Electronic supplementary information (ESI)

Enantioselective Friedel-Crafts reactions in water catalyzed by human telomeric G-quadruplex metalloenzyme

Changhao Wang, Yinghao Li, Guoqing Jia, Yan Liu, Shengmei Lu and Can Li

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

*To whom correspondence should be addressed. E-mail: canli@dicp.ac.cn

Tel: (+86) 411-84379070; Fax: (+86) 411-84694447.
# Table of Contents

General remarks........................................................................................................... S3  
Materials......................................................................................................................... S4  
Typical procedure............................................................................................................ S5  
Calculation the conversion of 1a.................................................................................... S6  
Scheme S1....................................................................................................................... S6  
Figure S1......................................................................................................................... S6  
Table S1.......................................................................................................................... S7  
Table S2.......................................................................................................................... S8  
Table S3.......................................................................................................................... S9  
References...................................................................................................................... S10  
$^1$H-NMR spectra and HPLC traces.............................................................................. S11
**General remarks**

Circular dichroism (CD) spectra were recorded on a dual beam DSM 1000 CD spectrophotometer (Olis, Bogart, GA) with a 10 mm quartz cell. Samples containing 10 μM oligomer were prepared and treated as described above before collecting CD spectra. Each measurement was recorded from 230 to 320 nm at room temperature (about 20 °C). The average scan for each sample was subtracted by a background CD spectrum of corresponding buffer solution. $^1$H-NMR spectrum was recorded on a Bruker DRX 400 MHz type ($^1$H, 400 MHz) with an internal reference tetramethylsilane. Data for $^1$H NMR spectra were recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration, coupling constant (Hz). High-performance liquid chromatography (HPLC) analysis was performed on an Agilent 1100 Series instrument with the eluents of hexane and isopropanol (i-PrOH), using a Daicel Chiralpak AD Column (250 × 4.6 mm) and Daicel Chiralcel OD Column (250 × 4.6 mm).
Materials

DNA oligodeoxynucleotides: 5'-G₃(TTAG₃)₃-3’ (ODN-1), 5'-G₃(TTG₃)₃-3’ (ODN-2), 5'-G₃(ATTG₃)₃-3’ (ODN-3), 5'-G₃(TATG₃)₃-3’ (ODN-4), 5'-G₃(AGAG₃)₃-3’ (ODN-5), 5'-G₃(AATG₃)₃-3’ (ODN-6), 5'-T₃(TTAT₃)₃-3’ (ODN-7), 5'-A₃(TTAA₃)₃-3’ (ODN-8), 5’-(TTA)₇-3’ (ODN-9) and 3-(N-morpholino)propanesulfonic acid (MOPS) were purchased from Sangon (Shanghai, China), and the strand concentrations were determined by measuring the absorbance at 260 nm using the extinction coefficient values published in the literature.¹ Cu(NO₃)₂·3H₂O (>99%), Zn(NO₃)₂·6H₂O (>99%), Co(NO₃)₂·6H₂O (>99%), Ni(NO₃)₂·6H₂O (>99%), NaCl (>99%), KCl (>99%) and PEG200 were purchased from Alfa Aesar (Tianjin, China). 5-methoxyindole (98%), indole (99%), 5-chloroindole (98%), 1-methylindole (98%) and 1-methylindole (98%) were purchased from J&K (Beijing, China). Water was distilled and deionized using a Milli-Q A10 water purification system. Other reagents and solvents were obtained from commercial sources and used without further purification. α,β-unsaturated 2-acyl imidazoles 1a-e were prepared according to the literature.²,³
Typical procedure

