Mild and Efficient Flavin-Catalyzed H_2O_2 Oxidations

Alexander B. E. Minidis and Jan-E. Bäckvall*[a]

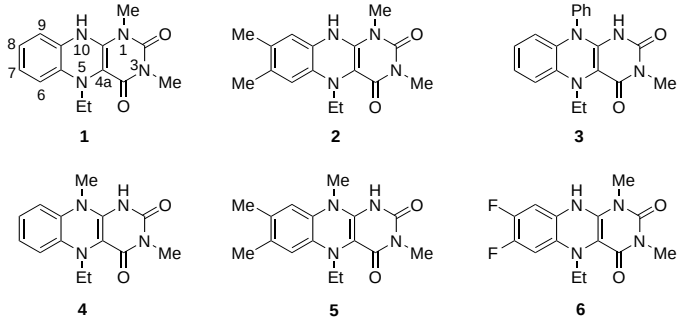
Abstract: Based on a previously discovered method for amine oxidations using flavins as catalysts and hydrogen peroxide as oxidant, a comparative kinetic study using NMR spectroscopy was undertaken with a series of flavins for amine and thioether oxidations. Included in this series is the newly prepared 7,8-difluoro-1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine. This study shows that flavins, which bear electron-donating groups on the aromatic ring and/or the *N*-10 position, are less active and are deactivated during the course of the reaction. Moreover, flavins that are alkylated at the *N*-1 position instead of the *N*-10 position and having either no substituents or electron-withdrawing groups on the aromatic ring, remain the most active and stable.

Keywords: flavins · homogeneous catalysis · hydrogen peroxide · oxidation

Introduction

The oxidation of organic substrates as for example amines and thioethers with stoichiometric flavin hydroperoxides has been known for more than two decades.[1] A more economical and environmentally friendly system with only catalytic amounts of flavin has so far been limited to a few publications involving the oxidation of secondary amines to nitrones,[2] sulfoxidations, [2, 3] and Baeyer–Villiger oxidation of selected substrates.[4] Only recently we discovered that flavin **1** could be used as catalyst in a mild and efficient oxidation of tertiary amines with hydrogen peroxide as terminal oxidant,[5] which also leads to a synthetically more viable reaction.

Because of the difference in catalytic activity of earlier employed flavins **2**–**5** compared with **1**,[1–5] we wanted to investigate if there was a correlation between the catalytic activity of these flavins and the substitution pattern and/or the electronic properties due to the substituents. Thus, a series of flavins (**1**–**6**) was prepared and employed in the oxidation of tertiary amines and thioethers. In addition to N oxidation,[5] the sulfoxidation is of current interest, since most methods for oxidation of thioethers to sulfoxides have several limitations.[6, 7]



Results and Discussion

Flavins **1**–**5** and the novel difluoro compound **6** were synthesized according to literature procedures,[4, 5a, 8, 9] and used as catalysts as described for the oxidation of tertiary amines.[5a] To observe conversion over a given time some reactions were followed by NMR spectroscopy, which also allows for initial rate determination based upon a pseudo-first order mechanism.[2]

Sulfoxidation with 1 as catalyst: We first studied the oxidation of a set of different thioethers to sulfoxides by H_2O_2 catalyzed by flavin **1** (Table 1). The results demonstrate the effectiveness and mildness of the new oxidation system. Only a small amount of catalyst **1** was necessary (1.8 mol%) and a minor excess of the final oxidant H_2O_2 (1.75 equiv) was used.[10] Methanol was chosen as a solvent and no inert reaction conditions such as dry solvents or an oxygen-free atmosphere were necessary.[1–3]

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry or from the author. Kinetic curves for the multiple addition experiments and a mass spectrum for **6** are available (four pages).

