Biomimetic asymmetric catalysis based on biological and synthetic macromolecular scaffolds
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Chapter 1 An introduction to biomimetic asymmetric catalysis

Over the past several decades, an abundance of enzyme mimetics based on various macromolecular scaffolds has been designed and fabricated by chemists. The resulting artificial enzymes, in some notable examples, brought new activity and selectivity to a variety of organic transformations. These reactions occur in well-defined environments and are characterized by different mode of actions, which include bringing the catalytic center and substrate in close proximity, increasing the effective molarity of the reactants, pre-organizing the catalyst and/or substrate and stabilization of the transition state. Unquestionably, these different pathways are highly related to the properties of the selected scaffolds (e.g., size, rigidity, and presence of functional groups). This chapter highlights the representative natural and synthetic macromolecular scaffolds that were chosen for the development of asymmetric artificial metallo-enzyme mimetics and their applications in homogeneous enantioselective organic transformations.
1.1 Introduction

The building blocks of nature’s living organisms, from small molecules (e.g., amino acids, nucleotides, monosaccharides) to macromolecules (e.g., proteins, nucleic acids, sugars), are all chiral. As a fact, more than 50% of the approved drugs are enantiopure compounds.\[^1\] Although chiral resolution techniques are widely used in industry, they are still hurdled by the high cost and low yield. In this respect, asymmetric catalysis is a suitable alternative since it produces an enantiomerically enriched compound with only a sub-stoichiometric amount of catalyst while a certain amount of solvent is consumed.\[^2\]

The catalysts for asymmetric reactions can be roughly classified into two groups: small molecule catalysts and enzymes. For a long period, enzymes attracted great research attention because they are highly selective and generally can accelerate the reaction rate under mild conditions. To date, the working principles of enzymes are often unclear. Nevertheless, stabilization of the transition state and/or binding substrate with a beneficial orientation and conformation in reaction pockets (active site) are considered as the origin of the high selectivity and reactivity in enzyme-catalyzed reactions.\[^3\]

Inspired by nature, scaffolds originating from biomolecules\[^4\] and synthetic cavities\[^5\] with hydrophobic pockets have been thoroughly applied for the design of artificial metallo-enzyme mimetics. These macromolecules which provide a combination of interactions (e.g. hydrogen bonding, π-π stacking, electrostatic and hydrophobic interactions) to the substrate, the transition state and the metal complex, are defined as the second coordination sphere. The interactions from these scaffolds play a key role in influencing the reaction rate and the selectivity. Due to the importance of the second coordination sphere, this chapter highlights the natural and synthetic macromolecular scaffolds that were chosen for the development of asymmetric artificial metallo-enzyme mimetics. The application of such scaffolds in homogeneous enantioselective organic transformations will be also discussed here.
1.2 Scaffolds based on biomolecules

In this field, chemists aim to combine the attractive features of natural and synthetic catalysts. A commonly used approach to achieve this is through the introduction of a transition metal complex into nature’s building blocks, i.e. DNA, RNA and proteins. This strategy makes use of the role separation between the metal complex, which contributes to the chemical activity, and the biomolecular scaffolds, which induce the selectivity and can also influence the reactivity in the reaction. Due to the modular build-up, the two components can be optimized separately by chemical or biological methods, allowing even the application of combinatorial synthesis approaches.

1.2.1 Protein scaffolds

Scheme 1.1. Schematic representation of the design of artificial metalloenzymes based on
biotin-(strept)avidin technique.