To a MOPS buffer (1 mL, 20 mM, pH 6.5) containing NaCl (50 mM), an aqueous solution of ODN-1 (5’-G3(TTAG3)3-3’, final conc. 100 μM) was added. After stirred for a half hour at 4 °C, a solution of Cu(NO3)2 (2 μL of a 25 mM solution, final conc. 50 μM) was added. Then, 2-acyl imidazole 1a in DMSO (10 μL of a 0.1 M solution) was added. The reaction was initiated by addition of nucleophile 2a in DMSO (10 μL of a 0.5 M solution, 5 equiv.) and the mixture was stirred for 24 hours, followed by the extraction with ethyl acetate (3 × 5 mL), and the solvent was removed under reduced pressure. After a short flash chromatography, the residue was directly analyzed by 1H-NMR and HPLC.4,5
Calculation the conversion of 1a

Conversions of 1a were calculated using the following formula:

\[
\text{Conversion of 1a} \% = \frac{\text{PA}_{3a}}{\text{PA}_{3a} + \text{PA}_{1a}/f}
\]

**Scheme S1**

Where \( \text{PA}_{1a} \) and \( \text{PA}_{3a} \) are the peak areas of 1a and 3a, respectively. And \( f \) is the correction factor determined to be 1.27 from a fitting curve (Fig. S1).

![Graph](image)

**Fig. S1** Determination of the correction factor. The HPLC ratios of peak areas (\( \text{PA}_{3a}/\text{PA}_{1a} \)) were determined with the standard molar ratios (\( n_{3a}/n_{1a} \)) of 1/20, 1/10, 1/5, 1/2, 1, 2, 5, 10, 20. The correction factor (\( f = 1.27 \)) was estimated from the fitting curve (\( R^2 = 0.992 \)).
Table S1 Enantioselective Friedel-Crafts reactions catalyzed by ODN-1-Cu$^{2+}$ by tuning the concentration of K$^+$ ions

Unless otherwise noted, all reactions were carried out in a typical procedure. $^b$ Determined by chiral-phase HPLC for the crude product (Scheme S1, ESI†). $^c$ Determined by chiral-phase HPLC.
**Table S2** Enantioselective Friedel-Crafts reactions catalyzed by ODN-1-Cu^{2+} by varying the amount of PEG200

\[ \text{Unless otherwise noted, all reactions were carried out in a typical procedure.} \]
\[ \text{Determined by chiral-phase HPLC for the crude product (Scheme S1, ESI†).} \]
\[ \text{Determined by chiral-phase HPLC.} \]
Table S3 Enantioselective Friedel-Crafts reactions catalyzed by various 21mer oligodeoxynucleotides combining with Cu\(^{2+}\) ions

 Unless otherwise noted, all reactions were carried out in a typical procedure. \(^{b}\) Determined by chiral-phase HPLC for the crude product (Scheme S1, ESI†). \(^{c}\) Determined by chiral-phase HPLC.
References


$^1$H-NMR spectra and HPLC traces

3-(5-methoxy-1H-indol-3-yl)-1-(1-methyl-1H-imidazol-2-yl)butan-1-one (3a).

$^1$H-NMR (CDCl$_3$, 400 MHz) δ 1.40 (d, $J = 6.9$ Hz, 3H), 3.40 (dd, $J = 15.6$, 8.4 Hz, 1H), 3.57 (dd, $J = 15.6$, 6.1 Hz, 1H), 3.77-3.82 (m, 1H), 3.86 (s, 3H), 3.94 (s, 3H), 6.82 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.01 (d, $J = 2.7$ Hz, 2H), 7.15 (s, 2H), 7.20 (d, $J = 8.8$ Hz, 1H), 8.18 (s, 1H).
HPLC condition: Daicel chiralpak-AD, hexane/i-PrOH 80:20, 1.0 mL/min, 254 nm.

Racemic 3a.

Retention times: 15.8 (+) and 21.9 (-) mins.
Product 3a from the F-C reaction catalyzed by ODN-1-Cu$^{2+}$ containing 50 mM NaCl (75% ee).

Retention times: 16.1 (+) and 22.2 (-) mins.
3-(1H-indol-3-yl)-1-(1-methyl-1H-imidazol-2-yl)butan-1-one (3b).