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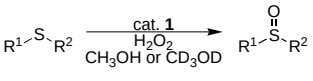
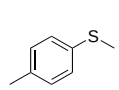
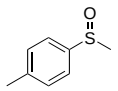
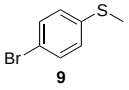
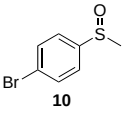
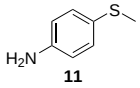
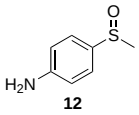
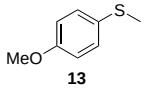
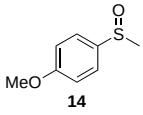
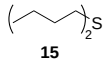
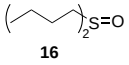
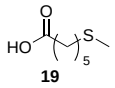
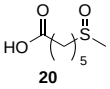
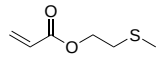
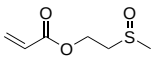
Table 1. Flavin-catalyzed sulfide oxidation.[a]



	Substrate	Product	mol % flavin	Time [min]	Conv./%[b] (yield/%)[c]	Rate enhancement[d]
1	 **7**	 **8**	1.83	60	100 (quant)	74:1 (7100:1)[e]
2	**7**	**8**	0.50	360[f]	99[g] (98)	n.d.
3	 **9**	 **10**	1.63	160	95.8	45:1 (4730:1)[e]
4	 **11**	 **12**	1.33	23	99.9	12:1 (1440:1)[e]
5	 **13**	 **14**	1.60	45	99.5	36:1 (3620:1)[e]
6	 **15**	 **16**	1.60	15	99 (quant)	12.5:1 (735:1)[e]
7	**15**	**16**	0.10	175	98.5	2:1 (2040:1)[e]
8	 **17**	 **18**	1.70	20	99[h]	n.d.
9	 **19**	 **20**	1.28	15	100 (quant)	n.d.
10	 **21**	 **22**	1.08	30	99.0	n.d.

[a] Substrate (0.223 mmol) was dissolved in methanol (600 μL, [D_4]MeOH for NMR measurement). Catalyst **1** (3–4 μmol) and H_2O_2 (40 μL, 30% aq. solution, 0.392 mmol) were added at 25 °C (no inert conditions). For the NMR experiments the tube was shaken well until a homogenous solution was obtained. [b] Determined by ^{1}H NMR spectra. [c] Isolated yield. [d] Describes the rate enhancement of catalyzed versus noncatalyzed reaction (see Experimental Section for details). In parenthesis the estimated ratio of reactivities of the catalytic flavin hydroperoxide and H_2O_2 is given (see [e]). [e] Estimated ratio of reactivities of the catalytic flavin hydroperoxide and H_2O_2, which is corrected for the amount of catalyst and amount of H_2O_2 to obtain an appropriate comparison of the two peroxides ({rate enhancement/amount catalyst)}·equiv. H_2O_2).[5] [f] Only 1.0 equiv H_2O_2 (30% in water) was used. [g] TON = 198. [h] With 2 equiv H_2O_2 no formation of 1,3-dioxide was detectable after 1 h.

As expected, aliphatic sulfides and electron-rich aryl alkyl sulfides are oxidized faster than electron-poor aryl alkyl sulfides (Table 1).[6, 7] It is noteworthy that no overoxidation was observed in any of the cases studied. Esters (e.g. **21**), acids (e.g. **19**), and alkenes (e.g. **21**) are also compatible with this oxidation system.[11] Other mild sulfoxidation methods such as catalytic MTO (methyltrioxorhenium) with H_2O_2 oxidize both the carbon–carbon double bond, as well as the sulfur of the thioether unit.[7e, 12] The aniline thioether **11** demonstrates, that deactivated amines are also compatible with this oxidation system. Only a quinone thioether could not be oxidized.[13] For dithiane **17** many procedures exist for its selective mono- and dioxidation, however, all of them have drawbacks such as the requirement of low temperature or strong oxidants.[14] The flavin/H_2O_2 system yields only the mono-oxide, even if two equivalents of hydrogen peroxide are employed.

Comparing the results in Table 1 with the previously reported results for N-oxidation,[5a] the rate enhancements are in general equally high for the S- and N-oxidation. Considering that the background reaction for dialkyl sulfides is fast, the rate enhancement achieved for such substrates is especially noteworthy. On the other hand, even though the background reaction for substrates such as diphenyl sulfide is very slow (11% conversion in four days), the catalyzed reaction (11% conversion in 160 min) results in a rate enhancement of approximately the same range as most other substrates (41:1 and 4280:1, respectively).

In addition, the reaction is not limited to the arbitrarily chosen amounts of catalyst and hydrogen peroxide. These amounts can be lowered to render an equally effective, albeit slower, system, which nevertheless gives full conversion (Table 1, entry 1 vs 2 and entry 6 vs 7).

