A decade of DNA-hybrid catalysis: from innovation to comprehension

Nicolas Duchemin,[a] Isabelle Heath-Apostolopoulos,[a] Michael Smietana,[b,*] Stellios Arseniyadis[a,*]

During a bit over a decade, the unique chirality of oligonucleotides has allowed the development of a variety of asymmetric synthetic transformations. The concept lies in embedding an achiral transition metal catalyst in a DNA double helix, which provides the necessary chiral microenvironment to selectively form one enantiomer of a given reaction product. The most recent efforts to unveil new reactivities have been accompanied with the willingness to understand the mechanisms by which the chirality is transferred and the influence of the interaction between DNA and the metallic co-factor on the selectivity. By offering a complete overview of the field, this review intends to highlight the intricate correlation between the structure of the chiral bio-inorganic scaffold and its catalytic efficacy.

1. Introduction

The development of efficient catalytic systems capable of promoting asymmetric transformations is one of the corner stone of synthetic chemistry. While a plethora of catalytic enantioselective transformations have been developed over the years, most of them imply the use of usually rare and expensive metals or chiral ligands. The use of biomolecules, which exhibit an inherent chirality, has been much less exploited in the context of asymmetric catalysis. The combination of these natural chiral objects with a specific metal appears to be an appealing approach for asymmetric synthesis and bio-inspired catalysis logically became a particularly attractive tool, combining homogeneous catalysis and bio-catalysis. These bio-inspired catalysts, which exhibit a chiral micro-environment generated by the ligation of a metallic co-factor to a macromolecule, have been engaged in a wide range of enantioselective transformations.[1-10] Interestingly, most of these systems involve the use of proteins and it is only in the last decade that DNA-based asymmetric catalysis emerged as a convincing approach, taking profit of the powerful chirality imposed by the DNA double helix. Moreover, the good accessibility of various and defined structures by highly effective automated oligonucleotide synthesis processes renders the concept even more attractive.

The concept of DNA-based asymmetric catalysis was first introduced by Roelfes and Feringa in 2005.[11] It relies on the use of an achiral transition metal catalyst imbedded in the DNA double helix, which provides the necessary chiral microenvironment to selectively form one enantiomer of a given reaction product. As depicted in previous reviews in the field,[12-17] a handful of highly enantioselective catalytic transformations have been carried out successfully, while several investigations have looked into deciphering the influence on the selectivity of each parameter, in particular the influence of the oligonucleotide, its topology, or the effect of the achiral metallic co-factor. This review intends to provide a complete overview of the field with a special emphasis given to the role of the ligands, their binding modes, and the different DNA architectures that have been used so far. We believe that this approach allows one to unveil more accurately the correlation between structure and selectivity, but also pays tribute to the improvements that were made in the control and understanding of natural or synthetic oligonucleotide assemblies.

[a] Queen Mary University of London, School of Biological and Chemical Sciences, Mile End Road, London, E1 4NS, UK. E-mail: s.arseniyadis@qmul.ac.uk
[b] Institut des Biomolécules Max Mousseron, UMR 5247 CNRS, Université de Montpellier, ENSCM Place Eugène Bataillon, 34095 Montpellier, France. E-mail: michael.smietana@umontpellier.fr

2. Supramolecular approach

For a chemist seeking to use the chirality of a macromolecule to achieve an enantioselective transformation, the most straightforward approach would be to incorporate an active catalytic centre in the vicinity of the macromolecule in order to create an appropriate chiral microenvironment. In this context, Roelfes and Feringa[11] developed a supramolecular approach which relied on the assembly of a DNA duplex and an achiral catalyst. They precisely characterized the binding modes of the catalytically active complexes which allowed a classification of the ligands used in two main groups: intercalators (**L1-L10**) and groove binders (**L11-L12**),[18-19] while another class of groove binders based on the Hoechst 33258 was recently introduced by our group (**L13-L16**) (Figure 1).[20] This purely structural detail is actually of the highest importance as it defines the geometry of the catalytic pocket and therefore enantioselectivity of the reaction. This section will therefore be organized in regards to this classification.

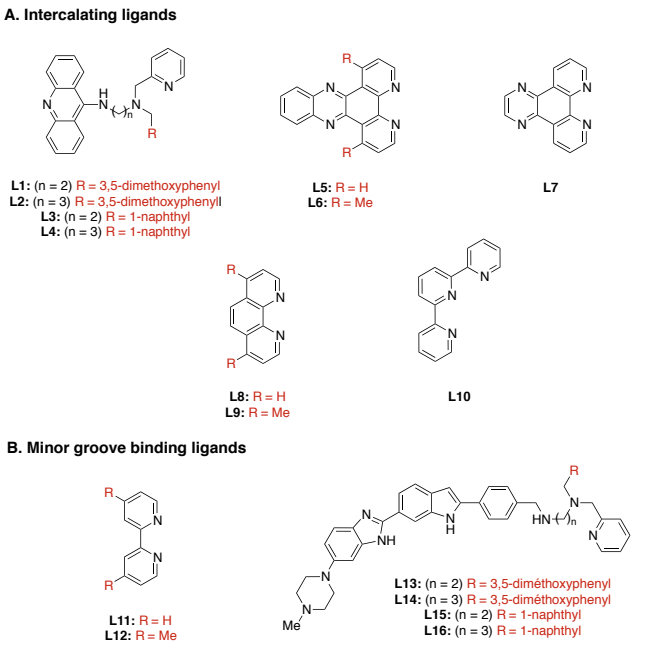
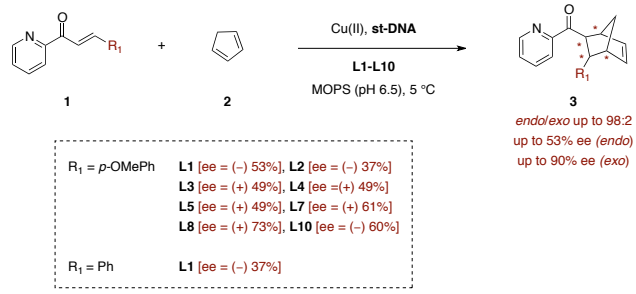


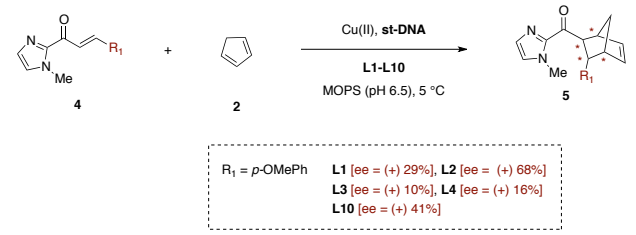
Figure 1. DNA-intercalating (**A**) or minor groove binding (**B**) ligands

2.1 Intercalative approach

The intercalation, which can be described as the positioning of the metallic co-factor between two base pairs of a duplex,[21] was the first approach envisaged in DNA-hybrid catalysis. Roelfes, Feringa and co-workers developed a copper(II)-catalysed Diels-Alder reaction between an azachalcone **1** and cyclopentadiene **2** in an aqueous media using commercially available salmon testes DNA (st-DNA) (Scheme 1).[11] The generation of the catalytically active chiral micro-environment was ensured by incorporating a copper(II)-binding site onto a spacer itself covalently bound to an acridine moiety, known to be an excellent DNA intercalating agent.[22] Various acridine-derived ligands, differing by the nature of the substituents on the ligation site or by the length of the spacer, were thus tested and some particularly encouraging enantioselectivities were achieved. Indeed, enantiomeric excesses as high as (–) 53% were obtained using the 3,5-dimethoxybenzyl-substituted ligand (**L1**) with an excellent *endo*/*exo* selectivity (up to 98:2).



Scheme 1. Diels-Alder cycloaddition between azachalcone and cyclopentadiene catalyzed by st-DNA/Cu(II)



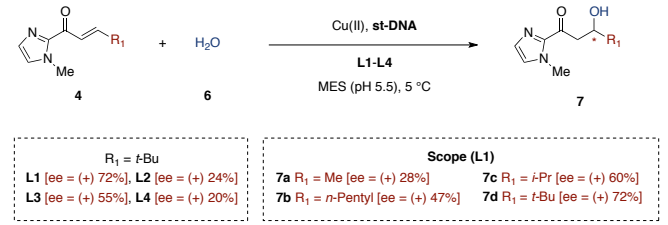
Scheme 2. Diels-Alder cycloaddition: influence of the ligands

These results were later improved by slightly modifying the structure of the dienophile. Indeed, by replacing the pyridyl group in **1** by a 2-methylimidazole and conducting the reaction under otherwise identical conditions, Boersma *et al.* were able to increase the *ee* to up to (+) 68% (Scheme 2).[23] It was demonstrated that for effective enantioselectivity, the spacer length and R_1 group (Figure 1) both played a vital role as significant *ee*s were only observed when the R_1 group was a 1-napthylmethyl or a 3,5-methoxybenzyl (**L1**-**L4**). The most effective ligands proved to be those containing arylmethyl groups supporting the idea that π-π stacking interactions occurred with the dienophile substrate.[24] The influence of the length of the spacer also highlighted the importance of the proximity to the duplex for an efficient chirality transfer onto the Diels-Alder product as a decrease in selectivity was observed when increasing the number of carbons between the acridine and the copper(II)-ligation site (**L2**, Figure 1).[11,23]

Although DNA is a powerful source of chirality, it was also found to decrease the reaction rates quite significantly.[25] This rather unfortunate discovery was counterbalanced by the observation of a strong influence of the oligonucleotidic sequence. Indeed, the chiral microenvironment created by the base pairs seams to affect the selectivity. Sequences with alternating GC base pairs were found to be the most effective, affording up to 62% *ee* with the poly(dG-dC). These results are consistent with acridine's preference for GC/CG base pairs;[26] the reaction therefore predominantly takes place within the duplex scaffold.

In a parallel study, the authors investigated the use of intercalating polypyridyl-based copper(II)-ligands on which the DNA intercalator and metal-binding moiety are combined into one (**L5**-**L10**).[27] Remarkably, for this class of ligand, a reverse correlation between binding affinity and the selectivity outcome was observed. Through the lens of this review, this particularity is actually of the highest importance as it seems to imply that the intercalative approach is not necessarily appropriate for the design of robust and efficient catalytic pockets. However, high selectivities could be achieved using these derivatives, with *ee*s up to (+) 73% (**L8**) (Scheme 2).[28]

Intercalating ligands were also applied to other copper(II)-catalysed reactions. The groups of Roelfes and Feringa first reported the DNA-mediated enatioselective *syn*-hydration of acylimidazole derivatives such as **4**, unprecedented in asymmetric catalysis (Scheme 3).[29] With acridine-based copper(II)-ligands (**L1**-**L4**), the reaction afforded extremely encouraging selectivities [*ee* up to (+) 72% with **L1**]. It is worth noting that the hydration reaction is reversible, making the selectivity strongly dependent on both the conversion and the ability of the reaction to occur outside the DNA-scaffold.

