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Asymmetric Catalysis

DNA-Based Hybrid Catalysts for Asymmetric Organic Synthesis

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asymmetric synthesis · DNA · hybrid catalyst · Lewis acid catalysis

Stereoselective hybrid systems based on metal-assisted catalysis with a chiral biomacromolecule form an attractive research area for the synthesis of enantiomerically pure compounds. Although various methods are available for this purpose, most rely on the use of enzymes, proteins, or RNA. The application of DNA-based hybrid catalysts for enantioselective synthesis emerged only a few years ago. DNA-based hybrid catalysts have been self-assembled from DNA and a metal complex with a specific ligand through supramolecular or covalent anchoring strategies and have demonstrated high stereoselectivity and rate enhancement in Lewis acid catalyzed reactions, such as Diels–Alder, Michael addition, and Friedel–Crafts reactions. For these reactions, cheap and commercially available salmon testes DNA has generally been used. In this Minireview, we summarize recent developments in the area of asymmetric catalysis with DNA-based hybrid catalysts.

1. Introduction

The development of efficient catalytic asymmetric reactions is a key objective in modern organic chemistry and is very important for the synthesis of natural products and the production of pharmaceuticals and agrochemicals. Although metal-catalyzed enantioselective transformations have been investigated extensively and have proven to be useful and versatile methods, the search for more efficient methods continues, and challenges still remain from economic and ecological points of view.[1] Many metal precursors that show high catalytic performance are derived from expensive rare metals and artificial chiral ligands, the construction of which requires time and effort, from their design to their synthesis, in contrast to the use of chiral biomolecules of natural origin. Furthermore, many of these metal complexes are sensitive to air or moisture. These features can be hurdles for the large-scale application of enantioselective catalysts as well as for the use of the inexpensive "green" solvent, water.

Stereoselective hybrid catalysts combining the catalytic power of a metal complex with the exquisite chirality of a biomacromolecule have received attention as alternative tools for the synthesis of enantiomerically pure compounds.[2] Considering the broad scope of transformations enabled by metal-catalyzed reactions and the vast diversity of natural and artificial biomolecules, this combination seems to be a very promising strategy. It would appear reasonable to use the double helix of DNA as a chiral environment in which reactions can take place. However, most stereoselective hybrid catalysts rely on the chiral architecture of a protein.[3] Indeed, only recently has significant success been achieved in DNA hybrid catalysis.

Since the three-dimensional structure of the DNA double helix was elucidated by Watson and Crick more than 50 years ago,[4] its double-helical structure with complementary hydrogen-bonded base pairs has come into the spotlight as an extraordinarily effective means for the storage and transfer of genetic information. However, the interest in DNA double-helix structures has now expanded from biology into various domains of science, including DNA nanotechnology.[5] From the viewpoint of a synthetic chemist, DNA is a notable material because of its unique chirality. The notion that the chiral environment of DNA has an influence on the stereochemical course of a reaction was established in 1960 following the observation that a stereoselective [2+2] photo-

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dimerization of thymine to the *cis syn* dimer occurred efficiently in DNA.[6] Furthermore, it has been found that the chirality of DNA plays a crucial role in the enantioselective recognition of chiral phenanthroline–metal complexes[7] and *P* helicenes.[8] In a variety of DNA-alkylating reagents, such as a benzo[*a*]pyrene diol epoxide,[9] duocarmycin,[10] and pyrrole–imidazole polyamides,[11] one of the enantiomers selectively forms a covalent bond with DNA. DNA-based catalysts, however, have not received as much attention in synthetic applications as catalytic RNAs, such as ribozymes, which have been employed successfully in a wide range of reactions, including enantioselective catalysis.[12] DNA was regarded as less catalytically competent than RNA because of the lack of a 2′-hydroxy group that can engage in hydrogen bonding.[13] In spite of an early concern about the ability of DNA as a catalyst, chirality transfer from DNA in stoichiometric DNA-templated reactions and the development of metallodeoxyribozymes suggest the potential of DNA in asymmetric catalysis.[14]

DNA is a promising candidate as a source of chirality in asymmetric catalysis for the following reasons: compared with RNA and proteins, DNA is chemically more stable and is readily available at lower cost in various sequences and lengths through highly efficient synthetic procedures and molecular-biological techniques. Although mainly B-DNA has been observed in organisms, there are many possible DNA conformations, including A-DNA and Z-DNA forms (Figure 1), and the high specificity of the A–T and G–C Watson–Crick hydrogen-bonding interactions enables the construction of various artificial structures on the basis of the simple four-letter alphabet (Scheme 1). DNA is a cheap and readily available biopolymer. For example, 1 kg of bulk DNA can be bought for about $100–200, and 1 g of purified salmon testes DNA (st-DNA) for about $77.[15] Furthermore, DNA is a suitable starting point for the development of a water-compatible catalyst because of its high solubility in water. Asymmetric catalysis in water is one of the most important research areas with respect to green chemistry.[16] Herein, we focus on the chirality of DNA and describe

