DNA-Based asymmetric catalysis as a synthetic tool

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Chapter 1
Asymmetric Catalysis with Helical (Bio-)Polymers

Inspired by Nature, the use of helical (bio)-polymer catalysts has emerged over the last years as a new approach to asymmetric catalysis. The use of helical polymers does not only open the ability to catalyze reactions asymmetrically but also enables easier recovery of the catalyst. In this chapter the various approaches and designs and their application in asymmetric catalysis will be discussed.

Parts of this chapter have been published: R.P. Megens, G. Roelfes, *Chem. Eur. J* **2011**, *17*, 8514-8523 and A.J. Boersma, R.P. Megens, B.L. Feringa, G. Roelfes *Chem. Soc. Rev.* **2010** *39*, 2083-2092

1.1 Introduction

The helical structure has always had a special attraction to chemists, especially since the discovery of the peptidic α-helix[1] and the DNA double helix structures[2], which have shown that helicity is a key element of biomolecular structure. Many efforts have been dedicated to re-creating these helical structures with synthetic macromolecules. This has resulted in a variety of helical polymers that have found widespread applications because of their interesting material properties.[3] Inspired by nature, the use of helical (bio-)polymers in enantioselective catalysis is starting to be explored. In this chapter this emerging field will be introduced. We have chosen not to distinguish between biopolymers, such as peptides, polynucleotides and other polymers. Instead, a more conceptual approach will be presented, focussing on the various design strategies that can be used to achieve asymmetric catalysis with helical (bio-)polymers.

Helical polymers can be divided in two main classes. First, there are the static helical polymers. These are polymers in which the helical sense is "fixed", that is, which cannot interconvert. This class can be subdivided in 1) polymers in which the helicity originates from the chirality in the side chains and 2) helical polymers that do not rely on chiral side chains; these include polymers with stereogenic centres in the main chain as a result of the use of chiral monomers and stable helical polymers of achiral monomers that were polymerized in a helix sense specific manner.

The second main class is that of the dynamic and/or responsive helical polymers. Responsive polymers respond to external physical, chemical or electrical stimuli resulting in a dramatic change in morphology, structure, shape or function.[4] These polymers become helical under specific reaction conditions and can interconvert to give the opposite helicity.

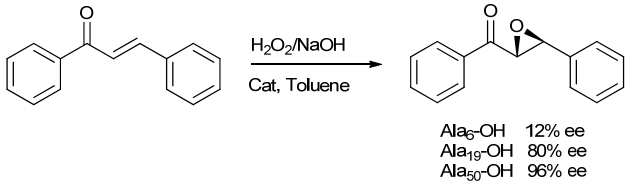
1.2 Static helical polymers

1.2.1 Helical polymers with side chain chirality

A variety of polymers need to be equipped with chiral side chains in order to maintain a stable helical structure in an enantiomerically pure form. In the case of peptides, the choice of the side chains is crucial to obtain a helical structure. Other polymers, such as, for example, polyacetylenes and, polyisocyanates do form helical structures by themselves, but their inversion barriers are low. Therefore, to stabilize them, chiral side chains are required.[3]

One of the early demonstrations of chiral polymers in catalysis was the use of polypeptides as catalyst in the enantioselective nucleophilic epoxidation of chalcone with hydrogen peroxide, in what has become known as the Julia-Colonna epoxidation.[5-8] Using polyalanine as the

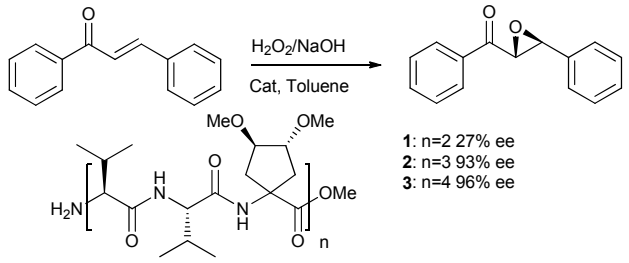
catalyst, the epoxide product could be obtained in up to 96 % ee, depending on the length of the polypeptide (Scheme 1.1). This was a first indication of a macromolecular amplification of chirality, albeit that a helical structure has not been proven for these peptides.



Scheme 1.1 Epoxidation of chalcone catalyzed by polypeptides.

Poly-alanine, leucine and isoleucine are among the most efficient catalysts for the Julia-Colonna epoxidation with a preference for longer polymer chain in terms of reaction rates and enantiomeric excess.[6]

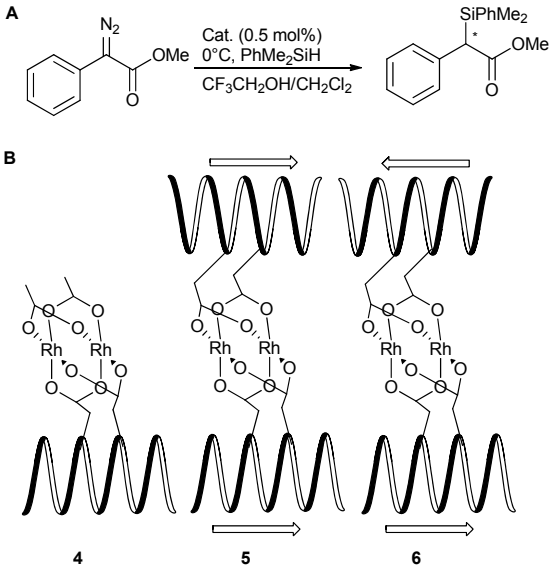
More recently, a chiral cyclic α-amino acid oligopeptide for the asymmetric epoxidation of chalcone was reported. X-ray crystallographic analysis has shown that these oligopeptides (**1-3**) form α-helical structures.[9] An increase in enantioselectivity was observed with increasing peptide length (Scheme 1.2). Which is a similar trend compared to the above mentioned peptides.



Scheme 1.2 Epoxidation of chalcone catalyzed by polypeptides **1-3**.