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.41 (d, $J = 6.9$ Hz, 3H), 3.46 (dd, $J = 15.9$, 8.2 Hz, 1H), 3.56 (dd, $J = 15.9$, 6.3 Hz, 1H), 3.93 (s, 3H), 6.99 (s, 1H), 7.31 (d, $J = 8.0$ Hz, 1H), 7.11–7.06 (m, 1H), 7.18–7.12 (m, 2H), 7.31 (d, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 7.9$ Hz, 1H), 8.23 (s, 1H).
HPLC condition: Daicel chiralpak-AD, hexane/PrOH 85:15, 1.0 mL/min, 254 nm.

Racemic 3b.

Retention times: 19.9 (+) and 28.7 (-) mins.
Product 3b from the F-C reaction catalyzed by ODN-1-Cu^{2+} containing 50 mM NaCl (67% ee).

Retention times: 19.9 (+) and 28.7 (-) mins.
3-(5-chloro-1H-indol-3-yl)-1-(1-methyl-1H-imidazol-2-yl)butan-1-one (3c).

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.40 (d, $J = 6.9$ Hz, 3H), 3.46 (dd, $J = 10.8$, 7.3 Hz, 2H), 3.83–3.71 (m, 1H), 3.93 (s, 3H), 7.02 (s, 1H), 7.05 (d, $J = 2.3$ Hz, 1H), 7.10 (dd, $J = 8.6$, 2.0 Hz, 1H), 7.16 (s, 1H), 7.22 (d, $J = 8.6$ Hz, 1H), 7.56 (d, $J = 1.8$ Hz, 1H), 8.31–8.22 (m, 1H).
HPLC condition: Daicel chiralpak-AD, hexane/i-PrOH 90:10, 1.0 mL/min, 254 nm.

Racemic 3c.

Retention times: 25.3 (+) and 32.7 (-) mins.
Product 3c from the F-C reaction catalyzed by ODN-1-Cu$^{2+}$ containing 50 mM NaCl (66% ee).

Retention times: 25.2 (+) and 33.1 (-) mins.
1-(1-methyl-1H-imidazol-2-yl)-3-(1-methyl-1H-indol-3-yl)butan-1-one (3d).

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$1.41 (d, $J$ = 6.9 Hz, 3H), 3.44 (dd, $J$ = 15.8, 8.0 Hz, 1H), 3.56 (dd, $J$ = 15.8, 6.5 Hz, 1H), 3.71 (s, 3H), 3.83 (dd, $J$ = 14.2, 7.0 Hz, 1H), 3.91 (s, 3H), 6.92 (s, 1H), 6.97 (s, 1H), 7.10–7.04 (m, 1H), 7.13 (d, $J$ = 0.8 Hz, 1H), 7.21–7.15 (m, 1H), 7.27–7.23 (m, 1H), 7.65 (d, $J$ = 7.9 Hz, 1H).
HPLC condition: Daicel chiralpak-AD, hexane/i-PrOH 95:5, 1.0 mL/min, 254 nm.

Racemic 3d.

Retention times: 16.1 (-) and 26.2 (+) mins.
Product 3d from the F-C reaction catalyzed by ODN-1-Cu$^{2+}$ containing 50 mM NaCl (-8% ee).

Retention times: 16.1 (-) and 26.3 (+) mins.

---

**Electronic Supplementary Material (ESI) for Chemical Communications**

This journal is © The Royal Society of Chemistry 2012

---

Signal 1: WDI A, Wavelength=254 nm

<table>
<thead>
<tr>
<th>#</th>
<th>Ret Time (min)</th>
<th>Width (min)</th>
<th>Area (mAU)</th>
<th>Peak Height (mAU)</th>
<th>Area (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.122</td>
<td>0.0074</td>
<td>1905.39505</td>
<td>70.80264</td>
<td>54.0762</td>
</tr>
<tr>
<td>2</td>
<td>26.380</td>
<td>0.6848</td>
<td>1686.07874</td>
<td>37.41811</td>
<td>48.5238</td>
</tr>
</tbody>
</table>