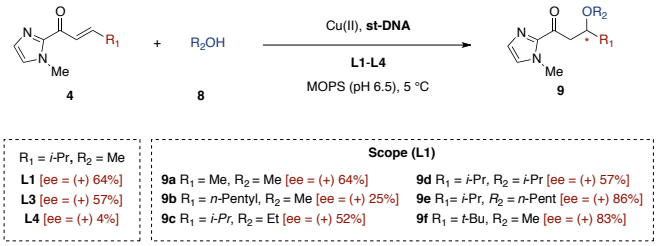


Scheme 3. *syn*-Hydration of acylimidazoles

A detailed analysis set the optimal reaction time to 24 hours, after which epimerisation occured although conversion kept increasing. A deeper investigation of the enantioselectivity outcome of the reaction was later conducted.[30] Mechanistically, the hydration was found to be strongly differing from the Diels-Alder reaction. Indeed, the use of water as nucleophile and its presence in the DNA solvation sphere completely changed the story, and it was demonstrated that for the reaction to occur with high levels of enantioselectivity, the metal co-factor had to be correctly positioned in the proximity of water molecules composing the hydration layer of the grooves. The hydration method was later applied to a one pot TEMPO-mediated oxidation/enantioselective hydration cascade.[31] Although only modest enantioselectivities were obtained, this proved DNA-mediated catalysis could easily be implemented in cascade processes.

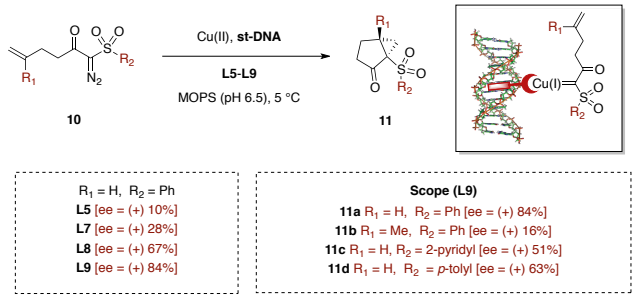
This DNA-catalysed C-O bond forming process was later applied to the oxa-Michael reactions (Scheme 4).[32] Enantioselectivities up to (+) 86% were reported using MeOH, *i*-PrOH or *n*-PrOH as nucleophiles. The latter were introduced

as co-solvents with water, which logically led to the formation of non-negligible amounts of hydration by-products.



Scheme 4. Oxa-Michael additions of acylimidazoles

In all the reactions reported so far, the metallic center was used as a Lewis acid to increase the electrophilicity of the enone. The development of an organometallic-based method involving DNA raised a certain number of questions as transition metal catalysts are usually poorly soluble or prone to degradation in aqueous media. Nevertheless, Roelfes and co-workers took advantage of the intercalative approach to develop the first example of a DNA-mediated Cu(I)-catalysed asymmetric intramolecular cyclopropanation of α-diazo-β-keto sulfones **10** (Scheme 5).[33] Through the formation of a copper-carbenoid intermediate, the mechanism leads to the cyclization on the terminal alkene and therefore requires the generation of Cu(I). This was easily achieved by reducing $Cu(NO_3)_2$ with the diazo moiety under inert atmosphere.



Scheme 5. Cu(I)-catalysed cyclopropanation

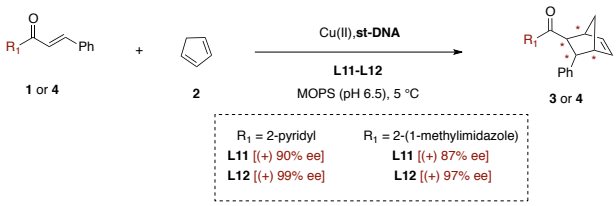
The authors also demonstrated that both the reactivity and the selectivity were intricately dependent on the presence of the bio-inorganic complex formed between DNA and the ligand (**L5**-**L9**). This study also revealed the importance of the binding affinity for the reaction outcome. Indeed, a strongly intercalating ligand such as **L9** was required to form a very stable catalytic pocket within the DNA, thus limiting the access of water molecules surrounding the substrastes. Ees as high as 86% were obtained which proved that oligonucleotide-based organometallic catalysis could be envisioned.

The intercalative approach truly initiated DNA-hybrid catalysis with the use of synthetically accessible ligands genuinely binding to DNA by intercalation between two base pairs. Various other anchorage strategies have however also been investigated such as the groove binding- and the covalent approach.

2.2 Groove binding approach

Taking advantage of the harnessing existing between oligonucleotide duplexes and ligands in asymmetric catalysis requires a clever mix between three main parameters: efficient chirality transfer, increased reactivity and duplex-ligand high affinity. The intercalating approach brought extremely satisfying results in terms of chirality transfer and diversity in catalysis. Yet, several studies showcased that reactivity and affinity weren't necessarily correlated with the highest enantioselectivities.[25,27] Although completing this triad seems highly challenging, it somehow sounds relevant to associate these three parameters to obtain efficient systems. The use of alternative binding modes was therefore envisaged to achieve this goal. Oligonucleotide duplexes present two dissymmetric grooves resulting from the association of both strands independently of the topology they adopt. In the B-type helix, the major groove is 22 Å wide and therefore easily accessible whereas the minor groove is narrower, with a 12 Å gap between successive strands. Thus, both represent interesting sites for asymmetric catalysis and were rapidly targeted.

The groove binding strategy was first envisaged with bipyridine-based ligands (**L11**-**L12,** Figure 1)[18] in the copper-catalysed reactions previously mentioned.[23,27] The use of bypiridine (**L11**) and later of 4,4'-dimethyl-2,2'-bipyridyl (dmbpy, **L12**) brought a dramatic increase in the enantioselectivity compared to the intercalative approach, with *ees* up to 99% in the Diels-Alder cycloaddition (Scheme 6). Remarkably, it was also found that the binding constants of these ligands for DNA were relatively close to those of



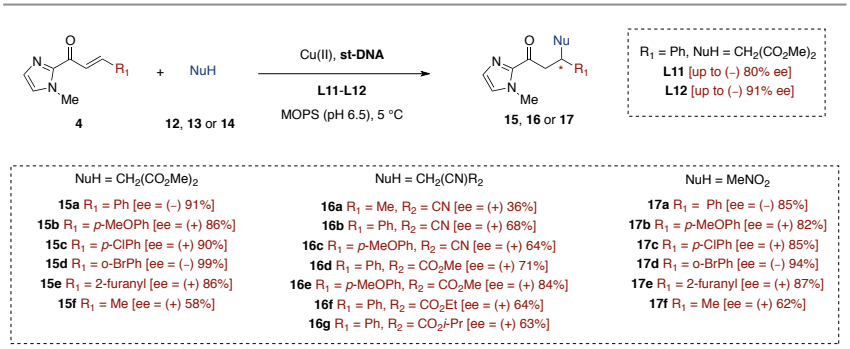
Oligonucleotide	K_b(DNA)/M^{-1}	k_{app}($M^{-1}.s^{-1}$)	*ee(%)*[a]
no DNA	-	5.05×10^{-3}	< 5
st-DNA	7.26×10^{3}	2.37×10^{-1}	(+) 98.5
$d(GCGCGCGC)_2$	9.42×10^{3}	2.98×10^{-2}	(+) 86
$d(AGGGCCCT)_2$	5.90×10^{3}	1.35×10^{-1}	(+) 97
$d(TCAGGGCCCTGA)_2$	9.59×10^{3}	5.00×10^{-1}	(+) 99.4
$d(GACTGACTAGTCAGTC)_2$	9.55×10^{3}	4.44×10^{-2}	(+) 78

R_1 = 2-(1-methylimidazole)

Scheme 6. Diels-Alder cycloaddition: influence of the ligands/sequences

acridine-based derivatives, thus ensuring a non labile interaction with the duplex.[27] The use of **L12**, the best ligand so far, was later fully investigated by Roelfes and Feringa.[34] Kinetic experiments revealed that in comparison with purely intercalative ligands, the sequence actually accelerated the reaction. In comparison with the use of $Cu(NO_3)_2$ alone, an impressive 58-fold increase in the reaction rate could be observed with st-DNA and Cu(**L12**). Therefore, in terms of reactivity and enantioselectivity, dmbpy (**L12**) rapidly appeared as the ligand of choice.

The same group later observed that a partial control of the enantioselectivity outcome was possible with ligands such as **L5-L10**.[28] Indeed, when using terpyridine-type ligands (**L10**) Roelfes, Feringa and co-workers observed an inversion of the selectivity obtained with bipyridine-type ligands **L11** and **L12**. This study clearly illustrates the fundamental importance of the binding mode between the metallic co-factor and the oligonucleotide duplex. The selectivity was once again found to be sequence-dependent. However, a different trend was observed for bipyridine-based ligands. With **L12**, the reaction reached 99.4% *ee* with the 12-mer oligonucleotide sequence d(TCAGGGCCCTGA)$_2$, as opposed to the preferred 16-mer sequence d(GACTGACTAGTCAGTC)$_2$ for the intercalative binding mode (Scheme 6). In addition to the high enantioselectivity achieved with this DNA sequence, the rate was also accelerated, twice as fast as the same reaction with st-DNA and 100-fold increase in comparison to the catalysis in the absence of DNA.



Scheme 7. Michael additions on acylimidazoles

The compatibility of the Diels-Alder reaction in organic co-solvent was rapidly investigated.[35] As a general trend, the reactions were most resilient to water-miscible organic solvents such as MeCN, alcohols, DMSO or DMF and could handle up to 33% v/v of the organic co-solvent without any noticeable loss in selectivity. Water non-miscible solvents such as CH_2Cl_2, ended up reducing both the *ee* and the conversion, likely due to precipitation of the DNA. Any increase in the concentration beyond this value led to a gradual decrease in selectivity and reaction rate. A non negligible drop in $K_{B(DNA)}$ (ligand binding constant to DNA) was concomitantly observed at >10% v/v of organic solvent. Base pair sequence and structure of the complex matter to the *ee*, as described earlier. Thus, a slight change in the structure of the DNA can lead to partial precipitation, which in turn can hamper the selectivity. Also, as the reaction is accelerated by the presence of water due to the hydrophobic effect, the gradual decrease in water content leads to a logical drop in rates. Nevertheless, the negligible influence on the enantioselectivity of high concentrations of organic solvents allows one to imagine a broader range of potential substrates for the different reactions developed.