The most widely used protein scaffold for the design of an artificial metalloenzyme is (strept)avidin, which shows strong interactions to biotinylated metal complexes (Scheme 1.1). In 1978, Whitesides and Wilson successfully demonstrated the first example of an artificial metalloenzyme using avidin as a scaffold. In their pioneering work, the supramolecular assembly of a biotinylated rhodium diphosphane complex with avidin was applied in an asymmetric hydrogenation reaction, albeit with a moderate ee of 41%.[6] Since 2003, Ward and coworkers have dedicated great efforts to the further development of this approach. By using streptavidin instead of avidin, they dramatically improved the catalytic performance with over 90% ee in the hydrogenation of N-acetamidoacrylic acid and N-acetamidocinnamic acid.[7] Further optimization was achieved with both chemical (e.g. different spacer between metal complex and biotin) and biological methodologies (e.g. different protein mutants). This chemogenetic approach gave rise to both enantiomers of the hydrogenation products with high enantioselectivities of up to 96% ee.[8] Following this design strategy, other transition metals, such as palladium, vanadium and ruthenium, were applied in several types of transformations, including allylic alkylation, oxidation of prochiral sulfides and transfer hydrogenation of prochiral ketones.[9] Current efforts are directed towards the challenging issues in organic chemistry. For instance, Ward and Rovis reported a rate-accelerated enantioselective electrophilic aromatic C-H activation reaction, which was catalyzed by a biotinylated cyclopentadienyl rhodium complex introduced into streptavidin (Scheme 1.2a). Up to 86% ee was achieved, and at the same time a 92-fold rate acceleration was observed compared to the reactions catalyzed by the pristine metal complex.[10a] To solve the general problem of the mutual inactivation of organometallic catalysts and enzymes when combining them to address synthetic challenges, a d⁶-piano stool complex was incorporated into streptavidin to generate an artificial transfer hydrogenase (ATHase) (Scheme 1.2b). Due to the steric separation, the resulting metalloenzyme showed full compatibility with several natural enzymes, thus enabling efficient concurrent cascade reactions.
Upon combining with a highly (S)-selective monoamine oxidases (MAO), they catalyze the double stereoselective deracemization of amines with up to 99% ee.[10b]

**Serum albumins** are a family of the most abundant proteins in blood plasma. Therefore, they are generally cheap, robust and easily accessible. Due to these features, they were often chosen as biological scaffolds for the fabrication of metalloenzymes (Scheme 1.3). In an early study, the 1:1 complex between an osmate ester and bovine serum albumin (BSA) was found to be effective as an enantioselective catalyst in the \(\text{cis}\)-hydroxylation of alkenes, affording diols of up to 68% ee.[11] Gross et al. generated an artificial oxidase by anchoring iron- and manganese-corroles to human serum albumin (HSA), which produced up to 74% \(ee\) in the asymmetric oxidation of thioethers.[12] Although these two examples successfully demonstrated the availability of serum albumins as second coordination scaffolds, the enantioselectivities were still moderate. In this respect, Reetz and coworkers reported several copper-phthalocyanine conjugates of different serum albumins as truly high enantioselective catalysts in Diels-Alder reactions with up to 98% \(ee\).[13]

![Scheme 1.2. Applications of artificial metalloenzymes based on biotin-(strept)avidin technique in a) an enantioselective electrophilic aromatic C-H activation reaction and b) in cascade reactions.](image)

**Apomyoglobin**, which represents the protein scaffold after removal of the cofactor of myoglobin, has been extensively used by the group of Watanabe (Scheme 1.4a). They constructed a series of artificial metalloenzymes with a variety of non-natural
cofactors, such as manganese-salen, chromium-salen and ruthenium -phebox complexes. However, the following test of these catalysts in the sulfoxidation of thioanisole generally gave low enantioselectivities.[14] Based on the same protein scaffold, Lu and coworkers improved the catalytic performance of apomyoglobin manganese-salen by a dual anchoring strategy, which was realized by covalent disulfide linkages between the cysteines on the protein scaffold and methane thiosulfonate groups on the metal complex (Scheme 1.4b). This type of catalyst yielded the sulfoxidation products with higher $ee$ values of up to 51%. [15] Moreover, the same group demonstrated that changing the anchoring positions on the protein scaffold resulted in an increased selectivity (up to 66% $ee$).[16]

Scheme 1.3. a) Schematic representation of the design of artificial metalloenzymes based on serum albumins and their applications in b) manganese catalyzed asymmetric sulfoxidation and c) copper catalyzed D-A reaction.
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Scheme 1.4. Schematic representation of a) the supramolecular and b) covalent anchoring of salen-based catalysts in apomyoglobin scaffolds and their applications in c) manganese catalyzed asymmetric sulfoxidation.

Scheme 1.5. Applications of artificial metalloenzymes based on the carbonic anhydrase scaffold in a) manganese catalyzed enantioselective epoxidation and in b) iridium catalyzed transfer hydrogenation reactions.
Another commonly used protein scaffold is derived from carbonic anhydrase. Replacement of the cofactor zinc by a manganese ion in the active site of this enzyme resulted in a new type of peroxidase (Scheme 1.5a), which can be used for the epoxidation of various styrene substrates with up to 67% ee.\textsuperscript{[17a,17b]} Instead of removing the zinc ion in human carbonic anhydrate, Ward used it as an anchoring site for an aryl-sulfonamide-bearing iridium pianostool complex (Scheme 1.5b). The combined units showed good reactivity and an ee value of up to 70% in the transfer hydrogenation of imines, using formate as the hydrogen source.\textsuperscript{[17c]}

