Electronic Supplementary Information for: Flavin-cyclodextrin conjugates as catalysts of enantioselective sulfoxidations with hydrogen peroxide in aqueous media

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1 Synthetic procedures and characterizations

1.1 General procedures

NMR spectra were acquired with spectrometers Bruker AVANCE 500 (¹H at 500.1 MHz and ¹³C at 125.8 MHz), AVANCE 600 (¹H at 600.1 MHz and ¹³C at 150.9 MHz) and Varian Mercury Plus (¹H at 299.97 MHz and ¹³C at 75.44 MHz) in $CDCl_3$, d₆-DMSO or D_2O at 300 K. Homonuclear 2D-NMR spectra (H,H-COSY) and heteronuclear 2D-NMR spectra (H,C-HSQC and H,C-HMBC) were used for structural assignment of proton and carbon signals of compounds 5 and 6. Mass spectra were measured either using ES ionization in positive or negative mode (Waters micromass ZQ). High resolution mass spectra were measured using nanoESI ionization on LTQ Orbitrap XL (Thermo Fisher Scientific). Optical rotations were recorded on AUTOPOL IV (Rudolph Research Analytical). Elemental analyses were carried out on Perkin Elmer 2400 II, determination of the content of sulfur was made by X-ray fluorescence spectrometry on SPECTRO iQ II. Preparative reversed-phase chromatography (RP) was carried out using medium pressure columns containing C-18 modified silica (Phenomenex Luna, 15 µm). Thin-layer (TLC) and reversed-phase thin-layer (RPTLC) chromatographies were performed with precoated Silica Gel 60F and RP-18F plates (E. Merck). HPLC analyses were recorded on Knauer Smartline with UV detector and detector of optical rotatory power CHIRALYSER. 2-(2-Methoxyethoxy)ethyl iodide¹ (9), 3-methylalloxazine^{2, 3} (10), 10-methylisoalloxazine⁴ (11) and heptahydrate of mono-6-deoxy-6-amino- β -cyclodextrin⁵ (12) were prepared according to the described procedures. All other chemicals used were commercially available. Correct elemental analysis for compounds 5 and 6 could not be obtained unless variable numbers of water molecules were taken into account. Thus, calculations based on accurate weights of these compounds (molarity, optical rotation, yields) were corrected with respect to the water content as deduced from elemental analysis.

1.2 Synthesis of substrate 13



1-[2-(2-Methoxyethoxy)ethoxy]-4-(methylsulfanyl)benzene (13). 4-(Methylsulfanyl)phenol (0.58 g, 4.16 mmol) was dissolved in DMF and potassium carbonate (3.14 g, 22.68 mmol) and iodide 9 (0.87 g, 3.78 mmol) was added. The reaction mixture was stirred at 40 °C overnight. The course of the reaction was monitored by TLC (DCM/MeOH – 30:1). The insolubles were

filtered off and the filtrate was evaporated in vacuo. Crude oily product was extracted with chloroform (3×25 mL), combined extracts were washed with water and dried over sodium sulfate. The solvent was evaporated and the crude product was subjected to column chromatography (ethyl acetate/hexane – 1:2) to give oily material (0.54 g, 59 %). ¹H-NMR[CDCl₃] δ : 2.44 (s, 3H), 3.39 (s, 3H), 3.58 (t, J = 4.5, 2H), 3.72 (t, J = 4.8, 2H), 3.85 (t, J = 4.5, 2H), 4.12 (t, J = 4.8, 2H), 6.86 (m, 2H), 7.24 (m, 2H). ¹³C-NMR[CDCl₃] δ : 18.1, 59.2, 67.8, 69.9, 70.9, 72.1, 115.6, 129.2, 130.2, 157.6. For C₁₂H₁₈O₃S (242.33) calculated: C 59.47 %, H 7.49 %, S 13.23 %; found: C 59.55 %, H 7.48 %, S 12.93 %. HR-MS (ESI): For C₁₂H₁₉O₃S [M+H]⁺ calculated 243.10494, found 243.10489.