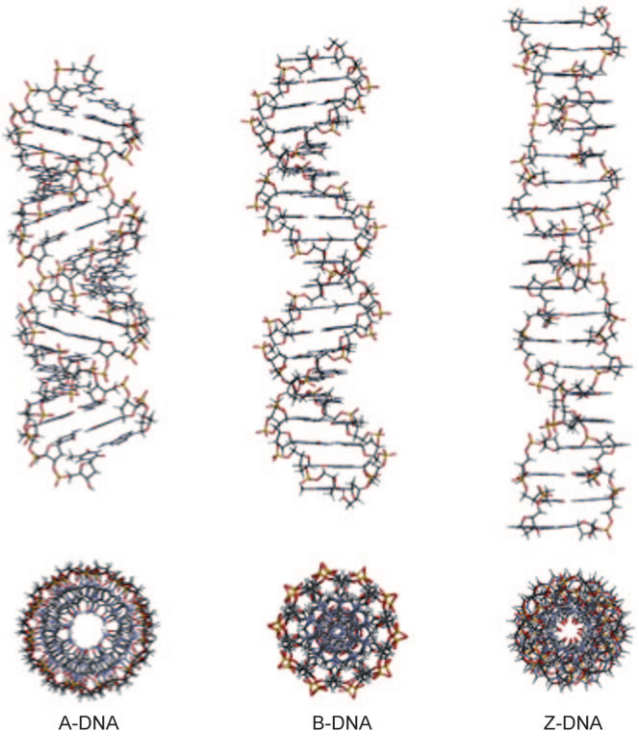
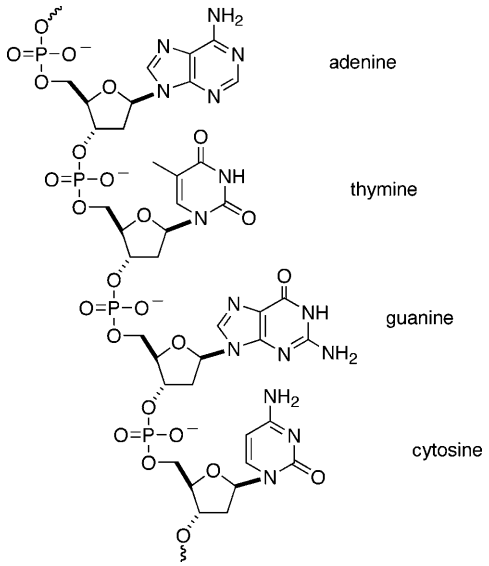


Figure 1. Three polymorphs of DNA.



Scheme 1. Chemical structure of DNA showing the connectivity of the four bases to the phosphate–sugar backbone.

Soyoung Park was born in Seoul, Korea in 1979. She received her MS in Chemistry from KAIST (Korea Advanced Institute of Science and Technology) under the guidance of Professor Sukbok Chang in 2005. In 2009, she completed her PhD at Kyoto University in Japan under the direction of Assistant Professor Ryo Shintani and Professor Tamio Hayashi. She is currently a postdoctoral fellow in the research group of Professor Hiroshi Sugiyama at Kyoto University. Her research interests include the development of new catalytic reactions, in particular for asymmetric synthesis.

Hiroshi Sugiyama received his PhD in 1984 with Teruo Matuura at Kyoto University. After postdoctoral studies at the University of Virginia with Sidney M. Hecht, he returned to Kyoto University in 1986 as an assistant professor and became an associate professor in 1993. In 1996, he joined the Institute of Biomaterials and Bioengineering at Tokyo Medical and Dental University. He has been a professor of chemical biology at Kyoto University since 2003. Among the honors he has received are the Nippon IBM Award and the Chemical Society of Japan Award for Creative Work.

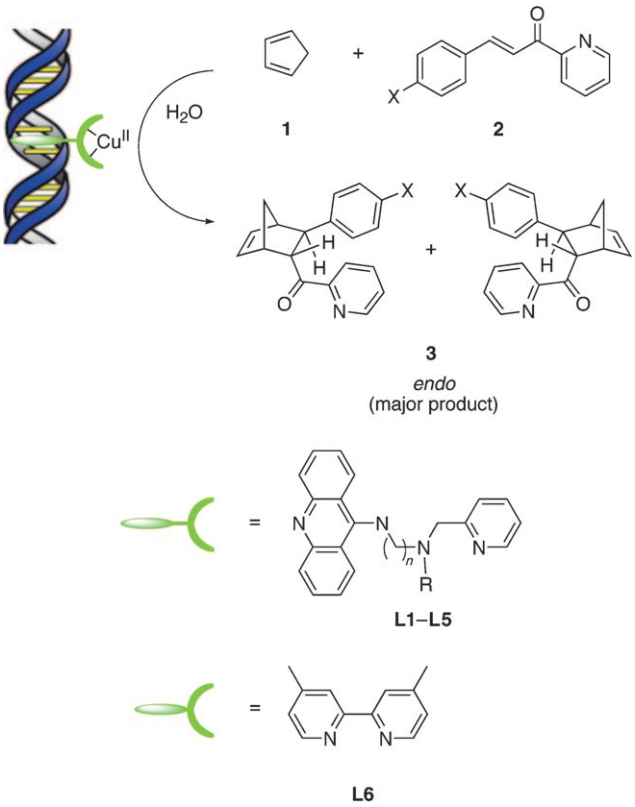
representative examples of catalytic asymmetric syntheses with DNA hybrid catalysts.

2. Catalytic Asymmetric Synthesis with DNA-Based Hybrid Catalysts

The application of DNA-based hybrid catalysts to asymmetric catalysis was first reported in the form of a copper(II)-catalyzed Diels–Alder reaction by Feringa and Roelfes in 2005.[17] They introduced the concept of a novel type of DNA-based asymmetric catalysis on the basis of supramolecular assembly by using a copper complex of a nonchiral ligand that can bind to DNA. Since then, DNA-based hybrid catalysts have been applied to various key asymmetric carbon–carbon bond-forming reactions.

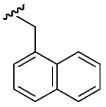
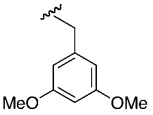
2.1. Diels–Alder Reaction

The potential of DNA-based hybrid catalysts for asymmetric catalysis was demonstrated for the first time in a Diels–Alder reaction combined with a supramolecular approach.[17] Feringa and Roelfes chose a copper(II)-catalyzed Diels–Alder reaction[18] between cyclopentadiene and an azachalcone in water as a model reaction (Scheme 2). The Cu^{II} center acted as a Lewis acid and activated the dienophile by coordination to the ketone oxygen atom and the pyridyl nitrogen atom. A catalytically active complex was formed in situ between Cu^{II} and a ligand that consisted of three functional components: a DNA-binding domain, such as 9-aminoacridine, a spacer moiety, and a metal-binding group. In the presence of st-DNA or calf thymus DNA (ct-DNA), the copper complex was anchored to the DNA double helix through the acridine intercalator. The reactions proceeded smoothly in water and were monitored to above 80% completion. Product **3** was obtained as a mixture of *endo* (major) and *exo* (minor) isomers, both with significant enantioselectivity. Without DNA, the products were obtained as racemates. Therefore, the enantioselectivity of the reaction originated from the DNA.