Total: 2671.46680 108.80875

---

*** End of Report ***
1-(1-methyl-1H-imidazol-2-yl)-3-(2-methyl-1H-indol-3-yl)butan-1-one (3e).

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.46 (d, $J = 7.1$ Hz, 3H), 2.41 (s, 3H), 3.61 (dd, $J = 7.3$, 1.7 Hz, 2H), 3.78 (dd, $J = 14.7$, 7.1 Hz, 1H), 3.85 (s, 3H), 6.93 (s, 1H), 7.08–7.00 (m, 2H), 7.09 (d, $J = 0.8$ Hz, 1H), 7.21 (dt, $J = 8.1$, 3.3 Hz, 1H), 7.65 (dd, $J = 8.1$, 6.7 Hz, 1H), 7.78–7.69 (m, 1H).
HPLC condition: Daicel chiralpak-AD, hexane/i-PrOH 85:15, 1.0 mL/min, 254 nm.

Racemic 3e.

Retention times: 22.3 (-) and 33.2 (+) mins.
Product 3e from the F-C reaction catalyzed by ODN-1-Cu\(^{2+}\) containing 50 mM NaCl (-44% ee). Retention times: 21.9 (-) and 32.8 (+) mins.
3-(5-methoxy-1H-indol-3-yl)-1-(1-methyl-1H-imidazol-2-yl)-3-phenyl-1-propanone (3f).

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 3.70 (s, 3H), 3.83 (dd, $J = 16.4$, 7.8 Hz, 1H), 3.88 (s, 3H), 3.99 (dd, $J = 16.5$, 7.5 Hz, 1H), 5.05 (t, $J = 7.6$ Hz, 1H), 6.98 (dd, $J = 12.8$, 6.2 Hz, 3H), 7.14 (dd, $J = 11.2$, 6.3 Hz, 3H), 7.22 (d, $J = 7.4$ Hz, 3H), 7.39 (d, $J = 7.5$ Hz, 2H), 7.48 (d, $J = 7.9$ Hz, 1H).
HPLC condition: Daicel chiralpak-AD, hexane/i-PrOH 80:20, 1.0 mL/min, 254 nm.

Racemic 3f.

Retention times: 29.5 and 38.6 mins.
Product 3f from the F-C reaction catalyzed by ODN-1-Cu$^{2+}$ containing 50 mM NaCl (21% ee).

Retention times: 29.6 and 38.6 mins.

---

Electronic Supplementary Material (ESI) for Chemical Communications
This journal is © The Royal Society of Chemistry 2012
---

### Area Percent Report

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorted By</td>
<td>Signal</td>
<td>Multiplier</td>
<td>1.0000</td>
<td>Dilution</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

Use Multiplier & Dilution Factor with ISTDs

#### Signal 1: Wavelength=254 nm

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RetTime</td>
<td>Type Width</td>
<td>Area Height Area %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 29.552</td>
<td>1.0256</td>
<td>843.03088 12.80160 60.4565</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 38.612</td>
<td>1.0247</td>
<td>566.03667 6.22000 39.5435</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Totals: 1409.06755 19.09440

---

*** End of Report ***
3-(4-bromophenyl)-3-(5-methoxy-1H-indol-3-yl)-1-(1-methyl-1H-imidazol-2-yl) propan-1-one (3g).

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 3.76 (s, 3H), 3.81 (dd, $J = 16.8$, 8.0 Hz, 1H), 3.91 (s, 3H), 3.95 (dd, $J = 16.8$, 7.2 Hz, 1H), 4.95 (t, $J = 7.6$ Hz, 1H), 6.79 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.86 (d, $J = 2.4$ Hz, 1H), 7.00 (s, 1H), 7.09 (d, $J = 2.1$ Hz, 1H), 7.15 (d, $J = 0.8$ Hz, 1H), 7.19 (d, $J = 8.8$ Hz, 1H), 7.25 (d, $J = 9.5$ Hz, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 8.11–8.01 (m, 1H).
HPLC condition: Daicel chiralpak-AD, hexane/i-PrOH 80:20, 1.0 mL/min, 254 nm.

