DNA-based catalysis and micellar catalysis
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Chapter 7

Conclusions and perspectives

In this chapter an overview of the science developed in this thesis is reported and overall conclusions are drawn. Furthermore, the future perspectives are evaluated.


7.1 Introduction

In the last decades, DNA’s role has been extended beyond that of the genetic blueprint of life. Because of its unique features, it has found applications in several fields. For instance, it represents one of the most exciting tools in nanoscience: the near-infinite choice of sequences that bind their complementary partners into a double helix, accordingly to precise base-pairing rules, has allowed for the construction of precisely programmed/controlled architectures and innovative functional systems.\textsuperscript{[1,2]} Moreover, the DNA molecule has also shown great potential in synthesis and catalysis.\textsuperscript{[3-7]} The recently discovered concept of DNA-based asymmetric catalysis\textsuperscript{[8-10]} has been successfully applied to several metal catalyzed reactions in water: the Cu\textsuperscript{II}-catalyzed Diels-Alder,\textsuperscript{[8,9,11,12]} Michael addition,\textsuperscript{[13]} Friedel-Crafts,\textsuperscript{[14]} syn-hydration of enones\textsuperscript{[15]} and fluorination reactions.\textsuperscript{[16]} In this case, DNA is used, in combination with an achiral Cu\textsuperscript{II} complex, as chiral scaffold whose chirality is transferred within the products of the metal catalyzed reaction (Figure 1).

**Figure 1.** Schematic representation of the DNA-double helix and of the DNA-based asymmetric catalysis concept.

![DNA Double Helix and Catalysis Concept](image)

The work described in this thesis aimed, firstly, to further develop the general concept of DNA-based asymmetric catalysis. The research efforts were directed towards the optimization of the design and of the performance of the DNA-based catalysts and, in particular, of those based on ligands of the first generation (Figure
1) in existing and novel reactivities, that is in the Cu\textsuperscript{II}-catalyzed Diels-Alder and syn-hydration reactions. Additionally, it was attempted to provide a deeper understanding about mechanistic aspects of the successful catalysts in those reactions. In the second part of the thesis, the focus was on the concept of micellar catalysis. Moreover, efforts have been made in order to merge the attractive features of both the DNA-based and micellar catalysis concepts, resulting in the construction of a new DNA-based micellar catalytic system. Since the attempts to achieve enantioselective micellar catalysis in the presence of DNA were not successful, a new design was introduced in the last part of the thesis. This implied the use of DNA in a modular-assembled micellar system, in which the DNA molecule acts as a tool to vary the position of the catalyst with respect to the surface of a micellar aggregate, thus tuning its activity.

### 7.2 Research overview

In Chapter 1 the concept of artificial metalloenzymes was introduced (Figure 2). Metalloenzymes aim to combine the attractive properties of homogeneous catalysis and biocatalysis, making use of the favourable interactions the second coordination sphere provided by the biomacromolecule can confer to a transition metal catalyzed reaction.

**Figure 2.** Schematic representation of the hybrid catalyst concept.

This concept has been applied successfully to a variety of metal catalyzed reactions in water and it represents the foundation of the DNA-based asymmetric catalysis concept. In fact, the non-covalent anchoring based on supramolecular interactions between the metal containing moiety and the biomolecular host, used in the construction of artificial metalloenzymes, has recently found one of its most successful applications in the DNA-based asymmetric catalysis approach which is
the object of Chapter 2. Herein, a detailed kinetic investigation of the DNA-based catalysts from ligands of the first generation (which comprise a metal-binding domain linked through a spacer to a 9-aminoacridine moiety) in the Cu\textsuperscript{II}-catalyzed Diels-Alder reaction in water between aza-chalcone and cyclopentadiene, was provided (Figure 3).

**Figure 3.** DNA-based asymmetric Cu\textsuperscript{II}-catalyzed Diels-Alder reaction in water promoted by catalysts from ligands of the first generation.

