# Supporting Information

# Deciphering the Stereoinduction Mechanism of DNA-Based Asymmetric Catalysis through Intramolecular Friedel–Crafts Alkylation

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# Materials

4-bromoaniline, 4-Fluoroaniline, ethyl 2-oxocyclohexane *p*-Anisidine, carboxylate, indole-3-butyric acid, sulfur trioxide pyridine complex, copper(II) nitrate hydrate, 4,4'-dimethyl-2,2'dipyridyl (dmbpy), 4,7-dichloro-1,10-phenanthroline (4,7-dcp), 3,4,7,8-tetramethyl-1,10-phenanthroline (3,4,7,8-tmp), 5,6-dimethyl-1,10-phenanthroline (5,6-dmp) were purchased from Sigma-Aldrich Chemicals Co. (Milwaukee, WI) and used without further purification. 1,10-phenanthroline (phen) monohydrate was received from Wako Chemicals. All other chemicals and solvents were purchased from Sigma-Aldrich Chemicals Co., Wako Pure Chemical Ind. Ltd., TCI, or Kanto Chemical Co. Inc. and used as 1,10-phenanthrolinopyrrole (php), dipyrido[3,2-d:2',3'-f]quinoxaline received. (dpq), dipyrido[1,3]diazepinone (dpda), dipyrido[3,2-1:2',3'-c]phenazine (dppz), 2-(2'-pyridinyl)imidazole (pimH) were prepared by following the literature procedures.<sup>1</sup> Substrates with tethered indole compounds were prepared as reported previously.<sup>2, 3</sup> Copper complexes were prepared using the procedures reported by Feringa and Roelfes.<sup>4</sup> Salmon testes DNA and synthetic oligonucleotides were obtained from Sigma-Aldrich Chemicals Co. Water was deionized (specific resistance of  $\geq 18.0 \text{ M}\Omega$  cm at 25°C) by a Milli-Q system (Millipore Corp.).

# Methods

NMR spectra were obtained on a JEOL JNM ECA-600 spectrometer operating at 600 MHz for <sup>1</sup>H NMR and 150 MHz for <sup>13</sup>C NMR in CDCl<sub>3</sub> unless otherwise noted. Flash column chromatography was performed employing Silica Gel 60 (70–230 mesh, Merck Chemicals). Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates from Silica gel 70  $PF_{254}$  (Wako Pure Chemical Ind. Ltd.). Enantiomeric excess (ee) determinations were performed by HPLC analysis (Chiralcel OD-H or Chiralpak AD-H) using UV-detection.

UV-melting studies were performed on V-650 UV/VIS spectrophotometer.



# Synthetic routes for substrates

Reagents and conditions: (i) NaNO<sub>2</sub>, NaBF<sub>4</sub>, HCl, 0 °C; (ii) ethyl 2-oxocyclohexane carboxylate, NaH, THF, reflux; (iii) HCl, EtOH, reflux; (iv) NaOH, EtOH, reflux; (v) neat, 220 °C; (vi) LAH, THF, reflux; (vii) Py•SO3, Et<sub>3</sub>N, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, MS 4Å, 0 °C; (viii) benzene, room temperature.

# Analytical Data for new substrates:



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.96 (s, 1H), 7.60 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 7.44 (d, <sup>3</sup>*J*<sub>HH</sub> = 14.3 Hz, 1H), 7.36 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.2 Hz, 1H), 7.18 (m, 3H), 7.11 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.2 Hz, 1H), 7.04 (s, 1H), 7.00 (d, <sup>4</sup>*J*<sub>HH</sub> = 2.0 Hz, 1H), 4.05 (s, 3H), 2.82 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H), 2.41 (q, <sup>3</sup>*J*<sub>HH</sub> = 6.8 Hz, 2H), 1.96 (sp, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  180.7, 148.7, 143.8, 136.4, 129.2, 127.5, 127.1, 126.5, 121.9, 121.4, 119.1, 118.9, 116.0, 111.1, 36.3, 32.4, 28.6, 24.7. HRMS (ESI-TOF) cald for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O (M+H<sup>+</sup>) 294.1606, found 294.1565.