Whereas the systems described above have attracted great research interests, other protein scaffolds have also been employed for the fabrication of metalloenzymes in asymmetric catalysis. Distefano et al. covalently attached an iodoacetamide functionalized phenanthroline to the unique cysteine of adipocyte lipid binding protein (ALBP). Upon copper complexation, the hybrid catalyst was used as artificial hydratase for activated esters and aryl amides with up to 86% ee.\textsuperscript{[18a]} The selectivity of the same ester hydrolysis reaction could be further improved to 94% ee by varying the attaching sites of the metal complex within mutated cavities.\textsuperscript{[18b]} Bovine \(\beta\)-lactoglobulin, equipped with Ru(II)/Rh(III) fatty acid derivatives formed active catalysts for the transfer hydrogenation of trifluoroacetophenone, albeit with only fair ee’s.\textsuperscript{[19]} Embedding an anionic manganese porphyrin complex into xylanase 10A (Xln10A) led to an enantioselective epoxidase for styrene derivatives by using KHSO\textsubscript{5} as oxidant.\textsuperscript{[20]} Kamer and coworkers covalently attached a phenanthroline copper conjugate to the sterol carrier protein type 2 like domain (SCP-2L) to generate an artificial Diels-Alderase with which a moderate ee of 25% was achieved.\textsuperscript{[21]} Other protein scaffolds, including photoactive yellow protein (PYP)\textsuperscript{[22]}, papain\textsuperscript{[23]}, the periplasmic nickel-binding protein NikA\textsuperscript{[24]}, and tubular protein [(gp5βf)\textsubscript{3}]\textsubscript{2} \textsuperscript{[25]} have also been combined with metal centers. However, the enantioselectivities produced by these systems were very low.
Scheme 1.6. Schematic representation of the design of artificial metalloenzymes by the creation of a new active site at the interface of the dimeric protein LmrR and their application in the copper catalyzed D-A reaction.

All of the protein scaffolds discussed above possess a defined binding pocket. In contrast, proteins that lack a pre-existing pocket were also employed for the construction of artificial metalloenzymes. As an example, Reetz and coworkers engineered a copper binding site in a thermostable protein, *Thermotoga maritime* (*tHisF*), with an appropriate combination of two histidine and one aspartic residue. The resulting system produced products with up to 46\% ee in the copper catalyzed Diels-Alder reaction.\[^{26}\] Recently, Bos and Roelfes have developed a novel concept for the design of artificial metalloenzymes, which involved the creation of a new active site at the interface of the dimeric protein *Lactococcal multidrug resistance Regulator* (*LmrR*) from *Lactococcus lactis* (Scheme 1.6). The reason for choosing LmrR as a proof-of-concept is related to the extremely high dimerization efficiency of this protein. With the as-formed catalyst, up to 97\% ee was obtained in the copper catalyzed Diels-Alder reaction\[^{27a}\], and at the same time up to 84\% ee was achieved in the hydration of a variety of \(\alpha,\beta\)-unsaturated ketones.\[^{27b}\]
1.2.2 Peptide scaffolds

Artificial metalloenzymes constructed from different host proteins have proven to be efficient for catalyzing several reactions with excellent enantioselectivities. However, this approach still faces some limitations. The host proteins are either costly compared to small chiral ligands or they need to be produced by recombinant expression, which might cause difficulties when generating large libraries.\cite{28} In this respect, chiral polypeptide ligands are a suitable alternative since they are readily accessible by standard solid phase synthesis and at the same time they have the potential to carry sufficient functionalities to form a well-defined second coordination sphere. A number of non-metal-containing peptide organocatalysts, which often exhibit excellent enantioselectivities have been reviewed by Miller and others.\cite{29} Here, the emphasis will only lie on oligo- and polypeptides that were complexed with metal ions to act as catalysts in enantioselective organic transformations.

