Challenges and Opportunities in DNA-based Asymmetric Catalysis

Michael Smietana, Stellios Arseniyadis

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Michael Smietana*a and Stellios Arseniyadis*b

Abstract: The biological importance of nucleic acids for the storage, expression and regulation of genetic information is now well understood. By taming the chemical synthesis of these biomolecules, chemists have been able to engineer new architectures based on the ability of DNA and RNA to fold into secondary or even more complex tertiary structures with applications in medicinal chemistry, diagnostics or even material sciences. Exploiting the fascinating helical structure of DNA and RNA to develop new chiral bio-hybrid catalysts capable of promoting highly stereoselective transformations under mild and eco-compatible conditions is also an emerging area of research. In this short review, we report our recent results in the field of DNA-based asymmetric catalysis as well as the challenges and promising perspectives that lie in front of us.

Keywords: Asymmetric catalysis · Bio-hybrid · Chirality · DNA · Double helix

Prof. Michael Smietana was educated at the Ecole Normale Supérieure in Paris. He received his PhD in 2001 from the University of Strasbourg under the guidance of the late Dr. Charles Mioskowski. He then joined Prof. Eric Kool's group at Stanford University as a Postdoctoral Fellow for two years working on the development of a new access to cyclic dinucleotides. In 2004, he moved to the University of Montpellier as an Assistant Professor, working in the Nucleic Acids Department of the Institute of Biomolecules Max Mousseron (IBMM). He was appointed Associate Professor in 2010 and Full Professor in 2012. In 2018, he received the Jean-Marie Lehn award from the Organic Chemistry Division of the French Chemical Society. His current research interests focus on molecular recognition and DNA-based asymmetric catalysis.

Dr. Stellios Arseniyadis overlapped with Prof. Michael Smietana in the Mioskowski group. He obtained his PhD in 2002 and joined Rhodia Chirex in Boston to work on various palladium- and copper-catalysed aryl bond-forming processes in collaboration with Prof. S. L. Buchwald at MIT. After a first academic postdoc with Prof. A. C. Spivey at Imperial College London working in the field of asymmetric organocatalysis, he joined Prof. K. C. Nicolaou's group at The Scripps Research Institute to work on the synthesis of new epothilone B analogues. In 2005, he joined the CNRS as a permanent researcher and was promoted to rank of Director in 2015. The same year, he joined Queen Mary University of London as a Reader in Organic Chemistry. His group is focussed on the development of new synthetic tools within the areas of transition metal catalysis, organocatalysis and, more recently, bio-hybrid catalysis.

1. Introduction

Mimicking enzymatic reactions by engineering artificial systems able to catalyse a wide variety of chemical transformations has been a continuous area of research for biologists and chemists since the late 1970s.[1] Inspired by the fascinating microenvironment provided by natural enzymes, considerable progress has been made toward the design of artificial systems capable of mirroring enzymatic active sites and achieve high catalytic capacity and substrate selectivity.[2] While initially based on peptides and protein scaffolds,[1c,2a,3] the construction of artificial metalloenzymes has been extended to a wide variety of architectures, including macrocyclic molecules such as cyclodextrins, calixarenes and cucurbiturils, and more recently nucleic acids, which have the particularity to adopt a plethora of secondary or even more complex tertiary structures (Fig. 1).[4]

Most of these systems rely on the incorporation of a metallic co-factor within a chiral macromolecular framework through a covalent, supramolecular or dative anchoring strategy (Fig. 2). Our group recently joined the task force with the aim of developing new nucleic acid-based artificial metalloenzymes with original catalytic activities; we will give here an account of some of our key achievements.

