Highly enantioselective DNA-based catalysis
Roelfes, Gerard; Boersma, Arnold J.; Feringa, B.L.

Published in:
ChemInform

IMPORTANT NOTE: You are advised to consult the publisher’s version (publisher’s PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher’s PDF, also known as Version of record

Publication date:
2006

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Figure S1. Induced CD spectra from [Cu(L4-7)(NO3)2] (150 µM) combined with salmon testes DNA (0.8 mg/ml) in Mops buffer (20 mM, pH 6.5). a) only st-DNA; b) [Cu(bipy)(NO3)2] / st-DNA; c) [Cu(dppz)(NO3)2] / st-DNA; d) [Cu(dpq)(NO3)2] / st-DNA; e) [Cu(phen)(NO3)2] / st-DNA.

Table S1: Effect of variation of the concentration of [Cu(bipy)(NO3)2], st-DNA and 2a on the results of the catalyzed reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration [Cu(bipy)(NO3)2] (mM)</th>
<th>Conc. DNA (mg/ml)</th>
<th>dienophile (mM)</th>
<th>Conversion (%)</th>
<th>Endo:Exo</th>
<th>E.e. Endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>1.3</td>
<td>1</td>
<td>&gt;80</td>
<td>97:3</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>0.10</td>
<td>1.3</td>
<td>1</td>
<td>&gt;80</td>
<td>98:2</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>0.15</td>
<td>1.3</td>
<td>1</td>
<td>&gt;80</td>
<td>98:2</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>0.30</td>
<td>1.3</td>
<td>1</td>
<td>&gt;80</td>
<td>98:2</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>0.45</td>
<td>1.3</td>
<td>1</td>
<td>&gt;80</td>
<td>98:2</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>0.60</td>
<td>1.3</td>
<td>1</td>
<td>&gt;80</td>
<td>98:2</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>0.15</td>
<td>0.65</td>
<td>1</td>
<td>68</td>
<td>98:2</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>0.30</td>
<td>0.65</td>
<td>1</td>
<td>&gt;80</td>
<td>98:2</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>0.30</td>
<td>1.3</td>
<td>0.3</td>
<td>Quant.</td>
<td>97:3</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>0.30</td>
<td>1.3</td>
<td>1.5</td>
<td>&gt;80</td>
<td>98:2</td>
<td>89</td>
</tr>
<tr>
<td>11</td>
<td>0.30</td>
<td>1.3</td>
<td>3</td>
<td>&gt;80</td>
<td>97:3</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>0.30</td>
<td>1.3</td>
<td>6</td>
<td>65</td>
<td>97:3</td>
<td>86</td>
</tr>
</tbody>
</table>
Table S2

<table>
<thead>
<tr>
<th>catalyst</th>
<th>T</th>
<th>endo:exo</th>
<th>e.e. endo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cu(NO&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt; / DNA</td>
<td>RT</td>
<td>95:5</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>DNA</td>
<td>5 °C</td>
<td>n.d.&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>[Cu(dppz)(NO&lt;sub&gt;3&lt;/sub&gt;)]&lt;sub&gt;2&lt;/sub&gt; / DNA</td>
<td>5 °C</td>
<td>94:6</td>
</tr>
</tbody>
</table>

Table S2, Selection of relevant control experiments, performed under standard conditions. a) conversion 50-60 %. b) conversion < 5%. c) cannot be determined due to the low conversion. d) conversion 52 %.

**Experimental and Synthetic Procedures**

**General remarks**

Salmon testes and calf thymus DNA were obtained from Sigma.

**Physical methods.**

Equilibrium binding constants to salmon testes DNA were determined by UV/Vis titration, following the procedure of Meehan.<sup>1</sup> After dissolution of salmon testes DNA (2 mg/ml), the stock solution was dialyzed extensively against Mops buffer (20 mM pH 6.5) prior to use. The concentration in base pairs was determined spectrophotometrically, using $\varepsilon_{260} = 12800 \text{ M}^{-1} \text{ cm}^{-1}$.<sup>1</sup> The absorbance ratio of $\lambda_{260}/\lambda_{280}$ was 1.8-1.9, indicating the DNA was sufficiently free of protein. The $K_b$ was determined by titration of DNA to a solution of copper complex in buffered solution. Concentrations of copper complexes generally were 30 $\mu$M, or 15 $\mu$M in case of Cu(dppz)(NO<sub>3</sub>)<sub>2</sub> and Cu(dpq)(NO<sub>3</sub>)<sub>2</sub>. Under conditions where the ratio of bound complex : DNA base pairs approaches zero, the $K_b$ can be determined using:

$$\frac{D}{\Delta \varepsilon_{ap}} = \frac{1}{\Delta \varepsilon} D + \frac{1}{\Delta \varepsilon K_b}$$

where $\Delta \varepsilon_{ap} = |\varepsilon_a - \varepsilon_f|$, $\Delta \varepsilon = |\varepsilon_b - \varepsilon_f|$, $\varepsilon_a$, $\varepsilon_f$, and $\varepsilon_b$ are the apparent, free and bound extinction coefficients for the complex, respectively, and $D$ is the DNA concentration in basepairs. In a plot of $D/\Delta \varepsilon_{ap}$ vs. $D$, $K_b$ is given by the ratio of the slope to the y intercept. A representative plot, for [Cu(bipy)(NO<sub>3</sub>)]<sub>2</sub>, is shown below.