\textbf{α-helices}, one of the most common secondary structures in proteins, have led to the development of metallopeptides in asymmetric catalysis. This structural motif was firstly employed by the group of Gilbertson in the 1990s (Scheme 1.7a).\cite{30} With the aid of solid phase synthesis, they designed and prepared a series of peptides incorporating diphenyl- and dicyclohexylphosphinoserine residues at the appropriate positions (\textit{i.e.} both of \textit{i} and \textit{i} + 1, 3, and 4).\cite{30a,30b,30c} Further evidences from NMR spectroscopy and X-ray crystallography confirmed that the α-helix structures were retained when complexed with rhodium.\cite{30d} In an initial trial, the resulting catalysts in the hydrogenation of 2-acetamidoacrylate gave a low \textit{ee} value of 8\%.\cite{30b} The optimization by a combinatorial synthesis approach on the solid phase resulted in significantly increased selectivity (up to 38\% \textit{ee}).\cite{30c,30e} Ball and coworkers recently described a \textit{de novo} design of metallopeptide by employing a metal chelating induced helical motif (Scheme 1.7b). In this special case, rhodium ion complexed with the carboxylate residues of aspartic acid at the \textit{i} and \textit{i} + 4 positions played an important role in stabilizing the secondary structure. In the absence of metal ion the peptide sequence is largely unstructured. Since these peptide ligands contained only natural
amino acids, an obvious advantage of this strategy is the avoidance of incorporating any nonnatural building blocks along with elaborate modification protocols for metal coordination. Based on this approach, a small library of 22 nonapeptides, which formed 44 parallel and antiparallel bis-peptide dirhodium complexes were generated. Screening of this library in an enantioselective Si-H insertion reaction revealed a sequence that produced the silane product with 92% ee. Following efforts of the same group aimed to speed up the screening process and to achieve both enantiomers in high optical purities without changing the handness of the amino acids. To this end, an on-bead screen was adopted with the assumption that the optimized mono-peptide complexes would generally be also selective as bis-peptide complexes. In a model cyclopropanation reaction, the high-throughput screening provided one sequence that gave up to 97% ee of the si product and another sequence that gave up to 90% ee of the re product.

![Scheme 1.7. Applications of metallopeptides based on α-helices in rhodium catalyzed enantioselective a) hydrogenation and b) Si-H insertion and cyclopropanation reactions.](image)

Gillbertson also reported a library of bisphosphine peptide ligands based on the well-known β-turn forming motif –Pro-Xxx-, where Xxx is a D-amino acid. These peptides were evaluated on solid support in palladium catalyzed allylic alkylation reactions (Scheme 1.8a). By varying phosphine substitution, up to 95% ee in solution and 88% ee on solid support were obtained. In order to elucidate the function of the structural motif, they prepared another control library of peptides which lacked β-turn structures. This resulted in a much lower number of hits and clearly showed the essential role of this structural confinement for the induction of enantioselectivity.
Landis disclosed a highly selective catalytic system built on a series of molecular scaffold orientated β-turn structures (Scheme 1.8b). The conformation of these peptides was stabilized via incorporating 3,4-diazaphospholane as a structural constraint. Up to 92% ee was obtained when applying them in a palladium catalyzed allylic substitution of diphenylallyl acetate. Ball introduced another design of metallopeptides based on turn structures, which were induced upon rhodium complexing with a single peptide sequence. Interestingly, they found that a phosphite additive that acted as an axial ligand for a dirhodium tetracarboxylate complex improved the enantioselectivity of Si-H insertion reactions. Albrecht and coworkers recently reported a tetrapeptide scaffold containing a C-bound histidylidene amino acid and a methionine residue. In this system, the double methylated histidine formed an N-heterocyclic carbene to act as a ligand for rhodium, while the sulfur of methionine acted as an extra chelator for the rhodium complex. The metal complexing induced the formation of stabilized turn structures. However, the asymmetric induction proved to be unsuccessful, which could be explained by the large distance between the chiral peptidic macrocycle and the active metal center.

\[32b\] \[32c\] \[32d\] \[32e\]

Scheme 1.8. Application of metallopeptides based on a) β-turn and b) molecular scaffold oriented β-turn structures in palladium catalyzed enantioselective allylic substitution reactions.

β-sheet formation is a crucial aspect during protein folding and design. Inspired by this motif, Breit and his group presented the design of β-sheet mimetics through a noncovalent self-assembly approach (Scheme 1.9). In their system, complementary hydrogen bonding between the amide functions of both peptide sequences occurred and was responsible for the formation of an antiparallel β-sheet structure. These
heterodimeric supramolecular assemblies in combination with rhodium catalyzed the hydroformylation of styrene with a moderate selectivity of up to 36% $ee^{[33]}$. 