Scheme 2. Diels–Alder reaction catalyzed by a supramolecular hybrid of a Cu^{II}–ligand complex and DNA.

Table 1: Effect of structural variation of the Cu^{II}–ligand–DNA hybrid catalyst.[a,b]

Entry	Ligand	X	*n*	R	DNA	*endo*/*exo*	*ee* (*endo*)	*ee* (*exo*)
1	**L1**	H	2		st-DNA	98:2	48 (+)	37 (+)
2	**L2**	H	3		st-DNA	98:2	49 (−)	18 (−)
3	**L3**	H	5		st-DNA	97:3	<5 (−)	<5 (−)
4	**L4**	H	2		ct-DNA	92:8	35 (+)	82 (+)
5	**L4**	OMe	2		st-DNA	91:9	53 (+)	90 (+)
6	**L5**	H	3		st-DNA	98:2	37 (+)	7 (+)
7	**L6**	–	–	–	st-DNA	>99:1		>99 (+)

[a] $Cu(NO_3)_2$ was used as the Cu^{II} source. Reaction conditions: Cu^{II}/ligand/DNA (1:1.3:3), 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer (pH 6.5), 5 °C, 3 days, >80% conversion. [b] Positive and negative *ee* values indicate the two enantiomers.

The enantioselectivity of the Diels–Alder reaction proved to be dependent on the substituent, R, of the ligand, and on the spacer length, *n*. When R was 1-naphthylmethyl, an *endo*/*exo* ratio of 98:2 was observed, and the *endo* isomer was obtained with 49% *ee* (Table 1, entry 2).In contrast, the *endo* isomer was formed with the opposite enantioselectivity with 37% *ee* when R was a 3,5-dimethoxybenzyl group (Table 1, entry 6). Furthermore, the absolute configuration of the product could be changed simply by changing the spacer (Table 1, entries 1 and 2). These stereochemical outcomes might be attributed to π–π stacking interactions between the ligand and the substrate and imply that each enantiomer can be obtained selectively through the appropriate design of the ligand, although the chirality of the DNA is identical. Elongation of the spacer ($n=5$) caused the *ee* value of the product to decrease dramatically (Table 1, entry 3). Irrespective of the source of the DNA used (st-DNA or ct-DNA), similar enantioselectivities were observed. An *ee* value of 53% was observed for the *endo* isomer when a ligand was used with a spacer length $n=2$, a 3,5-dimethoxybenzyl group as substituent R, and a methoxy group as substituent X (Table 1, entry 5).

DNA is expected to create a chiral environment to control the enantioselectivity of this reaction, and the mechanism can

be explained in terms of a two-step chirality transfer.[19] First, DNA imposes a chiral conformation on the catalyst, and then this DNA-derived chirality of the catalyst induces enantioselectivity in the catalyzed reaction. Hence, although **L1**–**L5** in the acridine-based system are achiral, the corresponding Cu^{II} complex is chiral. In fact, the conversion of an achiral or meso ligand–metal complex into a chiral complex by combination with an enantiomerically pure ligand as an exogenous chiral source is well-founded in asymmetric catalysis.[20]

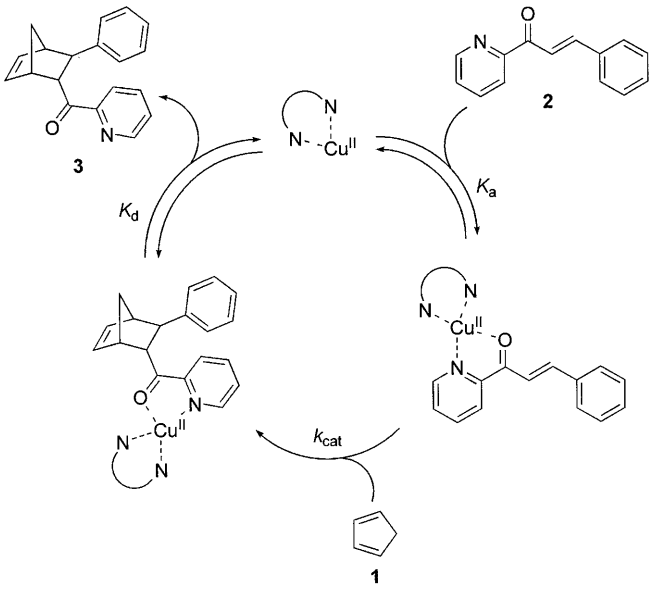
With **L1**–**L5**, the reaction rates were only slightly lower in the presence of DNA than for the corresponding reactions in solution without DNA. Because of the spacer in the ligand, the reactions are presumed to occur at a large enough distance from the DNA groove that the reaction rate is not affected significantly.[21] Interestingly, the selectivity of DNA-based Diels–Alder reactions was improved by removing the spacer between the copper binding site and the intercalator. When the nearly flat, symmetrical bipyridine-type ligand 4,4′-dimethyl-2,2′-bipyridine (dmbpy, **L6**) was used, complete regioselectivity (up to 99% *endo*) and high enantioselectivity (up to 99% *ee*) were observed (Table 1, entry 7).[22] In the case of the simple "second-generation" ligand dmbpy, the metal-binding domain and DNA anchor are incorporated into one moiety; thus, a spacer is no longer required. Accordingly, unlike with **L1**–**L5**, chirality is transferred directly from the DNA to the reaction components during catalysis, because the Cu^{II} center is located very close to the DNA, possibly inside the DNA groove, and **L6** is symmetrical as well as rigid.[19]