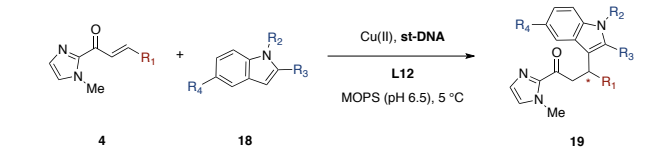
Along with the Diels-Alder reaction, several copper-catalysed C-C bond-forming reactions were developed using the highly efficient groove binding interaction. The Michael reaction – conjugate addition of a carbon nucleophile, in the form of an enolate, to an electron deficient carbon – was the first to draw the attention of the community. However, while highly enantioselective non DNA-catalysed Diels-Alder reactions are well reported in the literature,[36-39] only rare examples with significant selectivities were obtained in transition-metal catalysed Michael additions in water (up to 86% *ee*).[40] Yet, DNA-based catalysis rapidly enabled extremely appealing enantioselectivities for the Michael additions of both dimethyl malonate **12** and nitromethane **14** to α,β-unsaturated 2-acylimidazoles **4** (Scheme 7).[41] Unsurprisingly, **L12** was found to be the most effective ligand, affording up to 92% *ee* and 85% *ee* for dimethyl malonate **12** and nitromethane **14** respectively. Also, as expected for bipyridine-based groove binding ligands, the presence of DNA was shown to accelerate the reaction with conversions dropping from ≥75% to 54% in the absence of DNA. Variation in the R_1 group on the electrophile significantly affected the selectivities as well, with *ees* ranging from 58% to 99%. Interestingly, in sharp contrast with the malonate addition, the lower reactivity of nitromethane was clearly showcased. The reason unfortunately remains unclear as the proximity in the pKas (13.0 and 10.3 respectively) doesn't make the enolisation process accountable for the reactivity disparity. The use of organic co-solvents was also studied for the Michael addition by Megens and Roelfes[35] who observed that the reaction was less tolerant than the Diels-Alder cycloaddition to high concentrations of organic solvents as a decrease in selectivity starts to appear beyond 10% v/v. However, the reactivity was proved to be positively impacted with a general increase in conversion due to an acceleration of the dissociation step. Later, Zhao and co-workers took interest in the use of ionic solvents and glymes as alternative co-solvents in catalysis.[42]

Through a very detailed study, the authors observed that additions of glymes, glycols, deep eutectic solvents or ionic liquids in reasonable amounts had a negligible influence on the structure of the double stranded DNA and could also, in some cases, positively impact the enantioselectivity outcome of the reactions. High selectivities were indeed obtained for a wide range of substrates (up to >99% *ee*) with a 0.4 M concentration of glycerol. Moreover, the introduction of these co-solvents allowed to conduct the Michael additions at higher temperatures and thus drastically reduce the reaction times.

More recently, the group of Li reported a complementary study on DNA-mediated Michael additions using a groove binding approach.[43] With the aim of widening the class of useable nucleophiles, the authors took interest in the conjugate addition of malonitrile and various cyanoacetates on α,β-unsaturated 2-acylimidazoles **4** using the same conditions previously evoked (Scheme 7). These nucleophiles proved to be compatible with the reaction, with both good reactivities and selectivities (up to 84% *ee*). Only very moderate diastereoselectivity could unfortunately be observed. Interestingly, it was observed that the use of electron-withdrawing groups (such as *p*- or *o*-bromophenyl) on the electrophile was detrimental for the enantioselectivity when malonitrile was used as the nucleophile. This selectivity discrepancy was not observed by the group of Roelfes with the addition of dimethyl malonate **12** and nitromethane **14**. On the other hand, the addition of unsymmetrical cyanoacetates (**13b-d**) was proved to be less affected by the electrophile structure. Nonetheless, an increase in the size of the ester group ultimately led to a loss in enantioselectivities.

The Friedel-Crafts alkylation – addition of a heteroaromatic nucleophile to an activated electrophile – also met a frank success in DNA-hybrid catalysis. Interestingly, the reaction typically requires the absence of water, which truly makes it challenging to adapt to oligonucleotide-mediated catalysis. Nevertheless, several examples proved that the use of Lewis

acids as catalysts could increase the tolerance of the reaction for aqueous media.[44] The first enantioselective Friedel-Crafts alkylation with alkenes was achieved with a copper(II) complex.[45] In a similar approach to the Diels-Alder reaction, Roelfes and Feringa were able to develop a highly enantioselective Friedel-Crafts alkylation using α,β-unsaturated 2-acyl imidazoles **4** and diversely substituted indoles **18** (Scheme 8).[46] After screening a variety of ligands, the groove binding dmbpy (**L12**) led to the best results, with full conversions and up to 83% *ee*. The reaction proved to be compatible with a wide variety of indoles albeit aryl-substituted α,β-unsaturated 2-acyl imidazoles showcased lower reactivities than their alkyl analogues. By analogy with the Diels-Alder reaction, a strong influence of the sequence was observed; while AT-rich sequences lead to disappointing results, GC-centered short oligonucleotides afforded the best *ee*s. A complete scope of the reaction was conducted with $d(TCAGGGCCCTGA)_2$ and allowed good selectivities ranging from 69% to 93% *ee* (Scheme 8). Interestingly, this exact same sequence was also preferred in the Diels-Alder reaction.



4 18 19

19a R_1 = Me, R_2 = H, R_3 = H, R_4 = MeO [ee = (+) 83%]
19b R_1 = Me, R_2 = H, R_3 = H, R_4 = H [ee = (+) 72%]
19c R_1 = Me, R_2 = H, R_3 = H, R_4 = Cl [ee = (+) 72%]
19d R_1 = Me, R_2 = Me, R_3 = H, R_4 = H [ee = (–) 79%]
19e R_1 = Me, R_2 = H, R_3 = Me, R_4 = H [ee = (–) 81%]
19f R_1 = Ph, R_2 = H, R_3 = Me, R_4 = H [ee = (+) 75%]
19g R_1 = *o*-BrPh, R_2 = Me, R_3 = H, R_4 = H [ee = (+) 79%]
19h R_1 = *p*-MeOPh, R_2 = H, R_3 = H, R_4 = MeO [ee = (+) 69%]
19i R_1 = *p*-ClPh, R_2 = H, R_3 = H, R_4 = MeO [ee = (+) 79%]
19j R_1 = *n*-Pentyl, R_2 = Me, R_3 = H, R_4 = H [ee = (+) 76%]

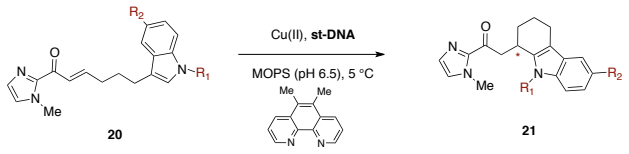
R_1 = Me, R_2 = R_3 = H, R_4 = MeO
st-DNA [ee = (+) 83% ee]
$d(ATATATATATAT)_2$ [ee = (+) 35% ee]
$d(TCAGTGCACTGA)_2$ [ee = (+) 63% ee]
$d(TCAGGGCCCTGA)_2$ [ee = (+) 93% ee]

Scheme 8. Friedel-Crafts alkylation between α,β-unsatured acylimidazoles and indoles

In a kinetic study around the Friedel-Crafts alkylation and the Michael addition, the data made evident that DNA, once again, increased the reactivity.[47] A 30-fold increase in the reaction rate was indeed measured in the presence of DNA. Yet surprisingly, the value of the constant characterizing the association between DNA and the metallic co-factor showed that only 16% of the complex was bound to the duplex. Nevertheless, an excellent selectivity was observed, which confirmed that the reaction rate was increased by the presence of the DNA, as an unbound free catalyst would catalyse the reaction in a racemic fashion. In other words, the DNA-bound catalyst is solely responsible of the selectivity.

The co-solvent compatibility was also studied and showed a satisfying tolerance of the reaction to various organic solvents,[35] with this time a decrease of the selectivity beyond 10% v/v. Attempts to increase the *ees* by lowering the temperature was also shown possible with co-solvents such as MeOH, EtOH, DMF, DMSO and 1,4-dioxane. Indeed, at 4 °C and –18 °C, the enantioselectivity of the Friedel-Crafts alkylation increased up to 90% with every solvent except EtOH and 1,4-dioxane, albeit with a mild decrease in the conversion. These results are particularly interesting as they represent the highest levels of enantioselectivity ever achieved so far for Friedel-Crafts alkylations with DNA.[46]

An intramolecular Friedel-Crafts alkylation was also reported by Sugiyama and co-workers (Scheme 9).[48] The reaction involved the cyclization of diversely functionalized fused indole-imidazoles **20** catalysed by Cu(II) complex in the presence of st-DNA or selected sequences, with up to 82% *ee* obtained using $d(TGTGTGCACACA)_2$. The sequence dependency was this time proven to differ from the classic intermolecular approach. Although the difference can be attributed to the reaction itself, the use of an intercalating ligand, 5,6-dimethylphenanthroline **L17**, instead of the usual **L12** used in the groove binding strategy may be the reason of such disparities. Once again this example confirms the clear influences of the binding mode topology, logically differing from one co-factor to another, on the chirality transfer. This latter characteristic was recently investigated theoretically by Morokuma and co-workers. A detailed analysis of the possible interactions between the metallic co-factor and a chosen sequence allowed to enlighten the most favoured conformation, leading to the formation of the *(S)*-enantiomer.[49]



20 21

21a R_1 = H, R_2 = H [ee = (+) 71%]
21b R_1 = H, R_2 = F [ee = (+) 70%]
21c R_1 = H, R_2 = Br [ee = (+) 77%]
21d R_1 = H, R_2 = OMe [ee = (+) 78%]
21e R_1 = Me, R_2 = H [ee = (+) 7%]
21f R_1 = Bn, R_2 = H [ee = (+) 4%]

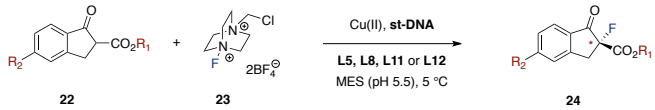
R_1 = H, R_2 = OMe
st-DNA [ee = (+) 78% ee]
$d(TGTGTGCACACA)_2$ [ee = (+) 82% ee]

Scheme 9. Intramolecular Friedel-Crafts alkylation

Recently, Roelfes and co-workers enriched the scope of the Friedel-Crafts alkylation using 2-methyl-1-(thiazol-2-yl)prop-2-en-1-one as electrophile.[50] This rather interesting structural change allowed to obtain a tertiary carbon center at the β position upon addition of various indoles and and subsequent reprotonation. **L12** still afforded the best results with *ee*s as high as 84%. Interestingly, the system was proven to afford the highest rate increase ever reported (up to 990-fold acceleration). The study indeed revealed that DNA is generally behaving like a micelle, binding the different substrates and therefore increasing the effective concentration in the vicinity of the oligonucleotide. However, the authors insisted on the fact that the binding affinity had to remain moderate in order to avoid any kind of inhibition caused by a high affinity of the reactants or products for the scaffold. Once again, this study clearly underlines the crucial importance of the dynamics and structural assets of the bio-hybrid catalyst for both the enantioselectivity and the reactivity.

Our group recently took interest in the use of copper-catalysed Friedel-Crafts alkylations to translate DNA-mediated catalysis, and especially the groove binding strategy, to RNA.[51] In an approach consisting in using selected short double stranded RNA sequences as chiral templates, we observed good reactivities albeit only moderate selectivities [up to (+) 54% *ee*]. Although a non-negligible decrease in the *ee* was observed when comparing the results to the ones obtained with DNA, this study underlined the possibility of using short RNA sequences in asymmetric catalysis rather than natural or synthetic ribozymes.[52-63] The latter were indeed used in a wide panel of reactions, but their structure and topology make them difficult to access synthetically. On the other hand, the results made clear that canonical double stranded architectures could lead to encouraging selectivities.

Several other transformations were developed by making use of the groove binding strategy and confirmed the applicability of this mode of interaction. Toru and co-workers, for instance, reported an early study on an enantioselective DNA-mediated fluorination reaction (Scheme 10).[64] Although this investigation has often been overshadowed by the simultaneous development of DNA-mediated C-C bond forming reactions by Roelfes and Feringa, it still represents the only example of C-F bond forming reaction in the domain. The authors were able to catalyse the fluorination of indanone carboxylates **22** with Selectfluor™ **23** with the groove binding complex Cu(**L12**). The mechanism proceeds *via* an enolate intermediate, which adopts a transition state resembling a distorted square planar conformation, in which the Cu(II) coordinates to the ligand and also chelates to the two carbonyl oxygen atoms. The efficacy of **L12** was rapidly observed and led to a wide range of enantioselectivities, from a moderate (+) 16% *ee* to a comparatively impressive (+) 74% *ee*, depending on the size of the ester moiety.