Kamer et. al. applied the natural cyclic peptide gramicidin S as a rigid scaffold for the development of a novel peptidic bisphosphine ligand (Scheme 1.10). Two phosphane-containing amino acids were inserted into the sequence to act as bidentate metal binding sites. The resultant rhodium complexes catalyzed asymmetric hydrogenation with up to 52% $ee$ while the corresponding palladium analogues allowed asymmetric allylic substitution with only 13–15% $ee^{[34]}$.

The group of Meldal demonstrated that peptides without any predefined secondary structure could be applied for inducing enantioselectivity as well. They synthesized a library of diphosphane and P-S peptidic ligands through the phosphinomethylation of
the primary and secondary amine of oligo-peptides on solid support. Then, the peptides were coordinated with palladium to generate metallopeptides. In a model allylic substitution reaction of diphenylallyl acetate, up to 21% ee was achieved with the diphosphane systems\(^{[35a]}\) and up to 60% ee was obtained with the P−S systems.\(^{[35b]}\)

In addition to the synthetic oligo-peptide structures discussed in the above sections, natural polypeptide scaffolds can also be utilized for metallopeptide design. In an example from Roelfes et. al, the natural peptidic hormone, **bovine pancreatic polypeptide (bpp)**, was truncated to 31 residues for synthetic convenience (Scheme 1.11). Furthermore, based on a calculated structural model, tryptophane at the 7\(^{th}\) position was selected as the mutation site for a variety of amino acids that are capable of binding copper ions. The results showed that peptides containing L-3-pyridylalanine provided good enantioselectivities of up to 83% ee in the D−A reaction and 86% ee in the Michael addition of dimethylmalonate to azachalcones, respectively. Moreover, a 3.5-fold rate acceleration was observed in the presence of peptide scaffold in the D−A reaction.\(^{[36]}\)

![Scheme 1.11](image.png)

**Scheme 1.11.** Application of metallopeptides based on natural peptidic hormone bpp in copper catalyzed enantioselective Michael addition and D-A reactions.

### 1.2.3 DNA scaffolds

The concept of DNA based asymmetric catalysis was pioneered by Roelfes and Feringa in 2005 (Scheme 1.12). In their seminal work, they demonstrated that the
chiral information of double helical DNA (salmon testes DNA, calf thymus DNA and synthetic duplexes) can be transferred directly to the copper catalyzed D-A reactions. This was realized by embedding a nonchiral DNA-intercalator modified ligand into the grooves of nucleic acid structures. This 1st generation catalyst provided D-A products with moderate ee values, ranging from 33% to 53%. Later, the 2nd generation of catalysts showed truly high enantioslectivities. In the new system, the DNA binding moiety and the ligand were integrated into one bidentate pyridyl ligand, without any spacer. This structural design rendered the reactive metal centre closer to the double helix, which gave rise to a significant increase in enantioselectivity (up to 99% ee) of the D-A reaction as in the earlier system. Then, the scope of the D-A reaction was investigated by employing a class of α,β-unsaturated 2-acyl imidazoles as substrates. The substrate variation demonstrated the practical applicability of the DNA based catalyst since the imidazole auxiliary could be removed readily and transformed after the reaction. In a comprehensive study, the authors found that both the enantioselectivity and the reactivity of D-A reaction were highly depending on the choices of DNA sequences, i.e. salmon testes DNA induced the highest enantioselectivity and also resulted in the largest (58-fold) rate acceleration. During the past decade, the DNA based catalytic systems have been extensively applied on a variety of organic transformations, such as hydrolytic kinetic resolution of pyridyloxiranes, electrophilic fluorination, Michael addition, F-C alkylation, syn-hydration of α,β-unsaturated ketones and intramolecular cyclopropanation of α-diazo-β-keto sulfones. These successful examples do not only demonstrate the broad applicability of DNA based asymmetric catalysis but also its potential capability to address challenging issues in catalysis.

In contrast to the supramolecular fabrication strategy, an alternative approach involves the covalent attachment of a catalytically active metal complex onto the DNA sequence to form an artificial metallo-DNAzyme. In this case, one can precisely locate the transition metal catalyst at desired positions of the scaffold. Roelfes and coworkers attached a carboxylic acid modified bipyridine ligand with the amino
group at the DNA terminus via amide bond formation (Scheme 1.13a). When this sequence in combination with a second oligonucleotide were hybridized with a complementary template, the resulting assembly induced up to 93% ee in the copper catalyzed D-A reactions between azachalcone and cyclopentadiene. In another example, Jäckke and his group reported a DNA-Diene-Iridium catalyzed allylic amination reaction which was beyond the scope of Lewis acid catalyzed reactions with copper ions (Scheme 1.13b). For the diene ligand conjugation, the clickable 4-triazolyl-deoxyuridine was inserted into a 19mer oligonucleotide by standard solid phase synthesis. Then the resulting sequence was reacted with primary amine functionalized ligands to form the desired DNA conjugates. Furthermore, complementary DNA and RNA strands were hybridized with the diene modified single strand to modulate the chiral microenviroment. Although the ee values observed in the model reaction were generally low (up to 27%), these results clearly showed that the abundant nitrogen donor-containing heterocyles on DNA bases did not obstruct the iridium coordination with diene ligand, and thus the suitability of DNA based catalysts in organometallic chemistry was successfully demonstrated.

