ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 6232–6234

www.rsc.org/chemcomm

COMMUNICATION

Enantioselective Friedel–Crafts reactions in water catalyzed by a human telomeric G-quadruplex DNA metalloenzyme†

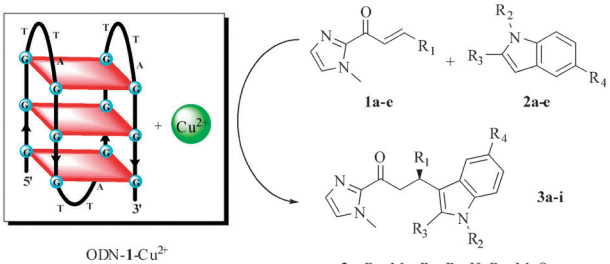
Changhao Wang,[ab] Yinghao Li,[ab] Guoqing Jia,[a] Yan Liu,[a] Shengmei Lu[a] and Can Li*[a]

Received 22nd February 2012, Accepted 2nd May 2012
DOI: 10.1039/c2cc31320k

A human telomeric G-quadruplex (G4DNA) metalloenzyme, assembled with G4DNA and Cu^{2+} ions, can catalyze the enantioselective Friedel–Crafts (F–C) reaction in water with good enantioselectivity (up to 75% ee). Furthermore, we found that the absolute configuration and the enantioselectivity of the product largely depend on the conformation and the sequence of G4DNA.

The Friedel–Crafts (F–C) reaction and its enantioselective variants are powerful carbon–carbon bond formation reactions in organic synthesis, and their application to alkylation of indole nucleus is an ongoing interest in the synthesis of natural products and potential medicinal intermediates.[1,2] In previous reports on the enantioselective F–C reactions, they were normally conducted under strictly anhydrous conditions, since only a few examples can tolerate even a small amount of water.[3] Boersma *et al.* reported the first catalytic enantioselective F–C alkylation in water using a DNA-based catalyst, which is composed of the double-stranded DNA and copper(II) complex with a special ligand.[4]

DNA, commonly existing in duplex structure, is an attractive scaffold for designing artificial metalloenzymes.[5] Recently, a series of chemical reactions have been achieved by DNA-based catalysts.[4,6] Amongst the possible conformations of DNA, G-quadruplex DNA (G4DNA) is found to form at the end of human telomeres, which is composed of a repeating string of TTAGGG units. The conformation of G4DNA is intrinsically tunable when factors such as strand orientation, loop type and arrangement, and glycosyl torsion angles are considered.[7] The variable topology of the G4DNA provides an opportunity to study the relationship between DNA structures and catalytic reaction performances. Until now, G4DNA has been used as a structural template to assist the catalytic functions,[8] and employed as a chiral scaffold to transfer the chirality.[6f] In this work, we report that the enantioselective F–C alkylations in water can be achieved using a human telomeric G4DNA metalloenzyme simply assembled by G4DNA and Cu^{2+} ions without additional ligands (Scheme 1). Furthermore, we found that the absolute configuration and the enantioselectivity of the product largely depend on the DNA sequence, and the loop sequence in the G4DNA metalloenzyme plays a crucial role in the chiral expression.



1a: R_1=Me
1b: R_1=Ph
1c: R_1=*p*-BrC_6H_4
1d: R_1=*p*-ClC_6H_4
1e: R_1=*p*-$MeOC_6H_4$

2a: R_2=R_3=H, R_4=MeO
2b: R_2=R_3=R_4=H
2c: R_2=R_3=H, R_4=Cl
2d: R_2=Me, R_3=R_4=H
2e: R_2=H, R_3=Me, R_4=H

3a: R_1=Me, R_2=R_3=H, R_4=MeO
3b: R_1=Me, R_2=R_3=R_4=H
3c: R_1=Me, R_2=R_3=H, R_4=Cl
3d: R_1=Me, R_2=Me, R_3=R_4=H
3e: R_1=Me, R_2=H, R_3=Me, R_4=H
3f: R_1=Ph, R_2=R_3=H, R_4=MeO
3g: R_1=*p*-BrC_6H_4, R_2=R_3=H, R_4=MeO
3h: R_1=*p*-ClC_6H_4, R_2=R_3=H, R_4=MeO
3i: R_1=*p*-$MeOC_6H_4$, R_2=R_3=H, R_4=MeO

Scheme 1 Schematic representation of the enantioselective F–C reactions in water catalyzed by the G4DNA metalloenzyme (ODN-**1**–Cu^{2+}).