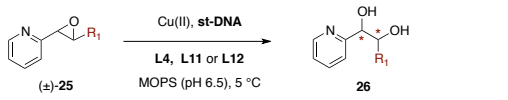
Scope (L12)

24a R_1 = Me, R_2 = H [ee = (+) 47%]
24b R_1 = Bn, R_2 = H [ee = (+) 24%]
24c R_1 = Et, R_2 = H [ee = (+) 54%]
24d R_1 = *i*-Pr, R_2 = H [ee = (+) 70%]
24e R_1 = *t*-Bu, R_2 = H [ee = (+) 74%]
24f R_1 = Me, R_2 = Br [ee = (+) 22%]

R_1 = Me, R_2 = H
L5 [up to (+) 12% ee]
L8 [up to (+) 14% ee]
L11 [up to (+) 28% ee]
L12 [up to (+) 47% ee]

Scheme 10. Fluoration of indanones

Roughly at the same time, Roelfes and co-workers took interest in yet another reaction: the DNA-based hydrolytic kinetic resolution of pyridyloxiranes **25** (Scheme 11).[65] Although the selectivities remained low (up to 63% *ee* at 74% conversion, *s* = 2.7), this study confirmed the potency of DNA in highly valuable transformations.



Scope (L12)

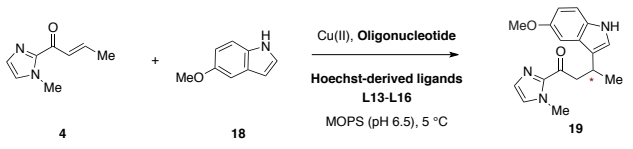
26a R_1 = H [up to (+) 10% ee, *s* = 1.5]
26b R_1 = Ph (*trans*) [up to (+) 63% ee, *s* = 2.7]
26c R_1 = Ph (*cis*) [up to (+) 4% ee, *s* = 1.2]
26d R_1 = *p*-MeOPh [up to (+) 7% ee, *s* = 1.2]

R_1 = Ph (*trans*)
L4 [up to (+) 12% ee, *s* = 1.1]
L11 [up to (+) 21% ee, *s* = 1.9]
L12 [up to (+) 63% ee, *s* = 2.7]

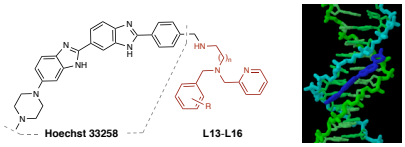
Scheme 11. Kinetic resolution of epoxides

As we clearly stated all along this section, the minor groove binding anchorage strategy allowed the development of highly enantioselective transformations. It is however worth to note that the precise characterization of the interaction existing between bipyridine-type ligands and the double strand has only been reported in 2015, nearly ten years after their introduction in DNA-mediated catalysis.[18] Consequently, the whole development of the strategy was conducted without a clear view of its intrinsic mechanism.

Lately, our group opted for a more rational minor groove anchorage approach.[20] Indeed, we envisaged the use of a new class of copper(II)-ligands (**L13**-**16**) based on the well-known minor groove binder Hoechst 33258. The idea was to develop sequence-specific targeted reactions (Scheme 12). A set of diversely substituted Hoechst 33258-derived ligands were therefore prepared before a complete spectroscopic characterization of the interaction between the ligands and selected oligonucleotides, followed by a molecular docking study was undertaken in order to ensure the minor groove binding anchorage mode. The screening of the ligands over various sequences allowed a clear determination of the short binding sites preferentially selected by the ligands. Their use in copper(II)-catalysed Friedel-Crafts alkylations showed an apparent correlation between their selectivity for the sequences and the enantioselectivity outcome. Although the selectivities remained rather moderate [up to (+) 47% *ee*], the use of Hoechst-derived ligands and their sequence specific targeting capabilities clearly offers compartmentalisation possibilities.



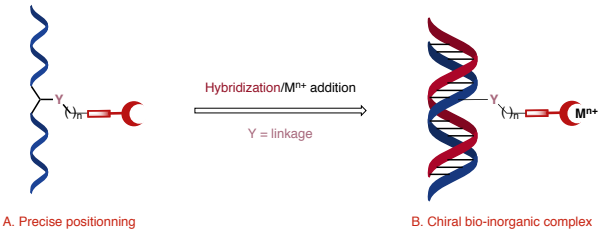
Oligonucleotide	L14	L16
ct-DNA	(+) 29% ee (K_a = 3.24 10^6 M^{-1})	(+) 47% ee (K_a = 2.40 10^6 M^{-1})
5'-d(CGAATTCGTTTTCGAATTCG)-3'	(–) 16% ee	(–) 26% ee
5'-d(CGTATACGTTTTCGTATACG)-3'	(–) 19% ee	(–) 23% ee



Scheme 12. Friedel-Crafts alkylation using Hoechst-derived ligands **L13-16**

3. Covalent approach

The supramolecular approach in DNA-based asymmetric catalysis has encountered a rapid success. As we stated in the previous section, both intercalation and groove binding modes allowed to unveil the power of oligonucleotides as easily accessible chiral scaffolds with seducing synthetic applications. But there is somehow a certain lack of completeness in this approach. Indeed, numerous studies have pointed out the influence of the sequence (length, nature or base content) on the selectivity and offered a first insight on the mechanism occurring during the chirality transfer. However, none of the intercalating or groove binding ligands used in the supramolecular approach present a sufficient affinity for specific sites to ensure a well defined positioning of the metallic co-factor. To address this site-selectivity matter, a more pragmatic or perhaps biased approach was to covalently attach the ligand onto a specific position and therefore develop oligonucleotide-conjugates for asymmetric catalysis purposes (Scheme 13).

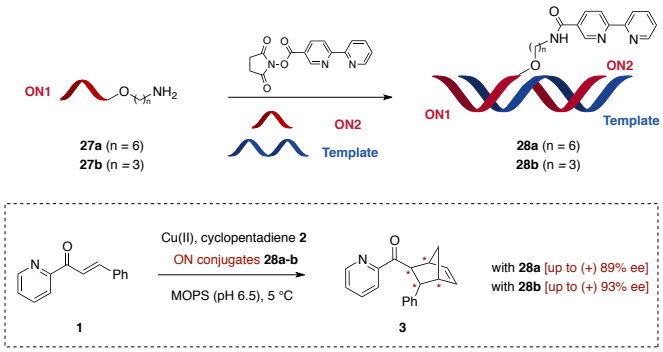


Scheme 13. Covalent attachment strategy

A covalent attachment allows the enforced generation of a chiral micro-environment, where the ligand is constrained in the helix or in its closest vicinity. Also, a covalent ligation strategy offers the possibility to control the exact location of the ligand and therefore, study the influence of the flanking or opposite bases by varying its position in the oligonucleotide (ON) sequence. Although the process of covalent anchorage to oligonucleotide can be seen as more time-consuming or complex, numerous methods have been developed to envisage direct and easy modifications of oligonucleotides.[66] This approach was eventually applied to various synthetic transformations, which will be reported in the following sections according to the type of metal used.[67-72]

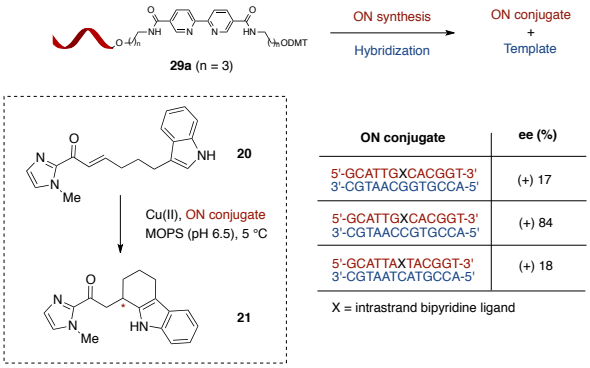
3.1 Cu(II)-catalysis

The excellent results reported with copper-catalysed reactions using the supramolecular assembly strategy encouraged several groups to turn their attention on the use of ON conjugates in asymmetric catalysis. Roelfes and co-workers first developed the concept with Diels-Alder cycloadditions,[73] using a ON conjugate formed by the covalent assembly between an NHS-activated bypiridine ester and 5'-amino-modified ON **27a**-**b** (Scheme 14). This ligand-bearing ON strand was then hybridized by combination with another ON strand (**ON2**) and a template strand complementary to both, to afford the duplexes **28a-b**, positioning the transition metal in between the **ON1** and **ON2** termini. Using this three-partner strategy, the environment surrounding the metallic co-factor could be modulated by simply changing **ON2** and the template strand. Using the main advantage of covalent assembly, *ie* the specific positioning of the Cu(II)/bipyridine-derived ligand complex on the ON, the authors reported extremely encouraging enantioselectivities, with *ee* up to 89% using a central positioning of the co-factor, G as flanking bases, and a complementary template. This selectivity could be increased to 93% using a shorter spacer (**28b**) showcasing the importance of the proximity to the chiral helix (Scheme 14).



Scheme 14. Single bipyridine attachment to ON, Diels-Alder cycloadditions

Another strategy was reported by the same group with a covalent anchorage of a cisplatin-derived copper ligand.[74] Although the type of attachment truly differs, the approach is structurally close to the previous one as it involves a covalent bond between the cisplatin moiety and the bases to ensure a stable anchorage to the duplex and the dangling ligand is free to interact with the duplex. Nevertheless, it is worth to note that although the cisplatin anchorage is very robust and represents a clever alternative to the supramolecular anchorage, it is unfortunately non-selective. The catalytic efficacy of the cisplatin anchorage was tested with st-DNA on the Diels-Alder cycloaddition and the Friedel-Crafts alkylation affording good selectivities (up to 73 and 64% *ee* respectively) though lower than those obtained with the supramolecular approach. Nevertheless, the major advance of the study was truly the possibility to covalently attach a metallic co-factor to a DNA scaffold and ensure its complete non-lability. Such stability is of course unreachable with the supramolecular approach.



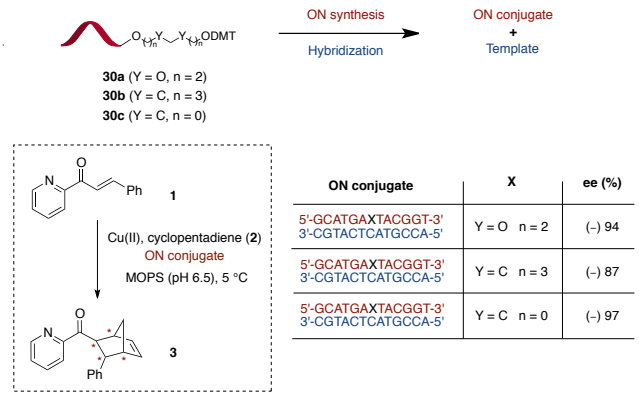
Scheme 15. Double bipyridine attachment to ON, intramolecular Friedel-Crafts alkylations

More recently, Sugiyama and co-workers developed another type of covalent anchorage consisting in the double attachment of a bipyridine derivative in 13-mer sequences as a base surrogate. These bioconjugates were eventually used in an intramolecular Friedel-Crafts alkylation after hybridization (Scheme 15).[75] An interesting screening of the counter base showed that the use of pyrimidines (C and T), smaller in size, was more favourable than the use of purines (A and G). Flanking bases showed a great influence as the use of G and C lead to a high selectivity (up to 84% *ee*) whereas A and T caused a dramatic decrease in the *ee*. The authors also conducted a complete model study to rationalise the oligonucleotide conjugates used in catalysis. They confirmed that the use of cytosine as the nucleic base facing the modification lead to the highest selectivities.