As mentioned earlier, the solvent of choice was methanol. However, other polar solvents such as acetonitrile, acetone, *tert*-butanol, and DMSO work almost equally well, although with lower rates (Table 2). Methylene chloride works fine with urea hydrogen peroxide, whereas with aqueous H_2O_2 the reaction stops after about 25% conversion due to phase separation and extraction of the flavin intermediate into the aqueous phase. Sodium peroxide as terminal oxidant gave almost no conversion.

Catalytic amine- and sulfide-oxidations have been described in the literature only for *N*,*N*-3,10-dimethylated flavin derivatives such as **4** and **5**.[1–3] Catalysts based on such a substitution pattern result only in low rate enhancements, whereas the *N*,*N*-1,3-dimethylated flavin **1** is a highly active catalyst as shown above for sulfoxidations and previously for amine oxidations.[5a] These findings led us to investigate the possible reasons for this difference in activity.

Relative rates of different flavins in catalytic N- and S-oxidation: To gain further insight into the influence of the substitution pattern of flavins on their catalytic activity, flavins **1**–**6** were prepared and compared in the H_2O_2 oxidation of tertiary amines (Figure 1) and sulfides (Figure 2). The new 7,8-difluoro derivative **6** was synthesized according to Scheme 1. Attempts to synthesize the 7,8-dichloro derivative of **1** failed under the reductive alkylation conditions employed for preparing such reduced flavin structures.[5a] Flavins bearing other electron-withdrawing substituents such as a nitrile would most likely fail under these conditions as well.[15]

0947-6539/01/0701-0298 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 1

Table 2. Solvents and oxidants in oxidation of **7**.

Oxidant	Solvent	mol% flavin **1**	Time [min]	Conv. [%][a]
30% H_2O_2	CD_3OD	–	60	7.5
30% H_2O_2	CD_3OD	1.6	55	100
30% H_2O_2	CD_3CN	1.7	60	76
30% H_2O_2	[D_6]acetone	1.7	60	23
30% H_2O_2	*t*BuOH	1.5	60	60
30% H_2O_2	[D_6]DMSO	2.9	60	14
30% H_2O_2	CD_2Cl_2	1.7	20[b]	26
H_2O_2·urea	CD_2Cl_2	1.7	60	100
H_2O_2·urea	MeOH	1.8	60	91
H_2O_2·urea	MeOH/H_2O (20:1)	1.7	60	100
H_2O_2·urea	abs. MeOH[c]	1.6	60	100
Na_2CO_3·1.5 H_2O_2	MeOH	1.8	60	13

[a] Conversion to sulfoxide **8**. [b] Reaction stopped after ca. 25% conversion due to phase separation and extraction of the flavin intermediate into the aqueous phase. [c] Methanol was dried over activated molecular sieves with a stream of argon passing through the solvent for 1 h.

A general trend (Figures 1 and 2) is that *N*,*N*,*N*-1,3,5-trisubstituted flavins (**1**, **2**, and **6**) show significantly higher activity than the corresponding *N*,*N*,*N*-3,5,10-trisubstituted analogues (**3**, **4**, and **5**). As can also be seen from the Figures, flavin **1** is an efficient catalyst with high initial rates resulting in full substrate conversions. Catalyst **6** gave full conversion within about 1 h, although the initial rate was slightly lower than that of **1**. Flavin **2** showed the same high initial rate as catalyst **1** in the N-oxidation, but the activity is lost during the course of the reaction. A similar deactivation of **2** was also observed in the S-oxidation. A likely explanation for the deactivation of **2** is that the electron-donating groups on the aromatic ring (7,8-dimethyl) make it electron rich enough to become sensitive towards oxidative degradation. Nevertheless, flavin **2** results in a much higher substrate conversion than catalysts **3**–**5**. Compounds **3**–**5** differ from **1** in that they have electron-donating substituents on the nitrogen in position 10 (i.e., they are *N*,*N*,*N*-3,5,10-trisubstituted) and when employed as catalysts they result in only a slightly enhanced activity over the noncatalyzed reaction. The very low activity of **5** actually seems to be the result of a disadvantageous substituent combination: electron-donating groups on the aromatic ring and trialkylation at nitrogens in positions 3, 5, and 10. Flavin **4**, which differs from **5** only in that the 7,8-dimethyl groups have been removed, was a better catalyst than **5**.