A model enantioselective F–C reaction using 2-acylimidazole (**1a**) and 5-methoxy indole (**2a**) as the substrates in 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer was chosen to probe the catalytic properties of G4DNA.[4] In the presence of Na^+ ions, we found that human telomeric DNA (ODN-**1**, 5′-$G_3(TTAG_3)_3$-3′) in antiparallel structure[9] could catalyze the F–C reaction and the corresponding product **3a** was obtained in an enantiomeric excess (ee) of 13% (Table 1, entry 2). Although the conversion and the enantioselectivity are not very high, it clearly shows that ODN-**1** can work as a direct chiral catalyst.

Ribozyme usually binds divalent metal ions to stabilize the structure but in some cases can promote the catalysis,[10] thus the same strategy could be applied to DNA. When a G4DNA metalloenzyme (ODN-**1**–Cu^{2+}) was assembled with G4DNA and Cu^{2+} ions, it is very interesting that ODN-**1**–Cu^{2+} shows remarkably higher catalytic performance than ODN-**1** (Table 1, entry 2) or Cu^{2+} ions (Table 1, entry 3), and generates the corresponding product **3a** in 75% ee and nearly quantitative conversion in 24 hours (Table 1, entry 4). In addition, nickel(II), zinc(II) and cobalt(II) nitrates were also introduced to form the DNA metalloenzymes for the enantioselective F–C

[a] *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China*
[b] *Graduate School of Chinese Academy of Sciences, Beijing 100049, China. E-mail: canli@dicp.ac.cn*

† Electronic supplementary information (ESI) available: Experimental details, supplementary figures and tables, ^{1}H-NMR spectra and HPLC traces. See DOI: 10.1039/c2cc31320k

Table 1 Enantioselective F–C reaction catalyzed by ODN-**1** and its metalloenzymes[a]

Entry	Catalyst	Conversion[b] (%)	ee[c] (%)
1	No	9	0
2	ODN-**1**	18	13
3	Cu^{2+}	62	0
4	ODN-**1**–Cu^{2+}	99	75
5	ODN-**1**–Ni^{2+}	20	11
6	ODN-**1**–Zn^{2+}	25	8
7	ODN-**1**–Co^{2+}	30	3

[a] Reaction conditions: **1a** (1 μmol, 1 eq.), **2a** (5 eq.), ODN-**1** (0.1 eq.), metal(II) nitrate (0.05 eq.), NaCl (50 mM), MOPS buffer (20 mM, pH 6.5), 4 °C, 24 h. All data are averaged by two experiments. [b] Determined by chiral-phase HPLC for the crude product (Scheme S1, ESI). Reproducible within ±5%. [c] Determined by chiral-phase HPLC. Reproducible within ±5%.

reaction. Compared with the F–C reaction catalyzed by ODN-**1**–Cu^{2+} (Table 1, entry 4), lower conversions and enantioselectivities were obtained by using ODN-**1**–Ni^{2+}, ODN-**1**–Zn^{2+} and ODN-**1**–Co^{2+} (Table 1, entries 5–7).

The conformation of G4DNA is tunable,[7] so it is possible to find out the effect of the ODN-**1** conformation on enantioselective induction in the F–C reaction. In the presence of Na^+ ions, ODN-**1** can fold intramolecularly into an antiparallel G-quadruplex conformation.[9] According to the circular dichroism (CD) spectra (Fig. 1b), the conformation of ODN-**1**–Cu^{2+} is in a labile state of antiparallel G-quadruplex structure without Na^+ ions, and the F–C reaction gives the product **3a** with 49% ee (Fig. 1a). As the concentration of Na^+ ions is increased, the antiparallel conformation of ODN-**1**–Cu^{2+} becomes stable and compact, resulting in the increased enantioselectivity for the F–C reaction (Fig. 1a and b). When the concentration of Na^+ ions attains 50 mM, ODN-**1**–Cu^{2+} provides **3a** in good enantioselectivity of up to 75% ee. The compact antiparallel conformation of ODN-**1**–Cu^{2+} is still maintained at higher concentration of Na^+ ions according to the CD spectra, but results in decreased enantioselectivity (Fig. 1a and b).