Scheme 1.12. Schematic representation of DNA-based asymmetric catalysis based on the supramolecular anchoring strategy developed by the groups of Roelfes and Feringa.
So far, the handedness of all the double stranded DNA scaffolds discussed above appeared to be right-handed. Therefore, the access to both enantiomers of the products mostly relied on the nature of ligand\cite{51} or the topology of the DNA\cite{52}. In contrast, Smietana and Arseniyadis developed an universal method by making use of the left-handed DNA strands which were accessible from a DNA synthesizer using commercially available L-nucleoside phosphoramidite building blocks. As expected, the L- and D-DNA gave rise to the mirror image products with nearly the same high enantioselectivities in the copper catalyzed F-C alkylation and Michael addition reactions.\cite{53}

In addition to the well-established systems based on double stranded DNA, \textbf{G-quadruplex DNA} has also been applied as scaffold for the construction of DNA-based asymmetric catalysts (Scheme 1.14). Compared to the double helix DNA, G-quadruplexes are structurally more complex and hence offer greater diversity in regard to the chiral microenvironment. Moses et. al. demonstrated the first modular construction of a G-quadruplex based chiral catalyst. A series of bidentate pyridyl ligands for copper coordination were employed to bind to G-quadruplex scaffolds in a supramolecular fashion. However, the resulting assemblies showed only weak chiral induction in the copper catalyzed D-A reactions.\cite{54} Similarly, Li and coworkers combined the human telomeric G-quadruplex DNA with a copper ion by a dative anchoring strategy, from which up to 74% and 75% ee were obtained in the D-A and

Scheme 1.13. Schematic representation of DNA-based asymmetric catalysis based on the covalent anchoring strategy.
F-C alkylation reactions, respectively. Interestingly, they found that the absolute configuration of the products could be reversed when the conformation of the G-quadruplex was switched from antiparallel to parallel under molecular (PEG200) crowding conditions.\cite{55} Recently, another hybrid catalyst composed of G-quadruplex DNA and copper porphyrin complex was introduced by Wilking and Hennecke. This supramolecular assembly gave rise to the same D-A products with up to 69\% ee. By means of nucleobase substitution experiments, residues which had an effect on enantiomeric outcome of the D-A reaction were identified.\cite{56}

Scheme 1.14. DNAzymes assembly based on G-quadruplex structures.
Scheme 1.15. Reaction scope of DNA-based asymmetric catalysis.
1.3 Synthetic macromolecular scaffolds

In addition to the naturally occurring biological scaffolds, synthetic oligomers and macromolecules with chiral microenvironments different from the bulk medium have also attracted interest in the field of biomimetic catalysis. These cavities have been proven to effectively enhance the rate of organic transformations in aqueous solution and at the same time they can influence the regio-, chemo- and stereo-selectivity of the chemical reactions. These effects are related to the unique properties of the cavities; however, the details concerning the working principles are often poorly understood. In this context, pre-organization of the substrates and stabilization of the transition states are the most widely accepted explanations. The flourishing developments of this field has been reviewed by others before.\[57\] Here, the focus will only lie on the transition metal-containing systems that were applied in homogeneous asymmetric catalysis.