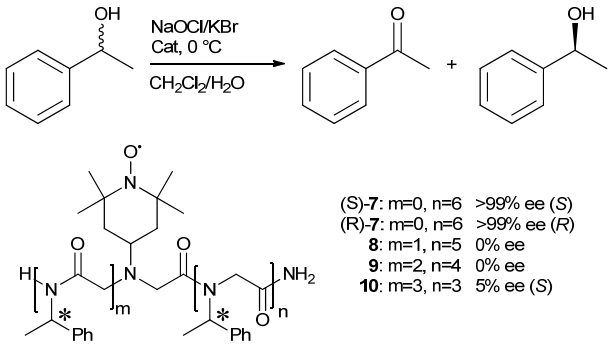
Whereas the Julia-Colonna type epoxidations represent an organocatalytic approach, also catalytically active transition metal complexes can be incorporated into a helical peptide structure. Ball and co-workers designed a peptide containing two carboxylate side chains which can coordinate to a di-rhodium metal center.[10] These metallopeptides proved to be active in diazo decomposition reactions,[11] however not in an asymmetric catalytic fashion. The design was changed slightly to nonapeptide (**4**), which catalyzed the insertion reaction of carbenes into $PhMe_2SiH$ (Scheme 1.3A) to afford the product in 32% ee.[12] To improve the chiral recognition, a *bis*-peptide catalyst was designed, in which the Asp side chains of two peptides were used to bridge the di-rhodium centre. (Scheme 1.3B).[12] The *bis*-peptide can be parallel (**5**) or antiparallel (**6**) isomers, albeit that to date it has not been established which isomer is which. The *bis*-peptide isomers afforded different enantioselectivity (20% and 45% ee, respectively)

which could be further improved by changing the peptide sequence (up to 92% ee). It was found that the residues adjacent to the catalytic moiety had the most significant effect on the enantioselectivity.



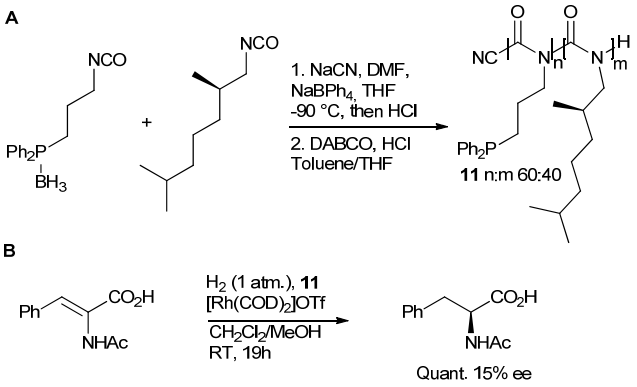
Scheme 1.3 A; Insertion reaction of $PhMe_2SiH$ into α-diazophenylacetate, B; Different Rhodium peptides as catalysts in insertion reaction.

Small peptoids have been used in the oxidative kinetic resolution of 1-phenylethanol by attaching TEMPO, a well known oxidation catalyst[13] (Scheme 1.4).[14] It was found that right-handed helical **7** preferentially oxidized *S*-1-phenylethanol to acetophenone, while left-handed **7** preferentially oxidized *R*-1-phenylethanol. Furthermore, the enantioselectivity was dependent on the position of the catalytic moiety within the peptide. Replacing the chiral phenylethyl substituents of the peptoid with benzyl substituents decreased the selectivity of the TEMPO-terminated peptoid **7**, but an increased selectivity was found with the TEMPO in the central position (**10**).



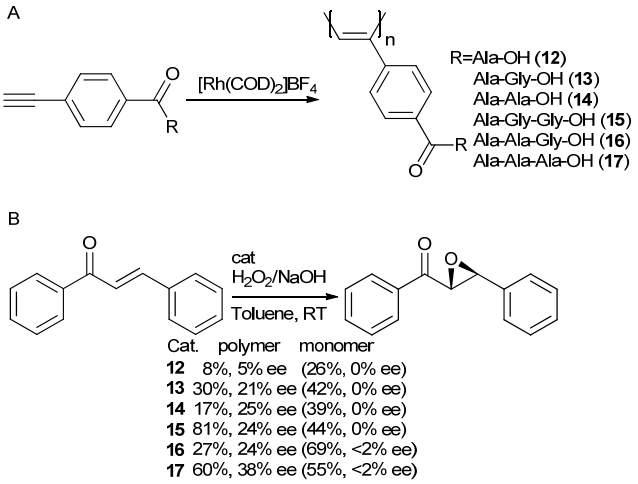
Scheme 1.4 Oxidative kinetic resolution of 1-phenylethanol.

A first example using a non-peptidic polymer involved a polyisocyanate in which an achiral monomer containing a phosphine ligand was co-polymerized with a chiral non-metal binding monomer (Scheme 1.5A).[15] In this way a single-sense helical polymer was created using a sub-stoichiometric number of chiral units.



Scheme 1.5 A; Synthesis of polyisocyanate co-polymers, B; Rhodium catalyzed asymmetric hydrogenation of N-acetamidocinnamic acid.

Upon complexation with $[Rh(COD)_2]OTf$, the co-polymer catalyst (**11**) was applied in the asymmetric hydrogenation of N-acetamidocinnamic acid. However, only low enantioselectivity of the hydrogenated product was achieved (Scheme 1.5B).

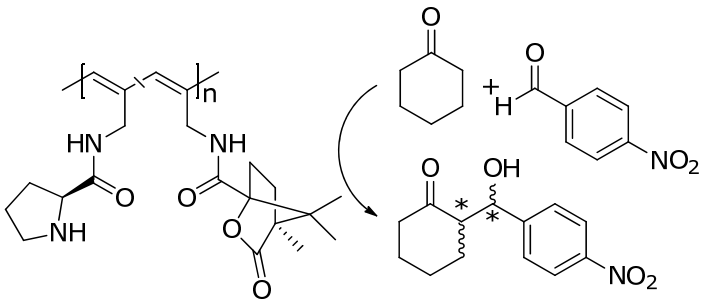


Scheme 1.6 Helical poly(phenylacetylene)s bearing oligopeptide pendants; A; Polymer synthesis, B; Epoxidation of chalcone catalyzed by helical polymers **12-17**.

Peptides as side chains can have a dual role, they are used to stabilize the helical structure of the polymer but can also be used as organocatalyst.[16] For example, a poly(phenylacetylene) with pendant

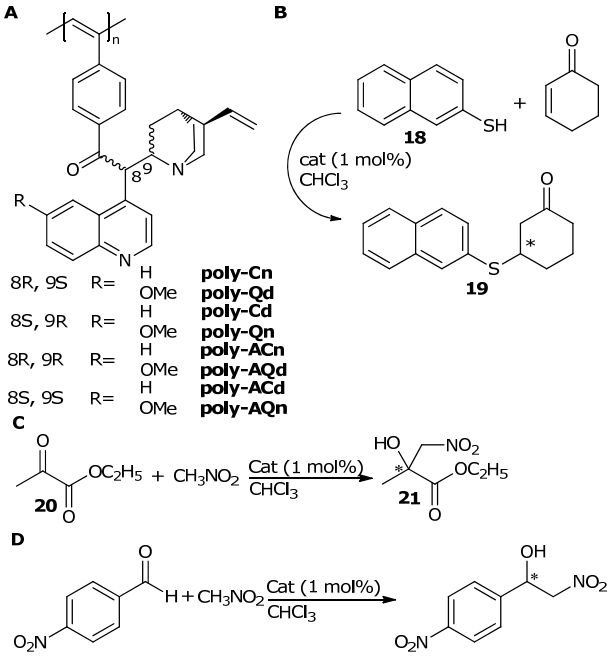
oligopeptide arms was shown to adopt a stable helical structure (Scheme 1.6A). Application of these polymers in the epoxidation of chalcones using H_2O_2 gave rise to moderate enantioselectivities of up to 38% (Scheme 1.6B). Since with the corresponding monomers no significant ee was obtained, it was suggested that the selectivity originates directly from the helical polymer and not from the chiral peptides.[17]

