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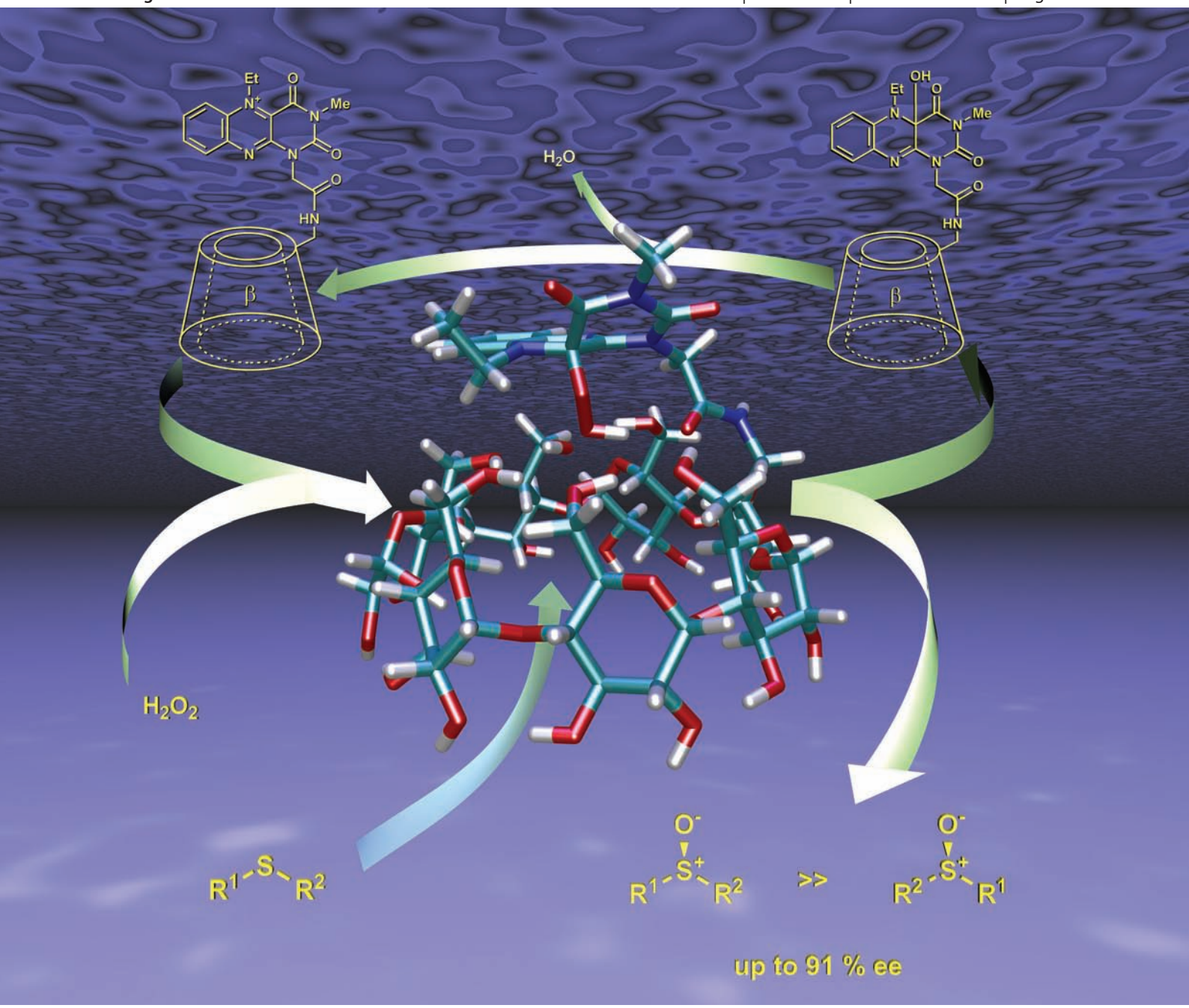

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PAPER

Alloxazine–cyclodextrin conjugates for organocatalytic enantioselective sulfoxidations†

Viktor Mojr,[a] Miloš Buděšínský,[b] Radek Cibulka*[a] and Tomáš Kraus*[b]

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Four structurally different alloxazine–cyclodextrin conjugates were prepared and tested as catalysts for the enantioselective oxidation of prochiral sulfides to sulfoxides by hydrogen peroxide in aqueous solutions. The alloxazinium unit was appended to the primary face of α- and β-cyclodextrins *via* a linker with variable length. A series of sulfides was used as substrates: *n*-alkyl methyl sulfides (*n*-alkyl = hexyl, octyl, decyl, dodecyl), cyclohexyl methyl sulfide, *tert*-butyl methyl sulfide, benzyl methyl sulfide and thioanisol. α-Cyclodextrin conjugate having alloxazinium unit attached *via* a short linker proved to be a suitable catalyst for oxidations of *n*-alkyl methyl sulfides, displaying conversions up to 98% and enantioselectivities up to 77% ee. β-Cyclodextrin conjugates were optimal catalysts for the oxidation of sulfides carrying bulkier substituents; *e.g. tert*-butyl methyl sulfide was oxidized with quantitative conversion and 91% ee. Low loadings (0.3–5 mol%) of the catalysts were used. No overoxidation to sulfones was observed in this study.

Introduction

Chiral sulfoxides represent an important class of compounds. Due to their high configurational stability, their efficiency at carrying chiral information, and their accessibility in both enantiomeric forms they serve as prominent chiral auxiliaries in organic asymmetric synthesis.[1] In medicinal chemistry, various structures containing chiral sulfoxide moieties exhibit remarkable biological activities;[2] for example, chiral sulfoxides appended to imidazole moiety-containing compounds constitute a large family of structures termed prazoles. These are known as gastric proton pump inhibitors (PPI), which are clinically used as antiulcer agents[1a,3] or psychostimulants (*e.g.* Modafinil[4]).

The most straightforward synthetic approach to chiral sulfoxides rests in the enantioselective oxidation of prochiral sulfides by chiral oxidants or by achiral oxidants under enantioselective catalysis.[1a,5] Historically, the most successful enantioselective catalytic approaches were realized with enzymes, namely monooxygenases[6] and peroxidases.[7] Both classes of these enzymes afforded good to excellent yields and enantioselectivities with a relatively wide range of substrates.[6f,6g,6i]

In the realm of transition metal catalysis several systems have been developed, oxidation under Sharpless conditions mediated by Ti(*O*-*i*Pr)$_4$/(*R*,*R*)-DET/*t*-BuOOH (Kagan and Modena protocols; DET = diethyl tartarate) being one of the most widely studied methods.[1a,5,8] When binol ligands were used in place of DET, enantioselectivities up to 96% enantiomeric excess (ee) were achieved in thioanisole oxidations.[9] Recently, oxidation systems employing hydrogen peroxide as the terminal oxidant have been studied due to their low cost and modest environmental impact. Metal-catalyzed oxidations with hydrogen peroxide are usually highly enantioselective (ee >90%) and require low loadings (1–2 mol%) of the catalyst. Mostly, these catalytic systems are based on salen complexes with vanadium,[10] aluminium,[11] or iron[12] formed *in situ* in the reaction mixture. Some of these catalysts, namely Fe(salan),[12d] Al(salalen)[11b] and platinum diphosphine[13] complexes were employed even in aqueous solutions.