2. DNA-based Catalysts in Asymmetric Synthesis

While catalytic nucleic acid-based architectures requiring metal ions as cofactors (also called DNA/RNAzymes) have been studied and optimized to catalyse a diverse range of reactions for more than three decades,[5] the use of DNA as a source of chirality in asymmetric catalysis was first reported by Roelfes and Feringa in 2005.[6] The concept was based on the supramolecular assembly of salmon testes DNA (st-DNA) and an achiral ligand composed of the well-known DNA-intercalating 9-aminoacridine attached to an aminomethyl pyridine moiety able to chelate a Cu(II) species. The catalytic activity of this bio-hybrid catalyst was first evaluated on a reaction known to be

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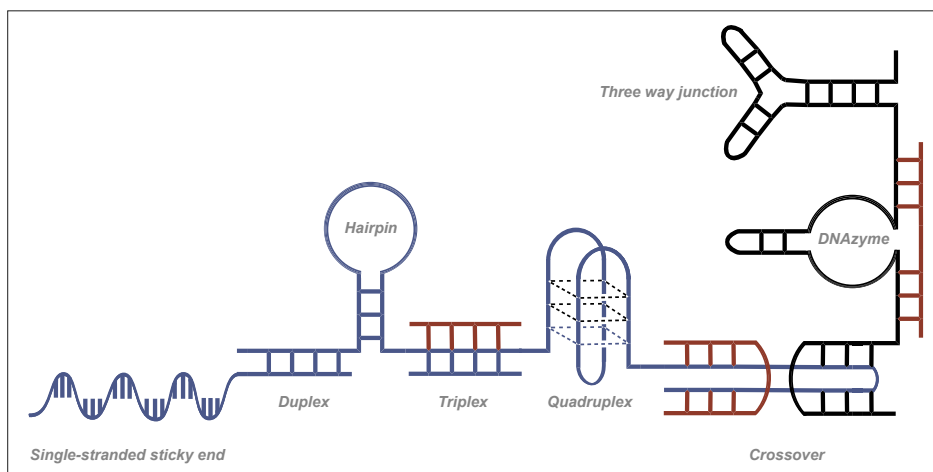Mile End Road
E1 4NS, London, UK

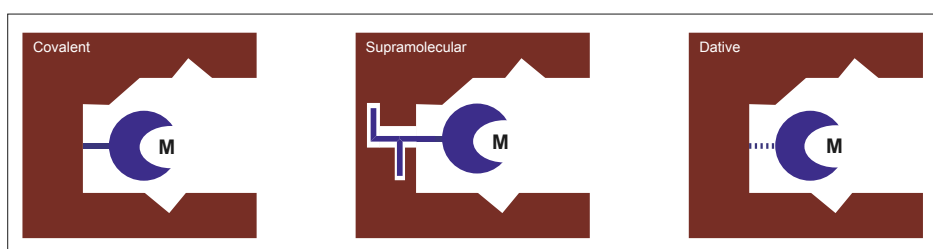Fig. 1. A few examples of structures adopted by DNA.

Fig. 2. Typical anchorage strategies.

water-compatible; namely the Diels Alder between aza-chalcones and cylopentadiene. The results were particularly interesting as a high *endo/exo* selectivity was obtained (98:2) along with a promising 53% ee of the major *endo* isomer (Scheme 1, top). In addition, they were also able to demonstrate that the absolute configuration of the product could be inverted by tuning the nature of the spacer. This benchmark reaction demonstrated that the right-handed DNA helix was suitable to create an appropriate chiral environment and induce an enantioselective catalytic transformation. Following these initial results the authors rapidly improved their system by introducing bipyridine and terpyridine-based Cu(II)-DNA binders[7] and by extending their scope to the more versatile 2-acyl imidazole derivatives (Scheme 1, bottom).[8]

The concept immediately caught the attention of the scientific community who, along with the Roelfes group, extended the use of DNA as a chiral scaffold to various other Cu(II)-catalysed reactions, including Michael[9a,b] and oxo-Michael additions,[9c] Friedel-Crafts alkylations,[9d,e] electrophilic fluorinations,[9f] hydrolytic kinetic resolutions of epoxides,[9g] *syn*-hydrations,[9h] and both inter-[9i] and intramolecular[9j] cyclopropanations (Schemes 2 and 3). Just last year, Roelfes and co-workers were able to show that the use of a Cu(II)-bipy-DNA complex in the context of a Friedel-Crafts alkylation also promoted a face-selective reprotonation of the highly

reactive transient enolate. These results were all the more remarkable considering that the reactions were run in water.[10]

