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DNA-based hybrid catalysis

Ana Rioz-Martínez and Gerard Roelfes[1]

In the past decade, DNA-based hybrid catalysis has merged as a promising novel approach to homogeneous (asymmetric) catalysis. A DNA hybrid catalysts comprises a transition metal complex that is covalently or supramolecularly bound to DNA. The chiral microenvironment and the second coordination sphere interactions provided by the DNA are key to achieve high enantioselectivities and, often, additional rate accelerations in catalysis. Nowadays, current efforts are focused on improved designs, understanding the origin of the enantioselectivity and DNA-induced rate accelerations, expanding the catalytic scope of the concept and further increasing the practicality of the method for applications in synthesis. Herein, the recent developments will be reviewed and the perspectives for the emerging field of DNA-based hybrid catalysis will be discussed.

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Introduction

Metalloenzymes are often considered the 'perfect' catalysts as they are capable of performing challenging reactions with high rates and high selectivity under mild conditions. It is increasingly recognized that the interactions provided by the so-called second coordination sphere to substrates and transition states are key elements in the highly efficient catalysis of metalloenzymes and this is what distinguishes them from 'traditional' homogeneous metal catalysts. This has resulted in a push to create hybrid catalysts in which transition metal complexes are embedded in biomolecular scaffolds such as protein or DNA, with the aim to take advantage of the second coordination sphere interactions provided by these scaffolds.

DNA-based hybrid catalysis was introduced 10 years ago [1]. It entails placing a catalytically active transition metal complex in close proximity to DNA using either supramolecular or covalent anchoring approaches. The chiral 2^{nd} coordination sphere provided by the DNA causes the reaction to proceed enantioselectively and, ideally, causes an additional rate acceleration [2].

The proof of concept studies and the early examples of DNA-based hybrid catalysis have been reviewed extensively [2,3]. In this contribution, the recent developments in the area of DNA-based hybrid catalysis will be discussed.

Supramolecular duplex DNA-based catalysis

Scope of DNA-based catalysis

The substrate scope of several previously developed Cu(II)-4,4′-dimethyl-2,2′-bipyridine/salmon testes DNA (Cu(II)-dmbpy/st-DNA) catalyzed reactions was expanded further. Li and co-workers reported cyanoacetates and malononitrile as effective nucleophiles for the DNA-based catalytic asymmetric Michael addition, giving rise to up to 84% ee [4].

Park and Sugiyama have reported an intramolecular conjugate addition of indoles, resulting in up to 71% ee when using st-DNA/Cu(II)-dmp (5,6-dimethyl-1,10-phenanthroline) as catalyst [5]. This was further improved to 77% by using the oligonucleotide d(TGTGTGCACACA)$_2$ (T = thymine, G = guanine, C = cytosine, A = Adenine). An intercalative binding mode for the Cu(II)-dmp complex was proposed. This was supported by computational studies, which showed that the pro-S structure of the substrate-Cu(II)-dmp complex bound to DNA complex is energetically more favorable than the pro-R structure. Additionally, the distance between the carbon atoms forming the new C–C bond in the product is shorter in the pro-S structure, suggesting the reaction to occur more easily. Finally, the pro-S structure was proposed to be only shallowly intercalated into the DNA, thus decreasing the energy required for conformational changes [6].

The catalytic scope of the previously established DNA-based hybrid catalysts comprising a Lewis acidic

[1] Web: http://roelfesgroup.nl/.