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.11 (s, 1H), 7.45 (d, <sup>3</sup>*J*<sub>HH</sub> = 15.6 Hz, 1H), 7.19 (m, 2H), 7.17 (s, 1H), 7.032 (s, 1H), 7.026 (dd, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz and <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H), 6.94 (s, 1H), 6.84 (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.5 Hz and <sup>4</sup>*J*<sub>HH</sub> = 2.4 Hz, 1H), 4.04 (s, 3H), 3.87 (s, 3H), 2.77 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H), 2.40 (q, <sup>3</sup>*J*<sub>HH</sub> = 6.8 Hz, 2H), 1.93 (sp, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  180.8, 153.9, 148.8, 143.8, 129.3, 127.2, 126.6, 122.4, 115.8, 112.2, 111.9, 100.9, 56.1, 36.4, 32.5, 28.5, 24.8. HRMS (ESI-TOF) cald for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub> (M+H<sup>+</sup>) 324.1712, found 324.1485.



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.40 (s, 1H), 7.69 (s, 1H), 7.42 (d,  ${}^{3}J_{\text{HH}} = 15.7$  Hz, 1H), 7.19 (m, 3H), 7.18 (s, 1H), 7.04 (s, 1H), 6.94 (s, 1H), 4.04 (s, 3H), 2.73 (t,  ${}^{3}J_{\text{HH}} = 7.5$  Hz, 2H), 2.36 (q,  ${}^{3}J_{\text{HH}} = 6.8$  Hz, 2H), 1.88 (sp,  ${}^{3}J_{\text{HH}} = 7.5$  Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 180.8, 148.5, 143.8, 135.1, 129.4, 129.3, 127.3, 126.7, 124.7, 122.8, 121.6, 115.8, 112.7, 112.5, 36.4, 32.4, 28.5, 24.6. HRMS (ESI-TOF) cald for C<sub>18</sub>H<sub>18</sub>BrN<sub>3</sub>O (M+H<sup>+</sup>) 372.0711, found 372.0667.



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.16 (s, 1H), 7.43 (d, <sup>3</sup>*J*<sub>HH</sub> = 15.6 Hz, 1H), 7.20 (m, 3H), 7.17 (s, 1H), 7.04 (s, 1H), 7.01 (s, 1H), 6.92 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.8 Hz, 1H), 4.05 (s, 3H), 2.75 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H), 2.38 (q, <sup>3</sup>*J*<sub>HH</sub> = 6.8 Hz, 2H), 1.91 (sp, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  180.8, 157.8 (d, <sup>1</sup>*J*<sub>CF</sub> = 235.2 Hz), 148.6, 143.9, 133.0, 129.3, 128.0 (d, <sup>3</sup>*J*<sub>CF</sub> = 8.6 Hz), 127.2, 126.7, 123.3, 116.3, 111.8 (d, <sup>3</sup>*J*<sub>CF</sub> = 8.6 Hz), 110.3 (d, <sup>2</sup>*J*<sub>CF</sub> = 25.8 Hz), 103.9 (d, <sup>2</sup>*J*<sub>CF</sub> = 22.9 Hz), 36.4, 32.5, 28.5, 24.7. HRMS (ESI-TOF) cald for C<sub>18</sub>H<sub>18</sub>FN<sub>3</sub>O (M+H<sup>+</sup>) 312.1512, found 312.1433.

S4



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.01 (s, 1H), 7.91 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H), 7.61 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 7.55 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.1 Hz, 1H), 7.46 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.8 Hz, 2H), 7.37 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.2 Hz, 1H), 7.20 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 7.11 (m, 2H), 7.00 (s, 1H), 6.88 (d, <sup>3</sup>*J*<sub>HH</sub> = 15.6 Hz, 1H), 2.85 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H), 2.41 (q, <sup>3</sup>*J*<sub>HH</sub> = 6.8 Hz, 2H), 1.97 (sp, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  191.1, 150.0, 138.1, 136.5, 132.7, 128.7, 128.6, 127.6, 126.3, 122.1, 121.5, 119.3, 119.0, 116.1, 111.3, 32.7, 28.8, 24.8. HRMS (ESI-TOF) cald for C<sub>20</sub>H<sub>19</sub>NO (M+H<sup>+</sup>) 290.1545, found 290.1532.