The direct incorporation of the metallic co-factor in the heart of the duplex was also investigated with other types of ligands. Hence, in 2015, Carrell's group envisioned the introduction of pyrazoles or salen as metal coordinating base pair surrogates to form a duplex stabilized by several copper complexations.[76] The coordination was studied with CD and UV-vis spectroscopy, which interestingly revealed the preference of the metallic center for pyrazole base pairs. An impressive increase in stability was observed upon copper addition, with melting temperatures (T_m) rising from 38 °C to 70 °C after only one ionic coordination. These different structures were later tested in the context of asymmetric catalysis with a model Diels-Alder cycloaddition. A rate-

acceleration was clearly observed but only modest selectivities were obtained (up to 39% *ee*). Interestingly, a rather counter-intuitive pH influence was unveiled with a progressive decrease in both selectivity and reactivity upon medium basification although the copper complexation is logically eased at higher pH. Other parameters, such as the variation of the duplex structure also need to be taken into account, nonetheless, this system did prove its efficacy in catalysis.

In a recent study, Park *et al.* promoted the concept of ligandoside approach, with the design of ligand-free catalysis.[77] They envisioned the use of hybrid cytosine/flexible linkers base pairs as coordination sites for copper(II) and observed excellent results in catalysis (Scheme 16). With a facing glycol base surrogate (from **30a**), the surrounding flanking bases proved to have a non-negligible influence on the selectivity of the site. Using the Diels-Alder cycloaddition as the model reaction, a wide range of *ees* were obtained, from (–) 13% using G as flanking bases to (–) 94% with T and A surrounding the spacer. This latter result was increased to (–) 97% when the linker was replaced by a propyl base surrogate (from **30c**). Relatively close selectivities were observed when a scope of the reaction was conducted, strengthening the idea that native DNA structures can exhibit catalytic activities.

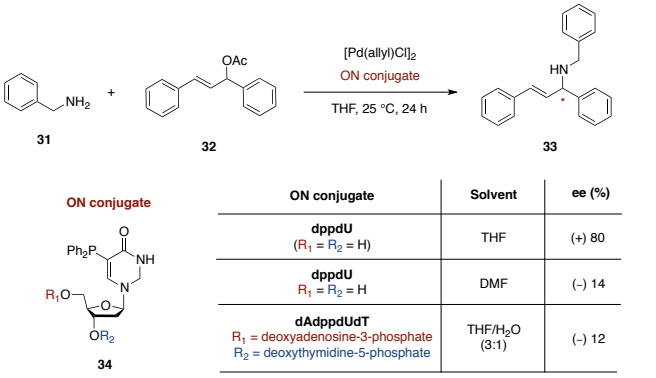


Scheme 16. Ligand-free approach, Diels-Alder cycloaddition

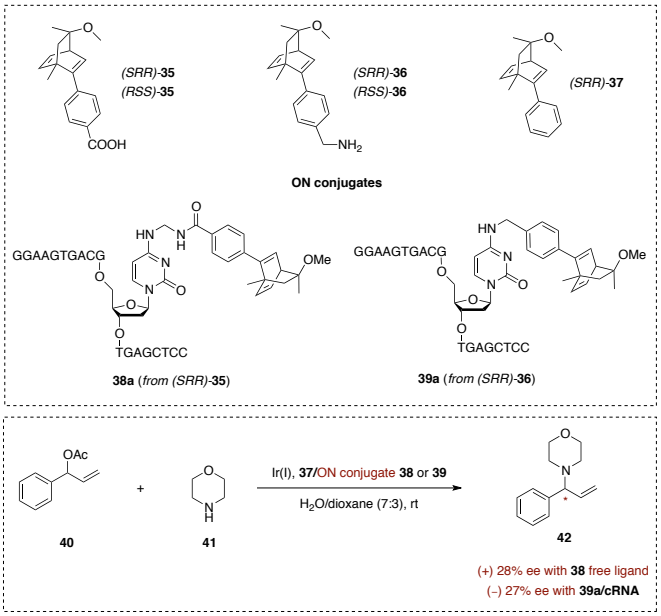
3.2 Pd and Ir-catalysed allylic aminations

The covalent approach also allowed to use new metals in DNA-mediated catalysis. The easy modification of oligonucleotides can indeed lead to the covalent attachment of non-DNA binding ligands and ensures their positioning in the close proximity of the duplex. The palladium-catalysed allylic amination was the first example of covalent assembly of the ligand to ON in DNA-based catalysis (Scheme 17).[78] The ON conjugate catalyst was obtained by functionalization of readily available 5-iodo-2'-deoxyuridine (IdU)-containing sequence to form the corresponding diphenylphosphine derivative **34**. The palladium bio-inorganic complexes were then generated using $[Pd(allyl)Cl_2]$ after duplex formation to catalyse the allylic amination between benzylamine **31** and 1,3-diphenyl-2-propenyl acetate **32** in THF (Scheme 17). High *ees* were reported (up to 80%) as well as an interesting solvent-dependent inversion of selectivity. Nevertheless, no real rationalization was suggested.

A rather similar approach was later envisaged by Jäschke and co-workers for the DNA-mediated Ir(I)-catalysed allylic amination of allyl acetate.[79] The authors developed a ON conjugate-diene-iridium(I) complex and evaluated its catalytic activity (Scheme 18). The ON strand was functionalised by a diene ligand and then hybridized with a complementary DNA or RNA strand. Both isomers of the chiral diene ligand were used in order to access either enantiomer. The functionalization was possible using commercially available 4-triazolyl-deoxyuridine. Post-synthetic conjugation with either **35** or **36** lead to the formation of the Ir(I) complexes which were eventually evaluated.



Scheme 17. Allylic amination of 1,3-diphenyl-2-propenyle acetate by benzylamine



Scheme 18. Structure of Ir(I)-ligands and 4-triazolyl-deoxyuridine functionalization

Interestingly, the non-hybridized ON conjugates afforded the same *ee* as the free ligand **37** (up to 23% *ee*), but upon addition of the complementary strand, the selectivity dramatically changed, with a general inversion in the *ees*, therefore proving that the duplex was sterically constraining the substrates. Unfortunately, only moderate chiral inductions were reported, the best *ee* being (–) 27% using RNA as the complementary sequence. Nevertheless, the striking inversion of selectivity between single and double strands once again proved that DNA and RNA could truly act as templates for asymmetric catalysis.

These last examples showcased several advantages of ON conjugates in catalysis, in particular the complete control of the positioning of the metallic co-factor. Moreover, the influence of other varying parameters such as the opposite or

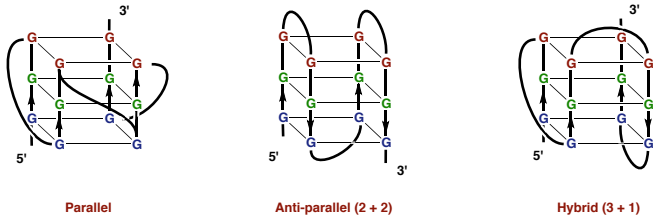
flanking bases can be easily evaluated which is a clear advantage over the supramoecular approach.

4. Non-canonical DNA structures

The previous sections demonstrated that DNA-duplexes could act as extremely efficient chiral templates for various types of metal-catalysed transformations. Although the duplex structure was established to be compulsory to attain satisfying levels of selectivity, single-stranded DNA catalysis did lead to some enantioselectivity.[34,46,76,79] The chirality of the duplex is actually insured by the ribose itself, which leads to the conclusion that any oligonucleotide-based secondary or tertiary structure, natural or synthetic, is chiral and can therefore be used in asymmetric catalysis. Considerable efforts have recently been devoted to the development and understanding of non-canonical scaffolds for catalysis, and very diverse applications were identified. Considering the great manoeuvrability of oligonucleotides, these structures are countless but a few were actually investigated. Natural assemblies, such as G-quadruplex, or synthetic, such as mirror-image or supported-DNA, led to very interesting results and therefore deserve careful examination.

4.1 G-quadruplex DNA in asymmetric catalysis

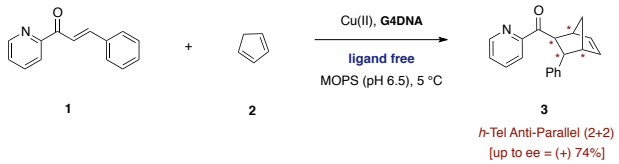
Unlike hybrids, such as DNA-RNA duplexes, which were not intensively evaluated,[79] G-quadruplexes recently met a growing success in catalysis, after being first wrongly considered as simple curiosities. G-quadruplex DNA (G4DNA) is one of the alternative conformation guanine-rich DNA strands can adopt.[80] The structure consists of the Hoogsteen base pairing of four guanines on a strand to form a tetramer,[81] while the rest of the strand loops round, forming other tetramers stacking above the latter. G4DNA have been identified in G-rich eukaryotic telomeres (*h*-tel) but also in non-telomeric DNA regions (*c*-myc). According to the base pair sequence, strand length and species with which it is in solution, G4DNA can adopt different topologies: parallel, antiparallel (2+2) or hybrid (3+1) (Scheme 19).[80] This has lead several groups to evaluate these chiral and tunable structures.



Scheme 19. Usual G4DNA conformations

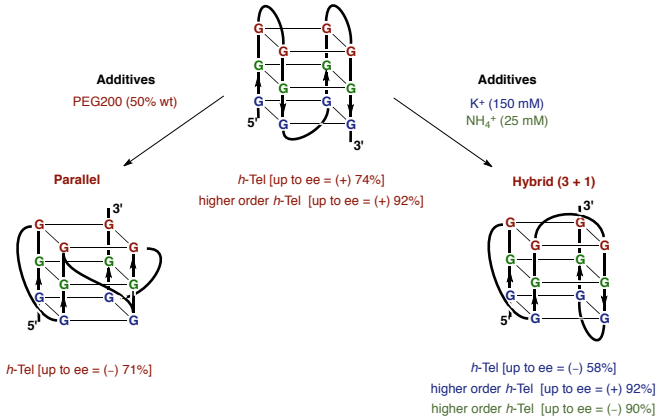
The first example of a G4DNA used as a chiral scaffold was reported by Moses and co-workers with the copper(II)-catalysed Diels-Alder reaction.[82] Using a bio-inorganic complex formed by a G4DNA scaffold of two different G-quadruplex forming sequences (*c*-kit and *h*-Tel), copper(II) and the groove binding ligand **L12**, the authors reported excellent *endo*/*exo* selectivities, up to 100:0, but moderate enantioselectivities, with *ee*s up to (–) 34%. A detailed spectroscopic study brought an interesting rational to this selectivity. Indeed, CD experiments made plain that various conformations of *h*-Tel were actually present in solution. Upon addition of the ligand, negligible changes in CD-spectra and thermal stabilities were observed, proving that no conformation was actually favoured. Two scenarios were therefore envisioned: catalysis conducted both on and off the G4DNA caused by the low binding affinity of the ligands, or the possibility that among the different conformations in solution, some may disfavour the desired enantioselection. As always, the heart of the matter seems to be residing in the control of the interaction between the chiral scaffold and the catalytically active species.

