DOI: 10.1002/ejoc.201000592

Planar Chiral Flavinium Salts – Prospective Catalysts for Enantioselective Sulfoxidation Reactions

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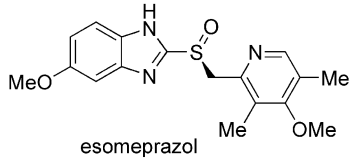
Keywords: Organocatalysis / Asymmetric catalysis / Sulfoxidation / Flavinium salts / Peroxides

A novel planar chiral flavinium salt, 3-benzyl-5-ethyl-10-(8-phenylnaphthalen-1-yl)isoalloxazinium perchlorate (**2b**), which bears a phenyl cap that covers one side of the isoalloxazinium skeleton plane, has been prepared as a potential catalyst for the enantioselective H_2O_2 oxidation of sulfides. The rate of H_2O_2 oxidation of sulfides in the presence of racemic **2b** is comparable to that of the reaction catalysed by 5-ethyl-3,10-dimethylisoalloxazinium perchlorate, which indicates that the bulky shielding substituent does not influence the catalytic activity of the flavinium unit. The turnover frequency for the oxidation of thioanisole with hydrogen peroxide with **2b** is 870 h^{-1}. The enantiomerically pure salts (+)-**2b** and (–)-**2b** were prepared from the pure enantiomers (+)-**3b** and (–)-**3b** of 3-benzyl-10-(8-phenylnaphthalen-1-yl)isoalloxazine (**3b**) obtained by HPLC separation of racemic **3b** on a chiral stationary phase. The enantiomerically pure salts (+)-**2b** and (–)-**2b** catalyse the H_2O_2 oxidation of *para*-substituted thioanisoles with enantiomeric excesses of 34–44 %. The highest enantioselectivity (54 % *ee*) was observed in the oxidation of methyl naphthyl sulfide.

Introduction

Methods for the preparation of enantiomerically pure chiral sulfoxides are currently of particular importance because they are useful as intermediates or chiral auxiliaries in organic synthesis.[1] Many drugs, including prazoles (proton pump inhibitors[2a]) or the psychostimulants modafinil[2b] and adrafinil,[2c] are racemic sulfoxides that challenge the so-called chiral switch, that is, the launch of an enantiomerically pure version of a formerly used racemic drug.[3] The proton-pump inhibitor esomeprasol [(*S*)-omeprazol, NEXIUM®],[4] a pharmaceutical "blockbuster", and psychostimulant armodafinil [(*R*)-modafinil, NUVIGIL™][5] are recent examples of enantiomerically pure sulfoxides used as pharmaceutical substances.



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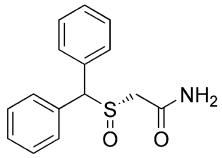

armodafinil

In addition to chiral stoichiometric oxidizing agents, several catalytic systems have been developed for enantioselective sulfoxidation reactions.[1a,4c,6] Recently, much interest has been focused on environmentally friendly oxidation reactions, in particular those using hydrogen peroxide or oxygen as terminal oxidants.[7] Interesting results have been obtained in biological sulfoxidation reactions.[1a,8] In particular, flavin- and haem-dependent monooxygenases and peroxidases are efficient catalysts achieving excellent enantioselectivity, but they are strongly dependent on the substrate structure. Steric factors also dramatically affect the yield of biological oxidation reactions. The majority of catalytic systems developed for sulfoxidation reactions are based on metal-ion complexes with chiral ligands that oxidize prochiral sulfides with good or even excellent enantioselectivity.[6,9] Although the loading of metal ions in oxidation reactions catalysed by these complexes has been reduced substantially, the removal of metal traces is a permanent problem in the pharmaceutical industry. Thus, the search for stereoselective, metal-free (organocatalytic) sulfoxidation systems is of high importance.[10]

Among the reported organocatalytic sulfoxidation methods,[10,11] that using 4a-hydroperoxyflavin (**Fl-OOH**), formed in situ from the corresponding flavinium salt (**$Fl^+ClO_4^-$**) and hydrogen peroxide (Scheme 1), seems to be the most promising.[10a,11] This method is highly chemoselective, producing sulfoxides without overoxidation to sulfones.[11–13] Hitherto, the vast majority of studies were performed with non-chiral flavinium salts and attention has been directed predominantly towards the efficiency and chemoselectivity of catalytic systems. There are only a few reports of chiral flavinium salts employed as catalysts in enantioselective oxidation reactions. The first involves the

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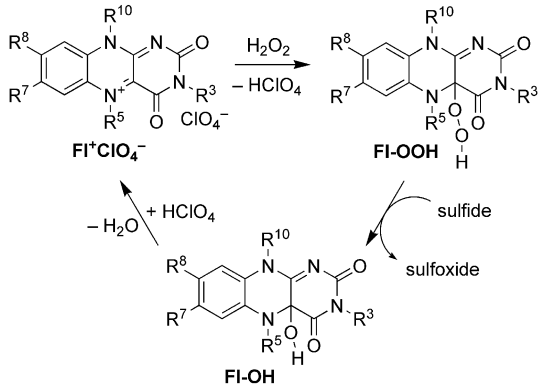
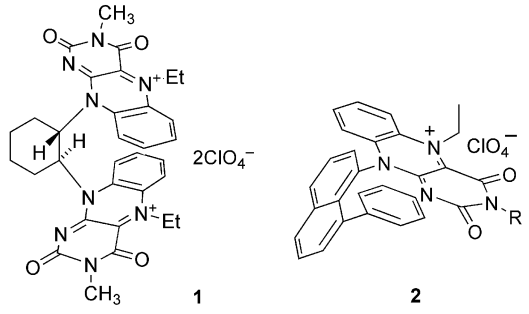
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000592.

