DNA-Based Catalysis

DOI: 10.1002/anie.201204850

Enantioselective Diels–Alder Reactions with G-Quadruplex DNA-Based Catalysts**

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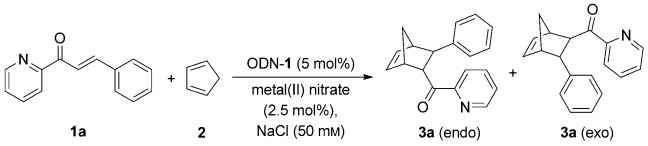
Deoxyribonucleic acid (DNA) is the genetic material of living organisms. In the past, double-stranded DNA (dsDNA) with its ubiquitous architecture has not been regarded as a catalytic species, since the duplex structure precludes the formation of catalytically competent tertiary structures.[1] To date, although no naturally occurring catalytic DNA has been reported, DNA for nonbiological applications has aroused much interest in chemists for applications in areas such as catalysis, encoding, and stereocontrol.[2] Among these applications, a series of DNA-based asymmetric catalysis have been developed, which use a hybrid catalyst composed of dsDNA and a copper(II) complex.[3] This same strategy was later applied to G-quadruplex DNA (G4DNA) and modest enantioselectivities in the Diels–Alder (D–A) reaction were obtained.[4] Very recently, a G4DNA metalloenzyme composed of G4DNA and copper(II) ions has been reported to be able to catalyze an enantioselective Friedel–Crafts reaction.[5] This biology/chemistry interface is an attractive area of research and awaits further extensive exploration. Herein, we report an enantioselective D–A reaction achieved through the use of human telomeric G4DNA-based catalysts. We show that the absolute configuration of the products can be reversed when the conformation of the G4DNA is switched from antiparallel to parallel. Furthermore, both the reaction rate and the enantioselectivity of the reaction were found to be dependent on the DNA sequence.

The D–A reaction is an important carbon–carbon bond forming reaction in organic synthesis. In the past few decades, it has received much attention in the development of innovative catalytic strategies to control the creation of the new carbon–carbon bonds and stereocenters. Among those strategies, biological molecules have been viewed as interesting and promising catalysts.[6] Herein, human telomeric G4DNA (ODN-**1**, 5′-$G_3(T_2AG_3)_3$-3′) was selected owing to its tunable conformation. As an initial attempt, a model D–A reaction[7] between aza-chalcone (**1a**) and cyclopentadiene (**2**) was chosen to probe the catalytic performance of ODN-**1**. We found that ODN-**1** alone in its antiparallel conformation[8] could promote the D–A reaction and the enantiomeric excess of the *endo* isomer of product **3a** is 17% (Table 1, entry 2).

Table 1: Diels–Alder reaction catalyzed by G4DNA-based catalysts.[a]



1a + **2** → **3a** (endo) + **3a** (exo)

Entry	Catalyst	Conversion [%][b]	*endo*/*exo*[b]	*ee* [%][c]
1	none	9	86:14	0
2	ODN-**1**	16	91:9	17
3	Cu^{2+}	68	92:8	0
4	ODN-**1**-Cu^{2+}	99	98:2	74
5[d]	ODN-**1**-Cu^{2+}	99	98:2	66
6	ODN-**1**-Ni^{2+}	20	92:8	32
7	ODN-**1**-Zn^{2+}	12	93:7	21
8	ODN-**1**-Co^{2+}	10	90:10	20

[a] See the Experimental Section for reaction details. All data are averaged over two experiments. [b] Determined for the crude product by HPLC analysis on a chiral stationary phase (Scheme S1); results are reproducible within ±5%. [c] Determined for the *endo* isomer by HPLC analysis on a chiral stationary phase; results are reproducible within ±5%. [d] $Cu(OTf)_2$ was used instead of $Cu(NO_3)_2$. OTf = trifluoromethanesulfonate.