1.3 Syntheses of flavin-carboxylic acids 3 and 4



2-(3-Methylalloxazin-1-yl)acetic acid (3). 3-Methylalloxazine (**10**) (2.0 g, 8.76 mmol) and dry potassium carbonate (1.20 g, 8.76 mmol) were suspended in dry DMF. Ethyl bromoacetate (1.26 mL, 17.53 mmol) was added by a syringe. Reaction mixture was stirred under nitrogen at ambient temperature for three days under monitoring by TLC (ethyl acetate/methanol – 30:1). Potassium carbonate was filtered off and DMF was removed under reduced pressure. Pale yellow solid (corresponding ester) was treated with hydrochloric acid (35 % in water, 50 mL) at 80 °C for 1 hour. Cold water (150 mL) was poured into the reaction mixture. Pale yellow precipitate was filtered off and recrystallised from 4 M acetic acid (200 mL). Yellow-green opalescent crystals (1.47 g, 58 %) were obtained, m. p. >300 °C. For $C_{13}H_{10}N_4O_4$ (286.24) calculated: C 54.55 %, H 3.52 %, N 19.57 %; found: C 54.48 %, H 3.15 %, N 19.60 %. MS (ESI⁻, DMSO): m/z (%): 285.1 (90) [M]⁻, 241.1 (100) [M – COO]⁻. For NMR characterization see Table S1 in chapter 1.5.



2-(10-Methylisoalloxazin-3-yl)acetic acid⁶ (4). 10-Methylisoalloxazine (**11**) (1.37 g, 6.0 mmol) and potassium carbonate (4.65 g, 33.6 mmol) were suspended in dry DMF (250 mL).

Then ethyl bromoacetate (2.53 mL, 22.8 mmol) was added. Reaction mixture was stirred overnight under nitrogen, then the solids were filtered off and DMF was evaporated. Wet residue was diluted with water (200 mL) and the solution was extracted with chloroform (2×200 mL). Combined extracts were dried over magnesium sulfate and chloroform was removed under reduced pressure. Light yellow solid (corresponding ester) was treated with hydrochloric acid (35 %, 25 mL) at 80 °C for 45 min. The reaction mixture was diluted with water (25 mL) and allowed to stand overnight. Brown precipitate was collected by filtration and recrystallised from 2M acetic acid (160 mL). Dark orange prisms (1.08 g, 64 %) were obtained, m. p. >300 °C. For C₁₃H₁₀N₄O₄ (286.24) calculated: C 54.55 %, H 3.52 %, N 19.57 %; found: C 54.42 %, H 3.25 %, N 19.59 %. For NMR characterization see Table S1 in chapter 1.5.

1.4 Syntheses of flavin-cyclodextrin conjugates



N-(6-Deoxy-β-cyclodextrin-6-yl) 2-(3-methylalloxazin-1-yl)acetamide (5). Acid 3 (16.4 mg, 57.3 μmol), aminocyclodextrin 12 (59.1 mg, 46.9 μmol, calculated for heptahydrate) and PyBOP (29.8 mg, 57.3 μmol) were dissolved in DMF. Then DIPEA (18.1 μL, 140 μmol) was added. The mixture was stirred overnight under inert atmosphere at ambient temperature. Then DMF was evaporated under reduced pressure, and the resulting solid was purified by reversed phase chromatography. Collected main fractions were concentrated in vacuo and lyophilized. Light yellow fluffy solid (49.9 mg, 72 %, calculated for tetrahydrate) was obtained. $[\alpha]_D^{20}$ +115.0 (*c* 0.113 in DMSO). For C₅₅H₇₉N₅O₃₇·4H₂O calculated: C 44.81 %, H 5.95 %, N 4.75 %; found: C 44.46 %, H 5.90 %, N 4.61 %. HR-MS (ESI): For C₅₅H₇₉N₅O₃₇Na [M + Na]⁺ calculated 1424.4352, found 1424.4346. For NMR characterization see Table S1 and Table S2 in chapter 1.5.



N-(6-Deoxy-β-cyclodextrin-6-yl) 2-(10-methylisoalloxazin-3-yl)acetamide (6). Acid 4 (32.5 mg, 113.5 μmol), aminocyclodextrin 12 (101.1 mg, 80.19 μmol, calculated for heptahydrate) and PyBOP (58.8 mg, 113.0 μmol) were dissolved in dry DMF (1.5 mL). Then DIPEA (35 mL, 201.0 μmol) was added. The mixture was stirred for 2 hours under inert atmosphere at room temperature. Then DMF was evaporated under reduced pressure, and the resulting solid was dissolved in water and purified by reversed phase chromatography. Collected main fractions were concentrated in vacuo and lyophilized. Light yellow fluffy solid (48 mg; 40 %, calculated for hexahydrate) was obtained. $[\alpha]_D^{20}$ +92.8 (*c* 0.097 in H₂O). For C₅₅H₇₉N₅O₃₇·6H₂O calculated: C 43.74 %, H 6.07 %, N 4.64 %; found: C 43.84 %, H 5.85 %, N 4.53 %. HR-MS (ESI): For C₅₅H₇₉N₅O₃₇Na [M + Na]⁺ calculated 1402.4537. For NMR characterization see Table S1 and Table S2 in chapter 1.5.