oxidation reactions of substituted thioanisoles[14a] and methyl naphthyl sulfide[14b] catalysed by chiral flavinium salts possessing a cyclophane moiety. The observed *ee* values were up to 65 and 72%, respectively. However, a relatively high loading of the catalyst (up to 12 mol-% relative to the substrate) was necessary to achieve the above-mentioned enantioselectivity. Another example of enantioselective oxidation catalysed by a chiral flavinium salt is the Baeyer–Villiger oxidation of *para*-substituted 3-phenylcyclobutanones. In the presence of the planar chiral bis-flavinium salt **1** the *ee* values of the resulting lactones ranged from 61 to 74%.[15]



Scheme 1. Catalytic cycle of H_2O_2 sulfoxidation mediated by a flavinium salt.

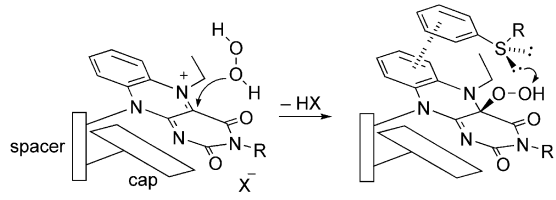


Herein we report the design, synthesis and study of novel planar chiral salts **2** as potential catalysts for enantioselective sulfoxidation reactions.

Results and Discussion

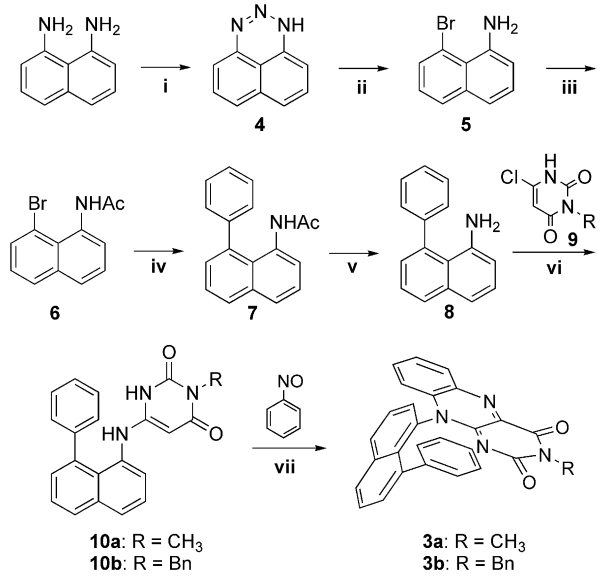
Design and Synthesis of the Flavinium Salts

The rationale for the design of the planar chiral flavinium salts **2** is shown in Scheme 2. The cap attached by a rigid spacer to a nitrogen atom at the 10-position of the flavin skeleton is expected to allow access of the substrate only from the "uncovered" face of the flavin moiety. Consequently, only one of the hydroperoxyflavin diastereomers formed in the reaction mixture can oxidize the substrate, which is supposed to be bound to the flavin moiety by π–π stacking. Owing to steric demands of the alkyl group in alkyl aryl sulfide, it is reasonable to assume mutual orientation of the substrate and the catalyst, as depicted in Scheme 2. In this arrangement the alkyl group is directed away from the flavin skeleton plane and only one of the enantiotopic lone-pair electrons at the sulfur atom can interact with the hydroperoxy function of the catalyst. As the covering cap and rigid spacer, we chose a phenyl group and a naphthalene-1,8-diyl, respectively. In comparison with the planar chiral flavinium salt **1** previously reported by Murahashi et al.,[15] we assume better blocking of the corresponding site of the isoalloxazinium skeleton plane.



Scheme 2. Proposed asymmetric induction in the oxidation of an aromatic substrate with a planar chiral flavinium salt "covered" with a cap.

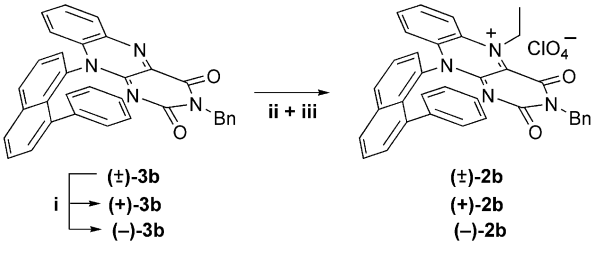
The key intermediates in the synthesis of flavinium salts **2** are non-quaternized flavins **3**, which were prepared starting from commercially available naphthalene-1,8-diamine (Scheme 3). First, naphthalene-1,8-diamine was converted into 8-bromonaphthalene-1-amine (**5**) via naphthotriazine (**4**).[16] After amino group protection,[17] the bromo derivative **6** was coupled with phenylboronic acid and the amide



Scheme 3. Synthesis of flavins **3**. Reagents and conditions: (i) 1 equiv. $NaNO_2$, AcOH, H_2O, –6 to 0 °C, 95%; (ii) 48% HBr, Cu, reflux, 67%; (iii) Ac_2O, pyridine, 100 °C, 90%; (iv) $PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, Na_2CO_3, *n*PrOH, H_2O, reflux, 93%; (v) HCl, EtOH, reflux, 90 (**10a**) or 95% (**10b**); (vi) 180 °C, 95%; (vii) AcOH, reflux, 65 (**3a**) or 69% (**3b**).