The enantioselectivity of the ODN-**1** promoted D–A reaction is significantly higher than that of the uncatalyzed reaction (Table 1, entry 2 vs. entry 1), which suggests that ODN-**1** might function as an enantioselective catalyst for the D–A reaction.

We assembled a complex between $Cu(NO_3)_2$ and ODN-**1** (ODN-**1**-Cu^{2+}) and tested its ability to enantioselectively catalyze the D–A reaction. ODN-**1**-Cu^{2+} provides a significant enhancement in the reaction rate (Table 1, entry 4) compared with the rates observed with ODN-**1** (Table 1, entry 2) or $Cu(NO_3)_2$ (Table 1, entry 3). We also observed an excellent diastereoselectivity for product **3a** (*endo*/*exo* of 98:2) and a good enantioselectivity (74% *ee*). These results suggest that ODN-**1**-Cu^{2+} can serve as a potent catalyst, providing stereoselectivity and enhancement in reaction rates. To further understand ODN-**1**-Cu^{2+}, we investigated the effects of different anions and cations in the divalent metal salts. A similar result to $Cu(NO_3)_2$ was obtained with other anions, such as $Cu(OTf)_2$ (Table 1, entry 5). This result indicates that the anion exerts a trivial influence on the D–A reaction. To

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[**] This work is financially supported by National Natural Science Foundation of China (grant numbers. 20773123, 20621063, 31000392). We thank Prof. Zhaochi Feng, Prof. Qihua Yang and Dr. Jun Li for helpful discussions, particular acknowledgement to Dr. Xin Zhang of the Scripps Research Institute for revising the manuscript.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204850.

test the effect of the choice of metal cations, G4DNA-metal(II) complexes were formed with nickel(II), zinc(II), and cobalt(II) nitrates. In all cases, lower conversions and enantioselectivities were obtained in the D–A reaction with these complexes (Table 1, entries 6–8 vs. entry 4).

To elucidate the catalytic activity of ODN-**1**-Cu^{2+}, we measured the initial rate (V_{init}) of the D–A reaction catalyzed by ODN-**1**, Cu^{2+} and ODN-**1**-Cu^{2+} (Supporting Information, Figure S2). The $V_{init\,ODN\text{-}1\text{-}Cu^{2+}}$ is greater than the $V_{init\,Cu^{2+}}$ and the $V_{init\,ODN\text{-}1}$ at a fixed concentration of **1a** (Figure S2), suggesting that ODN-**1** and the Cu^{2+} ion are assembled into an integrated G4DNA-Cu^{2+} complex. The small difference between the $V_{init\,ODN\text{-}1}$ and the $V_{init\,uncatalyzed}$ implies at most only a weak catalytic function of ODN-**1** (Figure S2, inset). The apparent second-order rate constant (k_{app}) was estimated from the initial rate of the D–A reaction.[7,9] ODN-**1** and Cu^{2+} increase the k_{app} by 1.9-fold and 11.0-fold, respectively (Table 2, entries 2 and 3), whereas ODN-**1**-Cu^{2+} gives rise to a rate acceleration of up to 33.0-fold (Table 2, entry 4). Compared with Cu^{2+} alone as the catalyst, ODN-**1**-Cu^{2+} provides a modest three-fold acceleration in the D–A reaction rate, which can most likely be attributed to the G4DNA ligand.[7,9]

Table 2: Kinetic parameters for ODN-**1**, Cu^{2+}, and ODN-**1**-Cu^{2+}.[a]

Entry	Catalyst	k_{app} [$M^{-1}s^{-1}$][b]	k_{rel}[c]
1	none	$(2.0\pm0.5)\times10^{-3}$	1.0
2	ODN-**1**	$(3.7\pm0.2)\times10^{-3}$	1.9
3	Cu^{2+}	$(2.2\pm0.1)\times10^{-2}$	11.0
4	ODN-**1**-Cu^{2+}	$(6.6\pm0.9)\times10^{-2}$	33.0