Cyclodextrins (CD) are a family of cyclic oligosaccharides, which are hydrophobic inside and hydrophilic outside. The hydrophobic cavity of cyclodextrins is able to interact with hydrophobic compounds to form inclusion complexes. This feature has been extensively utilized to design enzyme mimetics for various organic transformations.\[58\] Among them, however, only a few were enantioselective reactions that were catalyzed by cyclodextrin-based metalloenzymes (Scheme 1.16). Carofiglio et al. reported an ethylenediamine-functionalized β-CD structure which could coordinate with molybdenum ions to form an active catalyst in the oxidation of methyl phenyl sulfide. Up to 60% \textit{ee} was achieved by the presence of chiral cyclodextrins.\[59\] Following this work, another two series of β-CD derivatives were prepared to mimic oxidases for aromatic sulfides. Sakuraba and coworkers\[60\] modified β-CD with catechol-type ligands while Ji\[61\] et al. employed amino alcohol functions as metal coordination sites. When the resulting derivatives were complexed with molybdenum, they were applied in the oxidative transformation but, in both cases, only moderate enantioselectivities were obtained. In contrast, Woggon and coworkers demonstrated that the chiral induction of cyclodextrins can be significantly
improved when they were applied in the reduction of aromatic and aliphatic ketones. The transfer hydrogenation was carried out in the presence of amino alcohol linked β-CD and ruthenium ions.\cite{62} As one of the most widely used ligands, phosphines were successfully integrated into the cyclodextrin scaffold. Jia et al. prepared a novel bidentate β-CD-modified phosphine ligand and its rhodium and platinum complexes. The resulting catalysts were applied in the asymmetric reduction of olefins with up to 92% ee.\cite{63} Recently, Armspach and Matt reported a α-CD scaffold bearing two distinct phosphorous-containing chelators, a phosphane and a phosphite. This hybrid ligand was then evaluated in the rhodium-catalyzed hydrogenation of α-dehydroamino acid esters and hydroformylation of styrene with moderate ee’s.\cite{64}

![Scheme 1.16. Biomimetic catalysts based on cyclodextrins and their applications in a) molybdenum catalyzed asymmetric sulfoxidation and b) ruthenium catalyzed enantioselective transfer hydrogenation reactions.](image)

In addition to CD, the bowl-shaped calix[n]arenes are emerging as versatile building blocks for the construction of supramolecular structures and a number of intriguing catalytic systems were realized with this class of compounds. In particular, chiral calixarenes can be obtained by two distinct strategies: one is the ligation of chiral moieties at the upper or lower rim of non-chiral calixarenes; while the other consists of generating an unsymmetrical array of substituents on the calixarene skeletons to make them inherently chiral. The use of these structures in transition metal-based asymmetric catalysis is now attracting more and more interest (Scheme 1.17).\cite{65}
In the first attempt, Umani-Ronchi and coworkers demonstrated that the presence of achiral \( p\text{-}\text{tert}-\text{butyl} \)calix[4]arene was able to further promote the allylation of aldehydes catalyzed by (S)-BINOL zirconium complexes with slightly enhanced enantioselectivities. Moreover, this supramolecular system gave rise to the decrease of catalyst loading from 10% to less than 2%.\[^{66}\] Matt et al. synthesized a series of calix[4]arenes bearing two phosphorus groups. Three of them were inherently chiral with an AABC substitution pattern. Complexation of these diphosphines with palladium and rhodium afforded two types of catalysts. The palladium complexes were applied in the allylic substitution of diphenylallyl acetate with up to 67% ee. Up to 48% ee was observed in the rhodium catalyzed hydrogenation of dimethyl itaconate. The authors found that the chiral calixarenes, which showed effective chiral induction in catalysis, were the ones with more dissymmetric structures.\[^{67}\] High enantioselectivity in metallo-calixarene-catalyzed asymmetric reactions was first achieved by Kamer and van Leeuwen. They prepared a class of enantiopure
calix[4]-BINOL- and calix[4]-TADDOL-containing diphosphites by directly attaching three of the hydroxy groups of the calix[4]arene through a $\mu_3$-bridging phosphorus atom. The latter ones, upon coordination with rhodium, were able to catalyze the hydrogenation of prochiral olefins with up to 94% ee.$^{[68]}$ Vocanson and Pellet-Rostaing reported another efficient catalytic system based on chiral calix[4]arenes bearing $\beta$-amino alcohol groups. These ligands were synthesized by the introduction of glycidyl groups on the lower rim of the calix[4]arenes, followed by ring opening with amines. Their performance in ruthenium-catalyzed asymmetric transfer hydrogenation were evaluated. High reactivity as well as good enantioselectivity (up to 87% ee) were obtained when mono-functionalized calix[4]arene ligands were utilized.$^{[69]}$ Tomaselli and Sciotto introduced two calix-[4]arene-(salen) systems in asymmetric epoxidation reactions. In their first work, the calix[4]arene moiety was not able to effectively influence the selectivity through a molecular recognition mechanism. However, in a recent study, the calix[4]arene scaffold was fixed in an 1,3-alternate conformation and was attached to the salen unit by different spacers. In this way, the inherently chiral structures were more rigid, and hence resulted in better catalytic properties.$^{[70]}$ Other optically active calix[4]arene derivatives containing chiral moieties, including amino acid residues and binaphthyl phosphite, were applied in titanium-catalyzed aldol condensation$^{[71]}$ and rhodium-catalyzed hydroformylation reactions$^{[72]}$, respectively. However, the enantioselectivities were generally low.