In the presence of K^+ ions, the conformations of the G4DNA are usually in hybrid types.[11] Without K^+ ions, as mentioned above, ODN-**1**–Cu^{2+} is in a labile state and gives the F–C product in 49% ee (Fig. 1c and d). After a small amount of K^+ ions (2 mM) was added, the conformation of ODN-**1**–Cu^{2+} becomes compact (Fig. 1d), but the enantioselectivity is decreased to 9% ee (Fig. 1c). A little higher concentration of K^+ ions (5 mM) allows the ODN-**1**–Cu^{2+} to adopt the compact conformation, yet provides the reversed configuration of the product in 13% ee (Fig. 1c and d). As the concentration of K^+ ions is increased to 10–100 mM, the enantioselectivities of the F–C reaction do not change significantly (Table S1, ESI†), whereas the conformation of ODN-**1**–Cu^{2+} is converted to a hybrid type (Fig. 1d). In much higher concentration of K^+ ions (>200 mM), both the activity and the enantioselectivity decrease for the F–C reaction (Fig. 1c, Table S1 in ESI†).

Under molecular crowding conditions with PEG200, the conformation of ODN-**1**–Cu^{2+} can be switched from antiparallel type to parallel one by increasing the amount of PEG200 (Fig. 1f).[12] However, both the activity and the enantioselectivity of the enantioselective F–C reaction are decreasing (Fig. 1e, Table S2 in ESI†).

To investigate the sequence variations of the G4DNA metalloenzyme in the enantioselective F–C reaction, 21-mer oligodeoxynucleotides with different loop sequences were tested. In the presence of Na^+ ions, ODN-**1**–Cu^{2+} (loop sequence TTA) and ODN-**2**–Cu^{2+} (loop sequence TTT) generate the product **3a** with 75% ee and 6% ee, respectively (Table 2, entries 1 and 2). However, ODN-**3**–Cu^{2+} (loop sequence ATA), ODN-**4**–Cu^{2+} (loop sequence TAT), ODN-**5**–Cu^{2+}

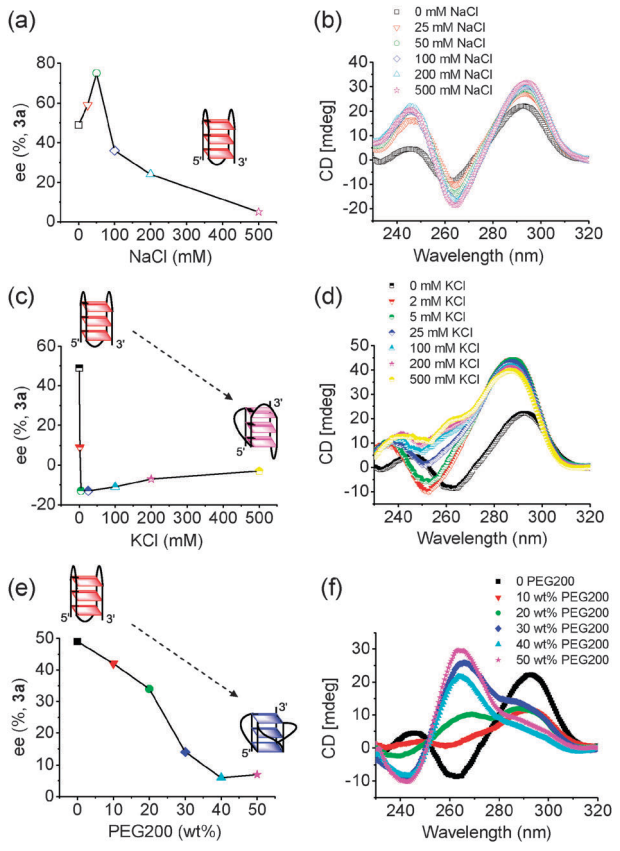


Fig. 1 The ee values of product **3a** for the F–C reaction catalyzed by ODN-**1**–Cu^{2+} with tuning the concentration of (a) Na^+ ions, (c) K^+ ions, and (e) PEG200. The corresponding CD spectra of ODN-**1**–Cu^{2+} by varying the concentration of (b) Na^+ ions, (d) K^+ ions, and (f) PEG200.