The mechanism of the flavin-catalyzed N- and S-oxidations is given in Scheme 2. Initial preactivation by molecular oxygen produces the flavin hydroperoxide **I**.[16] Transfer of the electrophilic oxygen to the substrate via **II** gives the 4a-hydroxy intermediate **III**. Elimination of the hydroxide ion from **III** gives **IV**, which can react with hydrogen peroxide to regenerate flavin hydroperoxide **I**. Taking into consideration the reaction mechanism in Scheme 2 and the fact that the oxygen transfer (**I** → **II** → **III**) to the substrate is most likely the rate-limiting step,[5a] electron-donating groups on the aromatic ring seem to stabilize the peroxo intermediate **I**, thus making it less reactive.[17] Consequently, a flavin with two

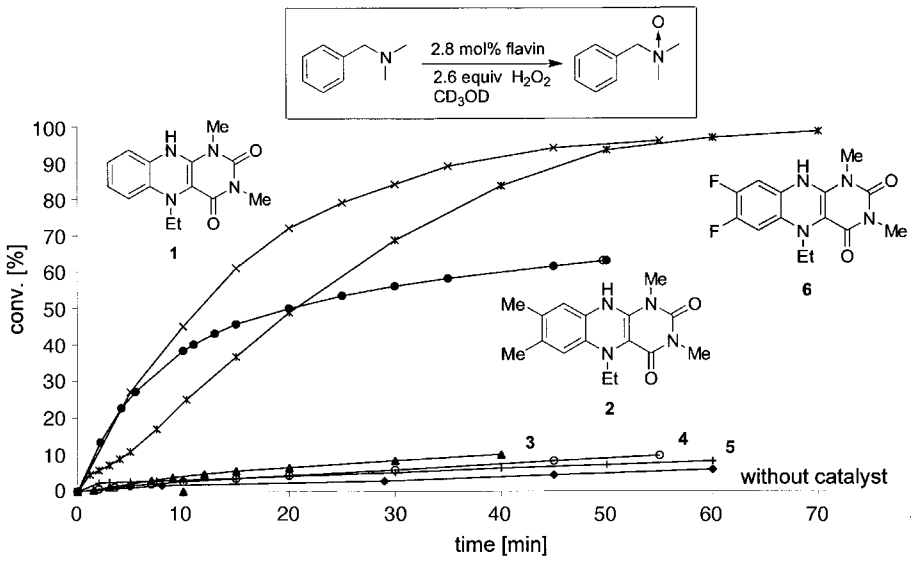


Figure 1. Comparison of flavins in the N-oxidation of *N*,*N*-dimethyl benzylamine.

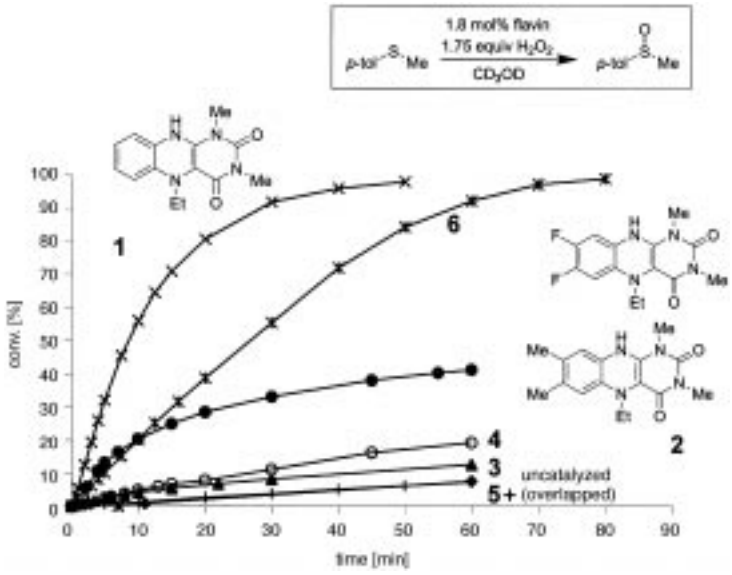
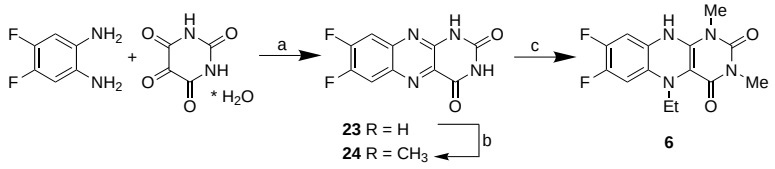
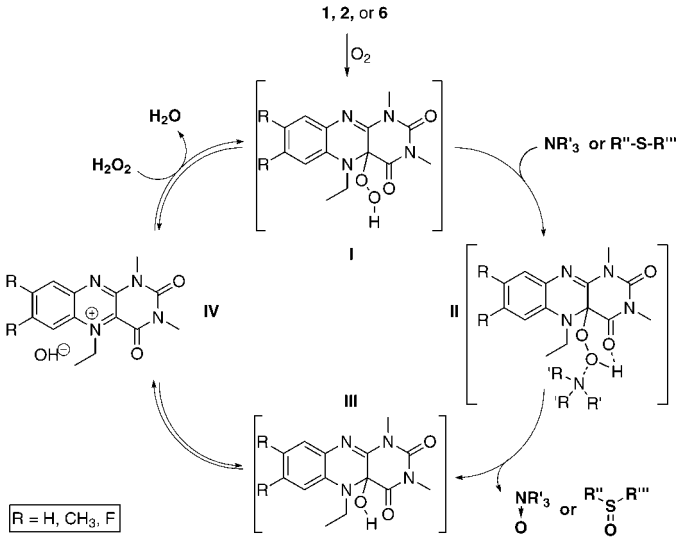