More recently, the group of Li, who rapidly became prominent in the domain, came up with several concepts which enabled to unlock the catalytic efficacy and applicability of G-quadruplexes. In two successive studies, they proved that a ligand-free approach could lead to interesting levels of selectivity in both the Diels-Alder cycloaddition and the Friedel-Crafts alkylation.[83,84] As we earlier stated with the ligandoside approach in the covalent attachment strategy, divalent cations chave a high affinity for nucleic acids. The authors therefore observed that the *h*-Tel sequence, in a specific anti-parallel conformation, could lead to very satisfying enantioselectivities even in the absence of ligands. Up to 75% *ee* could be obtained in the Friedel-Crafts alkylation and 74% *ee* in the Diels-Alder cycloaddition, while a clear increase in the reaction rates was observed in the presence of both copper(II) and G4DNA (Scheme 20).

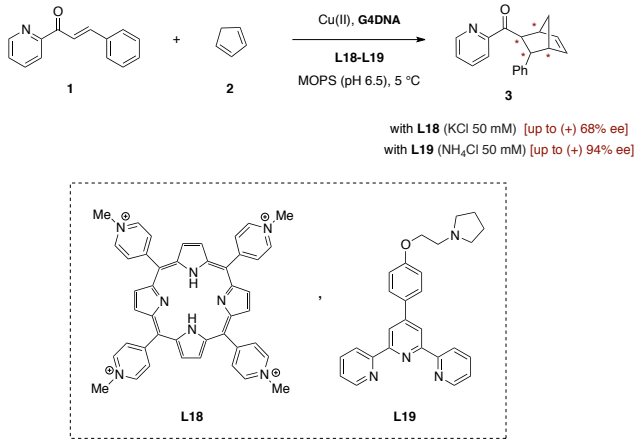


Scheme 20. *H*-Tel-mediated Diels-Alder cycloadditions

The use of a higher-order *h*-Tel sequence, which contains a greater amount of G-quartets, allowed to increase the selectivity (up to 92% *ee*) and the rate of the Diels-Alder reaction.[85] Interestingly, the architecture of the chiral scaffold was also proven to be easily tunable (Scheme 21). By first changing the sequence, a clear switch from the anti-parallel to the parallel conformation was observed in CD and correlated with a partial inversion in the enantioselectivity. The same type of phenomenon was detected upon gradual addition of NaCl, KCl or PEG200, causing dramatic changes in the conformation of the G4DNA. The compacity of the anti-parallel structure was reinforced by NaCl and reached its optimal efficacy at 50 mM for both Diels-Alder and Friedel-Crafts reactions, but a decrease in the *ee*s was observed beyond this concentration. KCl addition led to a gradual prominence of the hybrid confirmation and lower enantioselectivities. As for PEG200, molecular crowding led to the general appearance of the parallel conformations, causing loss of selectivities in the Friedel-Crafts alkylation, but inversions in *ee*s in the Diels-Alder cycloaddition [from 74% to (–) 47%]. The same group later reported the possibility to create a conformational switch in G4DNA using chosen Na^+/K^+ ratios.[86] They observed that a 100/0 mM ratio undoubtedly leads to a parallel conformation, evolving to a hybrid conformation at 50/25 mM. Although lower selectivities were obtained, this switch could once again lead to a partial inversion of the selectivity. A more efficient control of the selectivity was more recently achieved with higher order telomeric sequences using structure stabilizers



Scheme 21. Enantioselective Diels-Alder cycloaddition catalysed by higher-order h-Tel G4DNA.



Scheme 22. Supramolecular approach, application to Diels-Alder cycloadditions

such as potassium or ammonium ions.[87]

Removing the ligand parameter out of the equation therefore allows both excellent selectivities and reactivities and enables a very interesting rational to the catalytic effectiveness of the different conformations of G4DNA. However, the ligand-free approach unfortunately brings certain uncertainty on the structure and position of the catalyst in the scaffold. Hence, several studies turned their attention on the use of G4DNA-specific ligands in both supramolecular and covalent approaches.

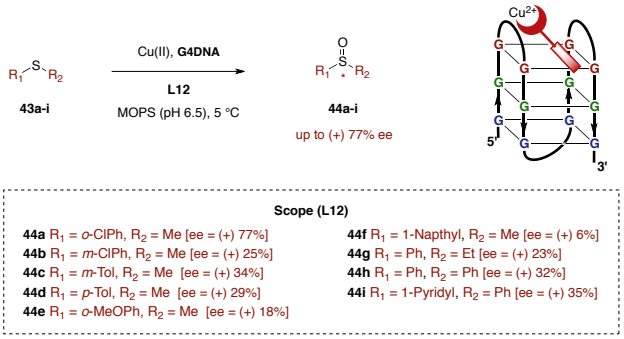
The founding work of Moses and co-workers showed that G-quadruplexes, in conjunction with bypiridine based ligands, could induce enantioselectivity in the copper-catalysed Diels-Alder cycloaddition. Michael additions were also investigated by Zhao *et al.* using a closely related approach based on bipyridine ligands.[88] Experimental parameters such as buffers, co-solvents or sonication times proved to be of the highest importance on the enantioselective outcome of the reaction. Yet once again, modest selectivities were observed and no structural comprehension seems easily reachable.

Wilking *et al.* envisioned to tackle this double issue by using known G-quadruplexes binders, cationic porphyrins **L18**, as copper ligands.[89] Their interaction with G4DNA occurs by π-stacking onto one of the two accessible G-quartet. Several cationic porphyrins were engaged in catalysis and led to encouraging enantioselectivities, as high as 56% *ee*, obtained with the Cu(**L18**) complex and *h*-Tel (Scheme 22). CD experiments once again demonstrated the great influence of sodium and potassium ions and confirmed the hybrid (3+1) as the adopted conformation. However, the sequence screening brought the most valuable information concerning the binding site of the ligands. Base substitutions on the 3'-end of the *h*-Tel-derived sequences indeed led to extremely varying selectivities whereas substitutions on the 5'-end had a limited impact. A binding on the 3'-end G-quartet was therefore logically suggested and enantiomeric excesses could be increased up to (+) 68% upon rationalized sequence optimization.

A new class of G-quartet stacking ligands was later developed by Li and co-workers for the same catalytic purpose (Scheme 22).[90] By taking advantage of the known affinity of terpyridine-metallic co-factors for G-quadruplexes, the authors were able to increase the catalytic activity of G4DNA for the Diels-Alder cycloaddition. Moreover, spectroscopic analysis (CD, UV and ITC) proved that the interaction with the chosen terpyridine-derived ligand **L19** was both stabilizing and regulating the G-quadruplex structure. The screening of various ligands later confirmed this influence, as a charged amino-alkyl side chain was shown to have a better affinity for the G-quartet. As previously stated, the selectivity could be further increased upon addition of stabilizing species such as ammonium cations, preforming and stabilizing the scaffold. A scope of the reaction was finally conducted after these optimizations and excellent enantioselectivities were observed on various substrates, with *ee*s ranging from (+) 93% to (+) 99%.

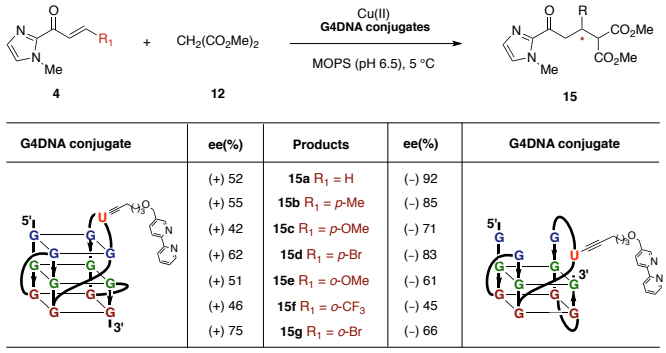
More recently, two major studies reintroduced the use of bipyridine-based ligands in order to widen the field of possibilities for G4DNA-mediated catalysis. Li and co-workers used dmbpy **L12** in a supramolecular fashion in order to develop an enantioselective sulfoxidation reaction (Scheme 23).[91] While several attempts were made to develop an asymmetric oxidation reaction with porphyrin-based ligands, no selectivity was observed. Interestingly, the use of **L12** in conjunction with a natural 21mer *h*-Tel sequence in its antiparallel stabilized conformation lead to 77% ee (Scheme 23). Yet, a pronounced substrate-specificity seems to occur (*ee*s ranging from 6% to 77%) and the observation of the very weak binding existing between the scaffold and the ligand surely keeps from having a clear view of the nature of the interaction.

To overcome this limitation, Jäschke and co-workers recently envisioned the covalent attachment of this specific ligand to the G4DNA scaffold.[92] As we previously stated, the covalent attachment is surely the best way to ensure the position of metallic co-factor and numerous studies confirmed its efficacy, especially with dmbpy **L12**. A specific type of sequence, *c*-kit wild type, was selected for its ability to adopt a parallel conformation. The introduction of the ligand was conducted by a Sonogishira coupling between bipyridine-derived alkynes and DMT-protected IdU. The corresponding amidites were then engaged in the automated synthesis of the c-kit derived sequences.



Scheme 23. G4DNA-mediated sulfoxidation reaction

By using a model copper-catalysed Michael addition on α,β-unsaturated acyl imidazoles such as **4** (Scheme 24), the authors were able to observe both good reactivities and unprecedented selectivities, with ees up to (–) 92% using an hexynyl-derived bipyridine introduced in position 10 of the c-kit. Moreover, they observed that the introduction of this modification on position 12 could lead to a very interesting reversal of selectivity to (+) 52% *ee* without any changes in the architecture of the scaffold. A complete scope of the reaction was conducted and the trend persisted, illustrating once again the importance of taming the microenvironment to improve the selectivities.

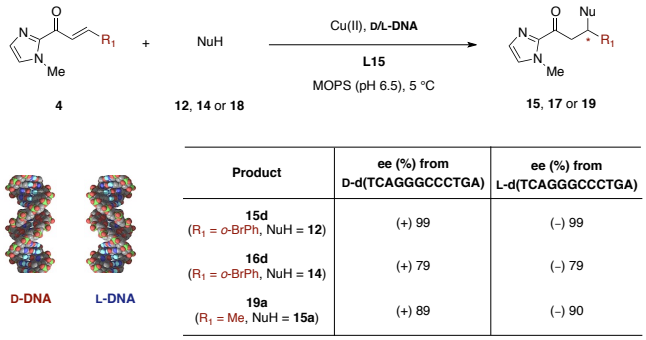


G4DNA conjugate	ee(%)	Products	ee(%)	G4DNA conjugate
	(+) 52	**15a** R_1 = H	(–) 92	
	(+) 55	**15b** R_1 = *p*-Me	(–) 85	
	(+) 42	**15c** R_1 = *p*-OMe	(–) 71	
	(+) 62	**15d** R_1 = *p*-Br	(–) 83	
	(+) 51	**15e** R_1 = *o*-OMe	(–) 61	
	(+) 46	**15f** R_1 = *o*-CF_3	(–) 45	
	(+) 75	**15g** R_1 = *o*-Br	(–) 66	

Scheme 24. Covalent approach, Michael additions of dimethyl malonate

4.2 Mirror-image DNA

A number of teams have been interested in controlling the enantioselectivity outcome of the various reactions developed so far. By varying the type of metallic co-factor, changing its position on the scaffold or tuning the conformation of the secondary structure, an inversion of the overall selectivity could be observed.[79,86,87,89,92] Nevertheless, these selectivity inversions remained reaction or substrate-specific and most of the time partial. To address this shortage, our group opted for the use of mirror-image oligonucleotides; by far the most reliable method to selectively access either enantiomer of any given reaction.[93] The mirror-image form of DNA, L-DNA is purely synthetic but possesses the same physical properties as common D-DNA.[94] The D and L equivalents of two different auto-complimentary sequences were thus prepared and evaluated (Scheme 25).