The majority of the described methods are efficient in the oxidation of alkyl aryl sulfides. In contrast, dialkyl sulfides are generally oxidized with only poor enantioselectivity and reports on their successful oxidation appeared only recently.[11,12d,14] Using Kagan or Modena protocol with cumyl hydroperoxide as stoichiometric reagent, methyl octyl sulfide[14c] and benzyl methyl sulfide[14a] were oxidized with ee 83% and 90%, respectively. Oxidation of benzyl methyl sulfide with urea–hydrogen peroxide adduct in methanol in the presence of 2 mol% of Ti(salen) complex proceeded with ee up to 93%.[14e] Oxidation of *tert*-butyl methyl sulfide with hydrogen peroxide in chloroform catalyzed by V(salan) complex or with PhIO in acetonitrile in the presence of Mn(salen) complex afforded sulfoxide with ee 76% in both cases.[14h,15] Fe(salan) complex is more general; it was applied as a catalyst for the enantioselective oxidation of various alkyl methyl sulfides (alkyl = octyl, decyl, dodecyl, cyclohexyl and benzyl) with hydrogen peroxide in water with ee values 87%–94%.[12d,14d] Metal catalysts are efficient

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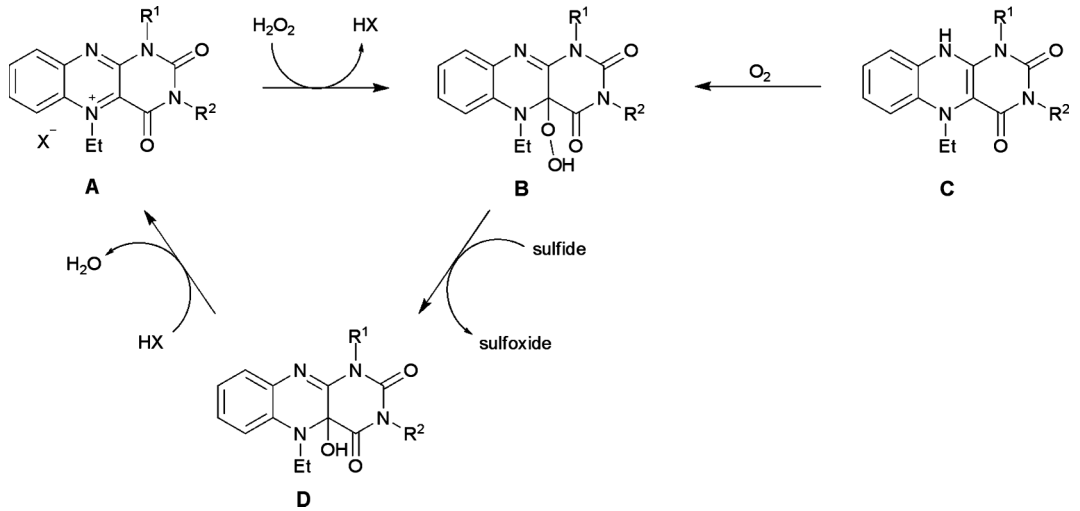


Scheme 1 Catalytic cycle of sulfoxidation by hydrogen peroxide mediated by alloxazinium salts.

in the enantioselective sulfoxidation of aromatic and aliphatic sulfides; with most of them, however, high enantioselectivities are achieved partly by overoxidation of one of the sulfoxide enantiomers to sulfone (kinetic resolution) at the expense of the yield.

Overoxidation to sulfones is usually absent in oxidation reactions promoted by organocatalysts.[16] Metal-free procedures are also attractive from the point of view of potential practical applications because removal of metal traces is a persisting problem in the pharmaceutical industry. However, enantioselectivities of organocatalytic sulfoxidations published so far have been only moderate in most cases. In general, 5-ethylflavin hydroperoxides formed *in situ* from the corresponding flavinium salts and hydrogen peroxide have been shown to oxidize sulfides efficiently.[17] When chiral flavinium catalysts with a cyclophane moiety were employed, substituted thioanisoles and methyl naphthyl sulfide were oxidized with ee up to 65 or 72%, respectively.[18] However, relatively high loading of the catalyst (up to 12 mol%) was necessary to achieve the above-mentioned enantioselectivity. Recently, the oxidation of aryl methyl sulfides using hydrogen peroxide in the presence of 5 mol% of planarly chiral flavinium salt affording ee up to 54% has been reported.[19]

The stereodiscrimination in oxidation reactions catalyzed by chiral flavin derivatives studied so far is assumed to be induced by weak π–π interactions between the oxidant (flavin hydroperoxide) and the aromatic substrate.[19–20] Therefore, flavin-based catalysts are inefficient for the oxidation of aliphatic sulfides in terms of enantioselectivity due to the absence of π–π interactions. Their performance thus could be improved by a chiral substrate-binding site attached to the molecule of the flavin catalyst. In particular, cyclodextrins forming inclusion complexes with a wide range of organic molecules could be used for this purpose since they were found to increase reaction rates of various transformations in aqueous media.[21] In addition, cyclodextrin cavities provide a chiral environment allowing, in principle, an enantioselective course of the reaction.[22] D'Souza observed an enhanced rate of the oxidation of benzylmercaptans to the corresponding disulfides[23] and of photooxidation of benzylalcohols to benzaldehydes[24] mediated by flavin moieties appended to β-cyclodextrin.

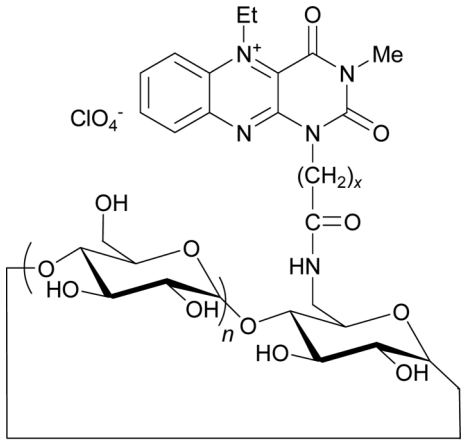
We have recently described[25] very efficient organocatalytic systems for the enantioselective oxidation of aromatic sulfides by hydrogen peroxide based on conjugates of β-cyclodextrin with 5-ethylflavin derivatives (both isoalloxazines and alloxazines). Presumably, these systems take advantage of the pre-coordination of the substrate with respect to the flavin-hydroperoxide (the actual oxidant) by means of its inclusion in the cyclodextrin cavity. In particular, the conjugate of β-cyclodextrin with alloxazine afforded excellent conversions within minute reaction times and enantioselectivities up to 80% ee in the oxidation of various aromatic sulfides with small amount (≤1 mol%) of the catalyst. In this paper, we describe the syntheses and catalytic properties of four structurally related alloxazine–cyclodextrin conjugates. We focused our attention on the oxidation of aliphatic sulfides, for which no organocatalysts have been reported so far.

Results and discussion

1. Design of catalysts

The accepted mechanism[17a,26] of sulfoxidations catalyzed by 5-ethylalloxazine derivatives is depicted in Scheme 1. Both oxidized[27] and reduced[26] forms, *i.e.* 5-ethylalloxazinium salt **A** and 5-ethyldihydroalloxazine **C**, can be used for catalysis. In the latter case, pre-activation of the alloxazine moiety with molecular oxygen precedes the catalytic cycle.