![Figure S2](image.png)

**Figure S2.** Representative plot of [DNA]/$\Delta \varepsilon_{ap}$ vs. [DNA] for [Cu(bipy)(NO<sub>3</sub>)]<sub>2</sub> (30 $\mu$M). The solid line represents the least squares linear fit of the data.
Catalytic Diels-Alder reactions, representative procedure.

A buffered solution (20 mM Mops, pH 6.5) of DNA bound catalyst (1.3 mg/ml salmon testes DNA and 0.3 mM [Cu(bipy)(NO₃)₂]) was prepared by mixing a solution of salmon testes DNA (10 ml of a 2 mg/ml solution in 30 mM Mops, prepared 24 h in advance) with an aqueous solution of catalyst (5 ml of a 0.9 mM solution, prepared by adding a solution of [Cu(bipy)(NO₃)₂] in a minimal amount of dms to 5 ml H₂O). An aliquot of a stock solution of dienophile 2a in CH₃CN (30 µL of a 0.5 M soln., final conc. 1 mM) was added and the mixture was cooled to 5 °C. The reaction was started by addition of cyclopentadiene (21 µL, final conc. 15 mM) and mixed by continuous inversion for 3 days, followed by extraction of the product with diethyl ether. After H-NMR analysis the e.e. was determined by chiral hplc (Daicel chiralcel-ODH column). Selected products were purified by column chromatography and analyzed on a Daicel chiralcel-ODH column or Daicel chiralpak-AD column to confirm the results obtained from analysis of the crude product.

HPLC conditions:
3a: Daicel chiralcel-ODH, heptane/iPrOH 98:2, 0.5 ml/min. Retention times: 11.4, 12.3 (exo isomer), 13.7 and 16.7 mins (endo isomer); Daicel chiralpak-AD, heptane/iPrOH 99:1, 1 ml/min. Retention times: 9.7, 10.6 (exo isomer), 12.5 and 14.6 mins (endo isomer).
3b: Daicel chiralpak-AD, heptane/iPrOH 98:2, 1 ml/min. Retention times: 13.5, 15.2 (exo isomer), 17.4 and 21.1 mins (endo isomer).
3c: Daicel chiralcel-ODH, heptane/iPrOH 99.75:0.25, 0.5 ml/min. Retention times: 13.9, 14.7 (exo isomer), 20.4 and 25.3 mins (endo isomer).

Figure S3. ¹H-NMR of the crude product 3a of the Diels-Alder reaction catalyzed by [Cu(dmbipy)(NO₃)₂] (table 1, entry 16). S denotes residual starting material 2a.
Figure S4. HPLC trace of the crude product 3a of the Diels-Alder reaction catalyzed by [Cu(dmbipy)(NO3)2] (table 1, entry 16). S denotes residual starting material 2a. The peak of one of the enantiomers of the exo product (at 11.4 min) is too small to detect.

**Synthesis**

**General remarks**

Dienophiles 2a-b,3 Cu(dppz)(NO3)2,4 Cu(dpq)(NO3)2,4 2-(2-pyridyl)imidazole (9)5 were prepared following published procedures.

(E)-4,4-dimethyl-1-(2-pyridinyl)-2-penten-1-one (2c). This compound was prepared following the procedure as described for 2a.3 Starting from 2-acetylpyridine (2.06 g, 17 mmol) and pivaldehyde (1.42 g, 16.5 mmol), after column chromatography (SiO2, heptane/ethyl acetate 8:1), 2c was obtained as a white solid. Yield: 706 mg, 3.7 mmol, 22 %.\(^1\)H-NMR (CDCl3, 400 MHz) \(\delta\) 1.18 (s, 9H), 7.24 (dd, 1H, \(J = 15.8\) Hz, \(J = 0.8\) Hz), 7.46 (m, 1H), 7.54 (d, 1H, \(J = 16.5\) Hz), 7.84 (m, 1H), 8.12 (d, 1H, \(J = 7.3\) Hz), 8.71 (m, 1H). \(^1\)H-NMR (CDCl3, 100 MHz) \(\delta\) 28.71 (q), 34.39 (s), 119.32 (d), 122.81 (d), 126.65 (d), 136.5 (d), 148.76 (d), 154.29 (s), 159.3 (d), 190.04 (d); Anal. Calcd for C\(_{12}\)H\(_{15}\)NO: C, 76.16 H, 7.99 N, 7.40. Found: C, 76.1 H, 8.04 N, 7.45.