In addition to implementing the concept to a broader range of reactions, intensive efforts have also been dedicated to getting some mechanistic insights as well as a better understanding of the various structural[7,11,12] and experimental[13] parameters that influence the selectivity. These are not covered here as it is beyond the scope of this account, however they can be found in some recent reviews.[14]

Our group joined this fascinating area of research in 2011, first by tackling a long-standing issue pertaining to bio-hybrid catalysis, which is the control of the enantioselectivity outcome. Indeed, while reaching high enantioselectivities can eas-

ily be achieved by fine-tuning the reaction conditions, selectively accessing a specific enantiomer in a given reaction is a more challenging task. Various strategies have been evaluated in the context of DNA-based asymmetric catalysis; these generally involved a fine-tuning of either the structure of the metallic co-factor or its position within the double-strand DNA platform. Unfortunately, the inversion of selectivity was in the best case only partial and usually very substrate-specific.[15] In this context, we were able to show that double strand-DNA made from L-nucleic acids instead of the natural occurring D-nucleic acids could be used to reverse the selectivity of any given reaction in a reliable and predictable fashion (Scheme 4).[16] These left-handed L-DNA sequences, mirror image of the corresponding right-handed D-DNA sequences, were readily synthesized using L-nucleotide phosphoramidites and evaluated in various Friedel-Crafts alkylations as well as in the conjugate addition of dimethyl malonate and nitromethane. In all cases, both enantiomers could be obtained selectively depending on the nature of the DNA helix.