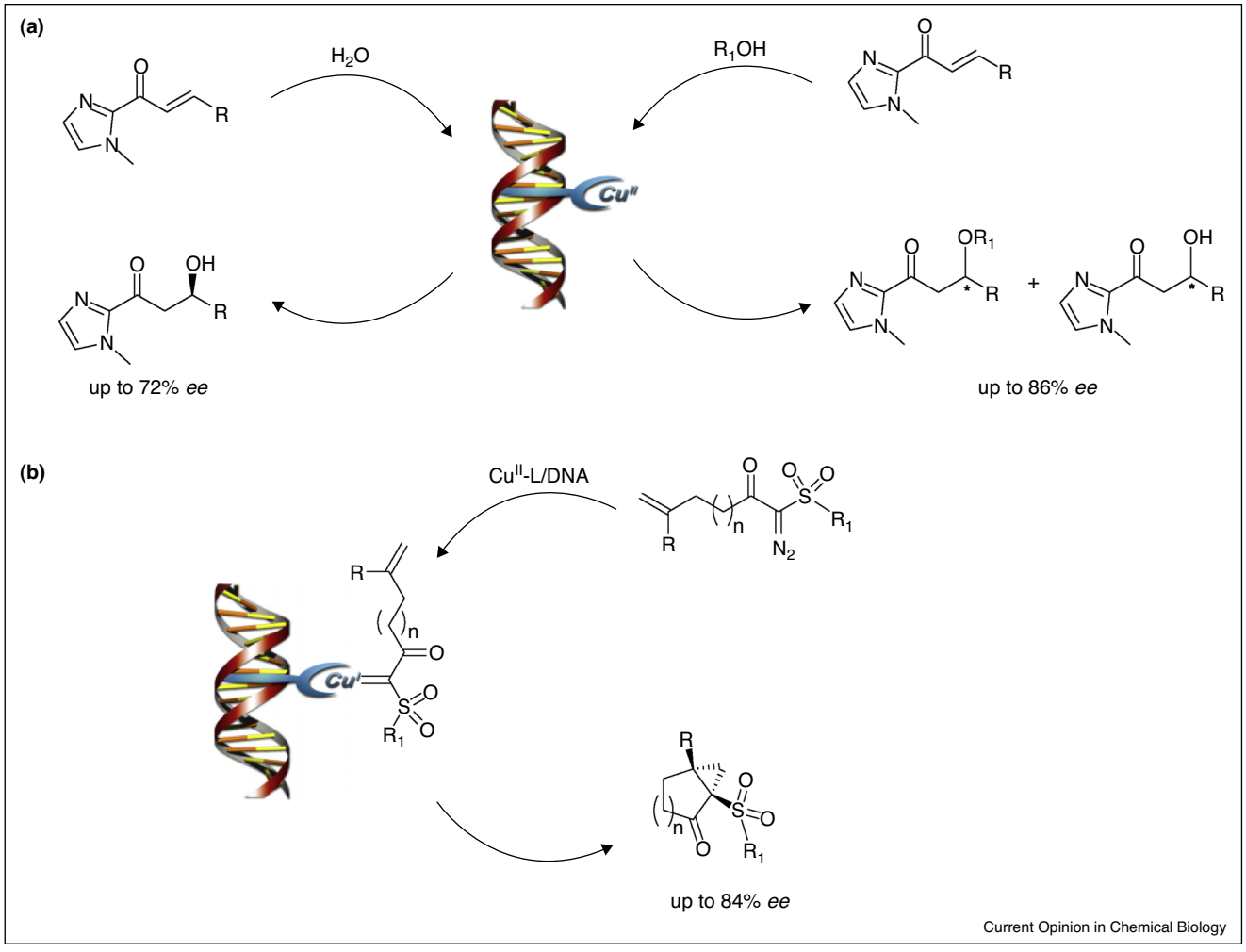
copper(II) complex in combination with duplex DNA, i.e. salmon testes DNA, has been further extended.

The Roelfes group had reported previously a catalytic enantioselective *syn* hydration of α,β-unsaturated ketones (Figure 1a), a reaction class for which there is no equivalent in homogeneous catalysis [7]. In a follow-up study, the first generation ligand structure was optimized and it was found that the AT rich DNA sequences gave rise to the highest enantioselectivities in the hydration reaction [8]. This is in marked contrast with all C–C bond forming reactions reported before, where actually GC rich sequences were most beneficial.