Racemic 3g.

Retention times: 34.6 and 41.4 mins.
Product $3g$ from the F-C reaction catalyzed by ODN-1-Cu$^{2+}$ containing 50 mM NaCl (7% ee).

Retention times: 33.4 and 40.5 mins.
3-(4-chlorophenyl)-3-(5-methoxy-1H-indol-3-yl)-1-(1-methyl-1H-imidazol-2-yl)propan-1-one (3h).

$^1$H-NMR (CDCl$_3$, 400 MHz) δ 3.72 (s, 3H), 3.80 (dd, $J = 16.4$, 8.0 Hz, 1H), 3.92 (s, 3H), 3.96 (dd, $J = 16.8$, 7.6 Hz, 1H), 4.98 (t, $J = 7.6$ Hz, 1H), 6.80 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.86 (d, $J = 2.4$ Hz, 1H), 7.00 (s, 1H), 7.11 (d, $J = 2.1$ Hz, 1H), 7.15 (d, $J = 0.8$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 3H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.96–7.89 (m, 1H).
HPLC condition: Daicel chiralcel-OD, hexane/i-PrOH 80:20, 1.0 mL/min, 254 nm.

Racemic 3h.

Retention times: 13.1 (+) and 15.3 (-) mins.
Product 3h from the F-C reaction catalyzed by ODN-1-Cu\textsuperscript{2+} containing 50 mM NaCl (-7% ee).

Retention times: 13.1 (+) and 15.3 (-) mins.

---

### Area Percent Report

**Sorted By:** Signal  
**Multiplier:** 1.0000  
**Dilution:** 1.0000  
**Use Multiplier & Dilution Factor with ISTDs**

**Signal 1: WVD1 A, Wavelength=264 nm**

<table>
<thead>
<tr>
<th>#</th>
<th>Ret Time [min]</th>
<th>Width [min]</th>
<th>Area [mAU]</th>
<th>Height [mAU]</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.100</td>
<td>0.4706</td>
<td>1270.62747</td>
<td>41.20019</td>
<td>46.4244</td>
</tr>
<tr>
<td>2</td>
<td>15.284</td>
<td>0.8346</td>
<td>1466.23621</td>
<td>37.96003</td>
<td>33.8756</td>
</tr>
</tbody>
</table>

**Totals:** 2736.76367 79.16012

---

***End of Report***
3-(5-methoxy-1H-indol-3-yl)-3-(4-methoxyphenyl)-1-(1-methyl-1H-imidazol-2-yl) propan-1-one (3i).

$^{1}$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 3.73 (s, 3H), 3.75 (s, 3H), 3.81 (dd, $J = 16.3, 8.2$ Hz, 1H), 3.89 (s, 3H), 3.95 (dd, $J = 16.3, 7.1$ Hz, 1H), 4.95 (t, $J = 7.6$ Hz, 1H), 6.80–6.73 (m, 3H), 6.92 (d, $J = 2.3$ Hz, 1H), 6.92 (d, $J = 2.3$ Hz, 1H), 6.98 (s, 1H), 7.05 (d, $J = 2.1$ Hz, 1H), 7.16 (d, $J = 9.0$ Hz, 2H), 7.27 (d, $J = 8.8$ Hz, 2H), 8.23 (s, 1H).
HPLC condition: Daicel chiralpak-AD, hexane/i-PrOH 80:20, 1.0 mL/min, 254 nm.

Racemic 3i.

Retention times: 53.4 (-) and 59.6 (+) mins.
Product 3i from the F-C reaction catalyzed by ODN-1-Cu$^{2+}$ containing 50 mM NaCl (-9% ee).

Retention times: 53.1 (-) and 59.5 (+) mins.