7 obtained in this fashion was hydrolysed to 8-phenylnaphthalene-1-amine (**8**). Heating of the amine **8** with chlorouracil **9** at 180 °C resulted in aminouracil **10**. Chlorouracils **9a** (R = CH_3) and **9b** (R = Bn) were obtained from commercially available methyl- or benzylurea via the corresponding barbituric acids[18] (for the synthesis of chlorouracils **9** see the Supporting Information). The flavin skeleton was formed by the reaction of aminouracil **10** with nitrosobenzene. We first applied the conditions described by Yoneda et al. for the preparation of simple flavins, that is, by heating the reagents in a mixture of acetic anhydride/acetic acid (4:1).[19] Unfortunately, in our case a lot of impurities resulted from the reaction mixture and flavins **3** were isolated in relatively low yields (23–28%). Optimization of the reaction conditions increased the yields to 65–69%; we found pure acetic acid to be a much better solvent for this cyclization. In this way, we prepared planar chiral flavins **3a** and **3b**.

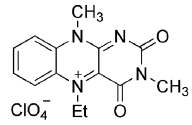
Our strategy for the synthesis of enantiomerically pure catalysts **2** was based on the separation of enantiomers of flavins **3** by HPLC on a chiral stationary phase followed by their transformation into the final optically pure salts (+)-**2** and (–)-**2** (Scheme 4). This approach was possible because of the rigidity of planar chiral flavins preventing racemization during the final step of the synthesis. Unfortunately, in preliminary experiments, we found the methyl derivative **3a** to be almost insoluble in solvents suitable as a mobile phase for HPLC separations. On the other hand, the solubility of the more lipophilic benzyl derivative **3b** was substantially higher and we succeeded in separating it even on the 100 mg scale using the Whelk stationary phase and the dichloromethane mobile phase (for details see the Exp. Sect. and the Supporting Information). The enantiomerically pure salts (+)-**2b** and (–)-**2b** were synthesized from optically pure flavins (+)-**3b** and (–)-**3b**, respectively, by reductive alkylation followed by oxidation of the thus-obtained 1,5-dihydroflavins (not isolated) with sodium nitrite in dilute perchloric acid. Racemic flavinium perchlorate (±)-**2b**, employed in the basic screening of catalytic activity, was obtained from (±)-**3b** in an analogous procedure (see Scheme 4).



Scheme 4. Synthesis of the flavinium catalyst **2b**. Reagents and conditions: (i) (*R*,*R*)-Whelk-O1, dichloromethane; (ii) CH_3CHO, 10% Pd/C, H_2, AcOH, H_2O, room temp.; (iii) $NaNO_2$, $HClO_4$, MeOH, H_2O, $NaClO_4$, 10 °C, 85% (two steps).

Catalytic Activity of (±)-2b in H_2O_2 Sulfoxidation Reactions

First, we wished to establish the effect of the phenyl cap on the catalytic activity of the flavinium salts. Therefore the efficiency of the racemic salt (±)-**2b** in sulfoxidation reactions of various substrates was compared with that of the simple "uncovered" salt **11**. The reactions were performed under the usual conditions, that is, with a small excess of hydrogen peroxide in the presence of 1.5 mol-% of the catalyst (relative to the substrate) at room temperature (for details see the Exp. Sect.).[12,13] The conversion can be monitored easily by ^1H NMR spectroscopy. Therefore the reactions were carried out in NMR tubes in deuteriated methanol as solvent. Based on our previous experience,[12c] we did not assume any isotope effect of the solvent on the reaction kinetics. For all the substrates used in this study, the oxidation reactions catalysed by both (±)-**2b** and **11** were chemoselective, no overoxidation to sulfones was observed in any case. The rate enhancements of the sulfoxidation reactions catalysed by (±)-**2b** and **11** are summarized in Table 1. A comparison of the kinetics of sulfoxidation catalysed by (±)-**2b** and **11** is shown in Figure 1; the given example represents the oxidation of thioanisole (for the data referring to other substrates, see the Supporting Information). The data show clearly that the catalytic efficiency of (±)-**2b** is practically the same as that of **11**, which indicates that the bulky shielding substituent does not diminish the catalytic activity of the flavinium unit. The catalytic activity of (±)-**2b** is very high: the rate enhancement of the oxidation of thioanisole performed under the afore-mentioned conditions is approx. 200 in comparison with the non-catalysed process and the turnover frequency of the catalyst calculated from the initial reaction rate is 870 h^{-1}. The observed high ratio of the rates of the reaction catalysed by (±)-**2b** and the non-catalysed reaction represents a necessary (although not sufficient) condition for enantioselective sulfoxidation catalysed by optically pure salts (+)-**2b** and (–)-**2b** as the non-catalysed side-reaction leads to racemic sulfoxides.



11

Table 1. Comparison of the catalytic efficiency of **2b** and **11** in H_2O_2 sulfoxidation reactions.

Entry	Substrate	Rate enhancement[a]	
		2b	**11**
1	Ph-S-Me	200	200
2	*p*-MePh-S-Me	170	180
3	*p*-ClPh-S-Me	170	150
4	*p*-NO_2Ph-S-Me	17	18[c]
5	Ph-S-Bn	120	100

[a] Rate enhancement was calculated as the ratio of the rates of the catalysed and non-catalysed reactions at low conversion[12,13] (up to 10%).