Table 2 Loop sequence variations of the G4DNA metalloenzyme[a]

Entry	Catalyst	ODN sequence	Conversion[b] (%)	ee[c] (%)
1	ODN-**1**–Cu^{2+}	5′-$G_3(TTAG_3)_3$-3′	99	75
2	ODN-**2**–Cu^{2+}	5′-$G_3(TTTG_3)_3$-3′	92	6
3	ODN-**3**–Cu^{2+}	5′-$G_3(ATAG_3)_3$-3′	95	−7
4	ODN-**4**–Cu^{2+}	5′-$G_3(TATG_3)_3$-3′	95	−6
5	ODN-**5**–Cu^{2+}	5′-$G_3(AAAG_3)_3$-3′	85	−17
6	ODN-**6**–Cu^{2+}	5′-$G_3(AATG_3)_3$-3′	95	−16

[a] Reaction conditions: **1a** (1 μmol, 1 eq.), **2a** (5 eq.), ODN (0.1 eq.), $Cu(NO_3)_2$ (0.05 eq.), NaCl (50 mM), MOPS buffer (20 mM, pH 6.5), 4 °C, 24 h. All data are averaged by two experiments. [b] Determined by chiral-phase HPLC for the crude product (Scheme S1, ESI). Reproducible within ±5%. [c] Determined by chiral-phase HPLC. Reproducible within ±5%.

Table 3 Substrate scope for the enantioselective F–C reactions[a]

Entry	1	2	3	Conversion[b] (%)	ee[c] (%)
1	**1a**	**2a**	**3a**	99	75
2	**1a**	**2b**	**3b**	99	67
3	**1a**	**2c**	**3c**	99	66
4	**1a**	**2d**	**3d**	93	8
5	**1a**	**2e**	**3e**	99	44
6	**1b**	**2a**	**3f**	91	21
7	**1c**	**2a**	**3g**	61	7
8	**1d**	**2a**	**3h**	72	7
9	**1e**	**2a**	**3i**	37	9

[a] Reaction conditions: **1** (1 μmol, 1 eq.), **2** (5 eq.), ODN-**1** (0.1 eq.), $Cu(NO_3)_2$ (0.05 eq.), NaCl (50 mM), MOPS buffer (20 mM, pH 6.5), 4 °C, 24 h. [b] Determined by ^{1}H-NMR for the crude product averaged by two experiments. Reproducible within ±10%. [c] Determined by chiral-phase HPLC. Reproducible within ±5%.

(loop sequence AAA) and ODN-**6**–Cu^{2+} (loop sequence AAT) provide the product **3a** in the reversed configuration of 7% ee, 6% ee, 17% ee and 16% ee, respectively (Table 2, entries 3–6). Minor mutations in the loop sequence of G4DNA can have a great effect on the enantioselective F–C reaction, which strongly suggests that the loop sequence plays a crucial role in the chiral induction of the reaction.[13] Compared to ODN-**1**–Cu^{2+}, non-structured 21-mer oligodeoxynucleotides containing d(TTA) combining with Cu^{2+} ions show the racemic products, indicating that the G-quadruplex structure is essential for the enantioselective F–C reaction (Table S3, ESI†).