[a] D–A reactions of **2** (1 mM) and **1a** at fixed concentrations (10, 15, 25, 35, and 50 μM), were carried out with ODN-**1** (50 μM), Cu^{2+} (25 μM), and ODN-**1**-Cu^{2+} composed of ODN-**1** (50 μM) and Cu^{2+} (25 μM), as well as without catalyst. Reactions conducted in 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer (20 mM, pH 6.5) with NaCl (50 mM), at 298 K. [b] The apparent second-order rate constant (k_{app}) was estimated from the initial rates ($k_{app}=V_{init}/([\mathbf{1a}]_0\cdot[\mathbf{2}]_0)$). [c] Rate acceleration (k_{rel}) is calculated by the ratio of $k_{app\,catalyst}/k_{app\,uncatalyzed}$, where $k_{app\,uncatalyzed}$ is the apparent second-order rate constant in the absence of the catalyst.

The conformation of G4DNA is inherently tunable,[10] so it provides a convenient system to probe the chiral induction effect of the ODN-**1** conformation in the D–A reaction. Without Na^+ ions, the conformation of ODN-**1**-Cu^{2+} is in a labile antiparallel G-quadruplex structure, as indicated by the circular dichroism (CD) spectrum (Figure 1b), and the product **3a** is obtained in 57% *ee* (Figure 1a). As the concentration of Na^+ ions increases, the antiparallel conformation of ODN-**1**-Cu^{2+} becomes stable, resulting in increased enantioselectivity of up to 74% *ee* (at 50 mM Na^+ ions) for product **3a**. Unexpectedly, higher Na^+ concentrations result in decreased enantioselectivity (Figure 1a), although the compact antiparallel conformation of ODN-**1**-Cu^{2+} is maintained (Figure 1b).

Under molecular crowding conditions, which can be generated by the addition of PEG200, the antiparallel ODN-**1** can be intramolecularly converted into a parallel

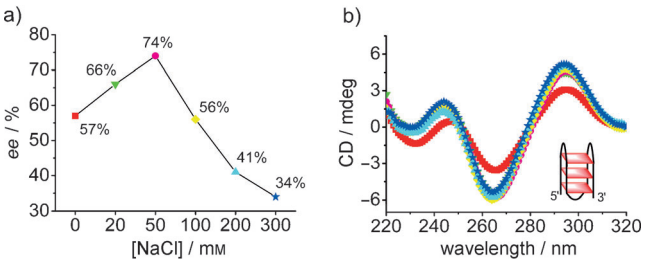


Figure 1. Effect of the concentration of Na^+ ions on the conformation of G4DNA and its correlation with the enantioselectivity of Diels–Alder reactions. a) The *ee* values of the *endo* isomer of **3a** from reactions catalyzed by ODN-**1**-Cu^{2+}. b) CD spectra of ODN-**1**-Cu^{2+} in MOPS buffer with varying concentrations of Na^+ ions. 0 mM (■), 20 mM (▼), 50 mM (●), 100 mM (◆), 200 mM (▲), and 300 mM (★).

conformation.[11] As mentioned above, without PEG200, ODN-**1**-Cu^{2+} is in a labile antiparallel conformation and gives **3a** in 57% *ee* (Figure 2a). As the concentration of PEG200 is increased to 10–20 wt%, the conformation of ODN-**1**-Cu^{2+} changes from antiparallel to a parallel/antiparallel hybrid (Figure 2b), and the enantioselectivity of the