Next, the substrate scope of this catalytic asymmetric oxa-Michael addition was expanded to include small alcohols as nucleophiles (Figure 1a) [9]. Using alcohol/water mixtures, the corresponding alcohol adducts were obtained in up to 81 and 86% ee for the methanol and *n*-propanol addition product, respectively. In all cases the β-hydroxy ketone resulting from conjugate addition of water was found as a major side-product. However, by lowering the reaction temperature, the formation of the side-product could be prevented: at −18 °C the methanol addition product was obtained almost exclusively, albeit that the reaction was somewhat slower at this temperature.

The DNA-based catalytic asymmetric hydration reaction was combined with a laccase/(2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) mediated oxidation in a one-pot-two-reactions process [10]. An undesired reaction of an oxidized TEMPO intermediate caused that the two reaction steps needed to be done stepwise. Thus, after the oxidation reaction was complete the enzyme was inhibited and the reactive TEMPO intermediate was reduced. Then, the hydration was started by adding

Figure 1



Recently reported reactions that expand the scope of DNA-based hybrid catalysis. **(a)** Asymmetric DNA-based copper catalyzed hydration and oxa-Michael reaction of α,β-unsaturated 2-acyl imidazoles in water. **(b)** DNA-based copper catalyzed asymmetric cyclopropanation of α-diazo-β-keto sulfones.

the copper(II) complex. Following this procedure, an efficient two-step one-pot sequence was achieved, resulting in formation of the product in 20% *ee*.

To date, almost all DNA-based catalytic reactions reported to date involve Lewis acid catalysis. Jäschke and co-workers had reported an Ir catalyzed allylic amination reaction that was compatible with DNA, albeit the ee's obtained were most likely due to the chiral ligand employed and not to the DNA [11]. Recently, the Roelfes group reported the first example of a DNA-based catalytic organometallic reaction that gives rise to good ee's (Figure 1b): the copper(I) catalyzed intramolecular cyclopropanation reaction of α-diazo-β-ketosulfones [12••]. The reaction was performed by using the copper(II) complexes also used in other DNA-based catalyzed reactions. The copper(II) ion was reduced *in situ* by the substrate to copper(I). It was found that, in contrast to most Lewis acid catalyzed reactions, strongly intercalating ligands such as dppz (dipyrido[3,2-*a*:2′,3′-*c*]phenazine) and dmdppz (3,6-dimethyl dipyridylphenazine) were required for the reaction to proceed efficiently. Up to 84% ee was obtained using dmdppz, albeit that the yields were low due to the formation of a considerable amount of side products. The side reaction was identified as the insertion of the carbenoid into the O–H bond of water resulting the α-hydroxysulfone, which then decomposes. While still far from practical, this report does demonstrate the feasibility of expanding the scope of DNA-based catalysis beyond Lewis acid catalysis.

Structural studies of DNA-based catalysts

Recent work by the Roelfes and Browne groups offers more understanding of the structure of DNA-based catalysts. A detailed spectroscopic study of the DNA-binding mode of various copper(II) complexes of second generation ligands was performed. It was found that Cu(II)-dmbpy (4,4′-dimethyl-2,2′-bipyridine) and Cu(II)-bpy (2,2′-bipyridine) are predominantly groove binding, whereas Cu(II)-phen (1,10-phenantroline) and Cu(II)-terpy (2,2′;6′,2″-terpyridine) are more mostly intercalating. Cu(II)-dpq (dipyrido[3,2-*f*:2′,3′-*h*]-quinoxaline) and Cu(II)-dppz are clear intercalators. Instead of relating the ee's to the DNA-binding modes, it is proposed that it is mainly the flexibility in binding of Cu(II)-dmbpy and Cu(II)-bpy which is important for the catalysis [13].

