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Highly enantioselective DNA-based catalysis

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Supplementary Information Accompanying

“Highly Enantioselective DNA-based Catalysis”

by

Gerard Roelfes, Arnold J. Boersma and Ben L. Feringa

Figure S1. Induced CD spectra from $[\text{Cu}(\text{L}_{4-7})(\text{NO}_3)_2]$ (150 μM) combined with salmon testes DNA (0.8 mg/ml) in Mops buffer (20 mM, pH 6.5). a) only st-DNA; b) $[\text{Cu}(\text{bipy})(\text{NO}_3)_2]$ / st-DNA; c) $[\text{Cu}(\text{dppz})(\text{NO}_3)_2]$ / st-DNA; d) $[\text{Cu}(\text{dpq})(\text{NO}_3)_2]$ / st-DNA; e) $[\text{Cu}(\text{phen})(\text{NO}_3)_2]$ / st-DNA.

Table S1: Effect of variation of the concentration of $[\text{Cu}(\text{bipy})(\text{NO}_3)_2]$, st-DNA and **2a** on the results of the catalyzed reaction.

Entry	Concentration $[\text{Cu}(\text{bipy})(\text{NO}_3)_2]$ (mM)	Conc. DNA (mg/ml)	dienophile (mM)	Conversion (%)	Endo:Exo	E.e. Endo
1	0.05	1.3	1	>80	97:3	89
2	0.10	1.3	1	>80	98:2	91
3	0.15	1.3	1	>80	98:2	91
4	0.30	1.3	1	>80	98:2	89
5	0.45	1.3	1	>80	98:2	85
6	0.60	1.3	1	>80	98:2	77
7	0.15	0.65	1	68	98:2	89
8	0.30	0.65	1	>80	98:2	84
9	0.30	1.3	0.3	Quant.	97:3	90
10	0.30	1.3	1.5	>80	98:2	89
11	0.30	1.3	3	>80	97:3	87
12	0.30	1.3	6	65	97:3	86

Table S2

	catalyst	T	endo:exo	e.e. endo (%)
1^a	Cu(NO ₃) ₂ / DNA	RT	95:5	10
2^b	DNA	5 °C	n.d. ^c	<5 %
3^d	[Cu(dppz)(NO ₃) ₂] / DNA	5 °C	94:6	-

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.¹ 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 $\epsilon_{260} = 12800 \text{ M}^{-1} \text{ cm}^{-1}$.² 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 μM , or 15 μM in case of Cu(dppz)(NO₃)₂ and Cu(dpq)(NO₃)₂. Under conditions where the ratio of bound complex : DNA base pairs approaches zero, the K_b can be determined using :

$$\frac{D}{\Delta\epsilon_{ap}} = \frac{1}{\Delta\epsilon} D + \frac{1}{\Delta\epsilon K_b}$$

where $\Delta\epsilon_{ap} = |\epsilon_a - \epsilon_f|$, $\Delta\epsilon = |\epsilon_b - \epsilon_f|$, ϵ_a , ϵ_f and ϵ_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 $D/\Delta\epsilon_{ap}$ vs. D , K_b is given by the ratio of the slope to the y intercept. A representative plot, for [Cu(bipy)(NO₃)₂], is shown below.

Figure S2. Representative plot of $[DNA]/\Delta\epsilon_{ap}$ vs. $[DNA]$ for [Cu(bipy)(NO₃)₂] (30 μM). 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 dmso to 5 ml H₂O). An aliquot of a stock solution of dienophile **2a** in CH₃CN (30 μ L of a 0.5 M soln., final conc. 1 mM) was added and the mixture was cooled to 5 $^{\circ}$ C. The reaction was started by addition of cyclopentadiene (21 μ L, 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 $[\text{Cu}(\text{dmbipy})(\text{NO}_3)_2]$ (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 $\text{Cu}(\text{dppz})(\text{NO}_3)_2$,⁴ $\text{Cu}(\text{dpq})(\text{NO}_3)_2$,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 (SiO_2 , heptane/ethyl acetate 8:1), **2c** was obtained as a white solid. Yield: 706 mg, 3.7 mmol, 22 %. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 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). $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ 28.71 (q), 34.39 (s), 119.32 (d), 122.81 (d), 126.65 (d), 136.85 (d), 148.76 (d), 154.29 (s), 159.89 (d), 190.04 (d); Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}$: 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)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 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 (CI): 256 (M+1); HRMS Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_1\text{O}_1$ 255.1623, found 255.1613.

$[\text{Cu}(\text{phen})(\text{NO}_3)_2]$. Following the procedure as described for $[\text{Cu}(\text{dppz})(\text{NO}_3)_2]$,⁴ starting from phenanthroline (70 mg, 0.35 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (94 mg, 1.1 eq), $[\text{Cu}(\text{phen})(\text{NO}_3)_2]$ was obtained as a blue solid. Yield: 114 mg, 0.31 mmol, 89 %. Anal. Calcd for $\text{C}_{12}\text{H}_8\text{CuN}_4\text{O}_6$: C, 39.19 H, 2.19 N, 15.23. Found: C, 39.25 H, 2.09 N, 15.15.

$[\text{Cu}(\text{bipy})(\text{NO}_3)_2]$. Following the procedure as described for $[\text{Cu}(\text{dppz})(\text{NO}_3)_2]$, starting from 2,2'-bipyridine (60 mg, 0.39 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (100 mg, 1.1 eq),⁴ $[\text{Cu}(\text{bipy})(\text{NO}_3)_2]$ was obtained as a blue solid. Yield: 86 mg, 0.25 mmol, 64 %. Anal. Calcd for $\text{C}_{10}\text{H}_8\text{CuN}_4\text{O}_6$: C, 34.94 H, 2.35 N, 16.30. Found: C, 35.1 H, 2.30 N, 16.15.

$[\text{Cu}(\text{2-(2-pyridyl)imidazole})(\text{NO}_3)_2 \cdot \text{H}_2\text{O}]$. To a solution of 2-(2-pyridyl)imidazole (**9**) (74 mg, 0.51 mmol) in ethanol (10 mL) was added $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (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 $\text{C}_8\text{H}_9\text{CuN}_5\text{O}_7$: C, 27.40 H, 2.59 N, 19.97. Found: C, 27.6 H, 2.49 N, 19.74.

[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.

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