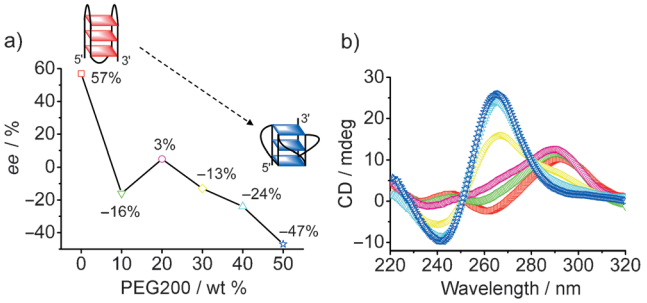


Figure 2. Effect of the concentration of PEG200 on the conformation of G4DNA and its correlation with the enantioselectivity of Diels–Alder reactions. a) The *ee* values of the *endo* isomer of **3a** from reactions catalyzed by ODN-**1**-Cu^{2+}. b) CD spectra of ODN-**1**-Cu^{2+} in MOPS buffer with varying PEG200 concentrations of 0 wt% (□), 10 wt% (▽), 20 wt% (○), 30 wt% (◇), 40 wt% (△), and 50 wt% (☆).

D–A reaction is low (Figure 2a). However, a higher PEG200 concentration (30 wt%) allows ODN-**1**-Cu^{2+} to adopt a parallel conformation,[11c] and product **3a** is obtained in 13% *ee* but as the opposite enantiomer. When the amount of PEG200 approaches to 50 wt%, the parallel conformation of ODN-**1**-Cu^{2+} becomes stable and the enantioselectivity increases to 47% *ee* for the opposite enantiomer. These results indicate that the addition of PEG200 changes the G4DNA structure and thus the active site, which results in production of the opposite enantiomer.

Experiments show that non-structured 21mer oligodeoxynucleotides combined with Cu^{2+} ions produce poor enantioselectivities (Figure S3e–i, Table S1), which further confirms that the G-quadruplex structure is essential for inducing enantioselectivity in the reaction. A series of control experiments were also conducted to demonstrate that significant enhancement in the D–A reaction occurs only when ODN-**1**-Cu^{2+} is involved (Table S2). Three strategies are introduced as

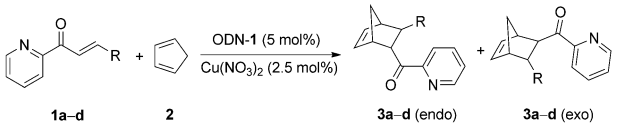
follows: 1) ODN-**1**-Cu^{2+}, 2) ODN-**1**-Cu(bipyridine),[4] and 3) ODN-**1**-Cu(**1a**), in which **1a** acts as a coplanar ligand. When ODN-**1** is in an antiparallel conformation, ODN-**1**-Cu^{2+} shows better catalytic performance in the D–A reaction than ODN-**1**-Cu(bipyridine) or ODN-**1**-Cu(**1a**) (Table S2, entry 1 vs. entries 2 and 3). These results unambiguously indicate that ODN-**1**-Cu^{2+} is more likely formed with the direct coordination of Cu^{2+} to ODN-**1**, which then acts as a G4DNA-Cu^{2+} complex to catalyze the reaction, whereas Cu(bipyridine) or Cu(**1a**) may interact with ODN-**1** through π–π stacking.[4] The above experiments were also carried out using the same strategies for the G4DNA in a parallel conformation, wherein a trend similar to that in the antiparallel G4DNA (Table S2, entries 4–6) studies was observed. Taken together, this work presents a different strategy for G4DNA-based asymmetric catalysis from the known method.[4]

With the primary catalytic results in hand, the substrate specificity of ODN-**1**-Cu^{2+} was tested with various substituted aza-chalcones (**1a–d**). ODN-**1**-Cu^{2+} was found to be an active catalyst for all the tested substrates in the D–A reaction. Although the *ee* values vary for products **3a–d**, the absolute configuration of each product can be reversed when the conformation of ODN-**1**-Cu^{2+} is switched from antiparallel to parallel (Table 3). We also investigated the k_{app} of the D–A reaction catalyzed by Cu^{2+} and ODN-**1**-Cu^{2+} for different substrates (Table S3). The modest rate accelerations ($k_{app\,ODN\text{-}1\text{-}Cu^{2+}}/k_{app\,Cu^{2+}}$) suggest that the Cu^{2+} ion primarily enhances the rate, whereas ODN-**1** mainly provides stereochemical control.