Another example of a helical polymer bearing peptides as side chains has appeared recently. In this example a co-polymer of polyacetylenes bearing prolineamide pendant groups and chiral bicycloheptanones was synthesized[18] (Scheme 1.7). An induced CD signal was found for these polymers and they were used in the aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde. Using a 1 to 1 co-polymer up to 80% conversion and 80% ee could be obtained. Unfortunately these results were not compared to proline itself. Furthermore, an unlikely mechanism was suggested that involved activation of the cyclohexanone via hydrogen bonding with the amide groups instead of formation of an enamine with benzaldehyde and proline.



Scheme 1.7. Aldol reaction of cyclohexanone with *p*-nitrobezaldehyde catalyzed by a proline bearing helical co-polymer.

A similar approach was taken by Yashima and *co*-workers.[19] They synthesized poly(phenylacetylene) but now bearing chinchona alkaloids as pendant groups (Scheme 1.8A) instead of peptides. These polymers exhibited an induced circular dichroism in the UV-visible region of the polymer backbone indicating that they formed a preferred-handedness helical polymer. These polymers were used in both the asymmetric conjugate addition of 2-naphthalenethiol (**18**) to 2-cyclohexanone (Scheme 1.8B) as well as the Henry reaction of ethylpyruvate (**20**) with nitromethane (Scheme 1.8C).



Scheme 1.8. Helical polymers bearing cinchona alkaloid pendant groups.

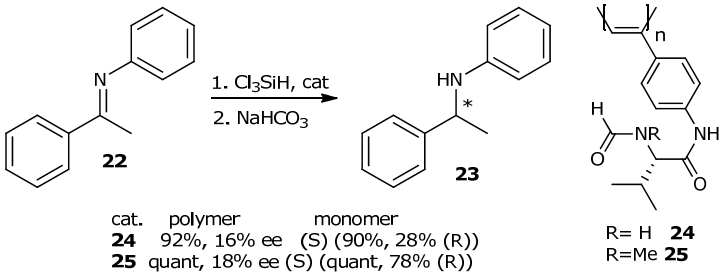
While all polymers gave conversions comparable to their monomers, only the polymer with cinchonidine pendant arms (**poly-Cd**) showed an slight increase in the enantioselectivity of the conjugate addition compared to the monomer, 32% vs. 14% ee, respectively.

The same trend holds for the Henry reaction of ethylpyruvate (**20**) with nitromethane. But now the polymer bearing the cinchonine pendant arms (**poly-Cn**) showed a slight increase in the enantioselectivity of the reaction, 26 and 14% ee , respectively.

More resently, the same alkaloid based helical polymers were used for the asymmetric Henry reaction of *p*-nitrobenzaldehyde with nitromethane (Scheme 1.8D).[20] In addition also amino-functionalized cinchona alkaloids (**ACd**, **ACn**, **AQn**, **AQd**) were prepared from commercially available natural cinchona alkaloids. **Poly-ACd** and **poly-ACn** gave similar results as the monomer whereas, **poly-AQn** and **poly-AQd** showed a much higher enantioselectivity compared to their monomeric counterparts. Using **poly-AQn** up to 94% ee of the Henry reaction product could be obtained.

However, when the chiral side chains themselves do give rise to enantioselectivity, there is the potential of a mismatch with the sense of helicity. This was observed in the reduction of ketimine (**22**) catalyzed by **24** or **25**.[21] The reaction catalyzed by the polymer gave a low ee of the opposite enantiomer compared to the monomer (Scheme 1.9). This indicates that the chirality of the side chain and the helicity of the main

chain of the polymer counteract each other (mismatched combination), resulting in low overall ee's.

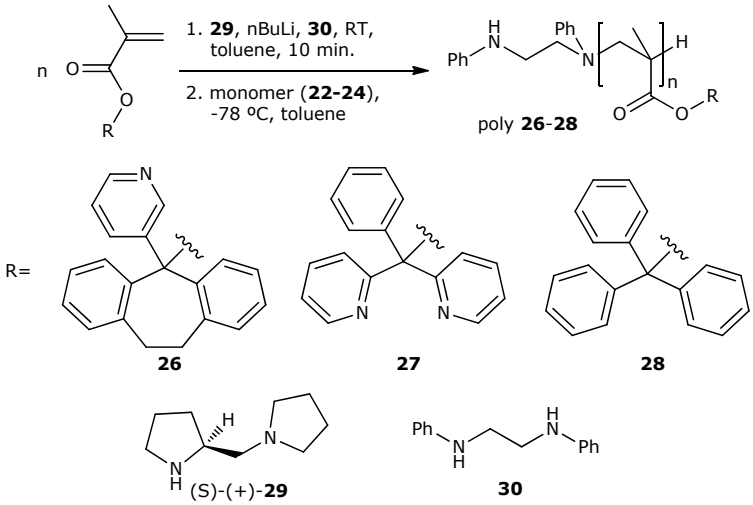


Scheme 1.9 Asymmetric reduction of ketimine catalyzed by **24** or **25**.

1.2.2 Helical polymers with backbone chirality

Enantioselective polymerization can give access to helical polymers that do not require chiral side chains, provided that their helical structure is stable.[22,23] In this process, the chirality in the polymer is induced during the polymerization by using a chiral initiator.

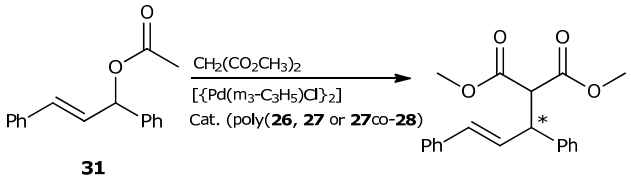
The group of Reggelin prepared helical polymers (poly **26**-**28**) by helix-sense selective anionic polymerization of methacrylates containing a pyridyl metal binding moiety using a chiral initiator. This initiator was made by treating a mixture of (*S*)- or (*R*)-1-(2-pyrrolidinomethyl)pyrrolidine (**29**) and N,N'-Diphenyl-ethylenediamine (**30**) with 1 eq. of *n*-BuLi (Scheme 1.10). This forms a chiral base complex which is able to initiate the helix-sense selective anionic polymerization.[15,24]



Scheme 1.10 Anionic helix-sense selective polymerization of methacrylates.