We have designed four alloxazine–cyclodextrin conjugates **1a**, **1b**, **2a** and **2b** (Fig. 1) which differ in the size of the cyclodextrin macrocycle and the length of the linker between the cyclodextrin and alloxazine moieties. A suitable size of the macrocycle for a particular substrate can be estimated using known stability constants of a broad range of cyclodextrin inclusion complexes.[28] It was expected that α-cyclodextrin macrocycles should preferably form inclusion complexes with aliphatic hydrocarbon chain-containing sulfides, whereas larger cavity of β-cyclodextrin should better accommodate sulfides bearing more bulky alkyl (cyclohexyl, *tert*-butyl) and aromatic substituents. Slight variation of the length of the linkage ($x = 1$ or 2) connecting cyclodextrin and alloxazine should allow the design of a catalyst with an optimal fit between the



1a (*x* = 1, *n* = 5)
1b (*x* = 1, *n* = 6)
2a (*x* = 2, *n* = 5)
2b (*x* = 2, *n* = 6)

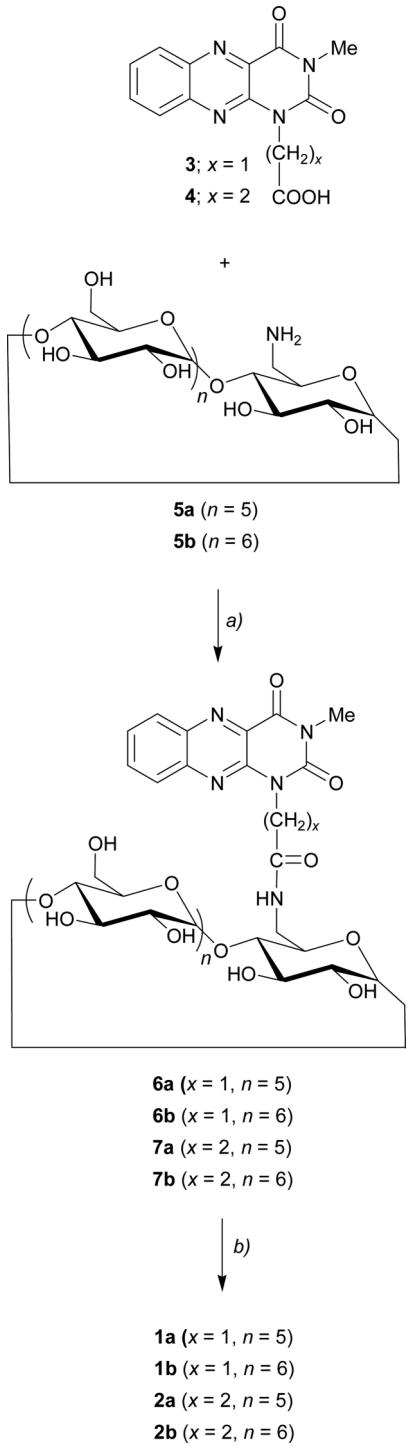
Fig. 1 Alloxazine–cyclodextrin conjugates prepared and tested as sulfoxidation catalysts.

alloxazinium moiety and the sulfide group in the binary inclusion complex. Amidic group was chosen as a connecting function because of its chemical stability under the reaction conditions employed and the viability of its formation from relatively easily accessible reacting components, *i.e.* alloxazine carboxylic acids and 6-amino-6-deoxy-cyclodextrins.

2. Synthesis

The synthesis commenced with the preparation of alloxazine carboxylic acids **3** and **4** (Scheme 2). 2-(3-Methylalloxazin-1-yl)acetic acid **3** was prepared by alkylation of 3-methylalloxazine with ethyl bromoacetate followed by acid hydrolysis.[25] 3-(3-Methylalloxazin-1-yl)propanoic acid **4** was obtained by addition of 3-methylalloxazine to methoxy poly(ethylene glycol) monoacrylate (mPEG-acrylate) under microwave irradiation[29] and removal of the PEG group by acid hydrolysis. Then conjugates **1a**, **1b**, **2a** and **2b** were prepared using the methodology recently described by us (Scheme 2).[25] In general, aminocyclodextrin was allowed to react with a slight excess of alloxazine carboxylic acid and PyBOP in the presence of *N*,*N*-diisopropylethylamine (DIPEA). Products **6a**, **6b**, **7a** and **7b** were isolated by means of reversed phase chromatography with yields 53–78%. The actual catalysts, *i.e.* *N*-ethylalloxazinium salts, were prepared by means of reductive alkylation[25] with acetaldehyde and hydrogen under catalysis by palladium in acidic media.

In principle, reduced forms of the catalysts, *i.e.* *N*-ethyl-1,5-dihydroalloxazine derivatives, are formed under these conditions.[25] However, both UV and mass spectrometries (*vide infra*) revealed that the primary products of the reaction undergo oxidation in the presence of air oxygen to the corresponding *N*-ethylalloxazinium salts **1a**, **1b**, **2a**, **2b**. Despite our great efforts, we were unable to record clear NMR spectra of the *N*-alkylated conjugates neither in their reduced nor oxidized forms due to peak broadening, presumably as a result of the presence of radical species. Nevertheless, in mass spectra only signals of alloxazinium ions (*i.e.* oxidized form; see mass spectra in ESI†) were found. UV spectra of all the prepared catalysts showed maxima at approximately 445 and 382 nm which are characteristic of alloxazinium salts.[30] As an example, the UV spectrum of **1b** is compared with that of an authentic sample of 5-ethyl-1,3-dimethylalloxazinium perchlorate and its reduced form in Fig. 2 (for the spectra of other conjugates **1a**, **2a** and **2b** see ESI†).



5a (*n* = 5)
5b (*n* = 6)

a)

6a (*x* = 1, *n* = 5)
6b (*x* = 1, *n* = 6)
7a (*x* = 2, *n* = 5)
7b (*x* = 2, *n* = 6)

b)

1a (*x* = 1, *n* = 5)
1b (*x* = 1, *n* = 6)
2a (*x* = 2, *n* = 5)
2b (*x* = 2, *n* = 6)

Scheme 2 Syntheses of flavin–cyclodextrin conjugates **1a**, **1b**, **2a** and **2b**; (a) PyBOP, DIPEA, DMF; (b) 1. CH_3CHO, Pd/C, H_2, EtOH, H_2O, $HClO_4$; 2. O_2, H_2O, $HClO_4$.

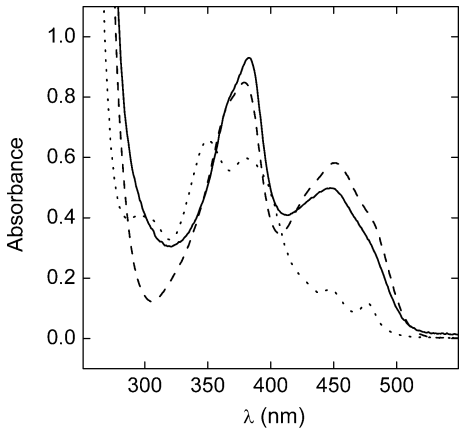
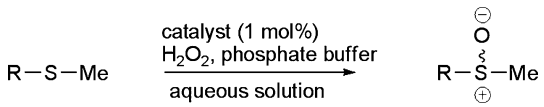


Fig. 2 UV–VIS spectra of the conjugate **1b** (—) and 5-ethyl-1,3-dimethylalloxazinium perchlorate (---) in aqueous solution at pH 2 (phosphate buffer). Spectrum of 5-ethyl-5,10-dihydro-1,3-dimethylalloxazine (· · ·) in acetonitrile is shown for comparison; $c = 5 \times 10^{-5}$ mol L^{-1}.