In a 2nd study, the interaction of the substrate, i.e. an azachalcone derivative, with the copper(II)complex/DNA hybrid was studied [14•]. It was observed that, in addition to the copper(II) complex, the substrate also binds to the DNA. Based on this work an explanation for the observed DNA-induced rate acceleration in catalysis is put forward. Both the substrate and copper(II) complex bind to DNA, resulting in a high effective molarity. This, combined with the fact that substrate and copper(II) complex bind with moderate affinity to the DNA and the resulting flexibility and dynamics in binding, leads to an increased formation of the substrate bound complex, resulting in an increase in reaction rate.

Control of the enantiomeric outcome of DNA-based catalysis

Since natural DNA is available in one chiral form only, an important challenge is to be able to access both enantiomers of a reaction product. Two solutions can be envisioned: the mirror image of the chiral DNA scaffold can be employed or the interaction of the metal complex with the DNA can be modulated by changing the structure of the ligand and, hence, the interaction of the complex with the DNA.

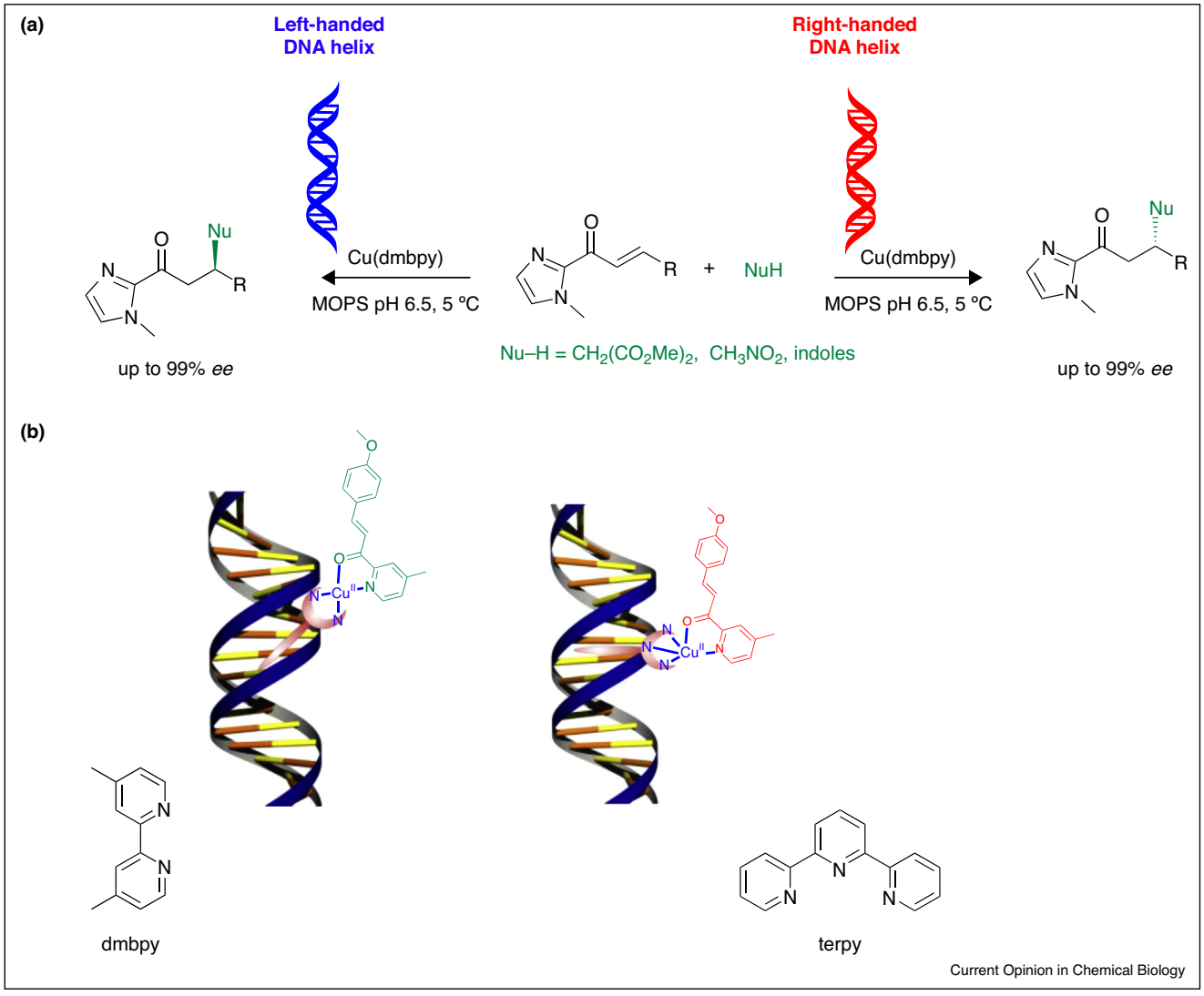
Smietana and Arseniyadis have reported the use of mirror image DNA in the catalytic asymmetric Michael addition and Friedel-Crafts alkylation reaction (Figure 2a) [15•]. Using the Cu(II)-dmbpy complex and the optimal synthetic DNA oligomers for these reactions, it was found that in all cases the opposite enantiomer of the product was obtained with the unnatural left handed *L*-DNA, compared to when using the natural right handed *D*-DNA.