1.5 NMR data of compounds 3, 4, 5 and 6



Figure S1: Numbering of heterocyclic skeletons used in Tables S1 and S2

| Ţ | ible S1: C | Carbon | ו and pro | ton NN | AR dat | a of con | punodu | ls 3 , 4, 5 | 5 and 6 | (aglycc | one part | () | |
|---|--------------------------------------|--------|----------------------------|-----------------|--------------------|--------------------------|-------------------|--------------------------|-------------------|------------------|-------------------|-------------------|--------|
| Compound (solv.; temp.) | C-2 | C-4 | C-4a | C-6a | C-6 | C-7 | C-8 | C-9 | C-9a | C-10a | N-CH ₃ | N-CH ₂ | C=0 |
| 3 (DMSO; 27 °C) | 150.49 | 159.28 | 130.80 | 139.39 | 130.33 | 129.54 | 134.25 | 127.64 | 142.06 | 144.89 | 28.92 | 43.40 | 169.36 |
| 4 (DMSO; 27 °C) | 159.24 | 154.21 | 137.31 | 133.62 | 132.00 | 126.65 | 135.76 | 117.01 | 135.34 | 149.82 | 32.25 | 42.61 | 169.54 |
| 4 (CD ₃ OD; 27 °C) | 161.39 | 157.46 | 138.34 | 137.21 | 133.29 | 128.06 | 137.23 | 117.71 | 135.22 | 151.35 | 32.91 | 43.68 | 171.86 |
| 5 (D ₂ O; 37 °C) | 154.30 | 163.51 | 132.81 | 145.11 | 129.85 | 137.50 | 132.84 | 132.40 | 142.25 | 147.48 | 31.9 | 48.27 | 172.18 |
| 6 (D ₂ O; 27 °C) | 159.39 | 163.60 | 138.33 | 136.22 | 119.35 | 139.90 | 130.65 | 134.32 | 138.47 | 152.04 | 35.47 | 46.58 | 172.09 |
| I | Compound (solv.; temp | p (; | 9-H | H | -1 | Н-8 | | 6-H | N-CH ₃ |)-N | CH ₂ | | |
| I | 3 (DMSO: 27 ° | | 8.03 ddd 8.5.1 7.0 7) | 8.01 | 1 ddd | 7.87 ddd (8 4·6 5·1 | 3 (7 | 3.28 ddd 1. 1 4. 0 7) | 3.41 s (3H) | 5.(| 30 s | | |
| | 4 (DMSO; 27 ⁶ | ç (ĵ | 8.18 m | 7.6 | 9 m | 8.00 m | | 8.00 m | 4.02 s (3H) | 4.5 (2 | 58 s (H) | | |
| | 4 (CD ₃ OD; 27 | °C) | 8.25 ddd 8.2; 1.5; 0.6) | 7.75 (8.2; 6 | 5 ddd (.7; 1.5) | 8.04 ddd (8.7; 6.7; 1 | 5) (8.7 | 3.02 ddd 7; 1.5; 0.6) | 4.18 s (3H) | 4.7 | 78 s (H) | | |
| | 5 (D ₂ 0; 37 °C | G | 8.13 dd (8.6; 1.4) | 8.2((8.6; 6 |) ddd (.8; 1.6) | 8.06 ddd (8.6; 6.8; 1 | _ (4. | 8.40 dd 8.6; 1.6) | 3.55 s (3H) | 5.22 d (16.3) | 4.98 d (16.3) | | |
| | 6 (D ₂ O; 27 °C | Û | 8.20 dd (8.3; 1.5) | 7.82 (8.3; 7 | 2 ddd '.1; 1.2) | 8.11 ddd (8.7; 7.1; 1 | .5) | 8.02 dd 8.7; 1.2) | 4.18 s (3H) | 4.91 d (16.2) | 4.70 d (16.2) | | |