The most important findings are that the role of DNA, in this case, is limited to being a chiral scaffold; no rate acceleration was observed in the presence of DNA. This was in contrast with what observed for catalysts based on ligands of the second generation (which bear bipyridine-type ligands) in all the Lewis-acid catalyzed enantioselective C-C bond forming reactions investigated so far. The differences are proposed to be related to the DNA microenvironment in which the catalyst resides and where the reaction takes place. Based on the results, it was concluded that the design of the ligand is an important aspect in the development of hybrid catalysts. The observed enantioselectivity proved to be highly dependent on the DNA-sequence; the optimal DNA-sequence for obtaining high enantioselectivities was identified (oligonucleotide containing alternating GC nucleotides). Finally, DNA has been shown to interact with the Cu\textsuperscript{II} complex to give a chiral structure.

Chapter 3 describes the optimization of the DNA-based catalyst design using ligands of the first generation in a novel reaction: the DNA-based Cu\textsuperscript{II}-catalyzed
asymmetric syn-hydration of enones. A comparison with the Diels-Alder reaction is reported (Figure 4). The optimization of the design resulted in a maximum ee of 83% in the hydration reaction and 75% in the Diels-Alder reaction which are the highest enantioselectivity observed with these catalysts in the two reactions, so far. Moreover, some guidelines for the design of the ligands of the first generation were formulated: in order to obtain high selectivities and reactivities a short spacer between the metal binding domain and the DNA interacting moiety is required; 2-aminomethylpyridine is the preferred metal binding moiety; the highest enantioselectivities are achieved with ligands where R’ is an arylmethyl group bearing electron donating substituents (Figure 1). By comparison with the DNA-based catalytic Diels-Alder reaction using the same st-DNA/Cu²⁺-L catalysts, it was concluded that the observed enantioselectivity in the hydration reaction is probably not the result of selective shielding of one π face of the enone. Instead, it was proposed that the structure of the ligand is important to position and orient the substrate bound CuⅡ complex optimally with respect to the structured first hydration layer of the DNA and that the DNA directs the H₂O nucleophile for attack to one preferred π face of the enone. This study clearly underlines the potential power of the second coordination sphere in enantioselective catalysis.

Chapter 4 provides a kinetic and sequence dependence study of the DNA-based CuⅡ-catalyzed asymmetric syn-hydration of enones using catalysts based on the first generation ligands. Based on the observed kinetic solvent isotope effect and on the proton inventory experiment, which showed that only one proton is involved in the rate determining step of the reaction, a concerted mechanism was suggested. Efforts to improve the observed enantioselectivity showed that sequences rich in consecutive A/T bases or containing ATAT/TATA central segments are responsible for higher enantioselectivity in D₂O (up to 82%).

Probably, in this case, the network of water molecules of the first hydration layer is responsible for directing the CuⅡ complex preferentially at the minor groove of the AT regions. In the CuⅡ-catalyzed Diels-Alder reaction, by using the same type of catalysts, a preference for the GC rich sequences was found (Chapter 2). Circular dichroism on a small series of synthetic oligonucleotides suggests that high ee values are related to a non-classical conformation of the DNA. In the presence of Cu(II) alone, both enantiomers of the product can be obtained depending on the DNA-sequence.
Figure 4. DNA-based Cu$^{II}$-catalyzed Diels-Alder and syn-hydration of enones reactions using catalysts from ligands of the first generation.

Finally, labeling experiments in deuterium oxide showed that in the case of substrate 4a (Figure 4) the reaction is diastereoselective; in case of the substrate carrying a methyl group on the β-position, both diastereoisomers are obtained. However at present it is unclear if this means that the diastereoselectivity is substrate dependent or if other processes are involved.

In the second part of the thesis, we focused on the concept of micellar catalysis. The use of Lewis acids in combination with surfactant molecules which form micellar aggregates under defined conditions, can lead to an increase of the rate of a chemical reaction. Recently, the concept of Lewis acid-surfactant combined catalysts (LASCs) for several Lewis-acid catalyzed reactions in water, was introduced. In Chapter 5 an extension of this concept is presented. The study reported revealed a dramatic acceleration of the copper catalyzed Friedel-Crafts reaction in water in the presence of an anionic surfactant (SDS) (Figure 5). The extremely short reaction times, the easy work up and the good product yields are the main advantages of this approach. The immediate step to follow in the research would be to develop enantioselective versions of the Lewis-acid catalyzed reactions in a micellar medium.
Figure 5. Cu\textsuperscript{II}-catalyzed Friedel-Crafts reaction in water in the presence of SDS aggregate.