Figure 2. Comparison of flavins in the S-oxidation of **7**.



Scheme 1. Synthesis of **6**. a) H_3BO_3, HOAc; b) K_2CO_3, MeI, DMF, 50 °C; c) H_2, Pd/C, CH_3CHO, HCl, $EtOH/H_2O$.

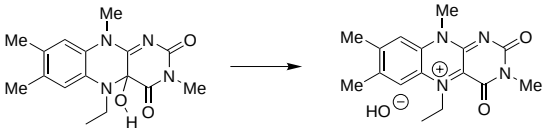


Scheme 2. Proposed catalytic cycle.

electron-withdrawing substituents in the 7- and 8-positions and methylated nitrogens in positions 1 and 3 is expected to result in increased reaction rates. When the 7,8-difluoro flavin **6** was employed as catalyst, this flavin did indeed show different properties compared with all other catalysts. There is a significant induction period, presumably due to the fact that the flavin precursor is less reactive towards activation by molecular oxygen.[18] After this initial phase though, the reaction proceeds quite rapidly.

If more substrate and oxidant are added at the end of the reaction, the subsequent reaction rates are as fast as in the first run in both the N- (Figure 1) and S oxidation (Figure 2). This was demonstrated for catalyst **6** in the S-oxidation of 4-methylphenyl methylsulfide (**7**) and N oxidation of *N*,*N*-dimethylbenzylamine and for catalyst **1** in S-oxidation of 4-methylphenyl methylsulfide (**7**) (see Supporting Information). The fact that **6** is obviously as stable as **1** in contrast to all other flavin catalysts supports the hypothesis of electron-donating groups having a negative effect on the catalytic properties. The reason why it does not show an overall higher reaction rate could be due to a change in the rate-limiting step. With **6**, the reoxidation of **III** → **I**, that is, **IV** → **I**, (Scheme 2) should be slower compared with that of **1**. If **I** turns into a more powerful oxidant (higher oxidation potential) because of the electron-withdrawing groups, it should be more difficult to reoxidize the corresponding reduced form **IV** back to **I**. Thus, the reoxidation may become the rate-determining step and there would not be full equilibrium between **IV** and **I**. Even if the reoxidation does not become the rate-limiting step the increased oxidation potential may shift the equilibrium between **I** and **III** so that the concentration of **I** becomes very low.[19] Consequently, even though step **I** → **II** may have become faster for **6**, a lower concentration of **I** will result in an overall reaction rate which is less than one would expect by just considering the oxidation potential of **I**.

