

Enantioselective Oxidation of Sulphides with Chiral 4a-Hydroperoxyflavin

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N(5)-Ethylated chiral flavinophane (+)-(1) acted as an asymmetric, autorecycling catalyst for mono-oxygenation of methyl aryl sulphides in the presence of excess H₂O₂.

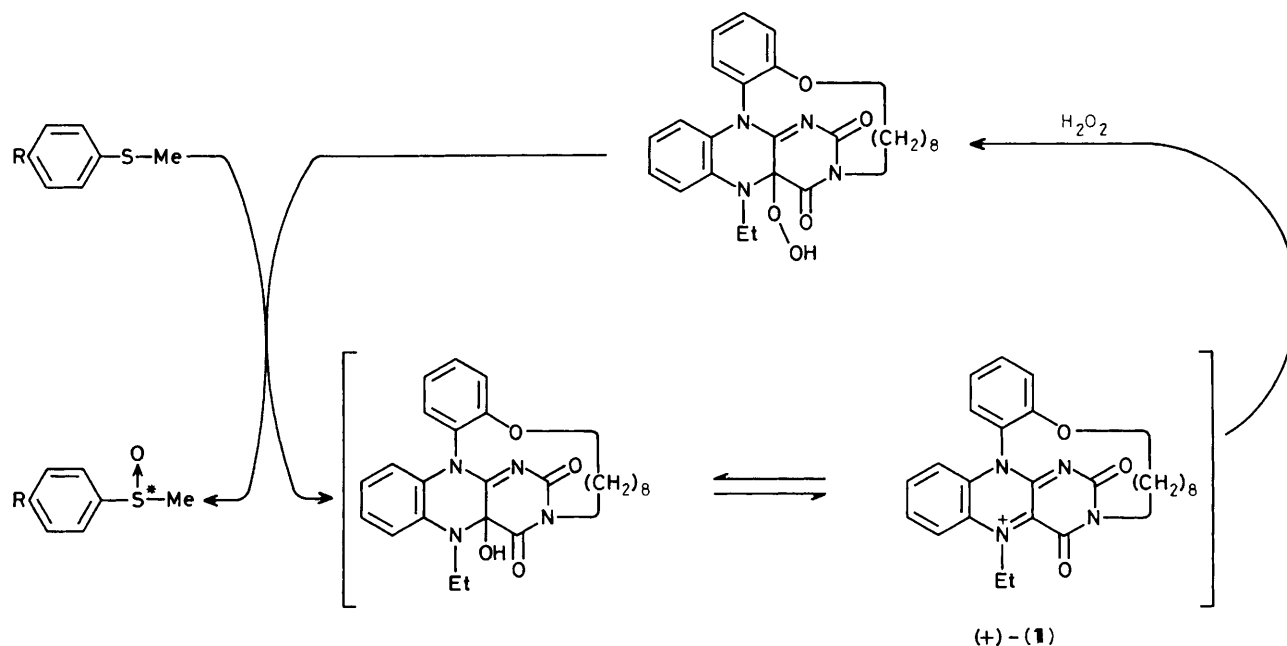
Biological oxygenation is mediated either by cytochromes P-450 or by flavin-dependent oxygenases. Several chemical models for cytochromes P-450 have been reported so far.¹ More recently, much of the research effort has been directed towards regioselective or asymmetric oxygenation of sub-

strates.¹⁻⁵ On the other hand, chemical models for flavin-dependent oxygenases have been reported by Bruice,⁶⁻⁹ Rastetter,^{10,11} and others.^{12,13} Bruice⁶⁻⁹ employed *N*(5)-ethylflavinium derivatives while Rastetter^{10,11} employed flavin *N*(5)-oxides. To the best of our knowledge, however,

Table 1. Asymmetric oxygenation of methyl aryl sulphides.