The enantioselectivity of the reaction through the direct transfer of chirality must rely strongly on the interaction between DNA and the Cu^{II} complex. In the case of the Cu^{II}–**L6**/st-DNA complex, a slightly decreased melting temperature was observed relative to that of st-DNA.[23] This observation suggests that Cu^{II}–**L6** forms a weak DNA-binding complex rather than intercalating with the DNA, because the presence of molecules that bind DNA strongly through intercalative binding often leads to an increase in the melting temperature. Surprisingly, the Cu^{II}–**L6**/st-DNA catalyst gave rise to a 58-fold rate acceleration relative to the reaction in the absence of DNA.[23] In an attempt to identify the origin of this rate acceleration by DNA, kinetic studies were carried out, and thermodynamic parameters were analyzed. As shown in Table 2, the K_a value did not change significantly as a result of the presence of DNA; however, the k_{cat} value increased by two orders of magnitude (Scheme 3). This result indicates that the rate enhancement is due to the acceleration of the irreversible Diels–Alder reaction in the presence of st-DNA rather than the affinity of dienophile **2** for the Cu^{II}–**L6**/st-DNA complex. Furthermore, this acceleration (k_{cat}) results from an increase in the rate of the reaction to form the major enantiomer and a lowering of the enthalpy barrier to catalysis. On the basis of this evidence, Feringa, Roelfes, and co-workers suggested that the DNA provides a suitable microenvironment as the catalytic pocket, which stabilizes the activated complex and thus promotes both rate acceleration and high enantioselectivity. This effect could derive from chemical or shape complementarity of the DNA groove, which may stabilize the transition state leading to the major enantiomer. In fact, this transition-state stabilization has also been proposed for antibody-catalyzed Diels–Alder reactions.[24]

Table 2: Kinetic and thermodynamic parameters: K_a, k_{cat}, $k_{(-)}$, $k_{(+)}$, and isobaric activation parameters at 298 K for the Diels–Alder reaction of **1** with **2** (Scheme 3).[a]

	Cu^{II}–**L6**	Cu^{II}–**L6**/st-DNA[b]
K_a [M^{-1}]	$(4.0\pm0.8)\times10^2$	$(5.0\pm1.4)\times10^2$
k_{cat} [$M^{-1}s^{-1}$]	$(4.5\pm1.2)\times10^{-2}$	3.8 ± 0.8
$k_{(-)}$ [$M^{-1}s^{-1}$]	$(2.2\pm0.6)\times10^{-2}$	$(5.8\pm1.2)\times10^{-2}$
$k_{(+)}$ [$M^{-1}s^{-1}$]	$(2.2\pm0.6)\times10^{-2}$	3.8 ± 0.8
$\Delta G^{\neq}$ [kcal mol^{-1}]	21 ± 1	18 ± 1
$\Delta H^{\neq}$ [kcal mol^{-1}]	10 ± 1	3.1 ± 0.5
$T\Delta S^{\neq}$ [kcal mol^{-1}]	-11 ± 1	-15 ± 1

[a] [Cu^{II}–**L6**] = 0.10–0.25 mM, 25 °C, MOPS buffer (pH 6.5), [**1**] = 6.0×10^{-3} M, [**2**] = 0.5–2.0 M (for the isobaric activation parameters, [Cu^{II}–**L6**] = 0.1 M). [b] Ratio: 1 Cu^{II}–**L6** complex per 6 base pairs of DNA.



Scheme 3. Proposed catalytic cycle for the copper(II)-catalyzed Diels–Alder reaction of **1** with **2**.

The sequence of st-DNA, a biopolymer of high molecular weight, can be considered to be random. Therefore, the Cu^{II}–**L6** complex may occupy different chiral microenvironments created by different base pairs in st-DNA. At this point, a question comes to the fore. Is it possible to control enantioselectivity according to a specific DNA sequence?—How does the DNA sequence affect the DNA-based hybrid catalyst?

The effect of the DNA sequence on catalysis was investigated by using synthetic oligonucleotides consisting of designated sequences.[21,23] Conspicuous changes in enantioselectivity were observed with various synthetic duplexes. Furthermore, the effectiveness of a particular DNA sequence depended on the ligand present in the DNA-based catalyst. In the case of the Cu^{II}–**L4** complex, an AT-rich sequence gave rise to very low enantioselectivity (Table 3, entry 1), whereas 62% *ee* was observed with poly[d(GC)] (Table 3, entry 2): a

higher value than that observed with st-DNA (37% *ee*).[17] Interestingly, the enantioselectivity could be changed greatly by modifying the order of the G and C nucleobases (Table 3, entries 3 and 4). Thus, GC-rich sequences may provide a suitable chiral environment for the reaction catalyzed by the Cu^{II}–**L4** complex. The suitability of such sequences can be explained by the affinity of acridine for GC-rich regions of DNA.[25]

Table 3: Dependence of enantioselectivity on the DNA sequence in the Cu^{II}–**L4**-catalyzed Diels–Alder reaction of **1** and **2**.[a]

Entry	DNA	*ee* [%]
	double-stranded DNA	
1	poly(dA-dT)(dA-dT)	6 (+)
2	poly(dG-dC)(dG-dC)	62 (+)
3	$d(GCGCGCGCGCGC)_2$	35 (+)
4	$d(CGCGCGCGCGCG)_2$	60 (+)
5	$d(CGCGGGCCCGCG)_2$	25 (+)
6	$d(TCAGGGCCCTGA)_2$	10 (+)
	single-stranded DNA	
7	d(GACTGACTAGTCAGTC)	34 (+)

[a] Reaction conditions: [**1**] = 16 mM, [**2**] = 1 mM, [Cu**L4**$(NO_3)_2$] = 0.3 mM, MOPS buffer (pH 6.5), 5 °C, 3 days.