The flavin hydroperoxide derived from O_2 and **5**, analogous to **I**, has been previously studied by Bruice[1c–e] and shown to be between 5×10^3 and 10^4 times as active as hydrogen peroxide in stoichiometric N oxidations. This rate enhancement is of the same order of magnitude as that estimated for the hydroperoxide of **1**.[5a] An interesting question therefore is why **5** does not work well in the catalytic reaction. To explain this one would have to assume that the reduced form **IIIb** (analogous to **III**) is not efficiently recycled to flavin hydroperoxide because of degradation and/or slow kinetics. It is likely that the slow step in this recycling is the dissociation of the hydroxy group to give the charged species **IVb**. This is supported by results by Murahashi,[2] who found that the rate-limiting step in S- and N oxidation with 7,8-dimethyl-*N*,*N*-3,10-dimethyl-flavin corresponding to **5**[20] is the elimination of the hydroxy ion from the 4a-hydroxy intermediate **IIIb** to give a cationic isoalloxazine (**IVb**). In fact, for the oxidation of a secondary amine the rate constant for step **IIIb** → **IVb** was 3600 times smaller than the rate constant for the O transfer from flavin hydroperoxide to nitrogen.[20] For the *N*,*N*-1,3-dimethylated flavins (**1**, **2**, and **6**) the step **III** → **IV** (Scheme 2) should be faster due to formation of a fused aromatic system (alloxazine).[21] Thus, the higher catalytic activity of **1**, **2**, and **6** would be due to a more efficient recycling of **III** to **I** (Scheme 2).



Conclusion

In summary, we have extended the use of our simple flavin/hydrogen peroxide system to the oxidation of thioethers to sulfoxides, which are accessible in short reaction times in quantitative yields. The comparative kinetic study of different flavin catalysts has shown that those based on the nitrogen substitution of the natural riboflavin with substituents on *N*-3 and *N*-10 are less active catalysts than their corresponding *N*,*N*-1,3-dialkylated counterparts. Furthermore, it was shown that flavins, which are alkylated at positions *N*-1 and *N*-3, having either no substituents such as **1** or electron-withdrawing groups such as **6** on the aromatic ring, result in highly efficient catalysts. The higher activity of *N*,*N*,*N*-1,3,5-trisubstituted flavins (alloxazine system, **1**, **2**, and **6**) over their *N*,*N*,*N*-3,5,10-trisubstituted counterparts (isoalloxazine sys-

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tem, **3**–**5**) is thought to be due to the higher rate of dissociation of the hydroxy group from the 4a-hydroxy intermediate of the former flavins to give an alloxazine (**III**). Flavins **1** and **6** are each accessible in only three steps with their precursors being much easier to handle than those bearing substituents at the *N*-10 instead of the *N*-1 position.[22] These two flavins are therefore the preferred choice of catalyst for the described mild and efficient N- and S oxidation. Finally, these results are also important in view of developing more efficient chiral flavin catalysts,[3] where a suppression of the relatively fast background reaction is essential.

Experimental Section

General: ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian 300 MHz and 400 MHz Gemini instruments. Chemical shifts are reported in ppm using residual solvent as internal standard.[23] IR spectra were measured on a Perkin–Elmer Spectrum One FTIR. MS spectra were measured on a Thermo Quest GCQ plus via direct inlet. Elemental analyses were performed by Analytische Laboratorien, Lindlar (Germany). Reagents were purchased from Lancaster or Aldrich, except 1,2-diamino-4,5-difluorobenzene (Apollo). Deuterated solvents were purchased from Cambridge Isotope Laboratories, except [D$_6$]acetone (Sigma) and CD$_3$CN (Dr. Blaser AG, Basel). 6-(Methylthio)hexanoic acid (**19**) was prepared according to Vederas and Liu.[24] Flavins **2**–**5** have all been previously described and were synthesized accordingly.[4, 8, 9] Flavin **1** was prepared according to Bergstad and Bäckvall.[5a] For the final work-up of **1**–**5**, the method described below for compound **6** was used.