3. Catalysis

We have studied the abilities of the four *N*-ethylalloxazinium salts **1a**, **1b**, **2a** and **2b** to catalyze the oxidation of sulfides by hydrogen peroxide (Scheme 3). A series of sulfides was used: *n*-alkyl methyl sulfides (*n*-alkyl = hexyl, octyl, decyl, dodecyl), cyclohexyl methyl sulfide, *tert*-butyl methyl sulfide and benzyl methyl sulfide. In addition, thioanisol was included in the series of sulfides as a representative of aromatic sulfides.



Scheme 3 Catalytic oxidation of sulfides by hydrogen peroxide.

In general, oxidation reactions (Tables 1–4) were carried out in aqueous buffered solutions (phosphate buffer, pH 7.5) with 1 mol% (except for entry 5, Table 1 and entries 6 and 14, Table 3) of the *N*-ethylalloxazinium salt as the catalyst and 2.3 equivalents of hydrogen peroxide. In addition, control oxidation experiments without conjugates were performed with selected substrates to check the rate of the non-catalyzed oxidations (Table 5). Since the sulfides were very poorly soluble in the reaction media and some of them tended to stick to the glass walls of the vials, preventing efficient stirring with a conventional magnetic stirrer, the reaction mixtures were vigorously shaken with a wrist-action shaker. Each substrate was allowed to react for an indicated period of time and then the oxidation was quenched by addition of sodium dithionite. Sulfoxide in common with remaining sulfide was extracted to deuterated chloroform and, subsequently, to tetrachloromethane. The conversion was determined as the ratio of peaks of the respective *S*-methyl groups in ^{1}H NMR spectra recorded in combined chloroform–tetrachloromethane solution. The enantiomeric excesses of the *n*-alkyl methyl sulfoxides were determined by ^{1}H NMR using (*R*)-(–)-3,5-dinitro-*N*-(1-phenylethyl)benzamide as a shift reagent.[31,32] This method proved less useful for aryl-, benzyl-, *tert*-butyl- and cyclohexyl methyl sulfoxides because of insufficient peak separation in the NMR spectra. In these cases, enantiomeric excess was determined by HPLC using a chiral phase column.

Table 1 H_2O_2-sulfoxidations catalyzed by conjugate **1a**[a]

Entry	Sulfide	Time [min]	Conv. [%][b]	ee [%]	Opt. rot.[e]
1	*n*-$C_6H_{13}SCH_3$	10	54	47[c]	(+)
2	*n*-$C_6H_{13}SCH_3$	20	90	47[c]	(+)
3	*n*-$C_8H_{17}SCH_3$	10	19	67[c] (70[d])	(+)
4	*n*-$C_8H_{17}SCH_3$	60	78	34[c] (37[d])	(+)
5	*n*-$C_8H_{17}SCH_3$	5 (5 mol%)	63	77[c] (76[d])	(+)
6	*n*-$C_{10}H_{21}SCH_3$	10	24	11[c]	(+)
7	*n*-$C_{10}H_{21}SCH_3$	20	98	9[c]	(+)
8	*n*-$C_{12}H_{25}SCH_3$	10	29	12[c]	(+)
9	*n*-$C_{12}H_{25}SCH_3$	20	98	12[c]	(+)
10	*t*-$C_4H_9SCH_3$	10	98	0[c]	
11	*c*-$C_6H_{11}SCH_3$	10	50	6[c]	(+)
12	*c*-$C_6H_{11}SCH_3$	60	68	8[d]	(+)
13	$BnSCH_3$	10	33	0[d]	
14	$BnSCH_3$	60	93	0[d]	
15	$PhSCH_3$	60	33	0[d]	

[a] Conditions: substrate (0.03–0.04 mmol), H_2O_2 (2.3 equiv.), phosphate buffer pH 7.5, R.T., catalyst loading 1 mol% (related to the substrate) if not stated otherwise; vigorous shaking; [b] conversion determined by ^{1}H-NMR; [c] enantiomeric excess determined by ^{1}H-NMR using chiral shift agent; [d] enantiomeric excess determined by HPLC on a chiral stationary phase (see ESI†); [e] sense of optical rotations derived from Chiralyser (426 nm) detector in the course of analyses in heptane–isopropyl alcohol mixture.

Table 2 H_2O_2-sulfoxidations catalyzed by conjugate **2a**[a]

Entry	Sulfide	Time [min]	Conv. [%][b]	ee [%]	Opt. rot.[e]
1	*n*-$C_6H_{13}SCH_3$	10	36	24[c]	(–)
2	*n*-$C_8H_{17}SCH_3$	10	13	17[c]	(–)
3	*n*-$C_{10}H_{21}SCH_3$	10	14	0[c]	
4	*n*-$C_{12}H_{25}SCH_3$	10	16	0[c]	
5	*t*-$C_4H_9SCH_3$	10	79	0[c]	
6	*c*-$C_6H_{11}SCH_3$	10	33	0[d]	
7	$BnSCH_3$	10	24	0[d]	
8	$PhSCH_3$	60	25	0[d]	

[a] Conditions: substrate (0.03–0.04 mmol), H_2O_2 (2.3 equiv.), phosphate buffer pH 7.5, R.T., catalyst loading 1 mol% (related to the substrate) if not stated otherwise; vigorous shaking; [b] conversion determined by ^{1}H-NMR; [c] enantiomeric excess determined by ^{1}H-NMR using chiral shift agent; [d] enantiomeric excess determined by HPLC on a chiral stationary phase (see ESI†); [e] sense of optical rotations derived from Chiralyser (426 nm) detector in the course of analyses in heptane–isopropyl alcohol mixture.

In addition, a set of randomly chosen samples representing all *n*-alkyl methyl sulfoxide structures was also analyzed by HPLC method using both UV and optical rotation (Chiralyser) detectors in order (*i*) to verify the consistency of the results obtained by the two approaches and (*ii*) to correlate the sense of optical rotations of the sulfoxides with the NMR shifts of the diastereomeric complexes. The latter allowed evaluation of the dependence of the configuration of a major enantiomer on the structure of the catalyst in all samples.