An alternative approach to obtaining the opposite enantiomer of the product in catalysis involved the use of tridentate ligands for copper(II), compared to the commonly used bidentate ligands (Figure 2b) [16]. Using natural st-DNA, with Cu(II)-terpy complexes also the opposite enantiomer of the Diels–Alder product were obtained compared to when using Cu(II)-bpy type complexes, albeit that the reaction was found to be much slower. Supported by calculations, this was attributed to the fact that in this complex, only one free coordination site is available in the equatorial plane of the copper(II), which means that the substrate binds a different orientation, with the carbonyl oxygen on the axial position. This affects the interaction of the substrate bound complex with DNA, thus forcing the diene or nucleophile to approach from the opposite prochiral face of the enone. Consequently the opposite enantiomer of the reaction product is obtained.

Increasing the applicability of DNA-based hybrid catalysis

In efforts to increase the practicality and scalability of the DNA-based catalysis concept, co-solvents and other additives have been explored [17]. It was reported that organic co-solvents such as methanol or acetonitrile can be added up to 30% v/v to the catalyzed Friedel-Crafts, Michael and Diels-Alder reactions, without a negative effect on the ee. However, the reaction rate is usually affected and depending on the reaction type and substrate, this effect was negative or positive. In the cases were a positive

Figure 2



Control of the enantiomeric outcome of DNA-based catalysis. **(a)** Asymmetric *L* and *D*-DNA-based copper catalyzed Friedel–Crafts and Michael reactions. **(b)** Binding of substrates to Cu(II)-dmbpy and Cu(II)-terpy complexes in DNA-based catalysis.

effect on the reaction rate was observed, this was attributed to an increase in the rate of dissociation of the product.

Recently, it was shown that also ionic liquids, inorganic salts, deep eutectic solvents, glymes and glycols could be added to the DNA-based catalytic Michael addition. In general, these additives were well accepted and in some cases actually the rate and selectivity of the reaction were increased [18].

Another important aspect is recyclability. It has been reported previously that the aqueous phase containing the DNA and the metal complex can be re-used several times without a negative effect on yield or ee [19,20]. However, this does not allow for recapturing of the DNA. For this purpose, Park and Sugiyama have developed a solid silica supported DNA-based catalyst [21]. This was successfully employed in the catalytic asymmetric Diels-Alder reaction of azachalcone with cyclopentadiene. After the reaction, the silica supported DNA was isolated, washed and then reused in catalysis after addition of fresh Cu(II)-dmbpy. After 10 cycles, still excellent conversions were achieved, albeit that the ee decreased slightly from 94 to 89%.