| Compound | C-1' | C-2' | C-3' | C-4' | C-5' | C-6' |
|--|---|---|--|---|--|---|
| (solv.; temp.) | | | | | | |
| 5 | 104.74 | 75.89 | 76.14 | 86.79 | 74.91 | 62.99 |
| (D ₂ O; 37 °C) | 104.66 (2) | 74.86 | 76.12 | 83.72 | 74.57 (3) | 62.93 |
| | 104.57 | 74.68 (2) | 76.04 (2) | 83.64 | 74.51 | 62.82 |
| | 104.27 | 74.65 (2) | 75.81 | 83.55 | 74.37 | 62.63 (2) |
| | 104.09 | 74.43 | 75.51 (2) | 83.34 | 73.95 | 62.61 |
| | 103.93 | | | 83.32 | | 44.05 |
| | | | | 83.23 | | |
| 6 | 104.59 | 74.66 | 75.68 | 85.82 | 74.31 (2) | 62.91 |
| (D ₂ O; 27 °C) | 104.46 (2) | 74.64 | 75.66 | 83.67 | 74.25 (2) | 62.78 |
| | 104.40 (2) | 74.62 (2) | 75.63 (2) | 83.59 | 74.21 (2) | 62.67 |
| | 104.38 | 74.57 (2) | 75.60 | 83.56 | 72.83 | 62.58 (2) |
| | 104.34 | 74.53 | 75.56 | 83.54 (2) | | 62.48 |
| | | | 75.38 | 83.40 | | 43.11 |
| | H-1, | н₋2, | Ц 3, | ц л, | Ц 5, | U 6'a L U 6'h |
| | 11 1 | 11-2 | 11-5 | 11-4 | 11-5 | п-0 a + п-0 0 |
| 5 | 5.093 | 3.672 | 3.984 | 3.660 | 3.950 | 3.998 + 3.903 |
| 5 (D ₂ O; 37 °C) | 5.093 5.093 | 3.672 3.645 | 3.984 3.969 | 3.660 3.608 | 3.950 3.850 | 3.998 + 3.903 3.69 + 3.48 |
| 5 (D ₂ O; 37 °C) | 5.093 5.093 5.067 | 3.672 3.645 3.643 | 3.984 3.969 3.899 | 3.660 3.608 3.552 | 3.950 3.850 3.500 (2) | $\frac{1+0}{3.998} + 3.903$ $3.69 + 3.48$ $3.97 + 3.883$ |
| 5 (D ₂ O; 37 °C) | 5.093 5.093 5.067 4.992 | 3.672 3.645 3.643 3.607 | 3.984 3.969 3.899 3.800 (2) | 3.660 3.608 3.552 3.488 | 3.950 3.850 3.500 (2) 3.480 | 3.998 + 3.903 3.69 + 3.48 3.97 + 3.883 3.352 + 3.241 |
| 5 (D ₂ O; 37 °C) | 5.093 5.093 5.067 4.992 4.958 | 3.672 3.645 3.643 3.607 3.589 | 3.984 3.969 3.899 3.800 (2) 3.729 | 3.660 3.608 3.552 3.488 3.410 | 3.950 3.850 3.500 (2) 3.480 3.046 | 3.998 + 3.903 3.69 + 3.48 3.97 + 3.883 3.352 + 3.241 3.573 + 3.404 |
| 5 (D ₂ O; 37 °C) | 5.093 5.093 5.067 4.992 4.958 4.901 | 3.672 3.645 3.643 3.607 3.589 3.519 | 3.984 3.969 3.899 3.800 (2) 3.729 3.575 | 3.660 3.608 3.552 3.488 3.410 3.400 | 3.950 3.850 3.500 (2) 3.480 3.046 2.803 | $\begin{array}{c} 3.998 + 3.903 \\ 3.69 + 3.48 \\ 3.97 + 3.883 \\ 3.352 + 3.241 \\ 3.573 + 3.404 \\ 3.768 + 3.645 \end{array}$ |
| 5 (D ₂ O; 37 °C) | 5.093 5.093 5.067 4.992 4.958 4.901 4.875 | 3.672 3.645 3.643 3.607 3.589 3.519 3.500 | 3.984 3.969 3.899 3.800 (2) 3.729 3.575 | 3.660 3.608 3.552 3.488 3.410 3.400 3.307 | 3.950 3.850 3.500 (2) 3.480 3.046 2.803 | $\begin{array}{c} 3.998 + 3.903 \\ 3.69 + 3.48 \\ 3.97 + 3.883 \\ 3.352 + 3.241 \\ 3.573 + 3.404 \\ 3.768 + 3.645 \\ 3.934 + 3.293 \end{array}$ |
| 5 (D ₂ O; 37 °C) 6 | 5.093 5.093 5.067 4.992 4.958 4.901 4.875 5.097 (2) | 3.672 3.645 3.643 3.643 3.589 3.519 3.500 3.693 | 3.984 3.969 3.899 3.800 (2) 3.729 3.575 3.963 (2) | 3.660 3.608 3.552 3.488 3.410 3.307 3.643 | 3.950 3.850 3.500 (2) 3.480 3.046 2.803 3.952 | $\begin{array}{c} 1.50 \ a+11.50 \ b\\ 3.998+3.903 \\ 3.69+3.48 \\ 3.97+3.883 \\ 3.352+3.241 \\ 3.573+3.404 \\ 3.768+3.645 \\ 3.934+3.293 \\ 4.01+3.915 \end{array}$ |