In Chapter 6 the design of a DNA-based micellar catalytic system was presented. The aim was to combine the excellent enantioselectivities obtained using DNA-based catalysts with the rate acceleration observed for several metal catalyzed reactions in water in the presence of surfactants. Since this initial approach proved unsuccessful, an alternative design (Figure 6 a, b) was proposed in which DNA was used as a tool to vary the position of the catalyst with respect to the surface of a micellar aggregate formed by a surfactant molecule (in the present case SDS), thus tuning its activity.

Figure 6. Control of chemical reactivity by positioning of the catalyst in the system.

a) CATALYSIS ON (or higher reactivity)

b) CATALYSIS OFF (or lower reactivity)

For the Cu\textsuperscript{II}-catalyzed Diels-Alder reaction the results are encouraging: a significant difference in reactivity between the two designs (Figure 6) was observed. Surprisingly, this was in contrast to what was observed for the Friedel-Crafts reaction: in this case, only a small difference exists between the two designs. By
optimization of the design (DNA-sequence and length of the oligonucleotide strands) it might be possible to achieve larger the difference in reactivity.

7.3 Future prospects

7.3.1 DNA-based asymmetric catalysis

In view of the impressive progress that has been achieved in this field in the last years, it is expected that the field of hybrid enzymes will live up to its promise and demonstrate that the best of the homogeneous catalysis and biocatalysis worlds really can be combined. It has been shown that the second coordination sphere in the artificial metalloenzymes has great potential for synthetic applications, affecting multiple parameters of a chemical reaction (vide supra). However, most synthetic chemists will likely still be hesitant to use an artificial metalloenzyme for their reactions. One important reason is that for almost all enantioselective transformations reported to date, good alternatives using conventional approaches, such as homogeneous or biocatalysis, are available even though the DNA-based catalytic reactions can be competitive with their “conventional” analogues, both in terms of practicality and cost. The DNA-based catalysis concept has proven to be really versatile and recently, as the syn-hydration of enones demonstrates, it has started to address some of the challenges in enantioselective catalysis for which there are no solutions available in conventional asymmetric catalysis, thereby making full use of the clear advantages that the second coordination sphere has to offer. Of course, challenges exist and further improvements can be foreseen.

- It is likely that other novel reactivities and selectivities can be found. The new procedures developed for selective transformations under mild conditions in water can represent a valuable starting point. Next step to follow would imply developing conjugate additions of other small molecule or hetero-aromatic nucleophiles, hydrolysis reactions, enantioselective protonation in water, intra/intermolecular reactions. Alternatively, in addition to Lewis-acid catalyzed reactions, also hydrogenations or oxidation reactions could be envisioned. Potential complications associated to the use of DNA may be the possible oxidation of DNA itself, with consequent strand scission albeit, oxidations in the presence of DNA are not unprece-dent. Additionally, the strong coordination of DNA bases to the metal ions...
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commonly used in catalysis\textsuperscript{[22]} could represent a problem; however, this might be overcome by appropriate choice of ligands and DNA structure.

- The substrates for DNA-based asymmetric catalysis can be easily synthesized in one step from commercially available compounds and easily purified; moreover, the imidazole moiety is readily removed from the products.\textsuperscript{[23]} However, in order to make the DNA approach more attractive for synthetic applications, the substrate scope should be expanded. The choice of the substrates in the DNA-based asymmetric catalysis was dictated by the necessity of having a bidentate coordination site in order to compete with water for coordination to copper(II). It would be desirable to employ monodentate substrates: ketones, aldehydes, esters, carboxylic acids. This might be achieved by using different metals with increased Lewis acid character and higher value of exchange rate with water molecules than copper (II) in order to make the metal available for binding the substrate.\textsuperscript{[24]}

Many successful examples of catalyzed reactions of monodentate substrates in aqueous solvents are reported using scandium(III) triflate,\textsuperscript{[25]} which therefore can be the metal of choice.