Alternative DNA architectures

In addition to duplex DNA, also other DNA architectures have attracted attention for application as scaffold in DNA-based catalysis.

Li and co-workers developed catalysts comprising DNA G-quadruplex structures in combination with copper(II), i.e. without ligand. Using human telomeric G-quadruplex sequences up to 75% ee was obtained in the catalyzed enantioselective Friedel-Crafts alkylation and up to 74% ee in the Diels-Alder reactions [22,23•]. The enantiomeric outcome of the reaction could be switched by addition of either Na^+ or K^+ ions, which was ascribed to the formation of either antiparallel or hybrid G-quadruplex structures, respectively [24].

McNaughton and co-workers reported the *in vitro* evolution of a DNA hybrid catalyst for Friedel-Crafts alkylation reactions [25]. Using a biotinylated indole, which was initially intended for use in a pull-down assay, in combination with 5′-linked acyl imidazole DNA library, catalytically active DNAs were selected by a gel-shift assay. This resulted in selection of a 72-mer oligonucleotide, called M14, which in combination with copper(II), in the absence of additional ligand, showed moderate activity in the in cis Friedel-Crafts alkylation reaction. Somewhat higher activity was found for the trans reaction. However, no enantioselectivities were reported.

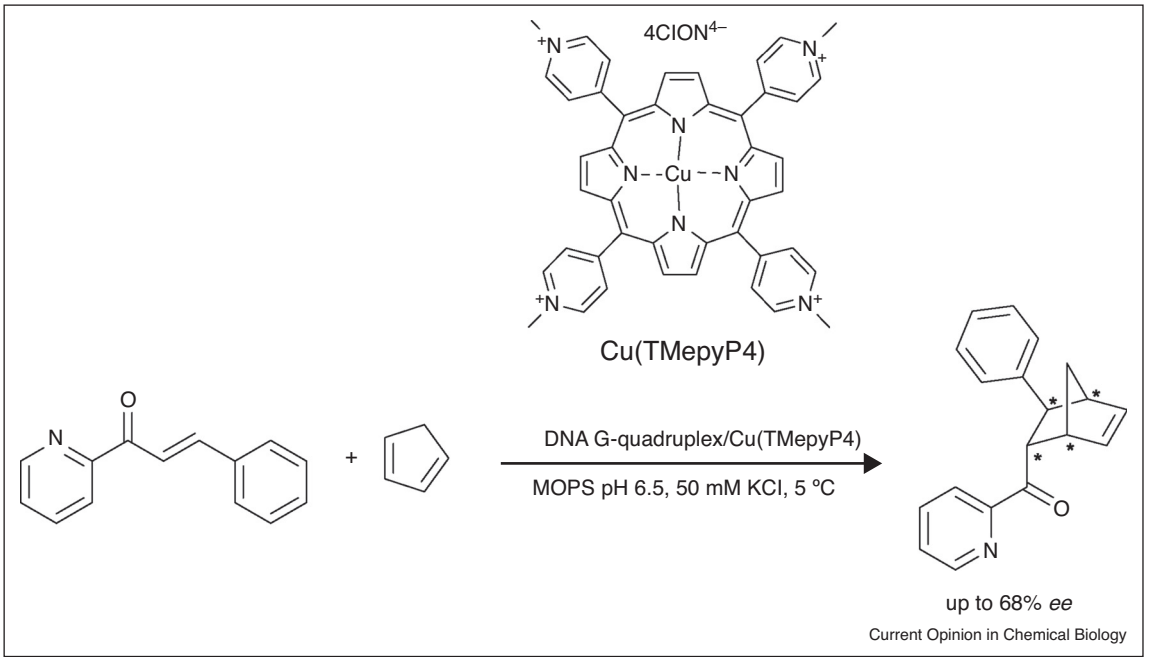
DNA G-quadruplexes were also explored in combination with copper(II) complexes. Cu(II)-phen in combination with human telomeric DNA sequences resulted in moderate enantioselectivity (up to 26% ee) in the catalyzed intramolecular Friedel-Crafts alkylation reaction.