| 5 (D ₂ O; 37 °C) 6 (D ₂ O; 27 °C) | 5.093 5.093 5.067 4.992 4.958 4.901 4.875 5.097 (2) 5.082 | 112 3.672 3.645 3.643 3.607 3.589 3.519 3.500 3.693 3.666 | 3.984 3.969 3.899 3.800 (2) 3.729 3.575 3.963 (2) 3.956 | 11-4 3.660 3.608 3.552 3.488 3.410 3.400 3.307 3.643 3.627 | 3.950 3.850 3.500 (2) 3.480 3.046 2.803 3.952 3.915 (2) | $\begin{array}{c} 1.50 \ a+11.50 \ b\\ \hline 3.998+3.903 \\ 3.69+3.48 \\ 3.97+3.883 \\ 3.352+3.241 \\ 3.573+3.404 \\ 3.768+3.645 \\ 3.934+3.293 \\ \hline 4.01+3.915 \\ 3.99+3.93 \end{array}$ |
| 5 (D ₂ O; 37 °C) 6 (D ₂ O; 27 °C) | 5.093 5.093 5.067 4.992 4.958 4.901 4.875 5.097 (2) 5.082 5.079 | 3.672 3.645 3.643 3.643 3.607 3.589 3.519 3.500 3.693 3.666 3.661 | 3.984 3.969 3.899 3.800 (2) 3.729 3.575 3.963 (2) 3.956 3.940 (2) | 11-4 3.660 3.608 3.552 3.488 3.410 3.400 3.307 3.643 3.627 3.595 | 3.950 3.850 3.500 (2) 3.480 3.046 2.803 3.952 3.915 (2) 3.867 | $\begin{array}{c} 1.50 \ a+11-0 \ b\\ \hline 3.998+3.903\\ \hline 3.69+3.48\\ \hline 3.97+3.883\\ \hline 3.352+3.241\\ \hline 3.573+3.404\\ \hline 3.768+3.645\\ \hline 3.934+3.293\\ \hline 4.01+3.915\\ \hline 3.99+3.93\\ \hline 3.95+3.41\\ \end{array}$ |
| 5 (D ₂ O; 37 °C) 6 (D ₂ O; 27 °C) | 5.093 5.093 5.067 4.992 4.958 4.901 4.875 5.097 (2) 5.082 5.079 5.042 | 3.672 3.645 3.643 3.643 3.589 3.519 3.500 3.693 3.666 3.661 3.639 (2) | 3.984 3.969 3.899 3.800 (2) 3.729 3.575 3.963 (2) 3.956 3.940 (2) 3.906 (2) | 11-4 3.660 3.608 3.552 3.488 3.410 3.400 3.307 3.643 3.627 3.595 3.58 | 3.950 3.850 3.500 (2) 3.480 3.046 2.803 3.952 3.915 (2) 3.867 3.826 | $\begin{array}{c} 1.50 \ a+11-0 \ b\\ \hline 3.998+3.903\\ \hline 3.69+3.48\\ \hline 3.97+3.883\\ \hline 3.352+3.241\\ \hline 3.573+3.404\\ \hline 3.768+3.645\\ \hline 3.934+3.293\\ \hline 4.01+3.915\\ \hline 3.99+3.93\\ \hline 3.95+3.41\\ \hline 3.895+3.85\end{array}$ |
| 5 (D ₂ O; 37 °C) 6 (D ₂ O; 27 °C) | 5.093 5.093 5.067 4.992 4.958 4.901 4.875 5.097 (2) 5.082 5.079 5.042 5.023 | 3.672 3.645 3.643 3.607 3.589 3.519 3.500 3.693 3.666 3.661 3.639 (2) 3.604 (2) | 11-3 3.984 3.969 3.899 3.800 (2) 3.729 3.575 3.963 (2) 3.956 3.940 (2) 3.906 (2) | 11-4 3.660 3.608 3.552 3.488 3.410 3.400 3.307 3.643 3.627 3.595 3.58 3.545 | 3.950 3.850 3.500 (2) 3.480 3.046 2.803 3.952 3.915 (2) 3.867 3.826 3.780 | $\begin{array}{c} 1.50 \ a + 11-0 \ b \\ \hline 3.998 + 3.903 \\ 3.69 + 3.48 \\ 3.97 + 3.883 \\ 3.352 + 3.241 \\ 3.573 + 3.404 \\ 3.768 + 3.645 \\ 3.934 + 3.293 \\ \hline 4.01 + 3.915 \\ 3.99 + 3.93 \\ 3.95 + 3.81 \\ 3.895 + 3.85 \\ 3.85 + 3.82 \end{array}$ |
| 5 (D ₂ O; 37 °C) 6 (D ₂ O; 27 °C) | 5.093 5.093 5.067 4.992 4.958 4.901 4.875 5.097 (2) 5.082 5.079 5.042 5.023 4.995 | 3.672 3.645 3.643 3.643 3.607 3.589 3.519 3.500 3.693 3.666 3.661 3.639 (2) 3.604 (2) | 3.984 3.969 3.899 3.800 (2) 3.729 3.575 3.963 (2) 3.956 3.940 (2) 3.906 (2) | 11-4 3.660 3.608 3.552 3.488 3.410 3.400 3.307 3.643 3.627 3.595 3.58 3.545 3.514 | 3.950 3.850 3.500 (2) 3.480 3.046 2.803 3.952 3.915 (2) 3.867 3.826 3.780 3.734 | $\begin{array}{c} 1.50 \ a+11-0 \ b\\ \hline 3.998+3.903\\ \hline 3.69+3.48\\ \hline 3.97+3.883\\ \hline 3.352+3.241\\ \hline 3.573+3.404\\ \hline 3.768+3.645\\ \hline 3.934+3.293\\ \hline 4.01+3.915\\ \hline 3.99+3.93\\ \hline 3.95+3.41\\ \hline 3.895+3.85\\ \hline 3.85+3.82\\ \hline 3.825+3.595\\ \hline \end{array}$ |