The α-cyclodextrin conjugate **1a** showed preferential catalytic activity in the oxidation reactions of aliphatic sulfides (Table 1). In this series of experiments, each reaction was first run for ten minutes; if the conversion was lower than 90%, then longer reaction time (20 or 60 min at maximum) was allowed. High conversions (≥90%) were attained within 20 min of reaction time with most aliphatic substrates except for octyl- and cyclohexyl-substituted sulfides which gave 78% and 68% conversions, respectively, in 60 min. Thioanisol afforded only 33% conversion. The rate acceleration in the course of reactions of decyl methyl

Table 3 H_2O_2-sulfoxidations catalyzed by conjugate **1b**[a]

Entry	Sulfide	Time [min]	Conv. [%][b]	ee [%]	Opt. rot.[e]
1	*n*-$C_6H_{13}SCH_3$	60	90	0[c] (0[d])	
2	*n*-$C_8H_{17}SCH_3$	60	99	18[c] (17[d])	(+)
3	*n*-$C_{10}H_{21}SCH_3$	60	99	9[c] (10[d])	(+)
4	*n*-$C_{12}H_{25}SCH_3$	60	91	4[c]	(+)
5	*t*-$C_4H_9SCH_3$	60	99	88[d]	(−)
6	*t*-$C_4H_9SCH_3$	60 (5 mol%)	99	91[d]	(−)
7	*c*-$C_6H_{11}SCH_3$	60	90	78[d]	(−)
8	*c*-$C_6H_{11}SCH_3$	60 (5 °C)	93	80[d]	(−)
9	$BnSCH_3$	60	84	30[d]	(+)
10	$PhSCH_3$	20	93	64[f]	(+)
11	$PhSCH_3$	60 (5 °C)	75	64[d]	(+)
12	*p*-$MePhSCH_3$	10	97	80[f]	(+)
13	*p*-$MePhSCH_3$	60 (5 °C)	74	80[d]	(+)
14[g]	*p*-$MePhSCH_3$	60 (0.3 mol%)	99 (91[h])	78[d]	(+)

[a] Conditions: substrate (0.03–0.04 mmol, unless otherwise stated), H_2O_2 (2.3 equiv.), phosphate buffer pH 7.5, R.T., catalyst loading 1 mol% (related to the substrate) if not stated otherwise; vigorous shaking; [b] conversion determined by ^{1}H-NMR; [c] enantiomeric excess determined by ^{1}H-NMR using chiral shift agent; [d] enantiomeric excess determined by HPLC on a chiral stationary phase (see ESI†); [e] sense of optical rotations derived from Chiralyser (426 nm) detector in the course of analyses in heptane–isopropyl alcohol mixture; [f] from ref. 25; [g] preparative run (4.86 mmol of substrate, 0.3 mol% of **1b**, 7.9 mmol H_2O_2); [h] isolated yield.

Table 4 H_2O_2-sulfoxidations catalyzed by conjugate **2b**[a]

Entry	Sulfide	Time [min]	Conv. [%][b]	ee [%]	Opt. rot.[e]
1	*n*-$C_6H_{13}SCH_3$	60	92	64[c] (61[d])	(−)
2	*n*-$C_8H_{17}SCH_3$	60	44	29[d]	(−)
3	*n*-$C_{10}H_{21}SCH_3$	60	99	0[c]	
4	*n*-$C_{12}H_{25}SCH_3$	60	98	0[c]	
5	*t*-$C_4H_9SCH_3$	60	98	86[d]	(−)
6	*c*-$C_6H_{11}SCH_3$	60	92	80[d]	(−)
7	$BnSCH_3$	60	92	58[d]	(+)
8	$PhSCH_3$	60	70	36[d]	(+)
9	*p*-$MePhSCH_3$	60	96	69[d]	(+)

[a] Conditions: substrate (0.03–0.04 mmol), H_2O_2 (2.3 equiv.), phosphate buffer pH 7.5, R.T., catalyst loading 1 mol% (related to the substrate) if not stated otherwise; vigorous shaking; [b] conversion determined by ^{1}H-NMR; [c] enantiomeric excess determined by ^{1}H-NMR using chiral shift agent; [d] enantiomeric excess determined by HPLC on a chiral stationary phase (see ESI†); [e] sense of optical rotations derived from Chiralyser (426 nm) detector in the course of analyses in heptane–isopropyl alcohol mixture.

Table 5 Control experiments for H_2O_2-sulfoxidations of sulfides[a]

Entry	Sulfide	Catalyst	Time [min]	Conv. [%][b]
1	*n*-$C_8H_{17}SCH_3$	α-CD	60	4
2	*n*-$C_8H_{17}SCH_3$	β-CD	60	3
3	*c*-$C_6H_{11}SCH_3$	α-CD	60	28
4	*c*-$C_6H_{11}SCH_3$	β-CD	60	31
5	*c*-$C_6H_{11}SCH_3$	—	60	39
6	*t*-$C_4H_9SCH_3$	α-CD	60	95
7	*t*-$C_4H_9SCH_3$	β-CD	60	95
8	*t*-$C_4H_9SCH_3$	—	60	98

[a] Conditions: substrate (0.1 mmol), H_2O_2 (2.3 equiv.), phosphate buffer pH 7.5, R.T., catalyst loading 1 mol% (related to the substrate) if not stated otherwise; vigorous shaking; [b] conversion determined by ^{1}H-NMR.

sulfide (*cf.* entries 6 and 7) and dodecyl methyl sulfide (*cf.* entries 8 and 9) is remarkable and difficult to understand at first sight. Lower activity of the catalyst in the initial period of time may be explained by the relatively slow oxidation of alloxazine moieties to alloxazinium salts by molecular oxygen in the initial step of the catalytic reaction. A similar induction period has been already observed in oxidation of thioanisoles with hydrogen peroxide catalyzed by 5-ethyldihydroalloxazines.[33] It must be noted that kinetics of oxidation reactions in this system could also be affected by the dissolution rate of poorly soluble sulfides. Last but not least, both starting materials and products may, in principal, form inclusion complexes of variable solubility which may also affect the activity of the catalyst.

The oxidation reactions of *n*-alkyl sulfides with **1a** revealed various degrees of enantioselectivity, the highest values being observed for *n*-hexyl methyl sulfoxide (47% ee) and *n*-octyl methyl sulfoxide (34–77%, entries 3–5, based on ^{1}H NMR). While with most substrates consistent values of enantiomeric excesses independent of reaction time were observed, the reaction of *n*-octyl methyl sulfide showed decreasing enantioselectivity with increasing reaction time. These results were reproduced in several repetitive experiments ruling out experimental artifacts. Since control experiments (Table 5, entries 1 and 2) showed negligible non-catalyzed oxidation of *n*-octyl methyl sulfide, we hypothesized that autoinhibition with the product might be the cause of the unexpected effect; with growing concentration of the product, a new equilibrium between inclusion complexes of **1a** with both starting material and the product could be established, the latter preventing proper pre-organization of the substrate with respect to flavinium moiety. The uncomplexed sulfide could be oxidized by alloxazinium moiety outside the cavity with lower (or without) transfer of chirality. Thus, an analogous experiment with 5 mol percent of the catalyst and shorter reaction time (Table 1, entry 5) was carried out, which allowed for 77% ee, supporting the hypothesis. No enantioselectivity was observed in the oxidation reaction of *tert*-butyl methyl sulfide, benzyl methyl sulfide or thioanisole.

The homologous catalyst **2a** having a longer linker between the cyclodextrin and flavin proved to be less efficient in terms of both conversions and enantioselectivities (Table 2). In most cases no enantioselectivity was observed at all, although a slight preference was encountered with hexyl and octyl sulfides (Table 2, entries 1 and 2). Therefore, this conjugate was not further investigated.