Run	[(1)]/mM	[<i>p</i> -R-C ₆ H ₄ SMe]/mM	H ₂ O:Me ₃ OH ^a	% Yield ^b	% e.e.	Configuration
1	1.2	R = H	11.0	0:100	360	(<i>R</i>)-(+)
2	1.3	R = H	11.0	15:85	400	(<i>R</i>)-(+)
3	1.2	R = H	11.0	33:67	800	(<i>R</i>)-(+)
4	1.2	R = Me	9.9	33:67	800	(<i>R</i>)-(+)
5	1.1	R = Bu ^t	7.6	29:71	220	(+) ^c
6	1.3	R = CN	10.0	33:67	24	(+) ^c

^a Ratio by volume. ^b Chemical yields were calculated on the basis of (+)-(1). ^c The absolute configurations are not known.

**Scheme 1**

there exists no successful precedent for asymmetric oxygen transfer from flavins. We recently synthesised new cyclic flavins with planar chirality (*i.e.*, chiral flavinophanes).^{14,15} It occurred to us that the *N*(5)-ethylflavinium derivative (1) may transfer mono-oxygen to the substrates in an asymmetric manner. We therefore tried the asymmetric oxidation of methyl aryl sulphides to the sulfoxides in the presence of H₂O₂.¹⁶

Compound (+)-(1) was synthesised from (+)-9'-oxa-10',11'-benzo[11](3,10)-isoalloxazinophane¹⁵ according to the method of Ghisla *et al.*¹⁷ The product (perchlorate salt; m.p. 198–200°C) was identified by i.r., n.m.r., and u.v.-visible spectra.¹⁷ The water-methanol mixed solution (15 ml) containing (+)-(1) and methyl aryl sulphide was stirred at –20°C in the dark. To this solution 2.5 µl of 35% H₂O₂ was added once a day. After 5 days (total amount 12.5 µl, [H₂O₂] = 9.6 mM), the solution was extracted with dichloromethane. After concentration *in vacuo*, the reaction mixture was subjected to a t.l.c. separation (silica gel chloroform).[†] The chemical yield and enantiomeric excess (e.e.) of the product (methyl aryl sulfoxide) were determined by the n.m.r.

[†] The sulfoxides slightly racemised (2% e.e.) during the t.l.c. separation.

method: in CDCl₃, the methyl signals of methyl aryl sulfoxide appeared separately in the presence of (*R*)-(+)-1,1'-bi-2-naphthol, the higher magnetic-field one being attributed to the (*R*)-(+)-isomer (see footnote to Table 1). The e.e. was determined from the integral intensity of each peak while the chemical yield was determined by comparing the integral intensity with that of (*R*)-(+)-1,1'-bi-2-naphthol. The results are summarised in Table 1

It is seen from Table 1 that (+)-(1) acts as an asymmetric, autorecycling oxygenation catalyst: the chemical yields far exceed 100% and the produced sulfoxides have the (*R*)-(+)-configuration. In the absence of (+)-(1), the sulphides were scarcely oxygenated by H₂O₂ (the yields of the sulfoxides were <1% at –20°C in the dark).

Apparently, the oxygenation has an electrophilic character because the chemical yield for methyl *p*-cyanophenyl sulphide is extremely low. Interestingly, both the chemical and the optical yield increase with increasing water concentration in the solvent: the highest enantiomeric excess (65.4% e.e.) is observed for methyl *p*-tolyl sulphide. The chemical yield of 800% [produced sulfoxide/(+)-(1) in feed] observed for runs no. 3 and 4 means that H₂O₂ added to the reaction system all reacted with the sulphides.

The foregoing findings suggest that (+)-(1) has a novel character as an asymmetric, autorecycling oxygenation cat-

alyst. This becomes possible because the planar chirality of (+)-(1) is firmly maintained through the oxygenation cycle. In fact, racemisation of (+)-(1) did not occur under the present reaction conditions. Therefore, this is a novel example of chiral multiplication achieved in the flavin-mediated mono-oxygenation system.

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