In addition to macrocycles, various families of porous organic-inorganic hybrid materials (e.g. zeolites, mesoporous silicas and metal organic frameworks (MOF)) have been extensively used as hosts for the incorporation of small chiral ligands (e.g. salen, binap, binol, N-heterocyclic carbene, amino acids and diamines). Under heterogeneous conditions, they have been successfully applied for a number of organic transformations, such as asymmetric epoxidation, hydrogenation, alkylation and aldol reactions. An obvious advantage of these heterogeneous catalytic systems is that they make the rather expensive chiral ligands easily recyclable and reusable.
More interestingly, in some cases, the small chiral catalysts encapsulated in confined porous structures gave rise to significantly higher enantioselectivity and reactivity compared to homogeneous conditions.\[73]\] These improvements could be generally attributed to the confinement effect of the pore, in which weak interactions, such as hydrogen bonding, van der Waals forces, and physical adsorption, might play an important role. More detailed discussions of this field can be found in several excellent reviews.\[74]\]

1.4 Aim and outline of this thesis

The overall goal of this thesis was to develop new strategies for the design of biomimetic, asymmetric catalytic systems, with the emphasis on exploring new scaffolds from either the biological or the synthetic pool as introduced in the previous paragraphs.

Compared to structurally complicated enzyme systems, peptide-based catalysts are intriguing analogues. Their folding relies on similar conformational determinants and functional group arrays as present in protein-based catalysts. The search for low molecular weight asymmetric catalysts based on such systems has attracted great interest because of their ease of synthetic accessibility and their low cost. However, the currently available peptide scaffolds based on well-known secondary structures do not allow variability in choice of amino acid composition. Moreover, most artificial metallopeptides require significant synthetic effort. In this context, Chapter 2 deals with a novel design of metallopeptides, which involves the formation of a stable cyclic peptide scaffold via an intramolecular disulfide linkage. In addition, our peptide ligand contained only natural amino acids avoiding synthesis of non-natural amino acids or elaborate post-modification protocols for metal coordination. In Chapter 2 it will be shown how this catalyst converts azachalcone derivatives in an asymmetric Diels-Alder reaction with cyclopentadiene.

In Chapter 3, the mechanism of the cyclic peptide catalyst is investigated in more detail. Therefore, we employed a method called alanine scanning, which is used in
biochemistry to explore the importance of different amino acid side chains for function of a protein. Here, it will be shown how the systematic exchange of each amino acid within the cyclic peptide scaffold into alanine allows to determine important residues for chiral induction. With this knowledge it was possible to broaden the scope of the reaction. This chapter will also demonstrate how a chiral Diels-Alder product is obtained, which could be further transformed into a valuable intermediate.

In **Chapter 4**, the size of the chiral ligand is further reduced. Instead of using a cyclic oligopeptide, it was explored if only a single amino acid is enough to achieve high enantioselectivity in a Diels-Alder reaction. It turned out that this goal is achievable, however, requires the addition of a non-chiral cavity, i.e. cucurbit[8]uril (CB[8]), a macrocycle that is obtained by reacting glycouril with formaldehyde. This chapter further deals with investigation of the mechanism of this supramolecular catalytic system. Therefore, optical spectroscopy plays an important role to reveal the structural arrangement of the amino acid, the CB[8], the diene and the dienophile. Moreover, it will be detailed how these optical techniques allow to explain the large rate acceleration found for this supramolecular catalyst.

In **Chapter 5**, transition metal catalysts were employed to produce amphiphilic DNA conjugates and DNA side-chain homopolymers. In this new synthetic strategy, nucleic acid modification and polymerization were carried out in organic medium by introducing a hydrophobic DNA-surfactant complex as a reactive scaffold. It will be demonstrated that amphiphilic DNA structures are accessible ranging from the introduction of small hydrophobic molecules to DNA side-chain homopolymers with high grafting density.

### 1.5 References


An introduction to biomimetic asymmetric catalysis


An introduction to biomimetic asymmetric catalysis