- Since the solubility of many of the reagents in water is poor, the use of surfactants forming micelles or of organic cosolvents, can be envisioned. The compatibility of DNA-based catalysts up to 30\% of organic solvent in the reaction mixture has been recently demonstrated.\textsuperscript{[21]} Eventually, for reactions which are incompatible or only partly compatible with water as solvent, it would be possible to still make use of the advantages provided by the DNA molecule and to perform DNA-based catalysis in pure organic solvent by using cationic surfactant to precipitate DNA with and by re-dissolving the collected complex in organic solvents.\textsuperscript{[26]}

- For some reactions, the recycling of the catalyst at low catalyst concentrations and in presence of synthetic oligonucleotides should be optimized (\textit{i.e.} in the Friedel-Crafts reaction with recycling, at low concentration of catalyst loss in enantioselectivity was detected).\textsuperscript{[9]}

- Finally, conversion and enantioselectivity can be improved in some reactions, especially when catalysts from the first generation ligands are involved. Improvements in the structure of the ligand and appropriate
choice of the DNA oligonucleotides via combinatorial or evolutionary approaches could be helpful.

- Further research efforts should be directed to address mechanistic issues. Still, the prediction of the accommodation, binding and conformation of the ligand-bound copper within the DNA helix is uncertain as well as the mechanism of transfer of chirality from DNA double helix within the products of the catalyzed reaction on study. The correlation between the structure of the ligands of both first and second generations and the outcome of the reactions investigated has still to be rationalized. Especially for the recently discovered syn-hydration of enones, several challenges exist. For instance, the next step to follow would be try to understand the origin of the Re-face addition so that would be also possible to increase the selectivity factor. Moreover, it would be interesting to understand why with the same catalytic species (copper complex from ligands of the second generation) a different preference for DNA bases (sequence selectivity) exists depending on the reaction (Diels-Alder and asymmetric syn-hydration reactions); also, the possibility of obtaining both enantiomers of the hydration product in presence of st-DNA and Cu(NO₃)₂ alone should be further investigated.

In conclusion, DNA-based asymmetric catalysis is rapidly emerging as a promising new concept in catalysis. Surely, the unique features provided by the DNA microenvironment to the catalysis will encourage further advances in this field, leading to the discovery of novel asymmetric reactivities in aqueous environment. Moreover, the efforts towards the elucidation of the mechanism of stereocontrol and enantioselectivity of DNA-based catalysis, will give a significant contribution to the mechanistic understanding of enzymatic catalysis.

### 7.3.2 DNA-based asymmetric micellar catalysis

The construction of the DNA-based micellar system described in Chapter 6, relies on the advantages presented by the modular assembly approach. Among these are the facile assembly by hybridization, the covalent functionalization of the oligonucleotides which allows for the control of the location and the geometry of the catalyst, the easy optimization by judicious design of the DNA strands, etc. In the presence of surfactant molecules, by different positioning of the catalyst with
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With respect to the surface of the resulting aggregate, we expected, based on what previously observed (Chapter 5), tuning of its activity. The close contact between the reaction partners at the micellar surface would ensure high reactivity; by contrast, the positioning of the catalyst further away with respect to the surface where the reaction is expected to occur more efficiently, would cause lower reactivity. This hypothesis was revealed to be true for the Cu$^{II}$-catalyzed Diels-Alder reaction, while almost no differences were observed in the Friedel-Crafts reaction. The optimization of this system in order to make this differences more dramatic could be achieved by changing the length of the oligonucleotides or the length of the spacer connecting the ligand-bound catalyst to the DNA strand. Alternatively, finding non-charged surfactant molecules which also could give acceleration of the reaction, can be useful reducing the complications due to the electrostatic repulsion between DNA and negatively charged surfactant. Exploring other reactivities for this system is imperative especially in view of the ultimate goal that would imply, by appropriate choice of the catalyst, to build a micellar system which, mimicking the living cell, can allow for performing different reactions in different environments simultaneously, based on the affinity of the substrates for a more apolar/polar medium.

7.4 References