7,8-Difluoroalloxazine (23): The procedure described by Bergstad and Bäckvall was followed[5a] using diamino-difluorobenzene (500 mg, 3.47 mmol) which gave a pale yellow powder (868 mg, 86 %). M.p. $>280\,^{\circ}$C;[25] ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 11.99$ (br, 1H; NH), 11.77 (br, 1H; NH), 8.27 (dd, $J = 8.4$, 10.8 Hz, 1H; arom H), 7.97 (dd, $J =$ 8.0, 11.6 Hz, 1H; arom H); ^{13}C NMR ([D$_6$]DMSO, 75.4 MHz): $\delta = 188.7$, 160.6, 150.5, 147.8, 139.0 (dd, $J = 444.8$, 12.2 Hz), 134.7 (dd, $J = 434.0$, 12.0 Hz), 116.6 (d, $J = 16.8$ Hz), 113.7 (d, $J = 18.3$ Hz); ^{19}F NMR ([D$_6$]DMSO, 376.3 MHz): $\delta = -126.8$ (ddd, $J = 20$, 11, 9 Hz, 1F), -133.9 (ddd, $J = 20$, 11, 9 Hz, 1F); MS (EI): m/z (%): 251 (15), 250 (100) $[M]^+$; IR (KBr): $\tilde{\nu} = 3564$ (m), 3478 (m), 3073 (s), 2932 (m), 2840 (s), 1747 (vs), 1724 (vs), 1685 (vs), 1635 (m), 1589 (s), 1578 (s), 1513 (vs), 1497 (s), 1446 (m), 1404 (m), 1354 (s), 1287 (s), 1245 (s), 1228 (s), 1159 (m), 1041 (w), 892 (s), 865 (m), 844 (m), 811 (m), 802 (m), 748 (m), 690 (w), 658 (m), 638 (w), 592 (m), 528 (s), 497 (s), 455 cm^{-1} (m); elemental analysis calcd (%) for C$_{10}$H$_4$F$_2$N$_4$O$_2$ (250.2): C 48.01, H 1.61; found C 47.01, H 1.71.

7,8-Difluoro-1,3-dimethylalloxazine (24): The procedure described by Bergstad and Bäckvall was followed,[5a] using 7,8-difluoroalloxazine (717 mg, 2.86 mmol) and yielded a yellow solid (785 mg, 98.5 %). M.p. 197 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 8.08$ (dd, $J = 8.0$, 9.6 Hz, 1H; arom H), 7.77 (dd, $J = 7.6$, 10.4 Hz, 1H; arom H), 3.80 (s, 3H; N-CH$_3$), 3.60 (s, 3H; N-CH$_3$); ^{13}C NMR (CDCl$_3$, 75.4 MHz): $\delta = 159.1$, 155.0 (dd, $J =$ 263.2, 16.1 Hz), 151.7 (dd, $J = 257.2$, 16.0 Hz), 150.2, 145.4, 141.1 (d, $J =$ 12.1 Hz), 136.8 (d, $J = 10.7$ Hz), 129.5, 115.9 (dd, $J = 17.5$, 2.3 Hz), 113.3 (d, $J = 18.3$ Hz), 29.7, 29.3; ^{19}F NMR (CDCl$_3$, 376.3 MHz): $\delta = -122.6$ (ddd, $J = 18.3$, 10.7, 7.6 Hz, 1F), -129.6 (ddd, $J = 18.3$, 10.7, 7.6 Hz, 1F); MS (EI): m/z (%): 280 (7), 279 (39), 278 (76) $[M]^+$, 167 (100); IR (KBr): $\tilde{\nu} =$ 3550 (m), 3476 (m), 3413 (s), 3044 (m), 2962 (w), 2924 (w), 1727 (s), 1680 (vs), 1637 (m), 1564 (s), 1513 (m), 1487 (s), 1432 (m), 1414 (s), 1379 (s), 1360 (m), 1299 (s), 1248 (s), 1198 (m), 1174 (m), 1101 (w), 1066 (w), 982 (w), 913 (m), 858 (m), 832 (w), 810 (w), 764 (vw), 745 (w), 731 (w), 645 (w), 615 (m), 568 (w), 489 (w), 478 (m), 459 cm^{-1} (m); elemental analysis calcd (%) for C$_{12}$H$_8$F$_2$N$_4$O$_2$ (278.2): C 51.81, H 2.90; found C 52.05, H 3.01.