In the case of the Cu^{II}–**L6** complex, the AT-rich sequence showed low enantioselectivity, similar to that observed with the Cu^{II}–**L4** complex. High enantioselectivities were observed in the presence of G-tract sequences (Table 4, entries 4–6): the product was obtained with 99.4% *ee* with $d(TCAGGGCCCTGA)_2$ (Table 4, entry 6), for which low enantioselectivity was observed in the presence of the Cu^{II}–**L4** complex (Table 3, entry 6). In the case of single-stranded DNA, although 81% *ee* was observed with the longer sequence tested, d(TCAGGGCACT), the reaction was much slower than with double-stranded DNA. Double-stranded DNA is thus required for both enantioselectivity and rate acceleration. In particular, with the Cu^{II}–**L6** complex, DNA sequences that induced the highest enantioselectivity also showed the largest rate enhancement: $d(TCAGGGCCCTGA)_2$ caused a two-fold rate acceleration relative to the reaction with st-DNA. In other words, a 100-fold reaction enhancement was observed as compared with the reaction in the absence of DNA. The correlation between reaction rate and DNA sequence indicates a significant point: of all the catalytic sites present in the DNA bound to the copper complex, the catalytic sites that lead to the highest enantioselectivity dominate the reaction, because they tend to increase the reactivity most.

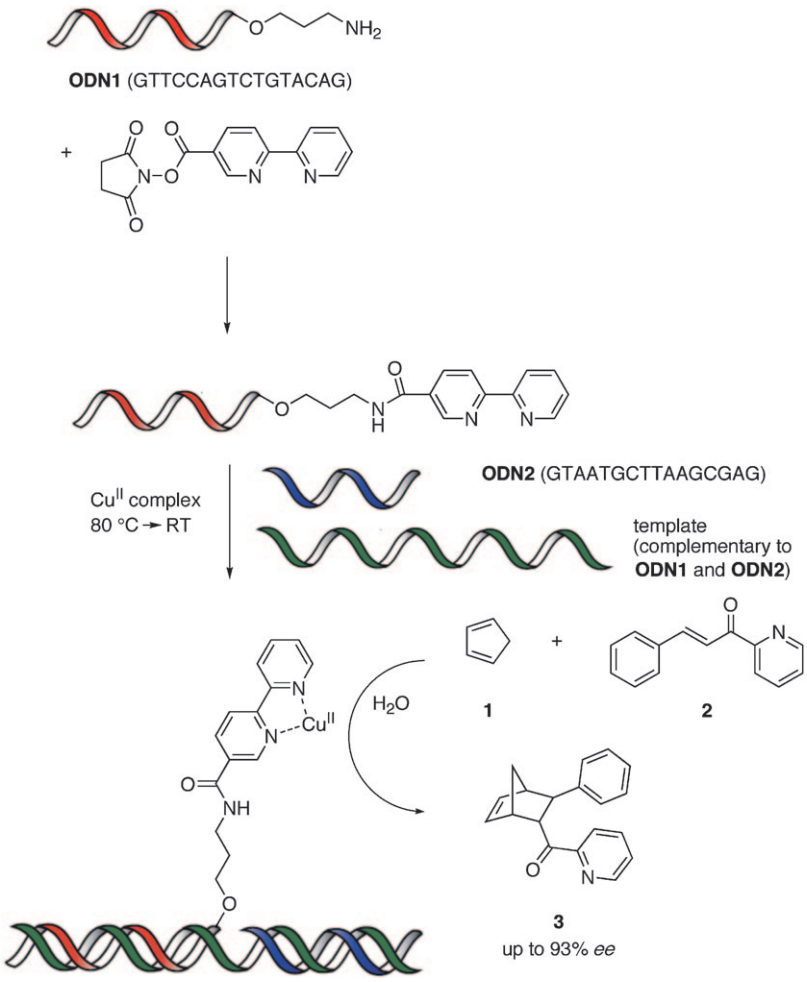
As a modular strategy for the screening of specific DNA sequences, Sancho Oltra and

Table 4: Dependence of enantioselectivity on the DNA sequence in the Cu^{II}–**L6**-catalyzed Diels–Alder reaction of **1** and **2**.[a]

Entry	DNA	*ee* [%]
	double-stranded DNA	
1	poly(dA-dT)(dA-dT)	15 (−)
2	poly(dG-dC)(dG-dC)	78 (+)
3	$d(GCGCGCGCGCGC)_2$	95 (+)
4	$d(TCGGGATCCCGA)_2$	98.4 (+)
5	$d(TCGGGTACCCGA)_2$	98.6 (+)
6	$d(TCAGGGCCCTGA)_2$	99.4 (+)
	single-stranded DNA	
7	d(GGG)	< 5 (+)
8	d(TCAGGGCACT)	81 (+)

[a] Reaction conditions: [**1**] = 8 mM, [**2**] = 1 mM, [Cu**L6**$(NO_3)_2$] = 0.30 mM, MOPS buffer (pH 6.5), 5 °C, 60 h.