Table S2: Carbon and proton NMR data of compounds **5** and **6** (β -cyclodextrin part)









Figure S4: ¹H and ¹³C NMR spectra of compound **5**



Figure S5: ¹H and ¹³C NMR spectra of compound **6**



1.6 Preparation of the catalysts 1 and 2

N-(6-Deoxy- β -cyclodextrin-6-yl) 2-(5-ethyl-5,10-dihydro-3-methylalloxazin-1-yl)acetamide (1). Acetaldehyde (170 µL, 3.03 mmol) and palladium on carbon (10%, 2.3 mg, 2.14 µmol) were added to a solution of 5 (15.0 mg, 10.4 µmol) in ethanol (800 µL), perchloric acid (0.1 M in water, 800 µL) and water (600 µL). The resulting mixture was stirred for 24 hours in the autoclave under hydrogen (0.6 MPa) at room temperature. Then the palladium-catalyst was filtered off under argon atmosphere, ethanol and resulting acetaldehyde were evaporated under reduced pressure. The solution of 1 was stored under argon atmosphere at -78 °C. The concentration of the catalyst 1 in the stock solution was recalculated with respect to the concentration. The activity of the prepared catalyst (aliquot of the catalyst according to the calculated concentration was used) was checked in oxidation of thioanisol under standard conditions (see chapter 2.1). The compound was identified by ESI HR-MS as oxidized form of the conjugate 1-ox (see below).

1-{[*N*-(6-Deoxy- β -cyclodextrin-6-yl)carbamoyl]methyl}-5-ethyl-3-methylalloxazin-5-ium perchlorate (1-ox). HR-MS (ESI): for C₅₇H₈₄N₅O₃₇ [M - ClO₄⁻]⁺ calculated 1430.48396, found 1430.48598.