β-Cyclodextrin conjugates **1b** and **2b** were expected to be better catalysts for the oxidation of bulkier substrates, such as phenyl-, *tert*-butyl-, cyclohexyl- and benzyl methyl sulfides. Our earlier preliminary results clearly showed that the conjugate **1b** was a very efficient catalyst for the oxidation of aromatic sulfides (thioanisoles) allowing high and rapid conversions in aqueous media with enantioselectivities up to 80% ee.[25] In the present study, we have tested its catalytic activity against a broader scope of substrates (Table 3). Unexpectedly, conjugate **1b** proved also efficient for the oxidation of *n*-alkyl methyl sulfides (Table 3, entries 1–4) allowing conversions 90–99% within 60 min of reaction time, for *n*-octyl methyl sulfide the conversion being even higher than in the case of **1a**. Enantioselectivities were low, up to 18% ee for *n*-octyl methyl sulfoxide (Table 3, entry 2). In contrast, *tert*-butyl methyl sulfide was oxidized not only with an excellent conversion but also with a significant enantioselectivity (88% ee; Table 3, entry 5). Since control experiments revealed that *tert*-butyl methyl sulfide is prone to rapid non-catalyzed oxidation (Table 5, entries 6–8) we assumed that the product could be contaminated with racemic sulfoxide arising from non-catalyzed reaction. Therefore, another

experiment was carried out with 5 mol% of the catalyst, which raised the enantiomeric excess to 91% (Table 3 entry 6) indicating only a slight influence of the non-catalyzed oxidation. Cyclohexyl methyl sulfide (Table 3, entry 7) also proved to be a good substrate for **1b**, allowing 90% conversion within 60 min and 78% ee. Benzyl methyl sulfide (Table 3, entry 9) allowed a good conversion (84% in 60 min) but a lower enantioselectivity (30% ee). Oxidation of phenyl- and *p*-tolyl methyl sulfides proceeded with the excellent conversions within 20 and 10 min and allowed 64% and 80% ee, respectively. Lowering the temperature of the reaction mixture to 5 °C had negligible effect on enantioselectivities in oxidation of selected substrates (Table 3, *cf.* entries 7–13). Finally, a preparative run (Table 3, entry 14) was carried out to demonstrate scalability of the catalytic system. Thus, oxidation of 4.9 mmol (672 mg) of *p*-tolyl methyl sulfide with 7.9 mmol of hydrogen peroxide catalyzed with only 0.3 mol% of the conjugate **1b** allowed 99% conversion (91% of isolated yield) in 60 min of reaction time and 78% ee.

The oxidation of *n*-alkyl methyl sulfides with the conjugate **2b** gave somewhat lower conversions (Table 4) as compared with **1b**. The enantioselectivities tended to decrease with the growing chain length; a remarkable 64% ee was achieved in the oxidation of *n*-hexyl methyl sulfide but no preference was observed for *n*-decyl- and *n*-dodecyl methyl sulfides. *tert*-Butyl and cyclohexyl methyl sulfides were oxidized with both high conversions and very good enantioselectivities (86% and 80% ee, respectively, Table 4, entries 5 and 6). Benzyl methyl sulfide (Table 4, entry 7) was oxidized with a slightly higher conversion and a significantly higher enantioselectivity (58% ee) as compared to **1b**. Thioanisole (Table 4, entry 8) was oxidized with moderate conversion and enantioselectivity while *p*-tolyl phenyl sulfide (Table 4, entry 9) showed high conversion but lower ee by 11% as compared with **1b**.

Finally, the control oxidations of selected substrates with or without α- or β-cyclodextrins showed no catalytic effect of native cyclodextrins (Table 5), thus confirming the indispensable role of the flavin moiety connected to the macrocycle. Unexpectedly, *tert*-butyl methyl sulfide showed high conversions under all conditions indicating that the competing non-catalyzed reaction could have significant impact on enantioselectivities of those catalyzed reactions that proceed with a slower rate. Cyclohexyl methyl sulfide also exhibited non-negligible conversions.

The sense of the optical rotations relevant to configurations of the preferred enantiomers tended to depend on the catalytic system used. Interestingly, a clear trend is observed for *n*-alkyl methyl sulfoxides: (+)-enantiomers were obtained with catalysts **1a** and **1b** while (–)-enantiomers were preferred with **2a** and **2b**. This suggests that the length of the linker between the flavinium group and the macrocycle rather than the size of the macrocycle is important for the absolute configuration of the products of oxidations of *n*-alkyl methyl sulfides. Other sulfoxides cannot be compared over the whole series of catalysts, yet limited conclusions can be drawn: the configurations of *tert*-butyl methyl sulfoxide, cyclohexyl methyl sulfoxide, benzyl methyl sulfoxide and phenyl methyl sulfoxide, respectively, obtained by the oxidation under catalysis with **1b** remained the same also under catalysis with **2b**.

Conclusions

Four structurally different alloxazine–cyclodextrin conjugates prepared in this study were tested as catalysts of the oxidation of sulfides to sulfoxides by hydrogen peroxide. The common denominator for all conjugates is the alloxazinium structural unit appended to cyclodextrin macrocycles of variable diameter *via* a linker with variable length. It was expected that smaller α-cyclodextrin conjugates should be better catalysts for the oxidation of *n*-alkyl methyl sulfides while the larger β-cyclodextrin conjugates should better accommodate bulkier substituents such as cyclohexyl or *tert*-butyl. However, *n*-alkyl methyl sulfides turned out to be the least predictable of all substrates used, being oxidized by α-cyclodextrin conjugate **1a** as well as by both β-cyclodextrin conjugates **1b** and **2b** with high conversions within 60 min in most cases. Within the series of *n*-alkyl methyl sulfides, catalysts **1a** and **2b** exerted a relatively high degree of enantioselectivity in the oxidation reactions of *n*-octyl and *n*-hexyl methyl sulfides, respectively.

Sulfides containing more bulky substituents, namely benzyl, phenyl, cyclohexyl or *tert*-butyl gave higher conversions and higher enantioselectivities with β-cyclodextrin-containing conjugates. The enantioselectivity of 91% ee achieved in the oxidation of *tert*-butyl methyl sulfide catalyzed by **1b** represents the highest value reported to date for this substrate taking into account synthetic (non-enzymatic) catalysts. Catalysis by the conjugate **1b** also afforded a very good enantioselectivity in the oxidation of cyclohexyl methyl sulfide.

Overall, the cyclodextrin–alloxazine conjugates reported in this paper proved to be very efficient organocatalysts of the oxidation of sulfides by hydrogen peroxide allowing good to excellent conversions within 60 min in aqueous media using 1 mol% of the organocatalyst. Importantly, no overoxidation to sulfones was observed in this study.

Experimental section

General procedures

NMR spectra were acquired with spectrometers Bruker AVANCE 500 (^{1}H at 500.1 MHz and ^{13}C at 125.8 MHz), AVANCE 600 (^{1}H at 600.1 MHz and ^{13}C at 150.9 MHz, equipped with a cryoprobe) and Varian Mercury Plus (^{1}H at 299.97 MHz and ^{13}C at 75.44 MHz) in $CDCl_3$, d_6-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 **6a**, **7a** and **7b**. Mass spectra were measured using ES ionization either in positive or negative mode (Waters micromass ZQ). High resolution mass spectra were measured using nanoESI ionization on LTQ Orbitrap XL (Thermo Fisher Scientific). Elemental analyses were carried out on Perkin Elmer 2400 II. UV spectra were measured on Varian Cary 50 spectrophotometer. 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 60 F and RP-18 F plates (E. Merck). HPLC analyses were recorded on Knauer Smartline with UV detector and detector of optical rotatory power CHIRALYSER.