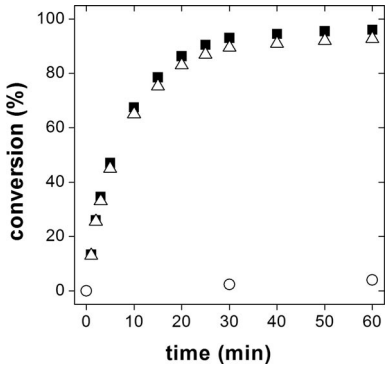


Figure 1. Oxidation of thioanisole with H_2O_2 catalysed by the flavinium salt (±)-**2b** (■) and the flavinium salt **11** (Δ). Non-catalysed reaction: (○).

Enantioselective Sulfoxidation Reactions Catalysed by 2b

The conditions for the enantioselective sulfoxidation reactions catalysed by single enantiomers of **2b** were optimized by using thioanisole as a model substrate. In these experiments we focused on the effects of the solvent, reaction temperature and concentration of the reagents. In each case the reaction was quenched at 70% conversion by the addition of sodium dithionate. The ratio of enantiomers in the isolated product was determined by HPLC on a Chiralcel OD column. The results are summarized in Table 2.

Table 2. The effects of solvent, temperature and concentration of reagents on asymmetric H_2O_2 sulfoxidation of thioanisole catalysed by the flavinium salt (+)-**2b**.

Entry	Solvent	*T* [°C]	*c* (substrate) [mol L^{-1}]	*ee* [%][a]
1	CH_3OH	0	0.2	8
2	CH_3OH	–20	0.2	11
3	CH_3OH	–20	0.01	14
4	$CF_3CH_2OH/CH_3OH/H_2O$ (6:3:1)	–20	0.2	17
5	$CF_3CH_2OH/CH_3OH/H_2O$ (6:3:1)	–20	0.01	24
6	CH_3OH/H_2O (3:1)	–20	0.01	29
7	CH_3OH/H_2O (2:1)	–20	0.01	34
8	CH_3OH/H_2O (2:1)	–40	0.01	35

[a] The enantiomeric ratios were determined by HPLC on a chiral stationary phase (Chiralcel OD column).

The choice of solvents was inspired by previous experience with enantioselective oxidations catalysed by chiral flavinium salts reported by Murahashi[14b,15] and Shinkai and their co-workers.[14a] Similarly, as in the case of sulfoxidation reactions catalysed by cyclophane-based flavinium salts,[14] the presence of water as well as the dilution of the reaction mixture were found to increase the enantioselectivity. The best results were obtained in a methanol/water (2:1, v/v) mixture. Unfortunately, a further increase in the water content led to inhomogeneity of the system. The presence of trifluoroethanol[15] in the reaction mixtures (entries 4 and 5) did not lead to higher enantioselectivity. As expected, a decrease of the reaction temperature increased the enantioselectivity. However, the observed effect was small and, below –20 °C, even negligible (entries 1 vs. 2 and 7 vs. 8).

The optimized conditions [methanol/water, 2:1, –20 °C, *c*(substrate) = 0.01 mol L^{-1}, 5 mol-% **2b** relative to the substrate] were used to investigate the enantioselectivity in the oxidation of various sulfides (Table 3). As expected, catalysis of the oxidation of thioanisole, both with (+)-**2b** and with (–)-**2b**, afforded the product with the same *ee* but of course with the opposite configuration (entries 1 and 2). In the case of *para*-substituted thioanisoles, the *ee* values ranged from 36 to 44% (entries 3–5). Interestingly, the effect of substitution at the *para* position of the phenyl ring on the enantioselectivity seems to be relatively small. The highest enantioselectivity (54% *ee*; entry 6) was observed in the oxidation of methyl 2-naphthyl sulfide, most probably due to its more extensive π system that may bind more efficiently to the catalyst. The enantioselectivity of the oxidation of alkyl phenyl sulfides is practically independent of the steric demands of the alkyl group; on going from the methyl (entries 1 and 2) to the isopropyl (entry 7) and the *tert*-butyl (entry 8) sulfides, the *ee* values decrease by only 3%. On the other hand, the enantioselectivities of dihydrobenzothiophene (entry 9) and cyclohexyl methyl sulfide (entry 10) oxidation are poor. This is in accordance with our assumption of the origin of the enantioselectivity of alkyl aryl sulfide oxidation catalysed by planar chiral flavinium salts **2** (Scheme 2). In the case of alkyl phenyl sulfides, the bulkiness of the alkyl group should not influence the course of the oxidation because of its orientation relative to the flavinium unit. However, decreased conformational flexibility of the cyclic sulfide dihydrobenzothiophene does not allow this substrate to adopt the optimum orientation depicted in Scheme 2 that is necessary for the enantioselectivity of sulfoxidation. Low enantioselectivity of the sulfoxidation of cyclohexyl methyl sulfide, which cannot be bound to the catalyst by π–π stacking, also supports our hypothesis of asymmetric induction (Scheme 2). 4-Nitrothioanisole is reported to afford high enantioselectivity

Table 3. Enantioselective H_2O_2 sulfoxidation reactions of various sulfides catalysed by the flavinium salts (+)-**2b** or (–)-**2b**.