7,8-Difluoro-1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine (6): A modified procedure from Bergstad and Bäckvall was followed,[5a] where a large excess of solid sodium dithionite instead of a dithionite solution was used during the work-up. Notably the product is highly air sensitive in solution and a rapid work-up is necessary. This demands that all necessary equipment must be assembled and accessible in advance. Reaction with 7,8-difluoro-1,3-dimethylalloxazine (600 mg, 2.15 mmol) yielded a yellow-green solid (65 mg, 10 %). Due to its oxygen sensitivity, the NMR sample of **6** was prepared under argon in degassed CDCl$_3$ having a layer of aqueous (D$_2$O) Na$_2$S$_2$O$_4$ on top; a MS spectra could also be obtained[26] using this solution directly after preparation. ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 6.71$ (dd, $J = 7.5$, 11.4 Hz, 1H; arom H), 6.38 (dd, $J = 7.2$, 10.2 Hz, 1H; arom H), 5.42 (br, 1H; NH), 3.45 (s, 3H; N-CH$_3$), ≈ 3.44 (overlap; q, $J = 7.2$ Hz, 2H; CH$_2$), 1.16 (t, $J = 6.9$ Hz, 3H; CH$_3$); ^{19}F NMR (CDCl$_3$, 282.2 MHz): $\delta =$ -142.2 (m, 1F), -143.7 (m, 1F); MS (EI): m/z (%): 309 (19), 308 (77) $[M]^+$, 307 (91), 279 (100).

General procedure for the kinetic study: The conversion rates of the reactions performed in the presence or absence of flavin catalyst were determined by integration of the corresponding ^{1}H NMR signals for the sulfide and product sulfoxide. For most compounds the R–S*Me* signals were integrated; however, in a few cases C*H*SMe or C*H*$_2$SMe signals were integrated due to better separation from other peaks. The rate enhancement was calculated by division of the rate at low conversion (≤ 10 %), for the catalyzed reactions usually after one minute reaction time.

A) With flavin catalyst

4-Methylphenyl methyl sulfoxide: Flavin **1** (1.06 mg, 3.89 μmol) was added to a solution of 4-methylphenyl methylsulfide (30 μL, 0.223 mmol) in [D$_4$]MeOH (600 μL) in an NMR tube. The tube was shaken well, followed by the addition of H_2O_2 (40 μL, 30 % aq. solution, 0.392 mmol) to the solution and the time measurement was started. If shaken well again, all of **1** dissolved immediately to give a yellow solution. The reaction was followed by ^{1}H NMR spectroscopy (usually at 1–2 min intervals for the first 10 min, then 5 min intervals for another 20 min and 10 min intervals until completion).[27] The NMR data for **8** was in accordance to the literature.[28]

Oxidation of other thioethers: The reactions were followed by ^{1}H NMR spectra for 20–60 min (1–2 min intervals for the first 5–10 min, thereafter 5 min intervals).[29] The NMR data of the products were in accordance to literature: 1-methanesulfinyl-4-methoxy-benzene (**14**),[28] 1-bromo-4-methanesulfinyl-benzene (**10**),[30] 4-methanesulfinyl-aniline (**12**),[31] 1,3-dithiane-1-oxide (**18**),[32] dibutylsulfoxide (**16**),[28] diphenylsulfoxide,[28] 6-(methylsulfinyl)hexanoic acid (**20**).[24]

B) Without flavin catalyst

4-Methylphenyl methyl sulfoxide: H_2O_2 (40 μL, 30 % aq. solution, 0.392 mmol) was added to a solution of **7** (30 μL, 0.223 mmol) in [D$_4$]MeOH (600 μL) in an NMR tube. The reaction was monitored immediately by ^{1}H NMR for 24 h (77 % conversion). The NMR data of product **8** was in accordance to literature data.[28]

Oxidation of other thioethers: The reactions were followed for 60–180 min for comparison and initial rate determination in connection with the catalyzed reactions. For diphenylsulfide the reaction was followed for 5 d (14 % conversion).

General procedure for preparation of sulfoxides (4-methylphenyl methyl sulfoxide): Flavin **1** (1.06 mg, 3.89 μmol) was added to a solution of 4-methylphenyl methylsulfide (30 μL, 0.223 mmol) in MeOH (600 μL), followed by the addition of H_2O_2 (40 μL, 30 % aq. solution, 0.392 mmol) and stirred for one hour. Alternatively the reaction mixture from the NMR experiments can be used and submitted to work-up as follows: A small amount of dithionite (ca. 10 mg) was added and the mixture diluted with diethyl ether (20 mL). Washing with water and drying over sodium sulfate gave a white solid (31.5 mg, >99 %). The NMR data of product **8** was in accordance to the literature.[25]

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