2-(3-Methylalloxazin-1-yl)acetic acid[25] **3**, 3-methylalloxazine,[27,34] 5-ethyl-1,3-dimethylalloxazinium perchlorate,[30] 5-ethyl-5,10-dihydro-1,3-dimethylalloxazine,[34] mono-6-deoxy-6-amino-β-cyclodextrin[35] **5b**, mono-6-deoxy-6-bromo-α-cyclodextrin,[36]

conjugate[25] **6b** and its *N*-ethylated derivative[25] **1b** were prepared according to the described procedures. All other chemicals used were commercially available. Correct elemental analysis for compounds **6a**, **7a** and **7b** 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. Hard copies of NMR and mass spectra of conjugates and compounds **4** and **5a** can be found in the ESI.†

Syntheses

3-(3-Methylalloxazin-1-yl)propionic acid (4). A mixture of 3-methylalloxazine (200 mg, 0.88 mmol), DABCO (98 mg, 0.88 mmol) and tetrabutylammonium bromide (56 mg, 0.18 mmol) was crushed in a mortar to give fine homogeneous powder. The mixture was mixed with mPEG-acrylate (1.55 mL, 3.50 mmol) and irradiated in a microwave reactor with max. power of 540 W under max. temperature at 130 °C for 40 min. Every 10 min (3 times) the reaction tube was removed from the reactor and a dose of mPEG-acrylate (0.39 mL, 0.88 mmol) was added, the mixture was dispersed by ultrasound and the reaction tube was placed back into the reactor. After that, the reaction tube was washed with DCM and the washings were collected and evaporated. Hydrochloric acid (35%, 10 mL) was added to the dry residue and the reaction mixture was heated to reflux for 45 min. Reaction mixture was diluted with water to approximately quadruple volume and filtered. Filter cake was washed with water and ether. Crude product was recrystallized from 2 M aqueous acetic acid (20 mL). Green–yellow crystals (75 mg, 29%) were obtained. M.p. 292–294 °C. ^{1}H-NMR[d_6-DMSO, 600.13 MHz] δ: 2.69 (2H, t, $J(1,2)$ = 7.8 Hz, CH_2), 3.39 (3H, s, CH_3), 4.53 (2H, t, $J(1,2)$ = 7.8 Hz, CH_2), 7.84 (1H, m, Ar-H), 7.99 (1H, m, Ar-H), 8.05 (1H, d, $J(1,2)$ = 7.0 Hz, Ar-H), 8.25 (1H, d, $J(1,2)$ = 7.0 Hz, Ar-H), 12.45 (1H, bs, COOH). ^{13}C-NMR[d_6-DMSO, 150.9 MHz] δ: 29.05, 32.05, 38.39, 127.99, 129.42, 130.45, 131.68, 134.08, 139.32, 142.51, 145.51, 150.69, 159.82, 172.92. MS (ESI) *m/z*: $[M]^-$ calcd for $C_{14}H_{12}N_4O_4$ 299, found 299. Anal. Calcd for $C_{14}H_{12}N_4O_4$: C 56.00%, H 4.03%, N 18.66%. Found: C 55.92%, H 4.08%, N 18.28%.

Mono-6-deoxy-6-amino-α-cyclodextrin (5a). Mono-6-deoxy-6-bromo-α-cyclodextrin (335 mg, 0.32 mmol) was dissolved in DMF (1.25 mL), then sodium azide (210 mg, 3.2 mmol) and potassium iodide (27 mg, 0.16 mmol) were added and the reaction mixture was heated at 80 °C overnight under stirring. Then the insoluble material was filtered off and the filtrate was evaporated and dried *in vacuo*. The resulting solid was purified by reversed phase chromatography. Collected main fractions containing mono-6-azido-6-deoxy-α-cyclodextrin were partly concentrated and the product was precipitated by addition of acetone. The precipitate was collected by means of centrifugation, then it was washed twice with acetone and dried *in vacuo*. The obtained white fine powder (220 mg) was dissolved in water (30 mL), 23 mg of palladium on charcoal (10%, 22 μmol) was added and the reaction mixture was stirred in an autoclave for 4 h under atmosphere of hydrogen (40 bar). After that the mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the product was precipitated by addition of acetone. The precipitate was separated by centrifugation, washed twice with acetone and dried *in vacuo*. White fine powder (185 mg, 58% over two steps) was obtained. ^{1}H NMR [D_2O, 600.13 MHz] δ: 5.091 (1H, d, $J(1,2)$ = 3.3 Hz, H-1); 5.074 (1H, d, $J(1,2)$ = 3.5 Hz, H-1); 5.058 (1H, d, $J(1,2)$ = 4.0 Hz, H-1); 5.051 (1H, d, $J(1,2)$ = 3.5 Hz, H-1); 5.046 (2H, d, $J(1,2)$ = 3.5 Hz, H-1); 4.00–3.95 (6H, m, 6 × H-3); 3.93–3.79 (16H, 6 × H-5, 5 × H-6a and 5 × H-6b); 3.66–3.61 (6H, m, 6 × H-2); 3.60–3.51 (6H, m, 6 × H-4); 3.47 (1H, dd, J(6a,6b) = 13.7 and J(6a,5) = 2.8 Hz, H-6a) and 3.15 (1H, dd, J(6b,6a) = 13.7 and J(6b,5) = 7.6 Hz, H-6b). ^{13}C NMR [D_2O, 150.9 MHz] δ: 104.12 (2 × C-1); 104.07 (2 × C-1); 104.03 (C-1); 103.86 (C-1); 84.05 (C-4); 83.98 (C-4); 83.93 (C-4); 83.91 (2 × C-4); 83.83 (C-4); 76.05 (C-3); 76.01 (C-3); 76.00 (C-3); 75.97 (C-3); 75.87 (C-3); 75.84 (C-3); 74.81 (C-5); 74.77 (2 × C-5); 74.72 (2 × C-5); 74.70 (C-5); 74.38 (2 × C-2); 74.35 (2 × C-2); 74.22 (C-2); 74.20 (C-2); 63.23 (C-6); 63.16 (3 × C-6); 63.11 (C-6); 43.55 (C-6). ^{1}H and ^{13}C NMR shifts were consistent with the published data.[37] MS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{36}H_{61}NO_{29}$ 994, found 994. Anal. Calcd for $C_{36}H_{61}NO_{29}\cdot 6H_2O$: C 40.04%, H 6.81%, N 1.30%. Found: C 40.21%, H 6.79%, N 1.33%.

***N*-(6-Deoxy-α-cyclodextrin-6-yl) 2-(3-methylalloxazin-1-yl)-acetamide (6a).** Acid **3** (26.5 mg, 92.6 μmol), mono-6-deoxy-6-amino-α-cyclodextrin **5a** (60.0 mg, 55.8 μmol, calculated for hexahydrate) and PyBOP (48.2 mg, 92.6 μmol) were dissolved in DMF (0.6 mL). Then DIPEA (43 μL, 0.25 mmol) was added. The mixture was stirred overnight under an 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 (39.4 mg, 53%, calculated for hexahydrate) was obtained. UV–VIS (nm): 328, 378. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{49}H_{69}N_5O_{32}$ 1262.38179, found 1262.38155. For ^{1}H NMR and ^{13}C NMR data: see Tables S1 and S2 in ESI.† Anal. Calcd for $C_{49}H_{69}N_5O_{32}\cdot 6H_2O$: C 43.65%, H 6.06%, N 5.19%. Found: C 43.89%, H 5.87%, N 5.16%.

