:

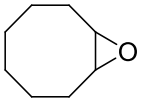
Column: Chiraldex γ-TA; Flow 0.9 mL/min, 40 °C for 5 min, then 4 °C/min up to 120 °C, 120 °C for 15 min, then 5 °C/min up to 140 °C;



τ_R (min) = 2.70 (cyclohexene), 8.60 (product), 11.00 (standard).

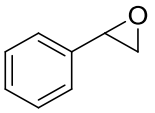


τ_R (min) = 11.00 (standard), 26.30 (methylcyclohexene), 29.60 (product).

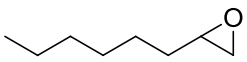


70 °C for 5 min, then 4 °C/min up to 120 °C, 120 °C for 15 min, then 5 °C/min up to 140 °C;

τ_R (min) = 2.70 (cyclooctene), 5.00 (standard), 11.60 (product).



τ_R (min) = 2.30 (styrene), 11.00 (standard), 18.50 (product).



τ_R (min) = 2.20 (1-octene), 11.00 (standard), 12.50 (product).

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9. Curriculum Vitae

For reasons of data protection,

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10. Publications and Conference Contributions

Publications

Florian Mummy, Jan Krämer, Jörg-M. Neudörfl, Albrecht Berkessel, and Rainer Haag; "Dendronized Fluoroalcohols as Catalysts for Alkene Epoxidation with Hydrogen Peroxide" submitted to Angewandte Chemie.

Florian Mummy, Hans-Ulrich Reissig, and Rainer Haag; "HMPA on Soluble Polymeric Support and its Application as Catalyst in the Aldol and Allylation Reaction", submitted to Synlett.

Conference contributions

1. **Netherlands' Catalysis and Chemistry Conference (NCCC IX)**, Noordwijkerhout (Netherlands), March 2008, poster presentation.

Florian Mummy, Rainer Haag "*A Polymer-Supported Phosphoramide as a Lewis-Base Catalyst for the Catalytic Aldol Reaction*."

2. **International Symposium on Homogeneous Catalysis (ISHC-XVI)**, Florence (Italy), July 2008, poster presentation.

Florian Mummy, Rainer Haag "*A Polmyer-Supported Phosphoramide as a Lewis-Base Catalyst for the Catalytic Aldol Reaction*."

3. **Netherlands' Catalysis and Chemistry Conference (NCCC X)**, Noordwijkerhout (Netherlands), March 2009, poster presentation.

Florian Mummy, Rainer Haag "*A Chiral Brønsted Acid Catalyst for the Organocatalytic Transfer Hydrogenation of Imines*."

4. **EuCheMS Chemistry Congress (3rd)**, Nürnberg (Germany), August/September 2010, poster presentation.

Florian Mummy, Rainer Haag "*Phosphoramides as Organocatalyst on Polymeric Support*."

5. **Orchem 2010**, 17. Lecture Conference, Weimar (Germany), September 2010, poster presentation.

Alberecht Berkessel, Jan Krämer, Florian Mummy, Rainer Haag "*Dendronized Fluorinated Alcohols as Catalyst for the Epoxidation of Alkenes with Hydrogen Peroxide*."

6. **Polydays 2010**, Berlin (Germany), October 2010, poster presentation.

7. **Joint International Symposium CRC 546 and UniCat**, Erkner (Germany), February 2011, poster presentation.

8. **Makromolekulares Kolloquium**, Freiburg (Germany), February 2011, poster presentation.

9. **International Symposium on Relations between Homogeneous and Heterogeneous Catalysis (ISHHC)**, Berlin (Germany), September 2011.

Florian Mummy, Rainer Haag "*Chiral Phosphoramides as Organocatalyst on Polymeric-Support*."

Research trips

April to July 2011 in the working group of Prof. Moshe Portnoy, School of Chemistry, Tel Aviv University, Tel Aviv, Israel.

February 2012 in the working group of Prof. Albrecht Berkessel, Department für Chemie, Universität zu Köln, Germany.