Various substituted 2-acylimidazoles (**1a–e**) and substituted indoles (**2a–e**) were tested for the enantioselective F–C reactions catalyzed by ODN-**1**–Cu^{2+}. We were pleased to find that the ODN-**1**–Cu^{2+} could provide nearly full conversions for the F–C reactions with 2-acylimidazole (**1a**) and a variety of substituted indoles (**2a–e**). Compared to the F–C reaction between **1a** and indole (**2b**) that generates 67% ee (Table 3, entry 2), the reactions with **1a** and 5-methoxy indole (**2a**) and 5-chloro indole (**2c**) provide the corresponding product **3a** in 75% ee and **3c** in 66% ee (Table 3, entries 1 and 3), which indicates that the electronic effect of the substitute substantially influences the F–C reaction. In addition, substituted indoles such as 1-methyl indole (**2d**) and 2-methyl indole (**2e**) reacted with **1a** to generate the corresponding products in 8% ee and 44% ee, respectively (Table 3, entries 4 and 5). Moreover, 2-acylimidazoles with aromatic moieties (**1b–e**) reacted with **2a** yield the corresponding F–C products in low enantioselectivities (Table 3, entries 6–9). Compared to the F–C reaction between **1b** and **2a** (Table 3, entry 6), the 2-acylimidazoles with another substituent (*p*-Br, *p*-Cl and *p*-MeO) in the aromatic moiety of R_1 reacted with **2a** yield the corresponding F–C products with decreased activities and enantioselectivities.

In summary, we found that human telomeric G4DNA can serve as a direct chiral catalyst for the enantioselective F–C reaction. When a G4DNA metalloenzyme is derived from Cu^{2+} ions and G4DNA, the activity and the enantioselectivity of the F–C reaction are considerably enhanced. Furthermore, we found that the absolute configuration and the enantioselectivity of the product are sensitive to the DNA sequence, and the loop sequence in the G4DNA metalloenzyme plays an important role in the chiral expression. This work opens a new avenue to construct a controllable DNA metalloenzyme for chemical and enzymatic synthesis using the accessible DNA.

We thank Prof. Z. Feng, Prof. Q. Yang and Dr J. Li for their helpful discussions. This work was supported by the NSFC (20773123, 20621063, 31000392).

Notes and references

1 (*a*) T. B. Poulsen and K. A. Jørgensen, *Chem. Rev.*, 2008, **108**, 2903; (*b*) S. L. You, Q. Cai and M. Zeng, *Chem. Soc. Rev.*, 2009, **38**, 2190.

2 (*a*) K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 160; (*b*) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370; (*c*) W. Zhuang, T. Hansen and K. A. Jørgensen, *Chem. Commun.*, 2001, 347; (*d*) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam and J. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 10780; (*e*) D. A. Evans, K. R. Fandrick and H. J. Song, *J. Am. Chem. Soc.*, 2005, **127**, 8942; (*f*) D. A. Evans, K. R. Fandrick, H. J. Song, K. A. Scheidt and R. Xu, *J. Am. Chem. Soc.*, 2007, **129**, 10029; (*g*) B. M. Trost and C. Müller, *J. Am. Chem. Soc.*, 2008, **130**, 2438; (*h*) Y. Liu, D. Shang, X. Zhou, Y. Zhu, L. Lin, X. Liu and X. Feng, *Org. Lett.*, 2010, **12**, 180; (*i*) Q. Yin and S. L. You, *Chem. Sci.*, 2011, **2**, 1344.

3 (*a*) J. Zhou, M. C. Ye, Z. Z. Huang and Y. Tang, *J. Org. Chem.*, 2004, **69**, 1309; (*b*) H. Ube, S. Fukuchi and M. Terada, *Tetrahedron: Asymmetry*, 2010, **21**, 1203; (*c*) F. Guo, D. Chang, G. Lai, T. Zhu, S. Xiong, S. Wang and Z. Wang, *Chem.–Eur. J.*, 2011, **17**, 11127.

4 A. J. Boersma, B. L. Feringa and G. Roelfes, *Angew. Chem., Int. Ed.*, 2009, **48**, 3346.

5 (*a*) A. J. Boersma, R. P. Megens, B. L. Feringa and G. Roelfes, *Chem. Soc. Rev.*, 2010, **39**, 2083; (*b*) S. K. Silverman, *Angew. Chem., Int. Ed.*, 2010, **49**, 7180; (*c*) T. R. Ward, *Acc. Chem. Res.*, 2011, **44**, 47.