Entry	Substrate	Catalyst	*ee* [%][a]	Config.[b]
1	Ph-S-Me	(–)-**2b**	34	(*S*)-(–)
2	Ph-S-Me	(+)-**2b**	34	(*R*)-(+)
3	*p*-MePh-S-Me	(–)-**2b**	42	(*S*)-(–)
4	*p*-MeOPh-S-Me	(–)-**2b**	36	(*S*)-(–)
5	*p*-ClPh-S-Me	(–)-**2b**	44	(*S*)-(–)
6	2-Naphthyl-S-Me	(–)-**2b**	54	(*S*)-(–)
7	Ph-S-*i*Pr	(–)-**2b**	32	(*S*)-(–)
8	Ph-S-*t*Bu	(–)-**2b**	31	(*S*)-(–)
9	2,3-Dihydrobenzo[*b*]thiophene	(–)-**2b**	5	(*R*)-(–)
10	Cyclohexyl-S-Me	(–)-**2b**	4	–

[a] The enantiomeric ratios were determined by HPLC on a chiral stationary phase (Chiralcel OD column) or by ^{1}H NMR (entry 10) in the presence of (*R*)-*N*-(3,5-dinitrobenzoyl)-1-phenylethan-1-amine as a chiral shift reagent.[20] [b] The absolute configurations were assigned by comparing optical rotations and HPLC elution orders with known literature data.[9e,21]

in the case of oxidation reactions catalysed by chiral metal complexes.[9] Unfortunately, in our case, the results of the oxidation of 4-nitrothioanisole were not reproducible because of its low solubility in the reaction mixture.

Conclusions

We have demonstrated that the novel planar chiral flavinium salt **2b** catalyses the enantioselective oxidation of alkyl aryl sulfides with hydrogen peroxide to yield the corresponding sulfoxides with up to 54% *ee*. The catalytic efficiency of **2b** towards various sulfides is relatively high, comparable to that of simple isoalloxazinium salts. However, the observed enantioselectivity is lower than that reported for chiral metal complexes. Nevertheless, it is comparable with the results obtained with the organocatalytic systems reported until now.[10,14] Moreover, the structure of the catalyst **2b** can be modified easily by substitution on the phenyl or pyrimidine ring, which could increase the enantioselectivity. The novel planar chiral flavinium salt **2b** may also be applied to other types of oxidation reactions, for example, Baeyer–Villiger oxidation reactions.

Experimental Section

General: Melting points were measured with a Boetius Block apparatus. NMR spectra were recorded with a Varian Mercury Plus 300 (299.97 MHz for ^{1}H anup>H and 125.77 MHz for ^{13}C), and a Bruker 600 Avance III spectrometer (600.13 MHz for ^{1}H and 150.92 MHz for ^{13}C). The ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. Optical rotations were measured with a Perkin–Elmer M-241 digital polarimeter. All reagents were purchased from commercial sources and used without any treatment unless otherwise indicated. TLC analyses were carried out on DC Alufolien Kieselgel 60H F254 (Merck). Preparative column chromatography was performed on Kieselgel 60 silica gel (0.040–0.063 mm, Merck). Elemental analyses were performed with a Perkin–Elmer 240 analyser. Preparative HPLC was carried out with an Agilent 1100 Series instrument.

3-Benzyl-5-ethyl-10-(8-phenylnaphthalen-1-yl)isoalloxazinium Perchlorate (2b): Palladium on charcoal (10%; 50 mg) and acetaldehyde (0.5 mL) were added to a solution of **3b** (101 mg, 0.2 mmol) in a mixture of acetic acid (20 mL) and water (2 mL). The resulting mixture was stirred for 36 h in an autoclave under H_2 (0.2 MPa) at room temperature. Then the catalyst was filtered off, acetic acid was evaporated under reduced pressure and the remaining solid was dried in vacuo. The residue was dissolved in a minimum volume of methanol (ca. 1 mL) and 2 M perchloric acid (2 mL) and sodium perchlorate (500 mg) were added. Sodium nitrite (110 mg) was added in several portions to the stirred mixture at 10 °C within 30 min. After stirring for an additional 45 min at the same temperature, the precipitate was filtered off, washed with water and dried. The solid obtained was dissolved in acetonitrile, reprecipitated by the addition of diethyl ether and dried in vacuo at room temperature to obtain **2b** (108 mg, 85%) as a black microcrystalline powder; m.p. 181–183 °C. ^{1}H NMR (CD_3CN, 600 MHz): δ = 1.82 (br. s, 3 H, $N^+CH_2CH_3$), 4.75–5.25 (br. s, 1 H), 5.09 (d, J = 14.1 Hz, 1 H), 5.24 (d, J = 14.3 Hz, 1 H), 5.40–5.90 (br. s, 1 H), 6.35 (m, 1 H), 6.49 (m, 1 H), 6.54 (t, J = 7.5 Hz, 1 H), 6.91 (d, J = 7.0 Hz, 1 H), 7.02 (m, 1 H), 7.19 (d, J = 8.2 Hz, 1 H), 7.25 (d, J = 7.0 Hz, 1 H), 7.34 (t, J = 7.2 Hz, 1 H), 7.39 (d, J = 7.2 Hz, 1 H), 7.39–7.41 (m, 2 H), 7.42–7.50 (m, 3 H), 7.69 (t, J = 7.5 Hz, 1 H), 7.85 (t, J = 7.8 Hz, 1 H), 7.88 (t, J = 7.8 Hz, 1 H), 7.97 (t, J = 7.7 Hz, 1 H), 8.22 (d, J = 8.5 Hz, 1 H), 8.35 (d, J = 7.9 Hz, 1 H), 8.40 (d, J = 8.5 Hz, 1 H) ppm. The signals are assigned in the Supporting Information. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.0, 47.0, 121.3, 122.7, 126.1, 127.1, 127.3, 127.4, 127.7, 127.8, 128.9, 129.1, 129.3, 129.4, 129.5, 129.6, 129.7, 130.7, 131.4, 131.7, 132.7, 134.0, 136.5, 136.6, 136.7, 136.74, 139.5, 140.6, 141.6, 151.3, 152.6, 155.3 ppm. $C_{35}H_{27}ClN_4O_6$ (634.16): calcd. C 66.19, H 4.29, N 8.82; found C 65.85, H 3.93, N 8.87.