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.70 (d, <sup>3</sup>*J*<sub>HH</sub> = 4.1 Hz, 1H), 8.13 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 8.05 (s, 1H), 7.84 (td, <sup>3</sup>*J*<sub>HH</sub> = 8.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.0 Hz, 1H), 7.63 (d, <sup>3</sup>*J*<sub>HH</sub> = 15.6 Hz, 1H), 7.62 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 7.45 (ddd, <sup>3</sup>*J*<sub>HH</sub> = 7.5 and 4.8 Hz and <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 1H), 7.35 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.2 Hz, 1H), 7.31 (m, 1H), 7.19 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.2 Hz, 1H), 7.12 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 6.99 (s, 1H), 2.84 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H), 2.45 (q, <sup>3</sup>*J*<sub>HH</sub> = 6.8 Hz, 2H), 1.98 (sp, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  189.7, 154.3, 150.4, 148.9, 137.1, 136.5, 127.6, 126.9, 124.8, 123.0, 122.0, 121.5, 119.3, 119.0, 116.2, 111.2, 32.9, 28.7, 24.9. HRMS (ESI-TOF) cald for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O (M+H<sup>+</sup>) 291.1497, found 291.1483.



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.58 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 7.44 (d, <sup>3</sup>*J*<sub>HH</sub> = 13.8 Hz, 1H), 7.27 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.5 Hz, 1H), 7.19 (m, 2H), 7.17 (s, 1H), 7.09 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 7.03 (s, 1H), 6.85 (s, 1H), 4.05 (s, 3H), 3.75 (s, 3H), 2.81 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H), 2.41 (q, <sup>3</sup>*J*<sub>HH</sub> = 6.8 Hz, 2H), 1.94 (sp, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  180.7, 148.6, 143.8, 137.1, 129.2, 127.9, 127.0, 126.5, 126.2, 121.5, 119.0, 118.6, 114.5, 109.1, 36.3, 32.6, 32.5, 28.8, 24.6. HRMS (ESI-TOF) cald for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O (M+H<sup>+</sup>) 308.1763, found 308.4206.



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.60 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 7.43 (d, <sup>3</sup>*J*<sub>HH</sub> = 15.7 Hz, 1H), 7.28 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.1 Hz, 2H), 7.24 (d, <sup>3</sup>*J*<sub>HH</sub> = 6.8 Hz, 2H), 7.16 (m, 3H), 7.10 (d, <sup>3</sup>*J*<sub>HH</sub> = 6.8 Hz, 2H), 7.09 (m, 1H), 7.02 (s, 1H), 6.91 (s, 1H), 5.27 (s, 2H), 4.03 (s, 3H), 2.82 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H), 2.41 (q, <sup>3</sup>*J*<sub>HH</sub> = 7.2 Hz, 2H), 1.95 (sp, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  180.8, 148.7, 143.9, 137.9, 136.9, 129.3, 128.8, 128.3, 127.6, 127.2, 126.9, 126.6, 125.7, 121.8, 119.3, 119.0, 115.4, 109.7, 50.0, 36.4, 32.6, 28.8, 24.8. HRMS (ESI-TOF) cald for C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O (M+H<sup>+</sup>) 384.2076, found 384.2635.



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.99 (s, 1H), 7.61 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 7.49 (d, <sup>3</sup>*J*<sub>HH</sub> = 15.6 Hz, 1H), 7.36 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 7.21 (m, 3H), 7.12 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.2 Hz, 1H), 7.04 (s, 1H), 7.03 (d, <sup>3</sup>*J*<sub>HH</sub> = 14.3 Hz, 1H), 4.05 (s, 3H), 3.00 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.8 Hz, 2H), 2.74 (q, <sup>3</sup>*J*<sub>HH</sub> = 7.0 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  180.7, 148.4, 143.7, 136.4, 129.2, 127.3, 127.1, 126.5, 122.0, 121.4, 119.3, 118.8, 115.4, 111.1, 36.3, 33.2, 24.0. HRMS (ESI-TOF) cald for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O (M+H<sup>+</sup>) 280.1450, found 280.1402.