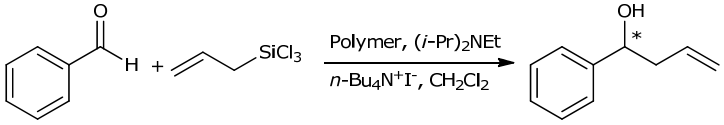
These polymers were used in the palladium-catalyzed enantioselective allylic substitution reaction of 1,3-diphenylprop-2-enyl acetate (**31**) with dimethylmalonate (Scheme 1.11). It was found that using **30** in catalysis did not give rise to any conversion.[24] Initiator **29** did result in conversion, with a slight enantiomeric excess of 10%. However, when (-)-poly-**26** was used, the product was obtained in 81% yield and 33% ee. Using the polymer with the opposite helicity resulted in preferred formation of the opposite enantiomer of the product with a similar enantioselectivity (32% ee).

Poly-**27**, which contains bidentate ligands, was designed because precipitation of palladium was observed when using the monodentate ligands.[15] A low optical activity was observed, which most likely indicates that a low excess of one of the helical forms of the polymer is present. Therefore also a co-polymer of **27** and **28** (poly(**27**co-**28**)) was prepared, which gave rise to an increased enantioselectivity of 60%.



Scheme 1.11 Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate.

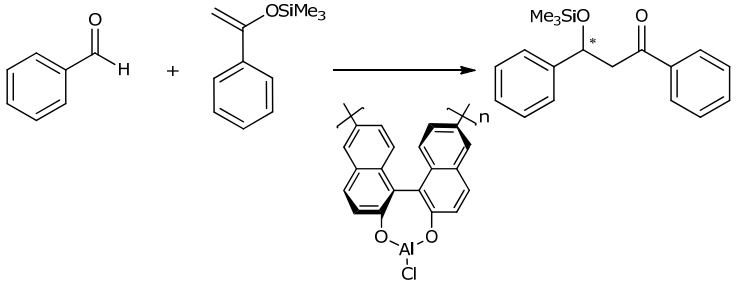
It was demonstrated that by oxidizing the pyridyl group to the corresponding pyridyl N-oxide with *m*-CPBA, these polymers could be used as Lewis base catalysts.[25] The N-oxide derived from polymer **26** proved to be active in the asymmetric allylation of benzaldehyde with allyltrichlorosilane (Scheme 1.12), resulting in the formation of the secondary alcohol in 56% yield and 19 % ee. In contrast, no reaction was observed with polymer **26**.



Scheme 1.12 Asymmetric allylation of benzaldehyde with allyltrichlorosilane.

Using chiral monomers also results in the formation of conformationally stable helical polymers. Binaphthols have been applied extensively in asymmetric organic reactions and have been shown to induce excellent chiral selectivity in many reactions.[26,27] Pu and co-workers, have used polybinaphthols to form rigid and sterically regular polymers. The polybinaphthol was treated with aluminum chloride and then used as a Lewis acid catalyst in the Mukaiyama aldol reaction (Scheme 1.13).[28,29] With the polymer (**32**) full conversion was obtained after 3.5h, while the monomeric aluminum complex gave only ~5%

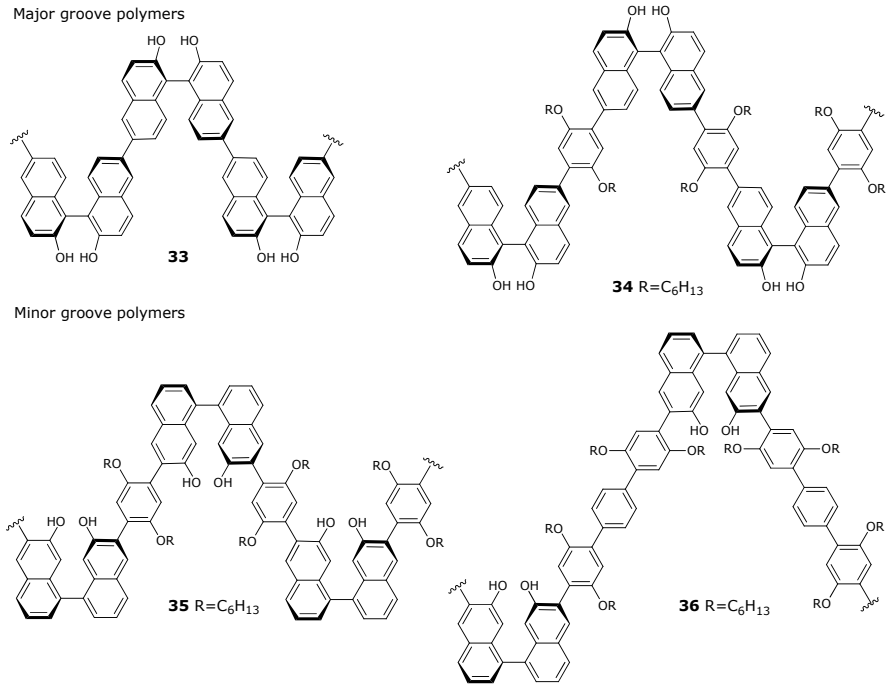
conversion in the same time. However no enantioselectivity was obtained in either case.



(*R*)-**32**

Scheme 1.13 Mukaiyama aldol condensation.

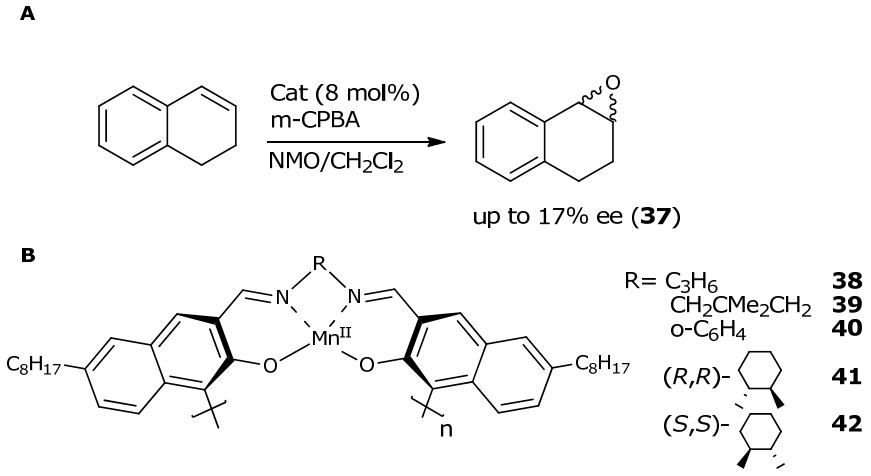
Polybinaphthyl (**33**-**36**) has been proposed to possess a "major" and a "minor" groove.[30,31] The 6,6'-polymerized binaphthols, in which the hydroxy groups point outwards, are designated "major groove" polybinaphthyls. When the binaphthol is polymerized at the 3,3'-position, a "minor-groove" polymer is obtained, with the hydroxy groups pointing inwards in the helical structure. A variety of minor and major groove polymers have been prepared (Scheme 1.14).[30-32]



Scheme 1.14 Variety of polybinaphthyls used in the reaction of benzaldehyde with diethylzinc.