Product	ee (%) from D-d(TCAGGGCCCTGA)	ee (%) from L-d(TCAGGGCCCTGA)
15d (R_1 = *o*-BrPh, NuH = **12**)	(+) 99	(–) 99
16d (R_1 = *o*-BrPh, NuH = **14**)	(+) 79	(–) 79
19a (R_1 = Me, NuH = **15a**)	(+) 89	(–) 90

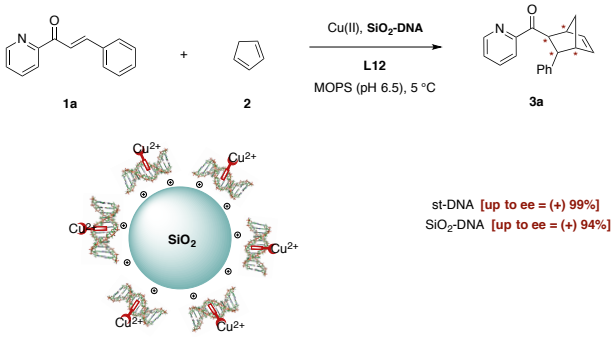
Scheme 25. Control of the stereoselectivity outcome using D- and L-DNA

Interestingly, we were able to selectively access either enantiomer by simply switching the orientation of the helix.

4.3 Solid-supported DNA

In order to increase the applicability of catalytic strategies, various paths can be explored. As far as DNA-mediated catalysis is concerned, the scalability of the reactions and reusability of the bio-inorganic complexes remained quite challenging until recently and the development of supported DNA-based catalysts. Recently, the concept has been successfully put into operation by making use of silica and cellulose as solid supports for oligonucleotides and tested in the Diels-Alder, Friedel-Crafts and Michael additions.[95,96]

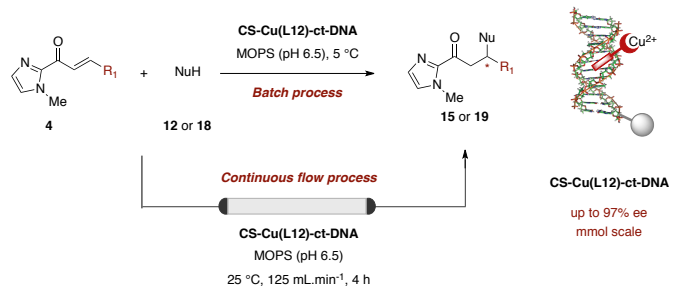
The first supported catalyst was reported by Sugiyama and co-workers and involved the immobilization of st-DNA onto ammonium-functionalised silica beads (Scheme 26).[95] Using the reported supramolecular strategy, the Diels-Alder reaction afforded an extremely satisfying 94% *ee*, comparable to the 99% *ee* achieved by the homogeneous Diels-Alder reaction. Recyclability was achieved using a rather simple washing protocol of the supported catalyst, followed by the re-addition of the metallic co-factor. Up to ten cycles could be successfully achieved using the same supported oligonucleotide with only moderate erosion of the *ee* over time.



Scheme 26. Silica-supported DNA

Our group was also involved in the development of a supported catalyst. Instead of ammonium-functionalised silica beads, we opted for cellulose supported-ct-DNA (Scheme 27).[96] The latter was tested in conjunctin with **L12** in the asymmetric Friedel-Crafts alkylation and in various Michael additions. Once again, high yields and high selectivities were obtained, while no loss in selectivity was observed after 10 runs.

We were also able to implement the method to a single-pass, continuous-flow process and for the first time perform reactions on a synthetically useful scale. The cellulose-ct-DNA-Cu(dmbpy) was simply loaded into a chromatography column, with the reagents being fed into the reaction *via* a syringe in a 30:1 MOPS buffer/MeOH solution. Using the Friedel-Crafts alkylation of 5-methoxyindole as model reaction, the concept afforded high selectivities (up to 80% *ee*) and an appealing and successful *mmol* scale protocol which is roughly a thousand times the scale typically run when using specific sequences.



Scheme 27. Cellulose-supported DNA

Conclusion & Perspectives

During the past decade, the use of oligonucleotides as a chiral framework for asymmetric transformations has met a growing success. From the pioneering work of Roefles and Feringa to the latest advances in tuning the conformation of G4DNA for the control of the selectivity, the spectrum of achievable transformations using oligonucleotides as chiral scaffolds has been tremendously broadened.

The comprehension of the binding modes of the metallic co-factor has also drawn the attention of many groups. Indeed, it rapidly became obvious that attaining the highest selectivities could only be achieved by a clear comprehension of the transfer of chirality from the oligonucleotide to the substrates, through the ligand, the key element of the chiral micro-environment. Many ligand-oriented strategies have therefore been envisaged. The supramolecular approach enabled the field to acquire its first distinctions, but was rapidly joined by the covalent strategy, which allowed, by tailoring the oligonucleotide scaffold, to gain precious insights on the positioning of the ligand and the influence of the surrounding environment. As for non-canonical structures, such as G-quadruplexes or supported-DNA, their use was proved to be extremely beneficial and appealing to achieve reactions at high levels of enantioselectivity or at synthetically relevant scales but also revealed new scaffold-ligands assemblies, showing unprecedented and useful features.

At this point, we have never been so close to unravelling a path to the perfect catalyst, simple and efficient, modular and universal. In a very recent study, Roelfes and co-workers reported a DNA-mediated carben transfer reaction,[97] making use of cationic iron porphyrin-derived complexes as metallic co-factors. Although interesting enantioselectivities were achieved, the authors highlighted another major facet of the concept. Indeed, the different porphyrin-based ligands showed wide-ranging behaviours in terms of catalytic efficacies, rightly attributed to the unique binding-modes showcased by each of these compounds. The key parameters are again eye-catching: the nature of the binding mode, the affinity for the oligonucleotide, and the proximity of the helix.

Among the large panel of metalloenzymes, oligonucleotides seem to stand out, but in order to ensure their success, the efforts now have to be carefully orchestrated. Nonethless, if the discovery of new reactions, systems, or useable topologies comes along with rational structure/selectivity correlation studies and a deeper understanding of the interactions existing between the scaffold and the ligands, the future of DNA-based asymmetric catalysis will be bright in the field of bio-hybrid catalysis. In a very recent study, Wagenknecht and co-workers enforced the applicability of DNA-based asymmetric catalysis by reporting a photocatalysed [2+2] cycloaddition using benzophenone-substituted DNA sequences.[98] Although the selectivity obtained with these chiral photoDNAzymes still remains moderate, this unprecedented methodology opens new perspectives in the field of DNA-based asymmetric catalysis.

Acknowledgements

We would like to thank the Agence Nationale de la Recherche for funding – NCiS project (ANR-2010-JCJC-715-1) and D-CYSIV project (ANR-2015-CE29-0021-01)] – as well as Dr Jean-Jacques Vasseur, Prof. Janine Cossy and NOXXON Pharma AG for their continuous support.

Notes and references

1 R. R. Davies and M. D. Distefano, *J. Am. Chem. Soc.*, 1997, **119**, 11643–11652.
2 R. S. Roy and B. Imperiali, *Protein Enginnering*, 1997, **10**, 691–698.
3 J. Collot, J. Gradinaru, N. Humbert, M. Skander, A. Zocchi and T. R. Ward, *J. Am. Chem. Soc.*, 2003, **125**, 9030–9031.
4 J. R. Carey, S. K. Ma, T. D. Pfister, D. K. Garner, H. K. Kim, J. A. Abramite, Z. Wang, Z. Guo and Y. Lu, *J. Am. Chem. Soc.*, 2004, **126**, 10812–10813.
5 C. Letondor, N. Humbert and T. R. Ward, *Proc. Natl. Acad. Sci. USA*, 2005, **102**, 4683–4687.
6 K. Okrasa and R. J. Kazlauskas, *Chem. Eur. J.*, 2006, **12**, 1587–1596.
7 M. D. Mihovilovic, *J. Chem. Technol. Biotechnol.*, 2007, **82**, 1067–1071.
8 J. Pierron, C. Malan, M. Creus, J. Gradinaru, I. Hafner, A. Ivanova, A. Sardo and T. R. Ward, *Angew. Chem.*, 2008, **120**, 713–717.
9 J. Steinreiber and T. R. Ward, *Coordination Chemistry Reviews*, 2008, **252**, 751–766.
10 V. Köhler, Y. M. Wilson, M. Dürrenberger, D. Ghislieri, E. Churakova, T. Quinto, L. Knörr, D. Häussinger, F. Hollmann, N. J. Turner and T. R. Ward, *Nature Chem*, 2012, **5**, 93–99.
11 G. Roelfes and B. L. Feringa, *Angew. Chem. Int. Ed.*, 2005, **44**, 3230–3232.
12 A. J. Boersma, R. P. Megens, B. L. Feringa and G. Roelfes, *Chem. Soc. Rev.*, 2010, **39**, 2083–2092.
13 F. Rosati and G. Roelfes, *ChemCatChem*, 2010, **2**, 916–927.
14 S. Park and H. Sugiyama, *Angew. Chem. Int. Ed.*, 2010, **49**, 3870–3878.
15 S. K. Silverman, *Angew. Chem. Int. Ed.*, 2010, **49**, 7180–7201.
16 I. Drienovská and G. Roelfes, *Isr. J. Chem.*, 2014, **55**, 21–31.
17 a) A. Rioz-Martínez and G. Roelfes, *Curr. Opin. Chem. Biol.*,