We applied the same approach with short double-stranded RNA sequences[17] with the idea that we could also potentially improve the selectivity due to the specific structural features pertaining to RNA. Indeed, compared to DNA, double-stranded RNA sequences adopt a compact A-form helix[18] characterized by a wide and shallow minor groove and a deep and narrow major groove. Interestingly, the inversion of selectivity was still observed when using D- and L-RNA instead of the corresponding D- and L-DNA sequences, however the enantioselectivities achieved were lower (up to 54% ee) (Scheme 5).
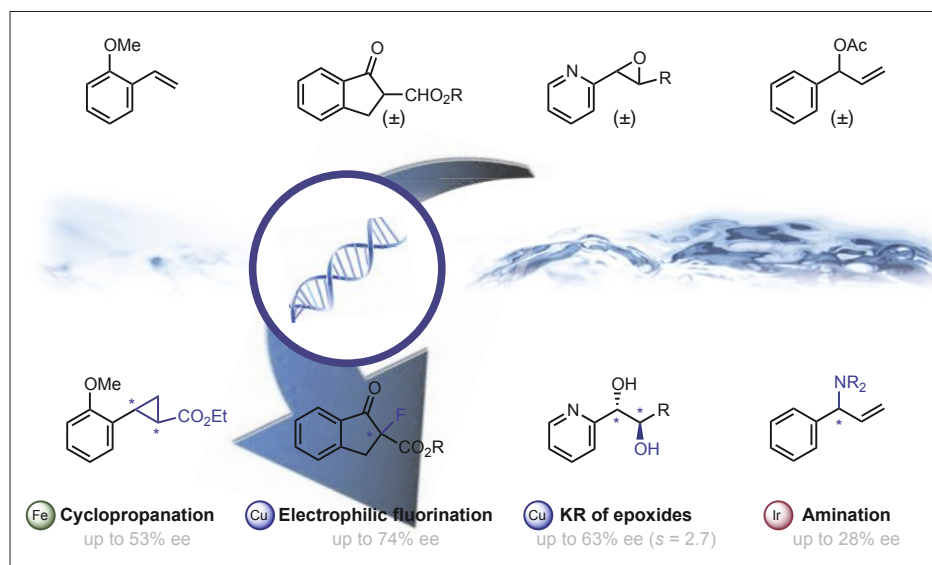
Following these results, we next evaluated the potential scalability of the process. To do so, we developed a DNA-based catalyst bound to a cellulose matrix (Scheme 6).[19] The chiral bio-hybrid material, which is commercially available, trivial
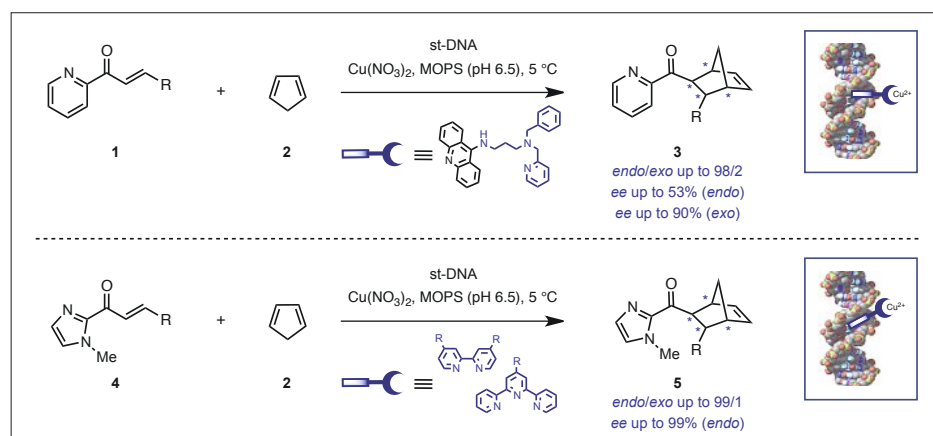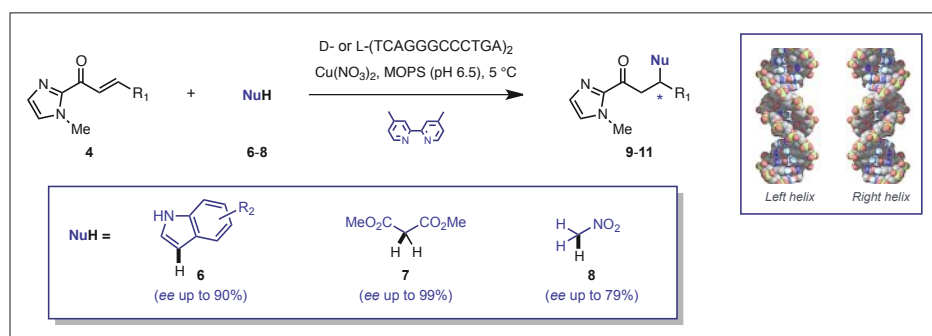