6 (*a*) G. Roelfes and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2005, **44**, 3230; (*b*) D. Coquière, B. L. Feringa and G. Roefles, *Angew. Chem., Int. Ed.*, 2007, **46**, 9308; (*c*) N. Shibata, H. Yasui, S. Nakamura and T. Toru, *Synlett*, 2007, 1153; (*d*) E. W. Dijk, B. L. Feringa and G. Roelfes, *Tetrahedron: Asymmetry*, 2008, **19**, 2374; (*e*) P. Fournier, R. Fiammengo and A. Jäschke, *Angew. Chem., Int. Ed.*, 2009, **48**, 4426; (*f*) S. Roe, D. J. Ritson, T. Garner, M. Searle and J. E. Moses, *Chem. Commun.*, 2010, **46**, 4309; (*g*) A. J. Boersma, D. Coquière, D. Geerdink, F. Rosati, B. L. Feringa and G. Roelfes, *Nat. Chem.*, 2010, **2**, 991.

7 *Quadruplex Nucleic Acids*, ed. S. Neidle and S. Balasubramanian, RSC publishing, Cambridge, 2006.

8 (*a*) Z. Tang and A. Marx, *Angew. Chem., Int. Ed.*, 2007, **46**, 7297; (*b*) Z. Tang, D. P. N. Gonçalves, M. Wieland, A. Marx and J. S. Hartig, *ChemBioChem*, 2008, **9**, 1061; (*c*) S. A. McManus and Y. Li, *J. Mol. Biol.*, 2008, **375**, 960; (*d*) S. Nakayama, J. Wang and H. O. Sintim, *Chem.–Eur. J.*, 2011, **17**, 5691.

9 Y. Wang and D. J. Patel, *Structure*, 1993, **1**, 263.

10 A. M. Pyle, *Science*, 1993, **261**, 709.

11 (*a*) A. Ambrus, D. Chen, J. Dai, T. Bialis, R. A. Jones and D. Yang, *Nucleic Acids Res.*, 2006, **34**, 2723; (*b*) K. N. Luu, A. T. Phan, V. Kuryavyi, L. Lacroix and D. J. Patel, *J. Am. Chem. Soc.*, 2006, **128**, 9963; (*c*) Y. Xu, Y. Noguchi and H. Sugiyama, *Bioorg. Med. Chem.*, 2006, **14**, 5584; (*d*) J. Dai, M. Carver, C. Punchihewa, R. A. Jones and D. Yang, *Nucleic Acids Res.*, 2007, **35**, 4927; (*e*) A. T. Phan, V. Kuryavyi, K. N. Luu and D. J. Patel, *Nucleic Acids Res.*, 2007, **35**, 6517; (*f*) K. W. Lim, S. Amrane, S. Bouaziz, W. Xu, Y. Mu, D. J. Patel, K. N. Luu and A. T. Phan, *J. Am. Chem. Soc.*, 2009, **131**, 4301.

12 (*a*) Y. Xue, Z. Y. Kan, Q. Wang, Y. Yao, J. Liu, Y. H. Hao and Z. Tan, *J. Am. Chem. Soc.*, 2007, **129**, 11185; (*b*) J. Zhou, C. Wei, G. Jia, X. Wang, Q. Tang, Z. Feng and C. Li, *Biophys. Chem.*, 2008, **136**, 124; (*c*) B. Heddi and A. T. Phan, *J. Am. Chem. Soc.*, 2011, **133**, 9824; (*d*) L. Petraccone, A. Malafronte, J. Amato and C. Giancola, *J. Phys. Chem. B*, 2012, **116**, 2294.

13 (*a*) H. Yu, X. Wang, M. Fu, J. Ren and X. Qu, *Nucleic Acids Res.*, 2008, **36**, 5695; (*b*) H. Yu, C. Zhao, Y. Chen, M. Fu, J. Ren and X. Qu, *J. Med. Chem.*, 2010, **53**, 492; (*c*) C. Zhao, J. Geng, L. Feng, J. Ren and X. Qu, *Chem.–Eur. J.*, 2011, **17**, 8209.