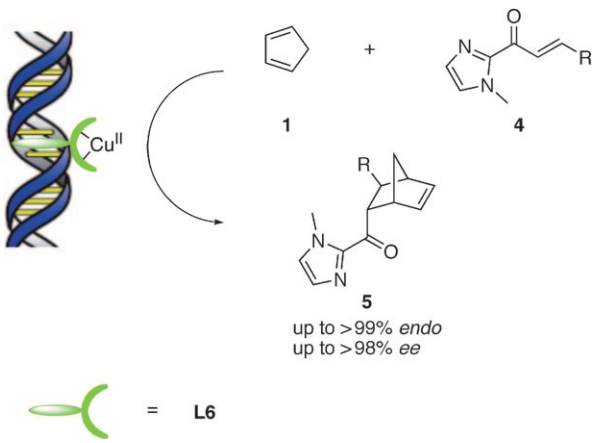
Roelfes introduced DNA hybrid catalysts containing a covalently anchored metal complex and demonstrated their effectiveness in asymmetric Diels–Alder reactions (Scheme 4).[26] This approach involves a functionalized oligonucleotide **ODN1** with a ligand, an unfunctionalized oligonucleotide **ODN2**, and a template oligonucleotide strand with a sequence that is complementary to both **ODN1** and **ODN2**. Through hybridization, the Cu^{II} complex is positioned inter-



Scheme 4. Schematic representation of the assembly of the DNA-based hybrid catalyst through a covalent anchoring strategy and general reaction scheme.

nally at the interface between **ODN1** and **ODN2**. In this covalent anchoring strategy, many variations of the second coordination sphere around the metal center could therefore be created readily by exchanging **ODN2** and the template. Compared with the use of st-DNA or ct-DNA, this approach might involve more time and a higher cost; however, the covalent anchoring strategy has the important feature of enabling the precise positioning of the metal complex relative to the DNA to create a fine-tuned second sphere based on the specific DNA sequence.

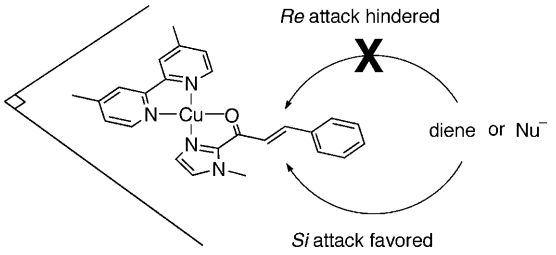
With respect to substrate scope, the 2-acyl pyridine moiety was found to be required in the dienophile, which has to be able to chelate the Cu^{II} complex, in terms of both activity and enantioselectivity. This feature is a potential concern for practical applications in synthesis because the pyridyl group can not be removed or transformed readily. However, the pyridine moiety could be replaced by a readily removable α,β-unsaturated 2-acyl imidazole auxiliary; substrates containing this functionality have proved useful in a variety of Lewis acid catalyzed reactions.[27] This alternative dienophile bound to the Cu^{II} ions in a bidentate fashion under aqueous conditions and gave the Diels–Alder adducts with high enantioselectivities (up to 98% *ee*; Scheme 5). If one considers the coordination environment around the Cu^{II} ion and the observed high enantioselectivity of the formation of **5**, DNA seems to block the *Re* face of the coordinated α,β-unsaturated 2-acyl imidazole effectively. Thus, an enantioselective Diels–Alder reaction with diene **1** might occur at the *Si* face of dienophile **4** because of the chiral microenvironment created by the DNA hybrid catalyst system (Scheme 6).



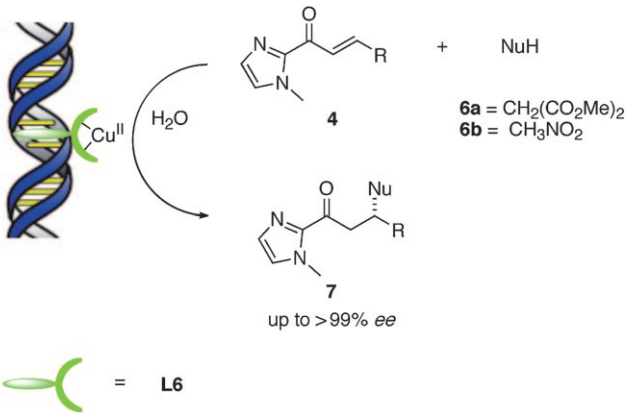
Scheme 5. Diels–Alder reaction of α,β-unsaturated 2-acyl imidazoles catalyzed by a supramolecular hybrid of the complex Cu^{II}–**L6** and DNA.

2.2. Michael Reaction

A DNA-based hybrid catalyst was used to promote a highly enantioselective Michael reaction in water (Scheme 7; the Michael adduct was obtained in some cases with >99% *ee*).[28] The maximum *ee* value observed previously for the product of a Michael reaction in water was 86% *ee* with a Pd–binap complex.[29]



Scheme 6. Stereofacial selectivity of the attack of the nucleophile in the DNA-based catalytic asymmetric Diels–Alder and Michael reactions of α,β-unsaturated 2-acyl imidazoles.



Scheme 7. Asymmetric Michael addition catalyzed by complexes formed between Cu^{II} ions and **L6** in the presence of DNA.

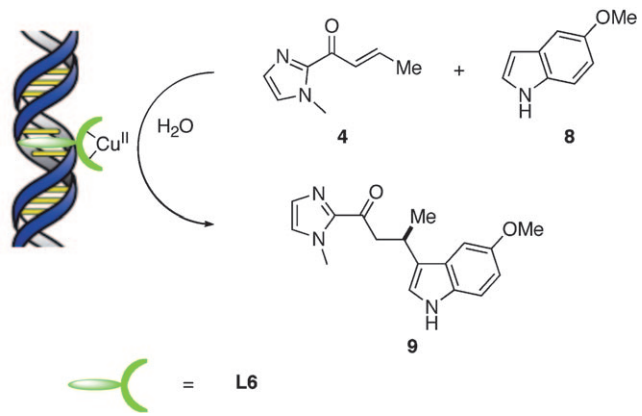
The DNA hybrid catalyst was self-assembled from st-DNA and a copper complex with **L6**; this catalyst also promoted Diels–Alder reactions with high enantioselectivity, as described in Section 2.1 (Schemes 2 and 5). The Michael adducts were obtained with up to 99% *ee* when dimethyl malonate was used as the nucleophile, and an α,β-unsaturated 2-acyl imidazole was used as the Michael acceptor. Nitromethane was also a good nucleophile in this reaction: the corresponding products were formed with up to 94% *ee*.