Compounds (+)-**2b** and (–)-**2b** were obtained from (+)-**3b** and (–)-**3b**, respectively, following the above-described procedure. Specific rotation: (+)-**2b**: $[\alpha]_D^{25}$ = 785 (c = 0.2, $CHCl_3$); (–)-**2b**: $[\alpha]_D^{25}$ = –798 (c = 0.2, $CHCl_3$).

3-Methyl-10-(8-phenylnaphthalen-1-yl)isoalloxazine (3a): A mixture of aminouracil **10a** (343 mg, 1 mmol) and nitrosobenzene (321 mg, 3 mmol) was stirred in acetic acid (8 mL) at reflux for 45 min. Then the solvent was evaporated and the residue was purified by column chromatography (chloroform/methanol, 100:2) and crystallization from chloroform/diethyl ether to afford **3a** (280 mg, 65%) as yellow needles; m.p. >350 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.49 (s, 3 H), 6.14 (d, J = 7.4 Hz, 1 H), 6.48 (t, J = 7.4 Hz, 1 H), 6.56 (d, J = 8.2 Hz, 1 H), 6.89 (t, J = 7.4 Hz, 1 H), 7.01 (t, J = 7.4 Hz, 1 H), 7.12 (d, J = 7.5 Hz, 1 H), 7.15 (d, J = 6.9 Hz, 1 H), 7.31 (d, J = 7.4 Hz, 1 H), 7.52 (m, 3 H), 7.69 (t, J = 8.0 Hz, 1 H), 8.04 (d, J = 8.2 Hz, 1 H), 8.15 (d, J = 8.2 Hz, 1 H), 8.18 (d, J = 8.2 Hz, 1 H) ppm. The signals are assigned in the Supporting Information. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.7, 117.3, 125.8, 126.0, 126.2, 126.4, 126.6, 127.0, 127.9, 128.6, 129.0, 129.4, 131.3, 131.5, 132.2, 132.3, 134.7, 135.7, 136.0, 136.9, 137.2, 140.3, 149.9, 155.6, 159.2 ppm. $C_{27}H_{18}N_4O_2$ (430.47): calcd. C 75.34, H 4.21, N 13.02; found C 75.16, H 4.34, N 10.99.

3-Benzyl-10-(8-phenylnaphthalen-1-yl)isoalloxazine (3b): Isoalloxazine **3b** was prepared analogously to **3a** from aminouracil **10b** (840 mg, 2 mmol) and nitrosobenzene (643 mg, 6 mmol) in acetic acid (15 mL). Column chromatography (chloroform/ethyl acetate, 4:1) and crystallization from chloroform/diethyl ether afforded **3b** (700 mg, 69%) as yellow needles; m.p. 289–291 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.24 (m, 2 H), 6.06 (d, J = 7.5 Hz, 1 H), 6.16 (t, J = 7.4 Hz, 1 H), 6.40 (t, J = 7.5 Hz, 1 H), 6.55 (d, J = 8.3 Hz, 1 H), 6.82 (t, J = 7.4 Hz, 1 H), 6.94 (d, J = 7.5 Hz, 1 H), 7.10 (d, J = 6.9 Hz, 1 H), 7.24–7.34 (m, 4 H), 7.40–7.54 (m, 3 H), 7.64–7.69 (m, 3 H), 8.01 (d, J = 8.2 Hz, 1 H), 8.11 (d, J = 7.9 Hz, 1 H), 8.16 (d, J = 8.2 Hz, 1 H) ppm. The signals are assigned in the Supporting Information. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 44.8, 117.2, 125.9, 126.0, 126.1, 126.3, 126.6, 126.7, 127.8, 128.3, 128.6, 128.9, 129.3, 129.9, 131.3, 131.5, 132.1, 132.2, 134.7, 134.8, 135.7, 135.9, 137.0, 137.2, 137.4, 140.2, 149.8, 155.1, 158.8 ppm. $C_{33}H_{22}N_4O_2$ (506.57): calcd. C 78.25, H 4.38, N 11.06; found C 78.31, H 4.32, N 11.02.

Resolution of Racemic Flavin 3b: Enantiomers of **3b** were separated by HPLC on a chiral stationary phase. Conditions for preparative chromatography: (*R*,*R*)-Whelk-O1 column (ø 1 cm, length 25 cm), dichloromethane as eluent, flow rate: 2.0 mL/min, detection: UV 254 nm; retention times: 15.2 [(–)-**3b**] and 28.5 min [(+)-**3b**]. Conditions for analytical chromatography: (*R*,*R*)-Whelk-O1 column (ø 0.46 cm, length 25 cm), dichloromethane as eluent, flow rate =

0.5 mL/min, detection: UV 254 nm, retention times: 10.3 [(–)-**3b**] and 19.3 min [(+)-**3b**]. For the chromatogram, see Figure S3 of the Supporting Information. Specific rotation: (+)-**3b**: $[a]_D$ = 870 (*c* = 0.5, $CHCl_3$); (–)-**3b**: $[a]_D^{25}$ = –879 (*c* = 0.5, $CHCl_3$).