Porphyrins are well-known G-quadruplex binders [26]. This has also been exploited for applications in catalysis. Heme bound to quadruplex DNA has been used extensively as a peroxidase, and has found applications as, for example, sensors. Sen and co-workers reported that DNA and RNA quadruplexes binding heme, are also efficient catalysts for oxygen transfer reactions such as the sulfoxidation of thioanisole, the oxidation of indole and the epoxidation of styrene [27].

In a study on the oxo-hydroxo tautomerism of Mn (III) tetra-(N-methyl-4-pyridyl)porphyrin) (TMPyP4) complexes, Pratviel and co-workers showed that Mn(III)TMPyP4 bound to DNA G-quadruplexes are capable of catalyzing epoxidation reactions, albeit that the activity was strongly reduced compared to Mn(III)-TMPyP4 alone [28].

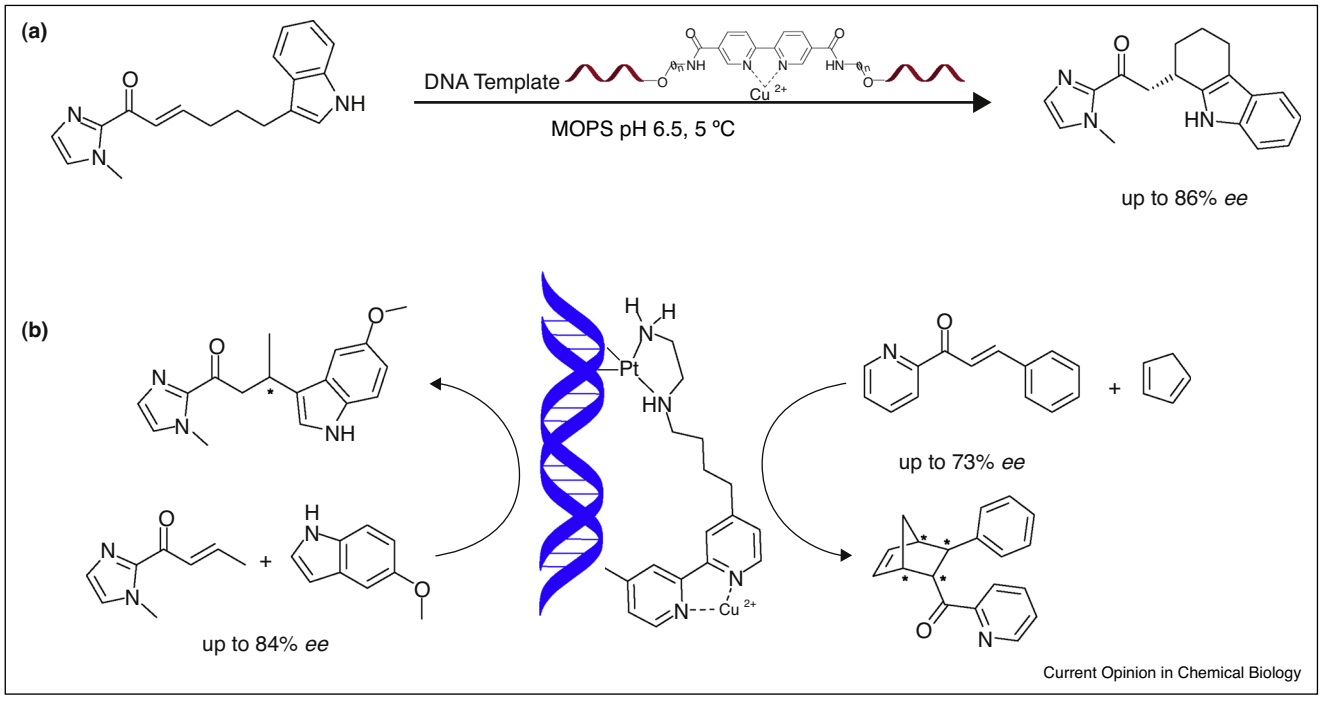
Hennecke and co-workers developed a hybrid catalyst comprising the copper(II) complex of TMPyP4 and G-quadruplex DNA (Figure 3) [29]. Depending on the sequence of the DNA, up to 68% ee was achieved in the catalyzed enantioselective Diels-Alder reactions. Nucleotide substitution experiments provided evidence for the CuTMPyP4 to be located at the 3′ face of the quadruplex and demonstrate that small changes in the residues of the G-quadruplexes can have a significant influence on the activity of the hybrid catalyst.