***N*-(6-Deoxy-α-cyclodextrin-6-yl) 3-(3-methylalloxazin-1-yl)-propanamide (7a).** Acid **4** (37.0 mg, 123 μmol), mono-6-deoxy-6-amino-α-cyclodextrin **5a** (100.0 mg, 93.0 μmol, calculated for hexahydrate) and PyBOP (64.0 mg, 123 μmol) were dissolved in DMF (1.0 mL). Then DIPEA (36 μL, 0.38 mmol) was added. The mixture was stirred overnight under an 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 (91.0 mg, 78%, calculated for pentahydrate) was obtained. UV–VIS (nm): 381, 328. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{50}H_{72}N_5O_{32}$ 1254.41549, found 1254.41595. For ^{1}H NMR and ^{13}C NMR data: see Tables S1 and S2 in ESI.† Anal. Calcd for $C_{50}H_{71}N_5O_{32}\cdot 5H_2O$: C 44.68%, H 6.07%, N 5.21%. Found: C 44.79%, H 6.13%, N 5.79%.

***N*-(6-Deoxy-β-cyclodextrin-6-yl) 3-(3-methylalloxazin-1-yl)-propanamide (7b).** Acid **4** (58.1 mg, 0.19 mmol), mono-6-deoxy-6-amino-β-cyclodextrin **5b** (200.0 mg, 0.16 mmol, calculated for heptahydrate) and PyBOP (101.0 mg, 0.19 mmol) were dissolved in DMF (2 mL). Then DIPEA (65 μL, 0.32 mmol) was added. The mixture was stirred overnight under an 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 (143.0 mg, 60%, calculated for tetrahydrate) was obtained. UV–VIS (nm): 318, 380. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{56}H_{81}N_5O_{37}$ 1438.4503, found 1438.4496. For ^1H NMR and ^{13}C NMR data: see Tables S1 and S2 in ESI.† Anal. Calcd for $C_{56}H_{81}N_5O_{37}\cdot 4H_2O$: C 45.23%, H 6.07%, N 4.44%; found: C 45.19%, H 6.03%, N 4.71%.

1-{[*N*-(6-Deoxy-α-cyclodextrin-6-yl)carbamoyl]methyl}-5-ethyl-3-methylalloxazin-5-ium perchlorate (1a). Acetaldehyde (170 μL, 3.03 mmol) and palladium on carbon (10%, 2.3 mg, 2.14 μmol) were added to a solution of **6a** (14.4 mg, 10.7 μmol) in ethanol (800 μL), perchloric acid (0.1 M in water, 800 μL) and water (600 μL). The resulting mixture was stirred for 18 h in the autoclave under hydrogen atmosphere (0.6 MPa) at room temperature. Then the catalyst was filtered off, ethanol and resulting acetaldehyde were evaporated under reduced pressure. The resulting solution of **1a** was diluted to 2 mL. This stock solution was frozen and stored at −78 °C. The concentration of the catalyst in the stock solution was recalculated with respect to the concentration of the conjugates prior to the alkylation and the actual volume of the sample. UV–VIS (nm): 383, 440; HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{51}H_{74}O_{32}N_5$ 1268.43114, found 1268.43000.

1-{2-[*N*-(6-Deoxy-α-cyclodextrin-6-yl)carbamoyl]ethyl}-5-ethyl-3-methylalloxazin-5-ium perchlorate (2a). Acetaldehyde (170 μL, 3.03 mmol) and palladium on carbon (10%, 2.3 mg, 2.14 μmol) were added to a solution of **7a** (14.3 mg, 10.8 μmol) in ethanol (800 μL), perchloric acid (0.1 M in water, 800 μL) and water (600 μL). The resulting mixture was stirred for 18 h in the autoclave under hydrogen atmosphere (0.6 MPa) at room temperature. Then the catalyst was filtered off, ethanol and resulting acetaldehyde were evaporated under reduced pressure. The resulting solution of **2a** was diluted to 2 mL. This stock solution was frozen and stored at −78 °C. The concentration of the catalyst in the stock solution was recalculated with respect to the concentration of the conjugates prior to the alkylation and the actual volume of the sample. UV–VIS (nm): 382, 444; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{52}H_{76}O_{32}N_5$ 1282.44679, found 1282.44373.

1-{2-[*N*-(6-Deoxy-β-cyclodextrin-6-yl)carbamoyl]ethyl}-5-ethyl-3-methylalloxazin-5-ium perchlorate (2b). Acetaldehyde (170 μL, 3.03 mmol) and palladium on carbon (10%, 2.3 mg, 2.14 μmol) were added to a solution of **7b** (15.5 mg, 10.3 μmol) in ethanol (800 μL), perchloric acid (0.1 M in water, 800 μL) and water (600 μL). The resulting mixture was stirred for 18 h in the autoclave under hydrogen atmosphere (0.6 MPa) at room temperature. Then the palladium-catalyst was filtered off, ethanol and resulting acetaldehyde were evaporated under reduced pressure. The resulting solution of **2b** was diluted to 2 mL. This stock solution was frozen and stored at −78 °C. The concentration of the catalyst in the stock solution was recalculated with respect to the concentration of the conjugates prior to the alkylation and the actual volume of the sample UV–VIS (nm): 382, 447; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{58}H_{86}O_{37}N_5$ 1444.49961; found 1444.49793.

Catalytic procedures

All catalytic oxidations of alkyl or aryl methyl sulfides were performed in 1 mL thick-walled screw-capped vial (Supelco). The reaction mixtures were prepared by addition of sodium-phosphate buffer (pH = 7.5, 0.05 M, 300 μL), liquid substrate ($3–4\times10^{-5}$ mol), appropriate volume of catalyst solution (1–5 mol%) and then the hydrogen peroxide (2.3 mol. eq. with respect to substrate). The vial was capped and the reaction mixture was shaken by wrist-action shaker for a given period of time. Then the reaction was quenched by addition of a solution of sodium dithionite in water (1.4 M, 170 μL). Product and remaining substrate were extracted to carbon tetrachloride (2×500 μL) and then to $CDCl_3$ (500 μL). Combined extracts were mixed and dried over sodium sulfate. One third of extracts was used for the NMR analysis of the conversion. Remaining solution was used for the analysis of enantiomeric excess of the isolated sulfoxides by NMR employing chiral shift reagent[31] or by HPLC on chiral phases (for details see ESI†).

Preparative oxidation of *p*-tolyl methyl sulfide

p-Tolyl methyl sulfide (672 mg, 4.86 mmol) was dissolved in sodium-phosphate buffer (pH = 7.5, 0.05 M, 40 mL) and solution of the catalyst **1b** (14.59 μmol) and hydrogen peroxide (1 mL, 7.94 mmol) were added. The reaction mixture was shaken in 125 mL bottle for 60 min using a wrist-action shaker. Then the reaction was quenched by addition of solution of sodium dithionite in water (1.4 M, 7 mL). Products were extracted to chloroform (3×40 mL). Collected extracts were dried over magnesium sulfate and filtered over sintered glass. The filtrate was evaporated and dried *in vacuo*. White solid (684 mg, 91%) was obtained. Analytical data were consistent with the published ones.[38]

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