1*H*-Naphtho[1,8,8a-*de*][1,2,3]triazine (4):[16a] A solution of $NaNO_2$ (9.12 g, 132 mmol) in water (53 mL) was added to a solution of naphthalene-1,8-diamine (20.00 g, 126 mmol) in a mixture of acetic acid (240 mL) and water (175 mL) at –6 °C. Then the reaction mixture was diluted with water (40 mL) and stirred at 0 °C for 45 min. The brown precipitate was filtered off, washed with water and dried at room temperature to give 20.30 g (95%) of a brown powder, which was sufficiently pure for the next synthesis. ^{1}H NMR ([D$_6$]-DMSO, 300 MHz): δ = 6.13 (d, *J* = 7.2 Hz, 1 H, Ar-H), 6.89 (d, *J* = 8.2 Hz, 1 H, Ar-H), 7.03 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.13 (t, *J* = 8.0 Hz, 1 H, Ar-H), 7.26 (m, 2 H, Ar-H), 13.29 (br. s, 1 H, NH) ppm.

8-Bromonaphthalene-1-amine (5):[16b] Copper powder (6.00 g, 94 mmol), activated by iodine,[16c] was added to a vigorously stirring solution of **4** (20.00 g, 118 mmol) in aqueous HBr (48%, 140 mL) at 50 °C. When the intense evolution of nitrogen had finished, the mixture was heated at reflux. The mixture was diluted with water (300 mL), heated to boiling and filtered. The residue was washed with boiling water (150 mL). The combined filtrates were neutralised with ammonia and extracted with diethyl ether. The ethereal solution was washed with water, filtered (to remove suspended solid) and dried with $MgSO_4$. The crude product obtained after solvent evaporation was purified by column chromatography (toluene) to afford **5** (17.61 g; 67%) as a pink solid; m.p. 90–91 °C (ref.[16b] 89–90 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.14 (br. s, 2 H, NH_2), 6.71–6.77 (m, 1 H, Ar-H), 7.11–7.17 (m, 1 H, Ar-H), 7.23–7.27 (m, 1 H, Ar-H), 7.62 (dd, *J* = 7.6, *J* = 1.2 Hz, 1 H, Ar-H), 7.69 (dd, *J* = 8.2, *J* = 1.2 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.0, 121.3, 121.5, 121.7, 124.4, 125.5, 125.7, 127.4, 134.9, 145.2 ppm.

***N*-(8-Bromonaphthalen-1-yl)acetamide (6):**[17] Acetic anhydride (7.1 mL, 75 mmol) was added to a solution of **5** (15.50 g, 70 mmol) in pyridine (40 mL). The mixture was heated at 100 °C for 1 h and then evaporated in vacuo. The solid residue obtained was crushed, washed with dilute hydrochloric acid (1:1) and water and then dried in air. The crude product was purified by crystallization from aqueous acetic acid (50%, w/w) to afford **6** (16.58 g; 90%) as colourless crystals; m.p. 142–144 °C (ref.[16] 143–144 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.29 (s, 3 H, $COCH_3$), 7.23 (t, *J* = 8.0 Hz, 1 H, Ar-H), 7.48 (t, *J* = 7.8 Hz, 1 H, Ar-H), 7.69 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.77 (d, *J* = 7.8 Hz, 1 H, Ar-H), 7.81 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.99 (d, *J* = 7.8 Hz, 1 H, Ar-H), 8.79 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 115.7, 124.5, 124.8, 125.9, 126.3, 127.0, 129.6, 132.0, 133.7, 136.6, 168.4 ppm.

***N*-(8-Phenylnaphthalene-1-yl)acetamide (7):** A solution of Na_2CO_3 (7.92 g, 75 mmol) in water (95 mL) was added under nitrogen to a solution of **6** (15.85 g, 60 mmol), phenylboronic acid (7.68 g, 63 mmol), palladium acetate (269 mg, 1.2 mmol) and triphenylphosphane (944 mg, 3.6 mmol) in propanol (300 mL). The mixture was heated at reflux for 6 h. The solvent was evaporated in vacuo and water was added to the residue. The mixture was extracted with chloroform and the extract was dried with Na_2SO_4. The crude product obtained after solvent evaporation was crystallized from ethyl acetate with charcoal to obtain **7** (14.58 g; 93%) as colourless crystals; m.p. 162–164 °C (ref.[22] 163–164 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.44 (s, 3 H, $COCH_3$), 7.03 (br. s, 1 H, NH), 7.28 (d, *J* = 7.8 Hz, 1 H, Ar-H), 7.42–7.56 (m, 7 H, Ar-H), 7.74 (d, *J* = 8.2 Hz, 1 H, Ar-H), 7.88 (d, *J* = 8.2 Hz, 1 H, Ar-H), 8.03 (d, *J* = 7.3 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0, 119.4, 121.0, 122.9, 123.1, 125.7, 125.8, 126.0, 127.7, 128.0, 133.0, 133.4, 134.4, 137.9, 138.7, 168.7 ppm.

8-Phenylnaphthalene-1-amine (8): A mixture of **7** (14.11 g, 54 mmol), ethanol (70 mL) and conc. hydrochloric acid (30 mL) was heated at reflux for 10 h. After evaporation of the solvents, the residue was stirred with diethyl ether (100 mL) and a solution of NaOH (5 g) in water (50 mL) until the solid was completely dissolved. The organic layer was separated and the aqueous layer extracted with diethyl ether (30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$ and evaporated to afford **8** (11.25 g, 95%) as a light-brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.72 (br. s, 2 H, NH_2), 6.64 (d, *J* = 7.3 Hz, 1 H, Ar-H), 7.17 (d, *J* = 7.0 Hz, 1 H, Ar-H), 7.27–7.49 (m, 8 H, Ar-H), 7.80 (d, *J* = 8.2 Hz, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 111.5, 119.3, 120.9, 124.8, 126.8, 127.7, 128.3, 128.5, 128.9, 129.5, 136.1, 138.5, 143.8, 144.0 ppm.