2015, **25**, 80–87. b) S. Park and H. Sugiyama, Molecules, 2012, **17**, 12792–12803.
18 A. Draksharapu, A. J. Boersma, M. Leising, A. Meetsma, W. R. Browne and G. Roelfes, *Dalton Trans.*, 2015, **44**, 3647–3655.
19 A. Draksharapu, A. J. Boersma, W. R. Browne and G. Roelfes, *Dalton Trans.*, 2015, **44**, 3656–3663.
20 K. Amirbekyan, N. Duchemin, E. Benedetti, R. Joseph, A. Colon, S. A. Markarian, L. Bethge, S. Vonhoff, S. Klussmann, J. Cossy, J.-J. Vasseur, S. Arseniyadis and M. Smietana, *ACS Catal.*, 2016, **6**, 3096–3105.
21 H.-K. Liu and P. J. Sadler, *Acc. Chem. Res.*, 2011, **44**, 349–359.
22 L. S. Lerman, *J. Mole. Biol.*, 1961, **3**, 18–30.
23 A. J. Boersma, B. L. Feringa and G. Roelfes, *Org. Lett.*, 2007, **9**, 3647–3650.
24 C. Janiak, *J. Chem. Soc., Dalton Trans.*, 2000, 3885–3896.
25 F. Rosati, A. J. Boersma, J. E. Klijn, A. Meetsma, B. L. Feringa and G. Roelfes, *Chem. Eur. J.*, 2009, **15**, 9596–9605.
26 C. Medhi, J. B. O. Mitchell, S. L. Price and A. B. Tabor, *Biopolymers*, 2000, **52**, 84–93.
27 G. Roelfes, A. J. Boersma and B. L. Feringa, *Chem. Commun.*, 2006, 635–637.
28 A. J. Boersma, B. de Bruin, B. L. Feringa and G. Roelfes, *Chem. Commun.*, 2012, **48**, 2394–2396.
29 A. J. Boersma, D. Coquière, D. Geerdink, F. Rosati, Ben L Feringa and G. Roelfes, *Nature Chem*, 2010, 991–995.
30 F. Rosati and G. Roelfes, *ChemCatChem*, 2011, **3**, 973–977.
31 J. S. Willemsen, R. P. Megens, G. Roelfes, J. C. M. van Hest and F. P. J. T. Rutjes, *Eur. J. Org. Chem.*, 2014, **2014**, 2892–2898.
32 R. P. Megens and G. Roelfes, *Chem. Commun.*, 2012, **48**, 6366–6368.
33 J. Oelerich and G. Roelfes, *Chem. Sci.*, 2013, **4**, 2013–2017.
34 A. J. Boersma, J. E. Klijn, B. L. Feringa and G. Roelfes, *J. Am. Chem. Soc.*, 2008, **130**, 11783–11790.
35 R. P. Megens and G. Roelfes, *Org. Biomol. Chem.*, 2010, **8**, 1387–1393.
36 J. W. Faller, A. R. Lavoie and B. J. Grimmond, *Organometallics*, 2002, **21**, 1662–1666.
37 M. P. Doyle, I. M. Phillips and W. Hu, *J. Am. Chem. Soc.*, 2001, **123**, 5366–5367.
38 H. Gotoh and Y. Hayashi, *Org. Lett.*, 2007, **9**, 2859–2862.
39 A. Berkessel and N. Vogl, *Eur. J. Org. Chem.*, 2006, **2006**, 5029–5035.
40 Y. Hamashima, D. Hotta, N. Umebayashi, Y. Tsuchiya, T. Suzuki and M. Sodeoka, *Adv. Synth. Catal.*, 2005, **347**, 1576–1586.
41 D. Coquière, B. L. Feringa and G. Roelfes, *Angew. Chem. Int. Ed.*, 2007, **46**, 9308–9311.
42 H. Zhao and K. Shen, *RSC Adv.*, 2014, **4**, 54051–54059.
43 Y. Li, C. Wang, G. Jia, S. Lu and C. Li, *Tetrahedron*, 2013, **69**, 6585–6590.
44 T. B. Poulsen and K. A. Jørgensen, *Chem. Rev.*, 2008, **108**, 2903–2915.
45 K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2001, **40**, 160–163.
46 A. J. Boersma, B. L. Feringa and G. Roelfes, *Angew. Chem. Int. Ed.*, 2009, **48**, 3346–3348.
47 E. W. Dijk, A. J. Boersma, B. L. Feringa and G. Roelfes, *Org. Biomol. Chem.*, 2010, **8**, 3868–3873.
48 S. Park, K. Ikehata, R. Watabe, Y. Hidaka, A. Rajendran and H. Sugiyama, *Chem. Commun.*, 2012, **48**, 10398–10400.
49 G. P. Petrova, Z. Ke, S. Park, H. Sugiyama and K. Morokuma, *Chem. Phys. Lett.*, 2014, **600**, 87–95.
50 A. García-Fernández, R. P. Megens, L. Villarino and G. Roelfes, *J. Am. Chem. Soc.*, 2016, **138**, 16308–16314.
51 N. Duchemin, E. Benedetti, L. Bethge, S. Vonhoff, S. Klussmann, J.-J. Vasseur, J. Cossy, M. Smietana and S. Arseniyadis, *Chem. Commun.*, 2016, **52**, 8604–8607.
52 W. L. Ward, K. Plakos and V. J. DeRose, *Chem. Rev.*, 2014, **114**, 4318–4342.
53 N. Preiswerk, T. Beck, J. D. Schulz, P. Milovnik, C. Mayer, J. B. Siegel, D. Baker and D. Hilvert, *Proc. Natl. Acad. Sci. USA*, 2014, **111**, 8013–8018.
54 R. R. Breaker and G. F. Joyce, *Chem. Biol.*, 2014, **21**, 1059–1065.
55 M. Chandra and S. K. Silverman, *J. Am. Chem. Soc.*, 2008, **130**, 2936–2937.
56 B. Seelig and A. Jäschke, *Chem. Biol.*, 1999, **6**, 167–176.
57 B. Seelig, S. Keiper, F. Stuhlmann and A. Jäschke, *Angew. Chem. Int. Ed.*, 2000, **39**, 4576–4579.
58 G. Sengle, A. Eisenführ, P. S. Arora, J. S. Nowick and M. Famulok, *Chem. Biol.*, 2001, **8**, 459–473.
59 S. Fusz, A. Eisenführ, S. G. Srivatsan, A. Heckel and M. Famulok, *Chem. Biol.*, 2005, **12**, 941–950.
60 M. Illangasekare, G. Sanchez, T. Nickles and M. Yarus, *Science*, 1995, **267**, 643–647.
61 N. V. Chumachenko, Y. Novikov and M. Yarus, *J. Am. Chem. Soc.*, 2009, **131**, 5257–5263.
62 P. A. Lohse and J. W. Szostak, *Nature*, 1996, **381**, 442–444.
63 T. R. Cech and B. Zhang, *Nature*, 1997, **390**, 96–100.
64 N. Shibata, H. Yasui, S. Nakamura and T. Toru, *Synlett*, 2007, **2007**, 1153–1157.
65 E. W. Dijk, Ben L Feringa and G. Roelfes, *Tetrahedron*, 2008, **19**, 2374–2377.
66 P. Murat, Y. Singh and E. Defrancq, *Chem. Soc. Rev.*, 2010, 2064–2070.
67 X. Li and D. R. Liu, *Angew. Chem. Int. Ed.*, 2004, **43**, 4848–4870.
68 T. N. Grossmann, A. Strohbach and O. Seitz, *ChemBioChem*, 2008, **9**, 2185–2192.
69 A. P. Silverman and E. T. Kool, *Chem. Rev.*, 2006, **106**, 3775–3789.
70 M. F. Jacobsen, E. Cló, A. Mokhir and K. V. Gothelf, *ChemMedChem*, 2007, **2**, 793–799.
71 J. Michaelis, A. Roloff and O. Seitz, *Org. Biomol. Chem.*, 2014, **12**, 2821–2833.
72 Z. Tang and A. Marx, *Angew. Chem. Int. Ed.*, 2007, **46**, 7297–7300.
73 N. S. Oltra and G. Roelfes, *Chem. Commun.*, 2008, 6039–6041.
74 L. Gjonaj and G. Roelfes, *ChemCatChem*, 2013, **5**, 1718–1721.
75 S. Park, L. Zheng, S. Kumakiri, S. Sakashita, H. Otomo, K. Ikehata and H. Sugiyama, *ACS Catal.*, 2014, **4**, 4070–4073.
76 M. Su, M. Tomás-Gamasa and T. Carell, *Chem. Sci.*, 2015, **6**, 632–638.
77 S. Park, I. Okamura, S. Sakashita, J. H. Yum, A. Chiranjit, L. Gao and H. Sugiyama, *ACS Catal.*, 2015, **5**, 4708–4712.
78 L. C. Ropartz, N. J. Meeuwenoord, G. A. van der Marel, P. W. N. M. van Leeuwen, A. M. Z. Slawin and P. C. J. Kamer, *Chem. Commun.*, 2007, 1556–1558.
79 P. Fournier, R. Fiammengo and A. Jäschke, *Angew. Chem. Int. Ed.*, 2009, **48**, 4426–4429.
80 S. Burge, G. N. Parkinson, P. Hazel, A. K. Todd and S. Neidle, *Nucleic Acids Res.*, 2006, **34**, 5402–5415.
81 E. N. Nikolova, E. Kim, A. A. Wise, P. J. O'Brien, I. Andricioaei and H. M. Al-Hashimi, *Nature*, 2011, **470**, 498–502.
82 S. Roe, D. J. Ritson, T. Garner, M. Searle and J. E. Moses, *Chem. Commun.*, 2010, **46**, 4309–4311.
83 C. Wang, G. Jia, J. Zhou, Y. Li, Y. Liu, S. Lu and C. Li, *Angew. Chem. Int. Ed.*, 2012, **51**, 9352–9355.
84 C. Wang, Y. Li, G. Jia, Y. Liu, S. Lu and C. Li, *Chem. Commun.*, 2012, **48**, 6232–6234.

85 Y. Li, G. Jia, C. Wang, M. Cheng and C. Li, *ChemBioChem*, 2015, **16**, 618–624.
86 C. Wang, G. Jia, Y. Li, S. Zhang and C. Li, *Chem. Commun.*, 2013, **49**, 11161–11163.
87 Y. Li, C. Wang, J. Hao, M. Cheng, G. Jia and C. Li, *Chem. Commun.*, 2015, **51**, 13174–13177.
88 H. Zhao and K. Shen, *Biotechnol Progress*, 2016, **32**, 891–898.
89 M. Wilking and U. Hennecke, *Org. Biomol. Chem.*, 2013, **11**, 6940–6.
90 Y. Li, M. Cheng, J. Hao, C. Wang, G. Jia and C. Li, *Chem. Sci.*, 2015, **6**, 5578–5585.
91 M. Cheng, Y. Li, J. Zhou, G. Jia, S.-M. Lu, Y. Yang and C. Li, *Chem. Commun.*, 2016, **52**, 9644–9647.
92 S. Dey and A. Jäschke, *Angew. Chem. Int. Ed.*, 2015, **54**, 11279–11282.
93 J. Wang, E. Benedetti, L. Bethge, S. Vonhoff, S. Klussmann, J.-J. Vasseur, J. Cossy, M. Smietana and S. Arseniyadis, *Angew. Chem. Int. Ed.*, 2013, **52**, 11546–11549.
94 H. Urata, K. Shinohara, E. Ogura, Y. Ueda and M. Akagi, *J. Am. Chem. Soc.*, 1991, **113**, 8174–8177.
95 S. Park, K. Ikehata and H. Sugiyama, *Biomater. Sci.*, 2013, **1**, 1034–1036.
96 E. Benedetti, N. Duchemin, L. Bethge, S. Vonhoff, S. Klussmann, J.-J. Vasseur, J. Cossy, M. Smietana and S. Arseniyadis, *Chem. Commun.*, 2015, **51**, 6076–6079.
97 A. Rioz-Martínez, J. Oelerich, N. Ségaud and G. Roelfes, *Angew. Chem. Int. Ed.*, 2016, **55**, 14136–14140.
98 N. Gaß, J. Gebhard and H.-A. Wagenknecht, *ChemPhotoChem*, 2016, 1–4.