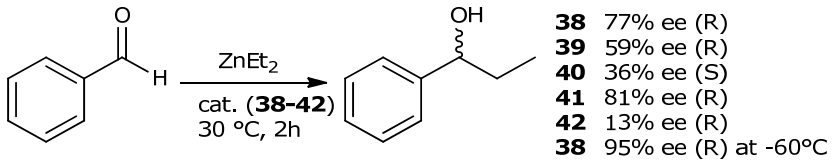
When the 1,2-addition reaction of benzaldehyde with diethylzinc was performed using the major groove polymers (**33, 34**) a rather low enantioselectivity was obtained and also considerable amounts of benzylalcohol were found as a side product.[30] Using the minor groove polybinaphthyl (**35**), high chemo- and enantioselectivities were obtained; by extending the spacer between the binaphthyl units (**36**) the selectivity could be further increased up to 98% ee.[32] This demonstrates the importance of the position of the catalyst in the polymer. These polymers were recovered readily by precipitation with methanol and used again without loss of activity and selectivity.[33]

A similar approach was followed by Takata and co-workers, using a poly(binaphthyl salen metal complex).[34,35] Salen manganese complexes (**38-40**) were shown to be capable of oxidizing alkenes, albeit with low enantioselectivity (Scheme 1.15A).



Scheme 1.15 A; Epoxidation of alkenes with **38-40**, B; Poly(binaphthyl salen Mangenese complexes (**38**-**42**).

When the same polymers were used in the 1,2-addition of diethylzinc to benzaldehyde, excellent yields and enantioselectivities, (i.e.) up to 81% ee for **37**, were obtained (Scheme 1.16), which could further be increased to 95% ee by lowering the temperature to -60 °C. Furthermore, a matched and mismatched combination was observed when introducing chirality in the amine linker.[35]



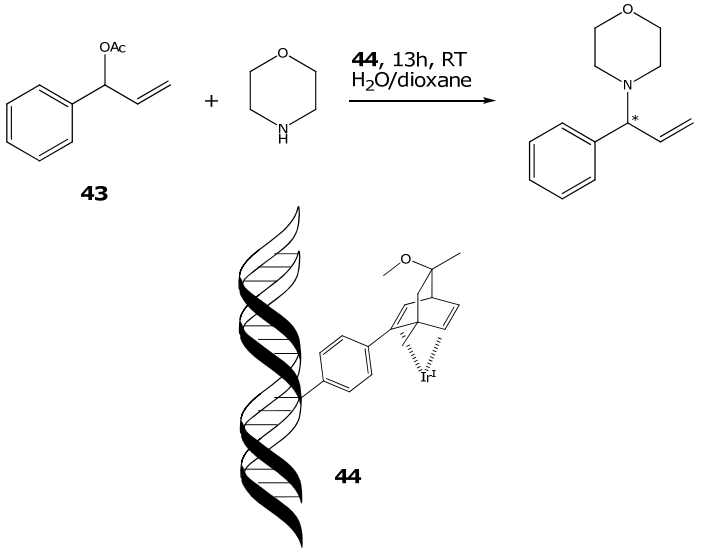
Scheme 1.16 Addition of diethylzinc to benzaldehyde.

1.3 DNA-based catalysis

The archetype helical polymer undoubtedly is DNA. Its unique double helical structure has been a source of inspiration for catalyst design. Asymmetric catalysis with DNA can be divided into two classes, which differ in the mode of attachment of the catalytic moiety, that is, using a covalent linkage or via non-covalent interactions.[36-38]

1.3.1 Covalent approach

Covalent anchoring involves binding of a transition metal complex via the ligand to the DNA using a small spacer moiety. Attachment sites in this case can be modified nucleobases or phosphate esters. Covalent anchoring is attractive since it allows for precise control over the positioning of the catalyst and, therefore, the structure and microenvironment of the catalytic site. However, covalent modification of DNA is laborious and very time consuming, which complicates the catalyst optimization process. This is illustrated by the fact that several approaches to the synthesis of ligand-DNA conjugates have been reported,[39-41] but in only a few cases successful catalysis has been achieved.

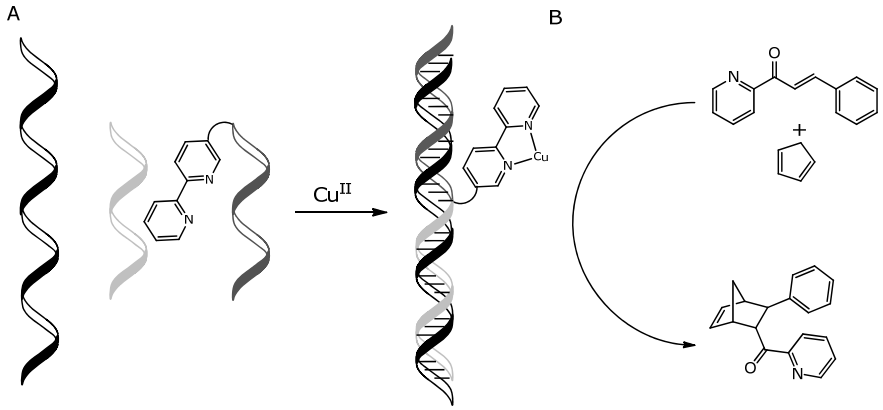


Scheme 1.17 DNA-based Ir-catalyzed allylic amination.

Jäschke and co-workers covalently attached diene ligands to DNA via a coupling of the diene ligand with an activated nucleoside 4-triazolyldeoxyuridine, which was introduced by solid-phase synthesis.[42] The corresponding Ir-complex (**44**) proved to be an efficient catalyst for the allylic amination of **43** with morpholine, resulting in a kinetic resolution of **43** (Scheme 1.17). The enantioselectivity of this reaction was modest (23 %) and can be attributed to the chirality of the ligand itself which gives 28% ee in the allylic amination reaction. However,

when a complementary RNA strand was used the opposite enantiomer of the product was formed in 27 % ee, indicating that a relationship exists between the structure of the polynucleotide and the enantioselectivity of the catalyzed reaction.