Scheme 1. DNA-catalysed Diels-Alder reaction.
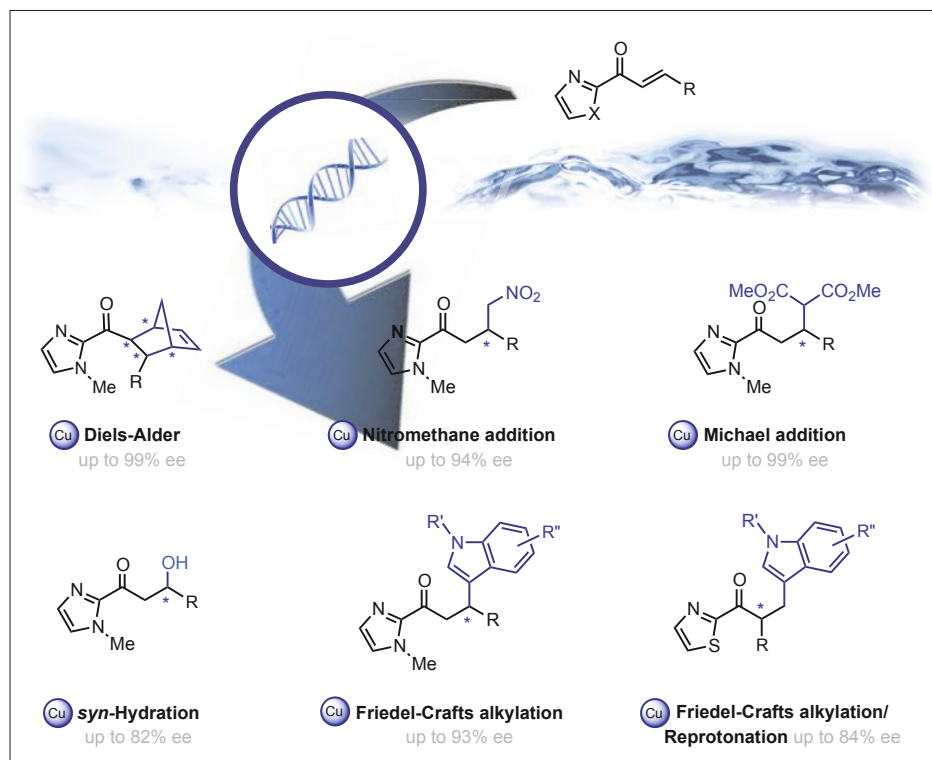
Scheme 2. Current scope in the field of DNA-based asymmetric catalysis.

Scheme 3 Current scope in the field of DNA-based asymmetric catalysis (continued).

Scheme 4. Use of L- and D-DNA for a reliable and predictable access to both enantiomers of a given reaction.

to use and fully recyclable proved to be a good alternative to the various immobilised DNA catalysts reported so far.[20] Most importantly, our solid-supported catalyst could be implemented to a single-pass continuous-flow process allowing fast conversions and high enantioselectivities at low catalyst loadings on mmol scale reactions.

More recently, we set out to design sequence-specific catalysts with the idea of ultimately being able to perform multi-catalytic processes in a one-pot fashion. With this in mind, we prepared a series of ligands derived from the well-known minor groove binder Hoechst-33258, which is also known to have a strong affinity for AT-rich regions of a B form duplex DNA (Scheme 7). An evaluation of the affinity of these new ligands by spectroscopic analysis confirmed their minor groove binding mode, while their use in Cu(II)-catalysed Friedel-Crafts alkylations showed a clear correlation between affinity and selectivity. Although the enantioselectivities observed were rather moderate (up to 47% ee obtained with ct-DNA and ligand **12b**), these results demonstrated that sequence-selectivity and thus compartmentalization could be achieved.[21]
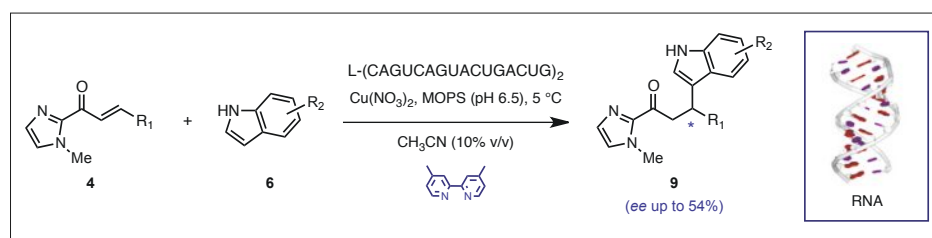
3. Conclusion and Outlook

DNA is an abundant, readily available and reasonably affordable source of chirality. Due to its highly charged phosphate backbone, it offers an interesting access to water-compatible asymmetric catalysts and thus a great alternative to the more traditional chiral organic ligands. The recyclability offered by solid-supported DNA catalysts associated with the compatibility of DNA with organic co-solvents further increase the attractivity of DNA for the development of large-scale enantioselective processes. The field of DNA-based asymmetric catalysis is however still in its infancy. Further mechanistic studies are indeed needed to assess the influence of the groove (minor *vs* major) and to fully understand and correlate the observed acceleration rates with the enantioselectivity. This will ultimately allow to better tame these bio-hybrid catalytic systems.