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  9.06 (s, 2H), 8.44 (d, <sup>3</sup>*J*<sub>HH</sub> = 4.0 Hz, 2H), 7.48 (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz and <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 2H), 7.40 (dd, <sup>3</sup>*J*<sub>HH</sub> = 7.8 and 4.4 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  163.5, 145.9, 145.8, 137.6, 128.9, 124.8. HRMS (ESI-TOF) cald for C<sub>11</sub>H<sub>8</sub>N<sub>4</sub>O (M+H<sup>+</sup>) 213.0776, found 213.0730.

# **Intramolecular Friedel-Crafts Alkylations**

The DNA-based hybrid catalyst was prepared in solution by mixing the copper complex with the respective ligand and DNA. The catalyst solution was prepared 12 h in advance before its use. The concentration of the copper complex was optimized as given in Table S1 and Figure S1. The reaction conditions were varied case by case. For example, in Table 1, 30 mol% of Cu-ligand in 5 mL water was mixed with 10 mL of 1.4 mg/mL solution of st-DNA in 20 mM MOPS buffer (pH 6.5). A stock solution of tethered indole starting material (1; 0.045 mM, 13.2 mg/500  $\mu$ L DMSO) prepared in advance was added to the catalyst solution, and the reaction mixture was stirred at 5 °C for two days. The product was extracted with Et<sub>2</sub>O and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent under reduced pressure, the residue was purified by silica gel PTLC using a solvent mixture of suitable polarity. In case of entry 4 in table 1, EtOAc:hexane = 2:3 was used to afford the product **2** as a yellow oil. The conditions for each reaction are given in the footnote of each table.

For ee determination, the racemic sample of **2** was prepared by using a copper complex with dmbpy as a ligand, and in the absence of DNA (Table S2). The ee of product **2** was determined on a Daicel Chiralcel OD-H column with a solvent mixture of suitable polarity. Hexane: 2-propanol = 9:1 was used with a flow rate of 0.8 mL/min. In this case, the retention times were 15.2 min (major enantiomer, *S*) and 17.7 min (minor enantiomer, *R*).

#### **Sequence-Dependent Studies**

A 1.5 mL Eppendorf screw-cap tube was loaded with a synthetic oligomer solution (240  $\mu$ L, 1.4 mg/mL) in 20 mM MOPS buffer (pH 6.5) and [Cu(5,6-dmp)](NO<sub>3</sub>)<sub>2</sub> complex (120  $\mu$ L, 30 mol%), and a stock solution of starting material (**1**, 12  $\mu$ L, 13.2 mg/500  $\mu$ L DMSO). The reaction mixture was shaken by using an Eppendorf mixer for 1 day at 5 °C. The product was extracted with Et<sub>2</sub>O and dried over Na<sub>2</sub>SO<sub>4</sub>. After the solvent removal under vacuum, product **2** 

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was analyzed by using HPLC.



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.92 (s, 1H), 7.46 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.2 Hz, 1H), 7.31 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 7.16 (s, 1H), 7.11 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.2 Hz, 1H), 7.06 (s, 1H), 7.05 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 4.08 (s, 3H), 3.58 (dd, <sup>2</sup>*J*<sub>HH</sub> = 13.9 Hz and <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 3.46 (dd, <sup>3</sup>*J*<sub>HH</sub> = 11.5 and 8.9 Hz, 2H), 2.72 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.1 Hz, 2H), 2.12 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.2 and 5.1 and 2.4 Hz, 1H), 2.00 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 14.3 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.2 and 6.1 and 2.4 Hz, 1H), 1.85 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.5 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.4 Hz, 1H), 1.78 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 12.9 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.5 and 5.8 and <sup>4</sup>*J*<sub>HH</sub> = 2.0 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  193.7, 143.0, 137.1, 135.7, 129.5, 127.6, 127.5, 121.2, 119.0, 118.1, 110.8, 110.2, 45.8, 36.5, 31.0, 29.7, 21.7, 21.3. HRMS (ESI-TOF) cald for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O (M+H<sup>+</sup>) 294.1606, found 294. 1393.