A method that allows for easier optimization involves the modular assembly of a DNA-based catalyst. This strategy involves two oligonucleotides, ON1 and ON2, with a covalently attached 2,2'-bipyridine ligand at the terminus of one of the strands (Scheme 1.18).[43] Upon hybridization of both oligonucleotides with a complementary template strand the catalytic moiety is placed in an internal position in the DNA duplex. Complexation of Cu^{II} to the bipyridine moiety produced the active DNA-based catalyst, which was found to be active in the asymmetric Diels-Alder reaction of azachalcone with cyclopentadiene. Ee's up to 93% were obtained, depending on the DNA sequence around the catalytic site and the length of the spacer.



Scheme 1.18 A; Modular assembly of a DNA-based system as catalyst for the B; Diels-Alder reaction of azachalcone with cyclopentadiene.

1.3.2 Non-covalent approach

Alternatively, a transition metal complex can be bound to the DNA using supramolecular interactions such as intercalation and/or groove binding. (Figure 1.1). The supramolecular anchoring approach is attractive because the catalyst is spontaneously self-assembled by combining the transition metal complex with the DNA, usually salmon testes DNA (st-DNA), which allows for rapid optimization. However, depending on the binding affinity and the DNA sequence selectivity, the catalyst may not be very well-defined; it is likely that the transition metal complex binds at multiple positions to the DNA. This method therefore results in a heterogeneous mixture of catalysts that reside in a different micro-environment and therefore will have different reactivity and selectivity.

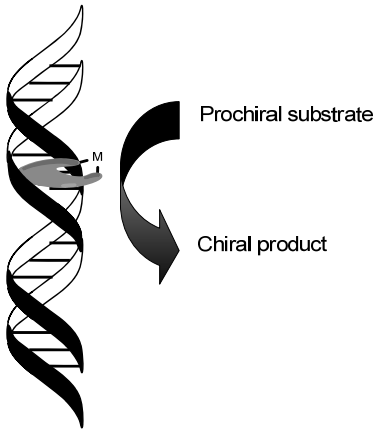
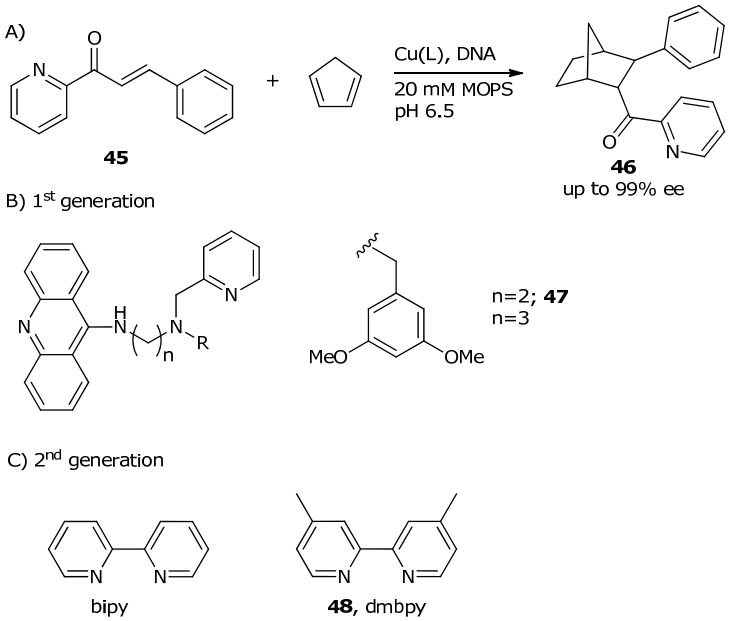


Figure 1.1 Schematic representation of non-covalent DNA-based catalysis.

The non-covalent approach to DNA-based catalysis has proven highly successful in a variety of reactions.[39,40] The Diels-Alder reaction of azachalcone (**45**) with cyclopentadiene was used initially to demonstrate the concept and has been used as the benchmark reaction for mechanistic studies. Using the first generation of ligands, which contain separated DNA intercalation and metal binding moieties that are connected via a spacer, up to 50% ee of **46** was found for this reaction (Scheme 1.19A and B).[44]

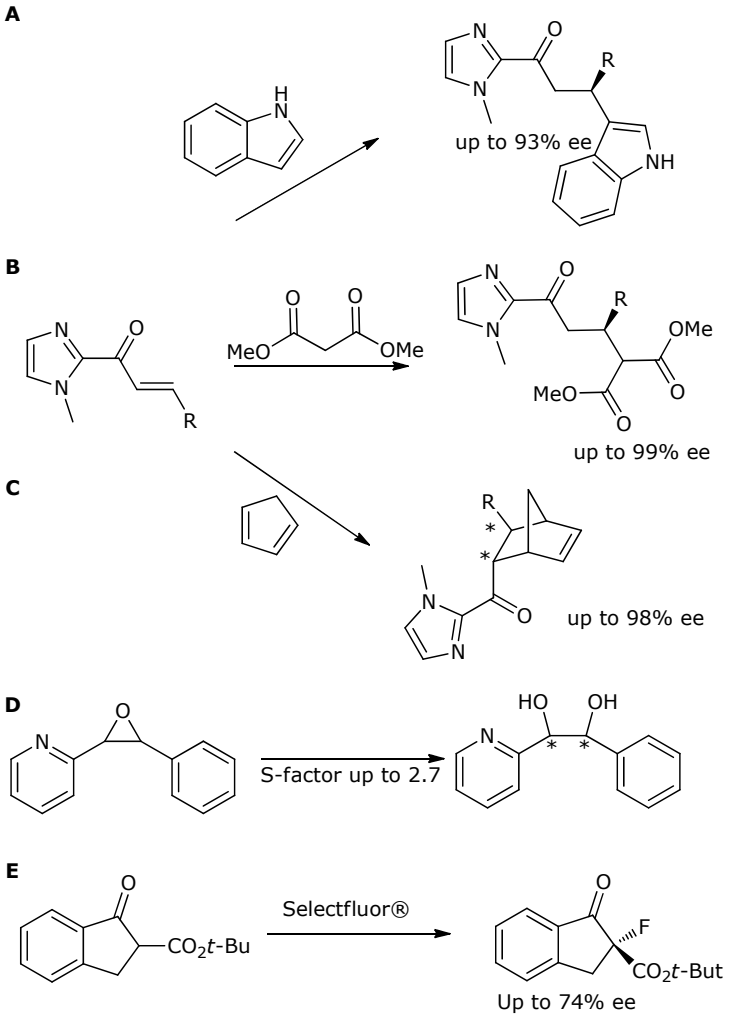


Scheme 1.19. A; Diels-Alder reaction of azachalcone (**45**) with cyclopentadiene catalyzed by 1st (B) and 2nd generation (C) DNA-binding ligands.