The coordination structure of metal ions or a metal complex to the host macromolecule in a metalloenzyme is crucial for catalytic performance, particularly in enantioselective reactions.[12] In an attempt to probe the localization of the Cu^{2+} ion in the G4DNA-Cu^{2+} complex, UV melting studies and UV Resonance Raman spectroscopy were employed. The two resulting curves nearly overlap, with a melting temperature of 54 °C (Figure S4b). This result implies that the Cu^{2+} ion has little or no destabilizing effect on the G-quadruplex structure in ODN-**1**-Cu^{2+}.[13] UV Resonance Raman spectroscopy was used to further confirm the G4DNA structure. When ODN-**1** interacts with the Cu^{2+} ion, the three characteristic Raman bands (1484, 1580, and 1605 cm^{-1}) are retained and the intensity of the two spectra is almost identical (Figure S4c), implying that the Hoogsteen hydrogen bonds and base-stacking interactions are not significantly affected.[14] According to the spectroscopic results, the accurate location of the Cu^{2+} ion is still unclear; more detailed characterizations are now underway.

The effect of the G4DNA sequence on the catalytic performance of the complex was investigated by loop mutation (Table 4). In the presence of Na^+ ions, ODN-**1–4** displayed antiparallel conformations, based on the CD spectra (Figure S3a–d). ODN-**1**-Cu^{2+} (loop sequence TTA) and ODN-**2**-Cu^{2+} (loop sequence ATA) generate product **3a** in 74% *ee* and 6% *ee*, respectively (Table 4, entries 1 and 2).

Table 3: Substrate specificity of ODN-**1**-Cu^{2+} for the Diels–Alder reaction.[a]



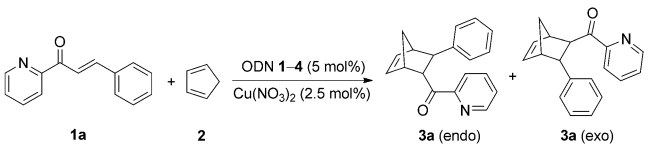
1a–d **2** **3a–d** (endo) **3a–d** (exo)

1a: R= C_6H_5 **1b**: R= *p*-$CH_3C_6H_4$ **1c**: R= *p*-$CH_3OC_6H_4$ **1d**: R= *p*-$NO_2C_6H_4$

Entry	Substrate	Conformation[b]	Conversion [%][c]	*endo*/*exo*[d]	*ee* [%][d]
1	**1a**	antiparallel	99	98:2	74
2	**1a**	parallel	97	97:3	−47
3	**1b**	antiparallel	62	97:3	21
4	**1b**	parallel	99	98:2	−51
5	**1c**	antiparallel	90	97:3	22
6	**1c**	parallel	80	91:9	−37
7	**1d**	antiparallel	90	96:4	47
8	**1d**	parallel	99	96:4	−71

[a] See the Experimental Section for reaction details. Reactions were run for 24 h (12 h for **1a**). All data are averaged over two experiments. [b] NaCl (50 mM) was added to form the antiparallel G4DNA-Cu^{2+} complex, and PEG200 (50 wt%) was added to form the parallel one. [c] Determined by ^1H NMR spectroscopy (HPLC for **3a**) of the crude product; results are reproducible within ±10%. [d] Determined for the *endo* isomer by HPLC analysis on a chiral stationary phase; results are reproducible within ±5%.