3-Methyl-6-[(8-phenylnaphthalen-1-yl)amino]uracil (10a): A mixture of **9a** (0.78 g, 5 mmol) and **8** (3.29 g, 15 mmol) was stirred under nitrogen at 180 °C for 40 min. After cooling, the resulting solid was filtered off, washed with diethyl ether (3 × 20 mL) and methanol (2 × 10 mL) and dried in vacuo to afford **10a** as a white solid (1.54 g, 90%); m.p. 294–296 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 2.95 (s, 3 H, CH_3), 3.80 (s, 1 H, CH=), 7.10–7.30 (m, 6 H, Ar-H), 7.37 (d, *J* = 7.3 Hz, 1 H, Ar-H), 7.57 (m, 2 H, Ar-H), 8.03 (m, 2 H, Ar-H), 9.46 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 26.6, 75.4, 126.2, 126.7, 127.0, 127.7, 128.0, 128.1, 129.1, 129.4, 129.5, 131.2, 133.0, 136.1, 138.7, 143.0, 151.1, 152.3, 163.6 ppm. $C_{21}H_{17}N_3O_2$ (343.39): calcd. C 73.45, H 4.99, N 12.24; found C 73.29, H 5.02, N 12.29.

3-Benzyl-6-[(8-phenylnaphthalen-1-yl)amino]uracil (10b): Aminouracil **10b** was prepared analogously to **10a** from **9b** (2.13 g, 9 mmol) and **8** (5.92 g, 27 mmol). The resulting solid was washed with diethyl ether (3 × 40 mL) and methanol (2 × 15 mL) and dried in vacuo to afford **10b** as a white solid (3.58 g, 95%); m.p. 296–298 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.79 (s, 1 H, CH=), 4.78 (s, 2 H, $PhCH_2$), 7.10–7.40 (m, 7 H, Ar-H), 7.50–7.61 (m, 2 H, Ar-H), 8.03 (d, *J* = 8.2 Hz, 2 H, Ar-H), 9.51 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 42.5, 75.2, 126.3, 126.7, 127.0, 127.5, 127.7, 128.0, 128.3, 128.8, 129.0, 129.4, 129.6, 131.2, 132.9, 136.1, 138.7, 139.0, 143.0, 120.9, 152.5, 163.2 ppm. $C_{27}H_{21}N_3O_2$ (419.49): calcd. C 77.31, H 5.05, N 10.02; found C 77.20, H 5.09, N 10.08.

5-Ethyl-3,10-dimethylisoalloxazinium Perchlorate (11): Salt **11** was prepared following a previously described procedure.[23] The NMR spectrum of **11** is in accord with that reported in the literature.[23]

Kinetic Measurements: Flavinium salt **2b** or **11** (3.8 μmol), the substrate (0.255 mmol) and [D$_4$]CD_3OD (600 μL) were charged into an NMR tube. The mixture was homogenized by sonication and tempered for 15 min at 25 °C. The reaction was started by adding 30% aqueous hydrogen peroxide (40 μL, 0.392 mmol). The conversions were calculated from the integrals of the corresponding signals in the ^{1}H NMR spectra. The spectra of the products corresponded to the spectra of authentic samples of the sulfoxide. For the oxidation of *p*-nitrothioanisole, half the amount of the flavinium salt as well as of the substrate and hydrogen peroxide was used.

Typical Procedure for the Asymmetric Sulfoxidation Reactions: Flavinium salt (+)-**2b** or (–)-**2b** (3.2 mg, 5 μmol) and the substrate (0.1 mmol) were dissolved in methanol/water (2:1, 10 mL). The mixture was homogenized by sonication and tempered for 30 min

at –20 °C. A 30% aqueous hydrogen peroxide solution (10.5 μL, 0.1 mmol) was added and the reaction mixture was stirred at –20 °C. The reaction was monitored by HPLC. When 70% conversion was reached, the reaction was quenched with 5% aqueous sodium bisulfite (5 mL). Methanol was carefully evaporated and the remaining aqueous solution was extracted with dichloromethane. After the evaporation of the solvents, the residue was purified by chromatography (ethyl acetate/hexane, 1:1). The enantiomeric ratios were determined by HPLC analysis on a Chiralcel OD column (hexane/2-PrOH, 9:1) or by ^{1}H NMR in the presence of (*R*)-*N*-(3,5-dinitrobenzoyl)-1-phenylethan-1-amine as a chiral shift reagent.[20]

Supporting Information (see also the footnote on the first page of this article): Experimental details for the synthesis of 3-alkyl-6-chlorouracils, ^{1}H NMR spectra of **2b**, **3a** and **3b**, chromatogram of the racemic mixture of flavin **3b** on a chiral HPLC column, CD spectra of (+)-**3b** and (–)-**3b** and the kinetics of the H_2O_2 sulfoxidation reactions catalysed by flavinium salt **2b**.

Acknowledgments

The authors wish to thank the Czech Science Foundation (Grant No. 203/07/1246) for financial support.

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Received: April 28, 2010
Published Online: August 3, 2010