100.00



<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  9.08 (s, 1H), 7.57 (s, 1H), 7.173 (s, 1H), 7.170 (d, <sup>3</sup>*J*<sub>HH</sub> = 6.1 Hz, 2H), 7.07 (s, 1H), 4.08 (s, 3H), 3.59 (dd, <sup>2</sup>*J*<sub>HH</sub> = 13.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 3.43 (dd, <sup>3</sup>*J*<sub>HH</sub> = 11.5 and 8.9 Hz, 1H), 2.66 (t, <sup>3</sup>*J*<sub>HH</sub> = 5.8 Hz, 2H), 2.10 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.1 and 5.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.4 Hz, 1H), 1.99 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.3 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.5 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.4 Hz, 1H), 1.83 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.9 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H), 1.77 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.2 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  193.7, 142.9, 138.6, 134.3, 129.5, 129.4, 127.6, 123.9, 120.8, 112.2, 110.0, 45.6, 36.6, 30.9, 29.7, 21.6, 21.1. HRMS (ESI-TOF) cald for C<sub>18</sub>H<sub>18</sub>BrN<sub>3</sub>O (M+H<sup>+</sup>) 372.0711, found 372.0509.





**Entry 2**. Yellow oil. 54% yield. The ee of the product was determined on a Daicel Chiralcel OD-H column with hexane:2-propanol = 9:1, flow = 0.8 mL/min. Retention times: 12.6 min

[major enantiomer], 17.8 min [minor enantiomer]. 38 % ee.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.69 (d, <sup>3</sup>*J*<sub>HH</sub> = 4.0 Hz, 1H), 8.67 (s, 1H), 8.13 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 7.88 (td, <sup>3</sup>*J*<sub>HH</sub> = 8.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.1 Hz, 1H), 7.50 (ddd, <sup>3</sup>*J*<sub>HH</sub> = 7.4 and 4.8 Hz and <sup>4</sup>*J*<sub>HH</sub> = 1.3 Hz, 1H), 7.47 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 7.29 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 7.11 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.1 Hz, 1H), 7.05 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 3.68 (dd, <sup>2</sup>*J*<sub>HH</sub> = 15.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 3.4 Hz, 1H), 3.63–3.54 (m, 2H). 2.74 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.1 Hz, 2H), 2.14 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 12.9 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.1 and 5.4 and <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H), 2.02 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.9 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.1 Hz, 1H), 1.88 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 14.3 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.1 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H), 1.81 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.1 and 5.5 and <sup>4</sup>*J*<sub>HH</sub> = 2.1 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  203.2, 153.4, 149.2, 137.3, 137.2, 135.7, 127.6, 127.5, 122.1, 121.3, 119.0, 118.1, 110.8, 110.2, 45.0, 31.0, 29.0, 21.6, 21.3. HRMS (ESI-TOF) cald for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O (M+H<sup>+</sup>) 291.1497, found 291.1438.



**Entry 4**. Yellow oil. 41% yield. The ee of the product was determined on a Daicel Chiralcel AD-H column with hexane:2-propanol = 12:1, flow = 0.8 mL/min. Retention times: 21.8 min [major enantiomer], 23.4 min [minor enantiomer]. 70 % ee (DNA-1).