Figure 3



Diels–Alder reaction catalyzed by DNA G-quadruplex/copper(II)-TMPyP4 hybrid catalyst.

Figure 4



Novel covalent anchoring approaches. **(a)** DNA-based intramolecular Friedel-Crafts alkylation catalyzed by a DNA-based hybrid catalyst with intrastand ligand. **(b)** DNA-based heteronuclear (Cu–Pt) catalyst applied in the asymmetric Friedel–Crafts alkylation and Diels–Alder cycloaddition reaction.

Novel covalent anchoring approaches

Covalent anchoring of the transition metal complex to the DNA in principle allows for control over the position of the metal complex and, hence, the 2nd coordination sphere. However, covalent anchoring entails chemically modifying DNA, which can be challenging and tedious and often gives rise to limited amounts of material.

Park and Sugiyama introduced a new design in which a 2,2′-bipyridine ligand was incorporated into the DNA backbone (Figure 4a). The corresponding DNA duplex was evaluated in the catalytic asymmetric intramolecular Friedel-Crafts alkylation reaction [30•]. The catalyst was optimized by variation of the nucleotides flanking the bipyridine moiety and opposite to it in the duplex strand. The highest ee's, up to 84%, were obtained with cytosine as the counter base.

The Roelfes group introduced a novel approach to covalently linking copper(II) complexes to natural salmon testes DNA via a tethered cisplatin moiety (Figure 4b) [31]. This novel heteronuclear (Cu–Pt) catalyst was applied in the asymmetric Friedel-Crafts alkylation and a Diels Alder reaction in water, achieving high conversions and ee's up to 64% and 73%, respectively, with a low catalyst loading (8 mol%). Moreover, the catalysts was recycled 10 times without loss of selectivity or activity. This method provides easy access to DNA-based hybrid catalysts using natural DNA, albeit that there is less control over the position of anchoring due to the moderate selectivity of cisplatin DNA binding.

Conclusions and perspectives

Since the first report in 2005, the concept of DNA-based hybrid catalysis has developed from a curiosity into a promising new approach to (enantioselective) catalysis in water. This concept has been applied successfully in a number of archetypal C–C and C–O bond forming reactions, such as the copper(II) catalyzed Diels-Alder, (oxa)-Michael addition and Friedel-Crafts alkylation reactions. DNA-based catalysis is attractive for these transformations since the reactions are experimentally straightforward and the catalyst is inexpensive, especially when compared to conventional alternatives. Therefore, recent and future efforts are focussing on optimizing the design of the catalyst and further increasing the practicality of this method. This includes exploring co-solvents, additives and immobilization protocols.

While the DNA-based hybrid catalysis concept has proven to be very powerful in combination with Lewis acid catalysis, there are still not many examples of other reaction classes. The recently reported copper(I) catalyzed intramolecular cyclopropanation reaction in this

regard is a very promising development as it demonstrates that DNA-based organometallic catalysis is feasible. Further developments in this area are expected.

Finally, through spectroscopic and computational studies the first insights into the origins of DNA-induced enantioselectivity and rate accelerations in catalysis have emerged. Understanding the 2nd coordination sphere interactions that are involved in catalysis and enantioselection will be key to future designs of DNA-based catalysts for novel reactions.

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