N-(6-Deoxy-β-cyclodextrin-6-yl) 2-(5-ethyl-5,10-dihydro-10-methylisoalloxazin-3-yl)acetamide (2). Acetaldehyde (170 μL, 3.03 mmol) and palladium on carbon (10%, 2.1 mg, 1.9 μmol) were added to a solution of 6 (13.8 mg, 9.3 μmol) in the mixture of ethanol (1.125 mL) and perchloric acid (0.1 M in water, 1.125 mL). The resulting mixture was stirred for 24 hours in the autoclave under hydrogen (0.6 MPa) at room temperature. Then the palladium-catalyst was filtered off under argon atmosphere, ethanol and resulting acetaldehyde were evaporated under reduced pressure. The solution of the catalyst **2** was stored under argon atmosphere at -78 °C. The concentration of the catalyst was recalculated with respect to the concentration. The activity of the catalyst (aliquot of the catalyst according to the calculated concentration was measured) was checked in oxidation of thioanisol under standard conditions (see chapter 2.1). In freshly prepared samples, the compound was identified by ESI HR-MS in its reduced form **2**. HR-MS (ESI): for C₅₇H₈₆N₅O₃₇ [M]⁺ calculated 1432.49961, found 1432.49798.

3-{[*N*-(6-Deoxy- β -cyclodextrin-6-yl)carbamoyl]methyl}-5-ethyl-10-methylisoalloxazin-5-ium perchlorate (2-ox). Solution of 2 was spontaneously oxidized by air oxygen for 1 hour to 2-ox. HR-MS (ESI): for C₅₇H₈₄N₅O₃₇ [M – ClO₄⁻]⁺ calculated 1430.48396, found 1430.48347.

1.7 HR-MS spectra of compounds 1-ox, 2 and 2-ox



Figure S6: High resolution mass spectrum of compound 1-ox



Figure S7: High resolution mass spectrum of compound 2



Figure S8: High resolution mass spectrum of compound 2-ox

1.8 Structure of flavinium salts 7 and 8



5-Ethyl-1,3-dimethylalloxazinium perchlorate (**7**) and 5-ethyl-3,10-dimethylisoalloxazinium perchlorate (**8**) were prepared according to the described procedures.⁷

2 Enantioselective sulfoxidations

2.1 General procedures

All catalytic oxidations of 4-substituted thioanisoles have been performed in 1 mL thick-walled cylindro-conical screw-capped vial, anchored on the shaking apparatus with axial shake. The reaction mixtures were prepared by adding sodium-phosphate buffer (0.05 M, 300 μ L), solid or liquid substrate (4.3 \cdot 10^{-5} mol), appropriate volume of catalyst solution and then the hydrogen peroxide (10 μ L, 30 %, 9.8 \cdot 10^{-5} mol). The vial was capped and the reaction mixture has been shaken for appropriate time. Then the reaction was quenched by solution of sodium dithionite in water (1.4 M, 100 μ L). Product and remaining substrate were extracted to chloroform (3×500 μ L) and reaction conversion was determined by NMR. In oxidations of 4-hydroxy- and 4-carboxy-thioanisoles, perchloric acid (0.1 M, 250 μ L) was added before extraction. Thus acidified mixture was extracted three times with ethyl acetate (3×1 mL). Combined extracts were evaporated and the NMR spectra were measured to determine the conversion of the catalytic reaction. Analysis of enantiomeric excess of the isolated sulfoxides was done by HPLC on chiral phases (for details see chapter 2.3).

2.2 NMR spectra of sulfoxides

| R | $-S-CH_3 \xrightarrow{\text{catalyst (1 mol%)}}_{H_2O_2, \text{ phosphate buffer}} R \xrightarrow{\bigcirc}_{\oplus} S \xrightarrow{\odot}_{\oplus} CH_3$ | | | |
|--------------|---|--|--|--|
| S-CH3 | Ar + p-R | | | |
| 2.73 (s, 3H) | 7.65 (m, 2H), 7.58-7.45 (m, 3H) | | | |
| 2.80 (s, 3H) | 7.61 (m, 2H), 7.02 (m, 2H) | | | |
| 2.71 (s, 3H) | 7.54 (m, 2H), 7.34 (m, 2H), 2.42 (s, 3H) | | | |
| 2.70 (s, 3H) | 7.60 (m, 2H), 7.04 (m, 2H), 3.86 (s, 3H) | | | |
| 2.81 (s, 3H) | 8.22 (m, 2H), 7.73 (m, 2H) | | | |
| 2.70 (s, 3H) | 7.58 (m, 2H), 7.05 (m, 2H), 4.19 (dd, 2H, J = 4.3, 5.4), 3.88 (dd, 2H, J = 4.2, 5.4), 3.72 (dt, 2H, J = 3.4, 8.3), 3.62-3.55 (m, 2H), 3.40 (s, 3H) | | | |
| | R-CH ₃ 2.73 (s, 3H) 2.80 (s, 3H) 2.71 (s, 3H) 2.70 (s, 3H) 2.81 (s, 3H) 2.70 (s, 3H) | | | |