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.99 (s, 1H), 7.20 (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.5 Hz and <sup>3</sup>*J*<sub>HF</sub> = 4.4 Hz, 1H), 7.16 (s, 1H), 7.07 (s, 1H), 7.09 (dd, <sup>3</sup>*J*<sub>HF</sub> = 9.5 Hz and <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H), 6.84 (td, <sup>3</sup>*J*<sub>HH</sub> = 8.9 Hz and <sup>4</sup>*J*<sub>HF</sub> = 2.7 Hz, 1H), 4.08 (s, 3H), 3.59 (dd, <sup>2</sup>*J*<sub>HH</sub> = 13.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 7.4 Hz, 1H), 3.44 (dd, <sup>3</sup>*J*<sub>HH</sub> = 12.1 and 8.8 Hz, 2H), 2.67 (t, <sup>3</sup>*J*<sub>HH</sub> = 5.8 Hz, 2H), 2.11 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 14.3 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.1 and 5.5 and <sup>4</sup>*J*<sub>HH</sub> = 2.0 Hz, 1H), 1.99 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 14.3 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.1 and 5.5 and <sup>4</sup>*J*<sub>HH</sub> = 12.2 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.8 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.0 Hz, 1H), 1.77 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.8 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.0 Hz, 1H), 1.77 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.8 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  193.7, 157.8 (d, <sup>1</sup>*J*<sub>CF</sub> = 232.3 Hz), 142.9, 139.2, 132.2, 129.5, 127.9 (d, <sup>3</sup>*J*<sub>CF</sub> = 8.6 Hz), 127.6, 111.2 (d, <sup>3</sup>*J*<sub>CF</sub> = 10.0 Hz), 110.5 (d, <sup>4</sup>*J*<sub>CF</sub> = 4.3 Hz), 109.2 (d, <sup>2</sup>*J*<sub>CF</sub> = 25.8 Hz), 103.1 (d, <sup>2</sup>*J*<sub>CF</sub> = 22.9 Hz), 45.6, 36.5, 30.9, 29.8, 21.7, 21.2. HRMS (ESI-TOF) cald for C<sub>18</sub>H<sub>18</sub>FN<sub>3</sub>O (M+H<sup>+</sup>) 312.1512, found 312.1509.





**Entry 6**. Yellow oil. 45% yield. The ee of the product was determined on a Daicel Chiralcel OD-H column with hexane:2-propanol = 9:1, flow = 0.8 mL/min. Retention times: 19.3 min [minor enantiomer], 21.1 min [major enantiomer]. 82 % ee (DNA-1).

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.78 (s, 1H), 7.19 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.9 Hz, 1H), 7.16 (s, 1H), 7.06 (s, 1H), 6.93 (d, <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H), 6.77 (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.8 Hz and <sup>4</sup>*J*<sub>HH</sub> = 2.0 Hz, 1H), 4.07 (s, 3H), 3.85 (s, 3H), 3.57 (dd, <sup>2</sup>*J*<sub>HH</sub> = 13.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 3.43 (dd, <sup>3</sup>*J*<sub>HH</sub> = 11.6 and 8.8 Hz, 2H), 2.69 (t, <sup>3</sup>*J*<sub>HH</sub> = 5.8 Hz, 2H), 2.10 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.2 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.1 and 5.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.4 Hz, 1H), 2.00 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 14.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.5 and 5.8 and <sup>4</sup>*J*<sub>HH</sub> = 2.3 Hz, 1H), 1.84 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.9 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H), 1.76 (dddd, <sup>2</sup>*J*<sub>HH</sub> = 13.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 8.8 and 6.1 and <sup>4</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  193.7, 153.9, 143.0, 138.1, 130.9, 129.5, 127.9, 127.5, 111.4, 111.04, 110.1, 100.5, 56.2, 45.7, 36.5, 31.0, 29.7, 21.8, 21.3. HRMS (ESI-TOF) cald for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub> (M+H<sup>+</sup>) 324.1712, found 324.1654.





**Entry 7**. Yellow oil. 91% yield. The ee of the product was determined on a Daicel Chiralcel OD-H column with hexane:2-propanol = 9:1, flow = 0.8 mL/min. Retention times: 14.3 min [major enantiomer], 17.4 min [minor enantiomer]. 7 % ee.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.49 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 7.28 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1H), 7.18 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.8 Hz, 1H), 7.16 (s, 1H), 7.08 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H), 7.06 (s, 1H), 4.06 (s, 3H), 3.77 (s, 3H), 3.70 (s, 1H), 3.45 (dd, <sup>2</sup>*J*<sub>HH</sub> = 16.3 Hz and <sup>3</sup>*J*<sub>HH</sub> = 10.9 Hz, 1H), 3.35 (dd, <sup>2</sup>*J*<sub>HH</sub> = 15.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H), 2.85 (dd, <sup>2</sup>*J*<sub>HH</sub> = 15.3 Hz and <sup>3</sup>*J*<sub>HH</sub> = 5.1 Hz, 1H), 2.64 (ddd, <sup>2</sup>*J*<sub>HH</sub> = 16.0 Hz and <sup>3</sup>*J*<sub>HH</sub> = 10.9 and 5.5 Hz, 1H), 2.00–1.85 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  191.9, 143.3, 137.8, 137.4, 129.4, 127.3, 127.2, 121.1, 118.8, 118.1, 109.9, 108.8, 43.5, 36.4, 29.5, 28.2, 27.8, 21.1, 18.6. HRMS (ESI-TOF) cald for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O (M+H<sup>+</sup>) 308.1763, found 308.1677.