By changing the design of the ligand, in particular the length of the spacer, the opposite enantiomer of the product could be obtained, which is of interest since natural DNA is available in one chiral form only. With the second generation of ligands (Scheme 1.19C), which do not contain a separate DNA-binding moiety, up to 99 % ee was obtained in the case of 4,4'-dimethyl-bipyridine (**48**).[45] The corresponding Cu^{II} complex, however, has only a moderate DNA-binding affinity and displays no sequence selectivity in binding. Moreover, the DNA-binding mode is not well-defined. In this light, the observed complete enantioselectivity is quite remarkable. This seeming paradox was solved by a kinetic and sequence dependence study, which revealed that the reaction is accelerated up to 2 orders of magnitude when the catalyst is bound to DNA. So the DNA is not just the chiral scaffold, but also participates actively in the reaction, most likely by providing favorable "second coordination sphere interactions".[37,46] Moreover, both the rate acceleration and the enantioselectivity were found to be sequence dependent, with the DNA sequences that give the highest ee, i.e. sequences containing G-tracts, also providing the largest rate acceleration.[47,48] Combined, this means that it is no problem that the catalyst is a heterogeneous mixture of many different species, since those that are in the optimum microenvironment which gives the highest ee's, dominate the outcome of the catalyzed reaction, since they also accelerate the reaction the most.

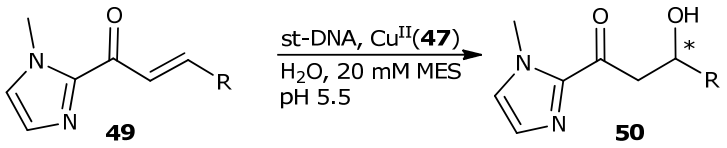
In addition to the Diels-Alder reaction, the Cu-dmbipy/st-DNA catalyst has been applied successfully in catalytic enantioselective Michael addition,[49,50] Friedel-Crafts alkylation,[51] fluorination[52] and epoxide ringopening reactions,[53] with in several cases ee's >90% (Scheme 1.20).

For the Friedel-Crafts alkylation and the Michael addition the same ligand and sequence dependency was obtained as with the Diels-Alder reaction. In these reactions dmbpy (**48**) gave the best results while 1st generation ligands gave much lower enantioselectivities. In these cases oligonucleotides containing G-tracts also proved to be the most effective with regard to the enantioselectivity. Furthermore, kinetics showed that the DNA, like in the Diels-Alder reaction, is beneficial for the reaction rate.



Scheme 1.20 Reaction scope of DNA-based catalysis, A; Friedel-Crafts alkylation, B; Michael addition, C; Diels-Alder reaction, D; Kinetic resolution of pyridyloxiranes, E; Fluorination reaction.

Recently it has also been demonstrated that DNA-based catalysis can be applied to a reaction for which there is no precedent using synthetic catalyst, namely the catalytic enantioselective and diastereospecific *syn* hydration of enones (Scheme 1.21).[54]



Scheme 1.21 Catalytic enantioselective *syn* hydration of enones.

In contrast to the other examples of DNA-based catalysis, the first generation ligands, that is, those based on a 9-aminoacridine intercalating moiety proved to be the most effective ligands for this reaction giving up to 79% ee. Furthermore, oligonucleotide containing central AT fragments displayed the highest selectivities, while G-tracts were shown to be the best sequences for the former developed reactions.

By performing the reaction in D_2O the ee could not only be improved to 82% ee but also the stereochemical course of the reaction could be elucidated, namely the addition of water goes in a *syn*-selective fashion. Interestingly, the reaction without DNA also results in the *syn*-selectivity, indicating that this might be dependent on the copper catalyst.

1.4 Dynamic and chirality-responsive helical polymers

Responsive polymers are polymers that react to external physical, chemical or electrical stimuli, resulting in a dramatic change in morphology, structure, shape or function. Such as, for example, helix inversion.[4] To date, a significant number of stimuli responsive polymers have been synthesized. Most often the chirality reponsive helical polymers contain functional pendant groups and upon addition of a chiral molecule, a conformational change of the polymer can be induced via non-covalent interactions (Figure 1.2).[55] These helical structures can be interconverted from right handed to the left handed and *vice versa* as in the case of polyisocyanates and poly(phenylacetylene).[56,57]

To date, only a few examples of asymmetric catalysis with responsive helical polymers have been reported. Yet, catalysts based on responsive helical polymers have great potential, since switching the helicity of the polymer with an external trigger makes it, in principle, possible to selectively obtain either enantiomer of a reaction product using the same catalyst.

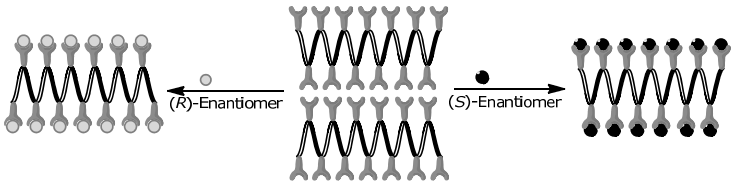
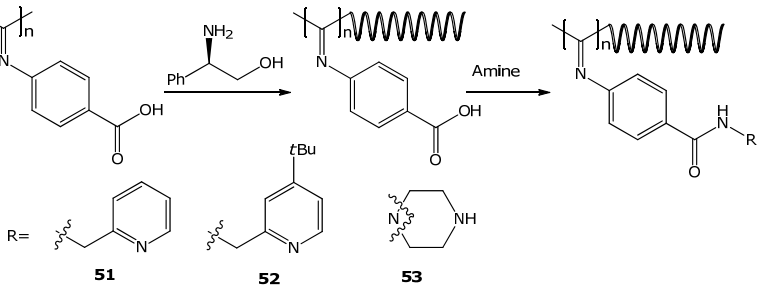


Figure 1.2 Schematic representation of a chirality-responsive polymer.