Like the stereochemical outcome of the Diels–Alder reaction,[22b] the observed high stereoselectivity can be explained as a consequence of the nucleophile attacking the *Si* face of the Michael acceptor because of the chiral environment provided by the DNA hybrid catalyst system (Scheme 6). Because the Cu^{II}–**L6**/st-DNA complex remains in the aqueous phase during extraction of the products, the DNA hybrid catalyst could be recovered. In the case of the DNA-mediated Michael reaction, the recovered catalyst solution was reused for another reaction on a 1 mmol scale without a significant decrease in the enantioselectivity or yield. These results demonstrate the potential of the DNA-based hybrid catalyst for practical applications in synthesis.

2.3. Friedel–Crafts Alkylation

A DNA-based hybrid catalyst also found application in the Friedel–Crafts alkylation, one of the most important Lewis acid mediated reactions; no other catalytic asymmetric

Friedel–Crafts alkylation of olefins has been described with water as the solvent.[30] The DNA-based hybrid catalyst was self-assembled by combining a Cu^{II} complex with st-DNA or oligonucleotides. The DNA-mediated catalytic enantioselective Friedel–Crafts alkylation reaction of 5-methoxyindole (**8**) in water was established by using α,β-unsaturated 2-acyl imidazoles as electrophiles under aqueous conditions (Scheme 8).



Scheme 8. Enantioselective Friedel–Crafts reaction catalyzed by a DNA-based hybrid catalyst.

The DNA sequence proved to be an important variable in the optimization of the reaction (Table 5). A series of synthetic double- and single-stranded DNA molecules were evaluated, and a similar pattern was observed to that found for the Diels–Alder reaction. The best results were obtained when Cu–dmbpy was used in combination with the self-complementary oligonucleotide d(TCAGGGCCCTGA)$_2$ (93% *ee*; Table 5, entry 2). This sequence also gave the best results in the Diels–Alder reaction (Table 4, entry 6).[23] The enantioselectivity decreased significantly with AT-rich duplexes and single-stranded DNA (Table 5, entries 4 and 5).

Table 5: Effect of the DNA sequence on the Cu^{II}–dmbpy–DNA-catalyzed Friedel–Crafts reaction.[a]

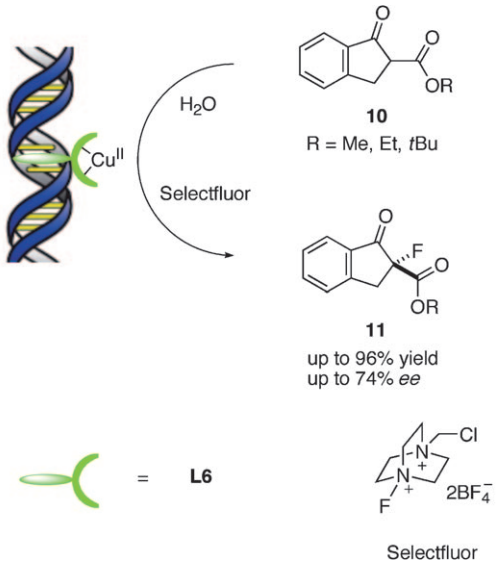
Entry	DNA	*ee* [%]
	double-stranded DNA	
1	st-DNA	83 (+)
2	d(TCAGGGCCCTGA)$_2$	93 (+)
3	d(GACTGACTAGTCAGTC)$_2$	55 (+)
4	d(ATATATATATAT)$_2$	35 (+)
	single-stranded DNA	
5	d(AGTCCCGTGA)	12 (+)

[a] Reaction conditions: [**4**] = 1 mM, [**8**] = 5 mM, [Cu^{II}-**L6**] = 0.3 mM, MOPS buffer (pH 6.5), 5 °C, 10 h.

In this reaction, not only was a 30-fold rate acceleration observed in the presence of DNA, but the reusability of the DNA-based hybrid catalyst was also verified. In the case of the reaction between **4** and **8** in entry 1 of Table 5, the catalyst solution was recovered at the end of the reaction by simple extraction and was reused for two more reactions. Undiminished activity was observed in terms of yield and enantioselectivity (second and third runs: 70 and 75% yield, 82 and 81% *ee*, respectively).

2.4. Fluorination

Although less studied than the above-mentioned carbon–carbon bond-forming reactions, the creation of carbon–heteroatom bonds with a DNA-based hybrid catalyst has also been demonstrated. Shibata, Toru, and co-workers developed the first DNA-based asymmetric C–F bond-forming reaction (Scheme 9)[31] by combining a chemical fluorination procedure and the DNA hybrid system established for the asymmetric Diels–Alder reaction by Roelfes and Feringa. The fluorination of indanone β-ketoesters with the Cu^{II}–dmbpy–DNA catalyst was carried out in an aqueous buffer with Selectfluor as the fluorine-transfer reagent. The effect of the ligand structure on the enantioselectivity is consistent with the previous observations for asymmetric Diels–Alder reactions. In the presence of dmbpy, fluorinated products were obtained with good DNA-induced enantioselectivity (up to 74% *ee*).