**Entry 8**. White solid. 12% yield. The ee of the product was determined on a Daicel Chiralcel OD-H column with hexane:2-propanol = 9:1, flow = 0.8 mL/min. Retention times: 15.2 min [major enantiomer], 18.8 min [minor enantiomer]. 4 % ee.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.51 (m, 1H), 7.18 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.2 Hz, 2H), 7.13 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.2 Hz, 2H), 7.10 (s, 1H), 7.08 (dd, <sup>3</sup>*J*<sub>HH</sub> = 7.4 Hz and <sup>4</sup>*J*<sub>HH</sub> = 2.1 Hz, 2H), 6.99 (s, 1H), 6.95 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H), 5.52 (d, <sup>4</sup>*J*<sub>HH</sub> = 2.6 Hz, 2H), 3.96 (s, 3H), 3.65 (m, 1H), 3.34 (dd, <sup>2</sup>*J*<sub>HH</sub> = 15.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 10.1 Hz, 1H), 3.26 (dd, <sup>2</sup>*J*<sub>HH</sub> = 15.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 2.7 Hz, 1H), 2.88 (ddd, <sup>2</sup>*J*<sub>HH</sub> = 15.6 Hz and <sup>3</sup>*J*<sub>HH</sub> = 5.4 and <sup>4</sup>*J*<sub>HH</sub> = 2.1 Hz, 1H), 2.68 (ddd, <sup>2</sup>*J*<sub>HH</sub> = 16.3 Hz and <sup>3</sup>*J*<sub>HH</sub> = 10.9 and 6.1 Hz, 1H), 2.04–1.81 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  191.8, 143.1, 138.6, 138.0, 137.2, 129.3, 128.7, 127.6, 127.2, 127.0, 126.0, 121.4, 119.0, 118.2, 110.5, 109.8, 46.4, 43.9, 36.3, 28.4, 28.0, 21.1, 18.5. HRMS (ESI-TOF) cald for C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O (M+H<sup>+</sup>) 384.2076, found 384.2132.

# **Optimization of the reaction conditions**



Figure S1. Structures of achiral ligands

Table S1. Screening of the ligands for the copper(II) catalyzed intramolecular Friedel–Crafts reaction in the presence of st-DNA.

entry	ligand	yield (%)	ee (%)
1	dmbpy	18	35
2	pimH	47	44
3	phen	32	58
4	5,6-dmp	64	71
5	4,7-dcp	26	51
6	3,4,7,8-tmp	64	49
7	php	28	48
8	dpq	30	38
9	dpda	42	65
10	dppz	60	33

All experiments were carried out with 0.045 mM substrate, 1.4 mg/mL st-DNA, 30 mol% Cu–ligand, at 5 °C, in 20 mM MOPS buffer (pH 6.5), for two days, unless otherwise indicated.

Table S2. Control experiments

		reaction condition	HN		
		20 mM MOPS buffer pH 6.5 5 °C, 1 day			
	entry	reaction conditions	yield (%)	ee (%)	
	1	st-DNA, Cu(5,6-dmp)	64	71	
	2	st-DNA, Cu(NO <sub>3</sub> ) <sub>2</sub>	30	18	
	3	Cu(NO <sub>3</sub> ) <sub>2</sub>	38	1	

HN	st-DNA, M 20 mM MOPS 5 °C,	I(5,6-dmp) S buffer pH 6.5 1 day	- HN O N NMe	
entry	metal	yield (%)	ee (%)	
1	Cu(NO <sub>3</sub> ) <sub>2</sub>	64	71	
2	CoCl₂ •6H₂O	no TM	—	
3	FeCl <sub>3</sub> ∙6H <sub>2</sub> O	7	5	
4	$Sc(SO_3CF_3)_3$	trace	2	
5 <sup>a</sup>	NiSO <sub>4</sub>	no TM	—	
6 <sup>a</sup>	NiCl <sub>2</sub>	no TM	_	

<sup>a</sup> 1,10-phenanthroline was used as a ligand.