In a first example a poly(4-carboxyphenyl isocyanide) was prepared and upon addition of (*R*)-phenylglycinol a single-handed helical structure was induced with a molar ellipticity at 357 nm of -10.6 $M^{-1}cm^{-1}$.[58] The induced helicity was memorized; after removal of the chiral amine and derivatization with an achiral amine containing a ligand moiety, the

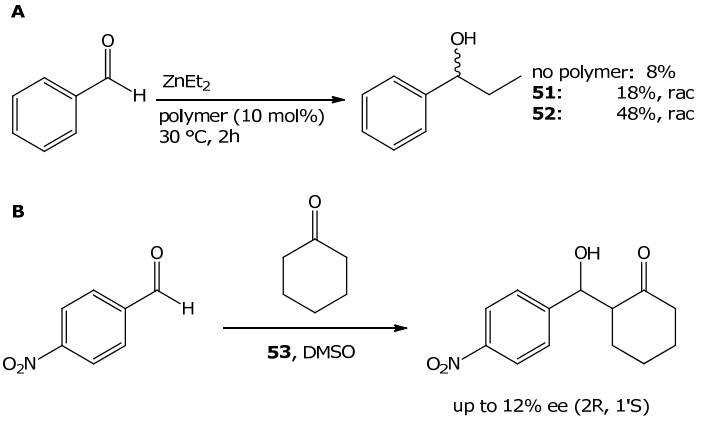
helical structure remained stable (Scheme 1.22); the amide moieties were found to increase the thermal stability of the helical polyisocyanide.[59]



Scheme 1.22 Schematic illustration for the helicity induction and memory of poly(4-carboxyphenyl isocyanide).

Using the polymers derivatized with pyridyl amines in the 1,2-addition reaction of diethylzinc to benzaldehyde (Scheme 1.23A) an acceleration of the reaction rate was obtained. However, no enantioselectivity was observed, which was attributed to the distance of the pyridyl group from the helical polymer.

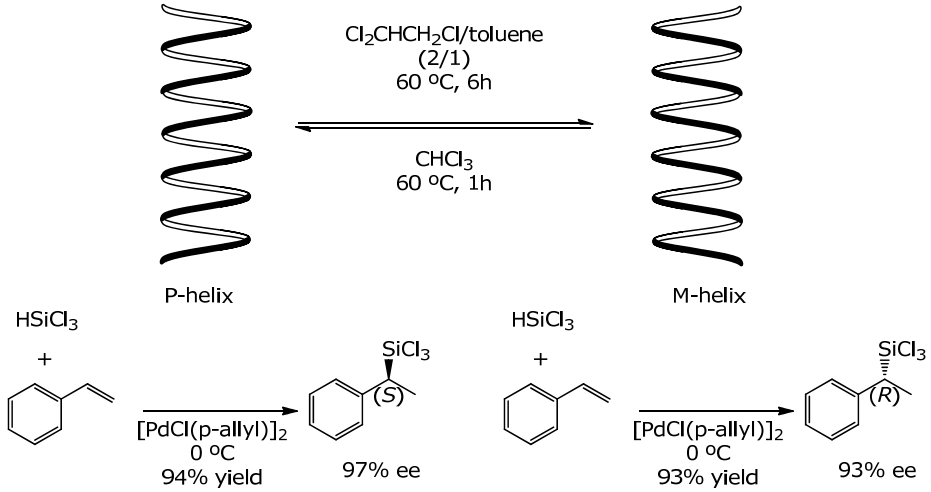
The piperazine bound helical polyisocyanide (**53**) was used as organocatalyst in the aldol reaction of benzaldehyde with cyclohexanone. Enantioselectivity was observed, albeit that the ee values were rather low, i.e. up to 12% (Scheme 1.23B).



Scheme 1.23 Reaction catalyzed by polymers with helical memory, A; Addition of diethylzinc to benzaldehyde, B; Aldol reaction of benzaldehyde with cyclohexanone.

An impressive demonstration of how helix interconversion can be used in asymmetric catalysis was recently reported by Suginome and co-workers.[60] They prepared a high-molecular-weight polymer based on a 20-mer polyquinoxaline-based phosphine (PQXphos) and used it in the palladium-catalyzed asymmetric hydrosilylation of styrenes (Scheme

1.24). Surprisingly, it was found that this polymer switches from P to M-helicity upon changing the solvent from chloroform to 1,1,2-trichloroethane/toluene (2:1). In catalysis, this resulted in 97% ee of the *S*-enantiomer with the P-helical form and 93% ee of the *R*-enantiomer with the M-helical form. Furthermore, the polymer was recycled up to 8 times without loss of selectivity, albeit that the palladium had to be recharged at the end of the 8th run, as a result of leaching.



Scheme 1.24 Asymmetric hydrosilylation using chirality responsive polymer.

1.5 Summary and outlook

In catalysis, polymers were for a long time only considered as scaffolds to create "heterogeneous" versions of homogeneous catalysts, with the idea that this would facilitate catalyst recovery and recycling.[61] From the examples described here, it is clear that asymmetric catalysis using helical (bio-)polymers has started to emerge as an attractive new approach. This is mainly due to the fact that these helical polymers can provide a chiral microenvironment for a catalyst, anologous to an enzyme active site, that can be used to direct the catalyzed reaction towards the selective formation of one enantiomer of a product. To date, the biopolymer-based catalysts, e.g. peptide and polynucleotide based catalysts, have proven to be most versatile and can already be used in a variety of important catalytic enantioselective reactions. The synthetic polymers have to date generally not achieved the same level of activity and selectivity in catalysis. One main difference, of course, is that synthetic polymers presently have less functional diversity, as they are built up from a smaller number of different monomeric units, and are not mono-disperse and structurally less well-defined compared to biopolymers. However, further advances in polymer preperation to

address these issues can be envisioned. Using dyamic and responsive polymers, new avenues in catalysis can be explored, such as using one catalyst to selectively prepare either enantiomer of a product, just by triggering a helix interconversion. Taken together, it can be concluded that helical (bio-)polymers are a promising and attractive new approach to enantioselective catalysis.

1.6 Aims and outline

The goal of the research described in this thesis is to explore the concept of DNA-based catalysis for practical use in synthetically interesting reactions. Our efforts have focused in two different directions: 1) optimization of the reaction conditions in terms of recyclability of the DNA with copper-catalyst and scale of the reaction. 2) the development of new reactions which are unknown or difficult to perform using conventional transition metal catalysis.

In chapter 2, attempts for covalently attaching DNA strands to gold nanoparticles for the use in DNA-based catalysis are described.

In chapter 3 describes the influence of the addition of organic co-solvents to DNA-based catalysis. The effects of these co-solvents on DNA-structure, yield, enantioselectivity and kinetics are investigated. The use of water-miscible co-solvents has resulted in the reduction of the catalyst loading to 0.75 mol% and increase of the enantioselectivity by performing the reaction at -18°C.

Chapter 4 describes the first transition metal catalyzed asymmetric intermolecular oxa-Michael addition of alcohols. This reaction was catalyzed by 1st generation DNA-based catalysts and provided ee's up to 86%.

In chapter 5, a novel approach to asymmetric protonation in water is presented. In our approach, 2nd generation DNA-based catalysis is used to perform a Friedel-Crafts alkylation/enantioselective protonation cascade with up to 60% ee.

Finally in chapter 6 the results in this thesis are summarized and combined with previous results. Furthermore an extensive future perspective is presented on the basis of ongoing projects.

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