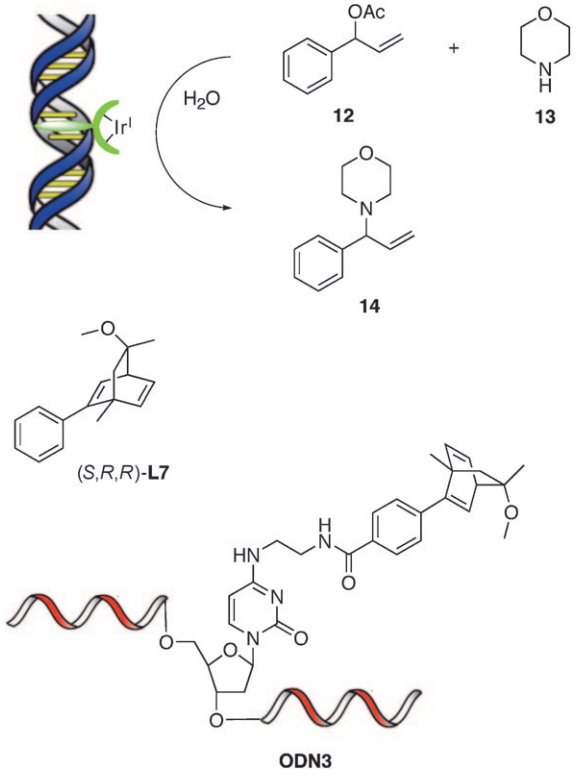
Scheme 9. Cu^{II}–dmbpy–DNA-mediated enantioselective C–F bond formation.

2.5. Allylic Amination with an Iridium(I)–Diene–DNA Hybrid Catalyst

The above-mentioned catalytic processes with DNA hybrid catalysts are restricted to Lewis acid catalyzed reactions with Cu^{II} ions. Two more examples of DNA-based asymmetric catalysis with copper complexes have been reported; however, the enantioselectivities in these cases were very low.[32] The use of DNA-conjugated transition-metal complexes that are not based on copper in organome-

tallic catalysis emerged only a short time ago.[33] Jäschke and co-workers demonstrated that the application of DNA hybrid catalysis could be extended to organometallic chemistry beyond Lewis acid catalysis.[33b]

A DNA-based system was utilized for an allylic substitution on the basis of iridium(I) diene chemistry in an aqueous medium. Bicyclo[2.2.2]octadiene ligands,[34] which had shown good activity in iridium(I)-catalyzed allylic substitution reactions, were selected and modified for use as anchoring ligands for DNA hybrid catalysis (Scheme 10). The DNA–



Scheme 10. Allylic amination by an iridium(I)–diene–DNA hybrid catalyst.

diene hybrid ligand was examined in the iridium-catalyzed allylic substitution of 1-phenylallyl acetate (**12**) with morpholine (**13**) in an aqueous medium (Scheme 10). In the presence of the DNA-based diene **ODN3**, a slightly higher activity was observed than with the iridium(I) complex of the free diene. These results show that the abundant nitrogen-containing heterocycles in DNA do not contend with the diene ligand for iridium coordination and do not obstruct the organometallic catalysis. Furthermore, the stereoselectivity of the DNA-based hybrid catalysts was demonstrated through the kinetic resolution of 1-phenylallyl acetate (**12**; Table 6). Complementary DNA and RNA strands were selected to modulate the chiral microenvironment surrounding the iridium–diene–DNA complex through hybridization, and 0.5 equivalents of morpholine were used to enable measurement of the *ee* values of 1-phenylallyl acetate (**12**) and the product at 50% conversion of **12**. The enantioselectivity observed depends on the distinct helix structure of the ligand and the complementary strand (single strand: no helix, DNA/DNA duplex: B-type helix, DNA/RNA duplex: A-type helix). Although the *ee* values observed remained low, these results clearly indicate chirality transfer from DNA to the iridium complex.

Table 6: Hybrid catalysts in the kinetic resolution of 1-phenylallyl acetate (**12**).[a]

Entry	Ligand[b]	Complementary strand	Yield [%][c]	**12** *ee* [%]	**14** *ee* [%]
1	**L7**	–	48	23	28
2	**ODN3**	–	49	16	23
3	**ODN3**	**cDNA3**	45	≤5	9
4	**ODN3**	**cRNA3**	48	−19	−27

[a] Reaction conditions: [**12**] = 50 mM, [**13**] = 25 mM, [{Ir(C$_2$H$_4$)$_2$Cl}$_2$] = 50 μM, [ligand] = 100 μM, water/dioxane (7:3), RT, 40 h. [b] **ODN3**: GCAGTGAAGGCTGAGCTCC. [c] The yield (based on **12**) was determined by GC.

3. Summary

In conclusion, we have discussed the development of DNA-based hybrid catalysts and the progress made in terms of their application in asymmetric catalysis. DNA-based hybrid catalysts were self-assembled from DNA and a metal complex with a specific ligand through supramolecular or covalent anchoring strategies and applied in asymmetric carbon–carbon or carbon–heteroatom bond-forming reactions. The use of DNA in Lewis acid catalyzed reactions, such as Diels–Alder, Michael addition, and Friedel–Craft reactions, led to high stereoselectivity and rate enhancement.

Although this research field is still in its infancy, the successful exploitation of helical chirality in asymmetric catalysis is a significant breakthrough. DNA hybrid catalysts should be beneficial to the development of green chemistry in academia and industry, because DNA-based catalytic systems can be used in aqueous media. As shown by an allylic amination with a DNA–diene–iridium(I) hybrid catalyst, the door is open for the incorporation of various metal complexes in DNA hybrid catalysts, and the optimization of new DNA-based hybrid catalysts will leap forward with the advance of molecular-biology techniques. However, challenges also lie ahead. For one thing, the water solubility of DNA can be a limitation, as many organic reagents are not soluble in water, and some are unstable in water. Can the DNA hybrid catalytic system be applied in organic media? Tanaka and Okahata reported a simple preparation of a DNA–lipid complex that is soluble in organic solvents, such as benzene, ethanol, and chloroform.[35] Such complexes might act as a stepping stone toward the extensive application of DNA hybrid catalysts.

We hope that this Minireview will inspire the active interest of many scientists in this area of asymmetric catalysis. We expect that DNA hybrid catalysis will find broad application as a complementary strategy to established approaches in asymmetric catalysis and will facilitate the asymmetric synthesis of enantiomerically pure target compounds.

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