Table S4. Effects of the catalyst loading on the enantioselectivity.

entry	Cu(5,6-dmp) (mol%)	ee (%)
1	0.03	47
2	0.05	56
3	0.1	65
4	0.3	72
5	0.5	73
6	1	75
7	3	76
8	5	77
9	10	80
10	20	78
11	30	73
12	35	70
13	40	69
14	50	61
15	60	48



Figure S2. Effects of the catalyst loading on the enantioselectivity



# **UV-melting studies**

 Blank : 20 mM MOPS buffer (pH 6.5)

 Cu(L) : 9.0 μM of Cu(NO<sub>3</sub>)<sub>2</sub> and 9.0 μM of Ligand in 20 mM MOPS buffer (pH 6.5)

 DNA-1 : 5.4 μM of DNA (5'-TGTGTGCACACA-3') in 20 mM MOPS buffer (pH 6.5)

 DNA-1,Cu(L) : 9.0 μM of Cu(NO<sub>3</sub>)<sub>2</sub>, 9.0 μM of Ligand, and 5.4 μM of DNA-1 in 20 mM MOPS buffer (pH 6.5)

Figure S3. UV absorption spectra of Cu(II)-ligand alone, DNA-1 in the absence and presence of Cu(II)-ligand.



Figure S4. UV melting curves of Cu(II)-ligand alone, DNA-1 in the absence and presence of Cu(II)-ligand.



Figure S5. Normalized UV melting curves of DNA-1 in the absence and presence of copper complex.



Figure S6. The viscosity measurement for st-DNA/ligand mixed solution. MOPS solution (20 mM, pH 6.5) was used as the buffer. The st-DNA solution (500  $\mu$ M per base pair, average length was 2000 bp) and samples were prepared to give total ligand/base pair ratios of 0.25 and 0.50. Each sample passed through an Ubbelohde-type viscometer. This flow time was measured four times at 30 °C.

Relative viscosity,  $(\eta/\eta^o)^{1/3}$ , is calculated in accordance with the theory of Cohen and Eisenberg.<sup>5</sup> The viscosity value  $\eta$  was calculated according to

$$\eta = (t-t_0) / t_0$$

where  $t_0$  is the measured flow time of the buffer and t is the observed flow time of the DNA/ligand mixed solution.  $\eta^o$  is the viscosity value of the st-DNA solution without ligand.

Average flow time [s] of each solution is shown below.

	buffer	st-DNA	st-DNA, EtBr	st-DNA, Cu(dmbpy)	st-DNA, Cu(phen)	st-DNA, Cu(5,6-dmp)	st-DNA, Cu(dppz)
[CuL/bp] = 0.25	$\textbf{258} \pm \textbf{0.5}$	$\textbf{520} \pm \textbf{1.7}$	$598 \pm 1.4$	$\textbf{531} \pm \textbf{2.2}$	$\textbf{562} \pm \textbf{1.0}$	$\textbf{580} \pm \textbf{0.5}$	$543\pm0.6$
= 0.50	-	-	$\textbf{668} \pm \textbf{0.8}$	$\textbf{521} \pm \textbf{2.9}$	$\textbf{561} \pm \textbf{1.0}$	$\textbf{636} \pm \textbf{3.6}$	$600\pm3.4$



Figure S7. CD spectra of  $d(C^{Me8}GCGC^{Me8}GCGC^{Me8}GCG)_2$  in 20 mM MOPS buffer, pH 6.5 at 4 °C at various concentration of Cu(5,6-dmp) complex (50 mM NaCl concentration, 10  $\mu$ M DNA concentration)

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