The recent extension of DNA-based asymmetric catalysis to other metallic co-factors[9i,22] and to photocatalysed processes[23] will undoubtedly open new avenues in the field. As far as we are concerned, our current efforts are focused on designing a 'universal' DNA-based catalyst capable of achieving high enantioselectivities on a wide range of reactions; these results will be reported shortly.

Scheme 5. Expanding bio-hybrid-mediated asymmetric catalysis into the realm of RNA.

Scheme 6. Cellulose-supported DNA-based asymmetric catalysis.

Scheme 7. Friedel-Crafts alkylation using Hoechst-derived ligands **12a** and **12b**.

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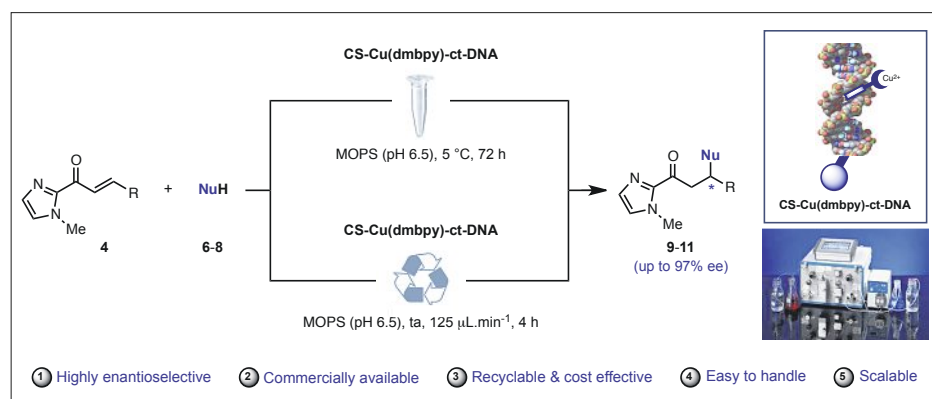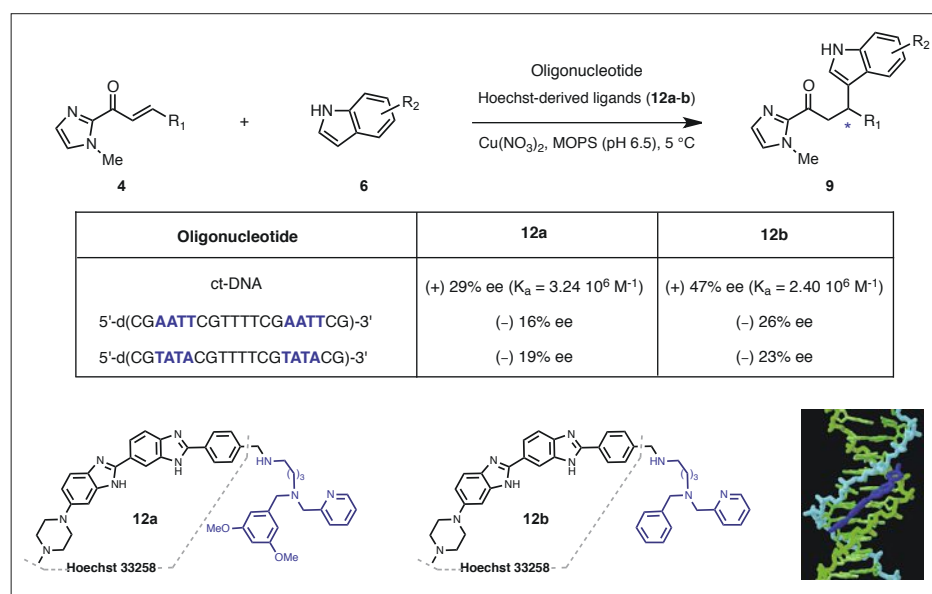
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