Table 4: Dependence of the enantioselectivity and the rate acceleration (k_{rel}) on the DNA sequence.[a]



1a **2** **3a** (endo) **3a** (exo)

Entry	5′–3′ sequence	Conformation[b]	*ee* [%][c]	k_{rel}[d]
1	ODN-**1**: $G_3(TTAG_3)_3$	antiparallel	74	3.0
2	ODN-**2**: $G_3(ATAG_3)_3$	antiparallel	6	0.9
3	ODN-**3**: $G_3(TATG_3)_3$	antiparallel	−27	1.0
4	ODN-**4**: $G_3(TTTG_3)_3$	antiparallel	−17	0.4
5	ODN-**1**: $G_3(TTAG_3)_3$	parallel	−47	1.5
6	ODN-**2**: $G_3(ATAG_3)_3$	parallel	−37	1.0
7	ODN-**3**: $G_3(TATG_3)_3$	parallel	−35	5.5
8	ODN-**4**: $G_3(TTTG_3)_3$	parallel	−66	1.0

[a] See the Experimental Section for reaction details. All data are the average of two experiments with conversions over 90%. [b] NaCl (50 mM) was added to form the antiparallel conformation of the G4DNA-Cu^{2+} complex, and PEG200 (50 wt%) was added to form the parallel one. [c] Determined for the *endo* isomer by HPLC on a chiral stationary phase; results are reproducible within ±5%. [d] Rate acceleration (k_{rel}) is the ratio of $k_{app\,ODN\text{-}1\text{-}Cu^{2+}}/k_{app\,Cu^{2+}}$ (for details, see Table S4).

However, ODN-**3**-Cu^{2+} (loop sequence TAT) and ODN-**4**-Cu^{2+} (loop sequence TTT) produce the opposite enantiomer of product **3a** in 27% *ee* and 17% *ee*, respectively (Table 4, entries 3 and 4). In contrast, under molecular crowding conditions, ODN-**1–4** all displayed parallel conformations (Figure S3a–d). Although the reactions catalyzed by the DNA-Cu^{2+} complex of ODN-**1–4** all produce the opposite enantiomer of product **3a**, the enantioselectivities vary with different loop sequences (Table 4, entries 5–8). These observations suggest that the loop sequence plays a crucial role in

chiral induction,[15] indicating that it is likely the enantioselective catalysis predominantly occurs in the loop region. We also investigated the rate acceleration ($k_{app\,ODN\text{-}\mathbf{1}\text{-}Cu^{2+}}/k_{app\,Cu^{2+}}$) for complexes of ODN-**1**–**4** (Table 4). Compared to Cu^{2+} alone, in two cases modest rate accelerations were observed (Table 4, entries 1 and 7), whereas in most cases the reaction rates are unaltered (Table 4, entries 3,6,8) or even reduced (Table 4, entries 2 and 4) in the presence of G4DNA. Taken together, both the reaction rate and the enantioselectivity are dependent on the DNA sequence.

In summary, we found that an enantioselective D–A reaction can be achieved by using human telomeric G4DNA-based catalysts. Furthermore, the absolute configuration of the product can be reversed when the G4DNA is switched from antiparallel to parallel. Our results demonstrate that the enantiomer produced, the enantioselectivity of the reaction, and the reaction rate are all dependent upon the DNA sequence chosen. This work provides a new method for the design of controllable DNA metalloenzymes for chemical and enzymatic synthesis.

Experimental Section

Standard Diels–Alder reaction procedure: An aqueous solution of ODN-**1** (5′-$G_3(TTAG_3)_3$-3′, 50 μM) was added to a 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer (2 mL, 20 mM, pH 6.5) containing either NaCl (50 mM) or PEG200 (50 wt%). After stirring for 30 min at 4 °C, a solution of $Cu(NO_3)_2$ (25 μM) was added. Then, aza-chalcone **1** in CH_3CN (20 μL of a 0.1M solution) was added. The reaction was initiated by the addition of freshly distilled cyclopentadiene **2** (15 μL) and the mixture was stirred for 12 h at 4 °C, followed by extraction with diethyl ether (3 × 5 mL). After drying the extracted mixture with anhydrous Na_2SO_4 and removal of the solvent, the crude products were directly analyzed by ^1H NMR spectroscopy and HPLC on a chiral stationary phase.

Received: June 21, 2012
Published online: August 15, 2012

Keywords: asymmetric catalysis · cycloaddition · Diels–Alder reaction · DNA · sequence-dependence

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