Table S3: NMR shifts of isolated sulfoxides from catalytic oxidations

^aCDCl₃, ^bCD₃OD, ^cCDCl₃/CD₃OD (6:1)

2.3 HPLC chromatograms



HPLC record of the separation of enantiomers of product of thioanisole oxidation catalyzed by 1 (1 mol%), (Entry 1, Table1, main text)

Figure S9: Conditions: Knauer® Eurocel 01 $5\mu m$ column, heptane/i-PrOH (17:3), 0.65 mL/min

492,406

100,0

100,0

Total

16712,202



HPLC record of the separation of enantiomers of product of thioanisole oxidation catalyzed by 2 (1 mol%), (Entry 2, Table1, main text)

Figure S10: Conditions: Knauer® Eurocel 01 5µm column, heptane/i-PrOH (17:3), 0.65 mL/min





Figure S11: Conditions: Knauer® Eurocel 01 5µm column, heptane/i-PrOH (17:3), 0.65 mL/min



HPLC record of the separation of enantiomers of product of thioanisole oxidation catalyzed by $8+\beta$ -CD (1 mol%), (Entry 4, Table1, main text)

Figure S12: Conditions: Knauer® Eurocel 01 5µm column, heptane/i-PrOH (17:3), 0.65 mL/min





Figure S13: Conditions: Knauer® Eurocel 01 $5\mu m$ column, heptane/i-PrOH (19:1), 0.5 mL/min



HPLC record of the separation of enantiomers of product of 4-hydroxythioanisole oxidation catalyzed by 2 (1 mol%), (Entry 6, Table1, main text)

Figure S14: Conditions: Knauer® Eurocel 01 5µm column, heptane/i-PrOH (19:1), 0.5 mL/min





Figure S15: Conditions: **Phenomenex® Lux 5u Amylose-2** column, heptane/i-PrOH (49:1), 0.65 mL/min





Figure S16: Conditions: **Phenomenex® Lux 5u Amylose-2** column, heptane/i-PrOH (49:1), 0.65 mL/min



enantiomers HPLC separation of of record of the product of 4-[2-(2methoxyethoxy]thioanisole oxidation catalyzed by 1 (1 mol%), (Entry 9, Table1, main text)

Figure S17: Conditions: Knauer® Eurocel 01 5µm column, heptane/i-PrOH (49:1), 0.65 mL/min

100,0

100,0

Total

26901,721





| | Table of results from CHIRALYSER (red line). | | | | | | | |
|---|--|-----------|---------|-------|--------|-------|--|--|
| | Reten. Time | Area | Height | Area | Height | W05 | | |
| | [min] | [mv.s] | [mv] | [%] | [%] | [min] | | |
| 1 | 68,760 | 23074,065 | 117,458 | 60,9 | 62,0 | 2,95 | | |
| 2 | 79,247 | 14830,705 | 72,122 | 39,1 | 38,0 | 3,08 | | |
| | Total | 37904,769 | 189,580 | 100,0 | 100,0 | | | |

Figure S18: Conditions: Knauer® Eurocel 01 5µm column, heptane/i-PrOH (9:1), 0.5 mL/min





Figure S19: Conditions: Daicel® Chiralcel OJ-H column, heptane/i-PrOH (5:1), 1 mL/min





Figure S20: Conditions: Daicel® Chiralcel OJ-H column, heptane/i-PrOH (5:1), 1 mL/min



HPLC record of the separation of enantiomers of product of 4-methylthioanisole oxidation catalyzed by 1 (1 mol%), (Entry 13, Table1, main text)

Figure S21: Conditions: **Phenomenex® Lux 5u Amylose-2** column, heptane/i-PrOH (17:3), 1 mL/min



HPLC record of the separation of enantiomers of product of 4-methylthioanisole oxidation catalyzed by 2 (1 mol%), (Entry 14, Table1, main text)

Figure S22: Conditions: **Phenomenex® Lux 5u Amylose-2** column, heptane/i-PrOH (17:3), 1 mL/min





Figure S23: Conditions: **Phenomenex® Lux 5u Amylose-2** column, heptane/i-PrOH (17:3), 1 mL/min





Figure S24: Conditions: **Phenomenex® Lux 5u Amylose-2** column, heptane/i-PrOH (17:3), 1 mL/min

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