[3-(tert-butyl)bicyclo[2.2.1]hept-5-en-2-yl](2-pyridinyl)methanone (3c, major isomer) \(^1\)H-NMR (CDCl3, 400 MHz) \(\delta\) 0.89 (s, 9H), 1.38 (m, 1H), 1.80 (m, 1H), 1.90 (dd, 1H, \(J = 6.2\) Hz, \(J = 1.5\) Hz), 2.76 (dd, 1H, \(J = 2.9\) Hz, \(J = 1.5\) Hz), 3.22 (m, 1H), 4.26 (dd, 1H, \(J = 6.2\) Hz, \(J = 2.9\) Hz), 5.69 (dd, 1H, \(J = 5.5\) Hz, \(J = 2.6\) Hz), 6.43 (dd, 1H, \(J = 5.5\) Hz, \(J = 2.9\) Hz), 7.44 (m, 1H), 7.78 (m, 1H), 7.97 (d, 1H, \(J = 7.7\) Hz), 8.71 Hz (d, 1H, \(J = 4.8\) Hz); MS (Cl): 256 (M+1); HRMS Calcd for C\(_{17}\)H\(_{21}\)N\(_1\)O\(_1\) 255.1623, found 255.1613.

[Cu(phen)(NO3)2]. Following the procedure as described for [Cu(dppz)(NO3)2], starting from phenanthroline (70 mg, 0.35 mmol) and Cu(NO3)\(_2\)-3H\(_2\)O (94 mg, 1.1 eq), [Cu(phen)(NO3)\(_2\)] was obtained as a blue solid. Yield: 114 mg, 0.31 mmol, 89 %. Anal. Calcd for C\(_{12}\)H\(_{10}\)CuN\(_4\)O\(_6\): C, 39.19 H, 2.19 N, 15.23. Found: C, 39.25 H, 2.09 N, 15.15.

[Cu(bipy)(NO3)2]. Following the procedure as described for [Cu(dppz)(NO3)2], starting from 2,2'-bipyridine (60 mg, 0.39 mmol) and Cu(NO3)\(_2\)-3H\(_2\)O (100 mg, 1.1 eq), [Cu(bipy)(NO3)\(_2\)] was obtained as a blue solid. Yield: 86 mg, 0.25 mmol, 64 %. Anal. Calcd for C\(_{10}\)H\(_{8}\)CuN\(_4\)O\(_6\): C, 34.94 H, 2.35 N, 16.30. Found: C, 35.1 H, 2.30 N, 16.15.

[Cu(2-(2-pyridyl)imidazole)(NO3)2·H\(_2\)O]. To a solution of 2-(2-pyridyl)imidazole (9) (74 mg, 0.51 mmol) in ethanol (10 mL) was added Cu(NO3)\(_2\)-3H\(_2\)O (123 mg, 0.51 mmol). The mixture was shaken until a clear green solution was obtained. The solution was placed in an ether bath for 2 days. The green crystals were filtered and washed with water and ethanol. Yield: 65 mg, 38%. Anal. Calcd for C\(_8\)H\(_9\)CuN\(_5\)O\(_7\): C, 34.94 H, 2.35 N, 1.15.
[Cu(2-(2-pyridyl)benzimidazole)(NO₃)₂ ⋅ H₂O]. To a solution of Cu(NO₃)₂ ⋅ 3H₂O (97 mg, 0.39 mmol) in a mixture of acetone (4 mL) and ethanol (0.3 ml) was added a solution of 2-(2-pyridyl)benzimidazole (10) (75 mg, 0.38 mmol) in ethyl acetate (4ml), through a small cotton plug. The dark green solution was filtered and the vial was closed with a cotton plug, allowing for slow evaporation of acetone. After one night a dark green solid had precipitated, which was washed with a small volume of ethyl acetate. Yield: 135 mg, 89 %. Anal. Calcd for C₁₂H₁₁CuN₅O₇: C, 35.96 H, 2.77 N, 17.47. Found: C, 36.30 H, 2.83 N, 17.04.

[Cu(4,4’-dimethyl-2,2’-dipyridyl)(NO₃)₂]. To a solution of Cu(NO₃)₂ ⋅ 3H₂O (0.10 g, 0.41 mmol) in ethanol was added 4,4’-dimethyl-2,2’-dipyridyl (11) (38 mg, 0.24 mmol), dissolved in ethanol. The solution was placed in an ethyl acetate bath and left standing for 2 days. The blue solid was filtered and washed with ethanol. Yield: 49 mg, 59%. Anal. Calcd for C₁₀H₈CuN₄O₆: C, 38.8 H, 3.25 N, 15.07. Found: C, 38.5 H, 3.14 N, 14.80.

Reference List