# Asymmetric Oxidation of Sulfides Catalysed by an Iron Complex of $C_2$-Chiral Strapped Porphyrin as a Conceptually New P-450 Model Catalyst

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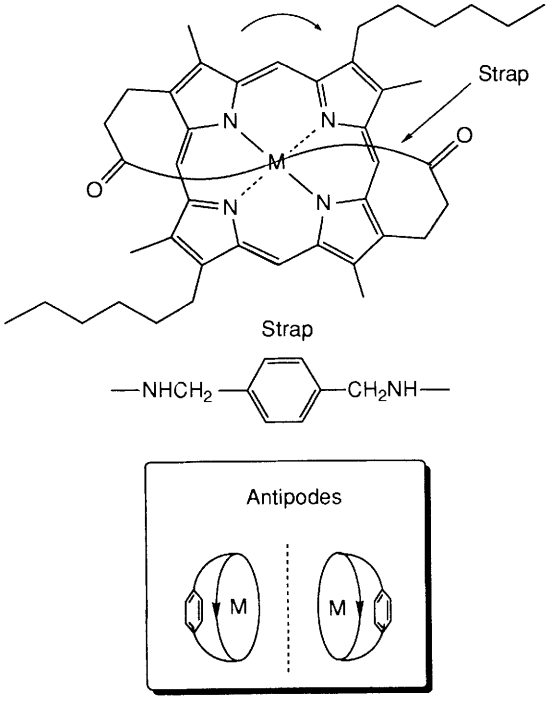
Asymmetric oxidation of aryl sulfides by iodosobenzene has been achieved using the novel iron porphyrin catalysts derived from the antipodes of a $C_2$-chiral 1,4-xylylene-strapped porphyrin, affording the corresponding sulfoxides in 18–71% enantiomeric excess.

In relation to the asymmetric oxygen transfer mediated by cytochrome P-450[1] and from a synthetic viewpoint, various chiral metalloporphyrin catalysts have been reported,[2] which bear chiral auxiliaries linked to achiral porphyrin moieties, and are intended to mimic the possible function of the chiral protein molecule in asymmetric induction. Very recently, we have exploited conceptually new chiral metal complexes of a strapped porphyrin **1**, which has no chiral substituents on the porphyrin moiety but has diastereotopic porphyrin faces. The porphyrin ligand of **1** was derived from dihexyldeutero-

**Table 1** Asymmetric oxidation of sulfides catalysed by **1**-FeCl[a]

| Run | Catalyst **1**-FeCl | Sulfide (ArSR) Ar | R | $[Im]_0$/$[Catalyst]_0$ | $T$/°C | $t$/h | Turnover number[b] | E.e. (%)[c] | Config.[c,d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | (+) | Ph | Me | 0 | −43 | 2.0 | 67 | 0 | — |
| 2 | (+) | | | 600 | −43 | 2.0 | 142 | 43 | (*S*) |
| 3 | (−) | | | 100 | −43 | 3.0 | 108 | 33 | (*R*) |
| 4 | (−) | | | 600 | −43 | 2.0 | 150 | 33 | (*R*) |
| 5 | (−) | *p*-$MeC_6H_4$ | Me | 100 | −43 | 2.0 | 92 | 23 | (*R*) |
| 6 | (−) | *p*-$BrC_6H_4$ | Me | 0 | −23 | 2.5 | 178 | 0 | — |
| 7 | (−) | | | 100 | −23 | 3.5 | 30 | 36 | (*R*)[e] |
| 8 | (−) | *p*-$NO_2C_6H_4$ | Me | 100 | −43 | 4.5 | 36 | 40 | (*R*) |
| 9 | (−) | $C_6F_5$ | Me | 0 | −15 | 1.5 | 15 | 36 | (*S*) |
| 10 | (−) | | | 100 | −15 | 1.5 | 55 | 30 | (*S*) |
| 11 | (+) | *p*-$Me(O)HNC_6H_4$ | Me | 0 | −15 | 1.5 | 107 | 23 | (*R*) |
| 12 | (+) | | | 600[f] | −15 | 2.0 | 60 | 18 | (*R*) |
| 13 | (−) | Ph | Et | 100 | −20 | >48.0 | <2 | 18 | (*R*) |
| 14 | (+) | Ph | $CH_2OMe$ | 0 | −43 | 2.0 | 30 | 0 | — |
| 15 | (+) | | | 100 | −43 | 2.0 | 40 | 71 | (*R*) |
| 16 | (+) | | | 600 | −43 | 2.0 | 22 | 70 | (*R*) |
| 17 | (−) | | | 600 | −43 | 2.0 | 20 | 67 | (*S*) |

[a] In $CH_2Cl_2$ under nitrogen using 900 μmol of sulfide, 360 μmol of PhIO and 1.8 μmol of **1**-FeCl. [b] Calculated from the yield of sulfoxide (GC or gravimetry after isolation) and the amount of **1**-FeCl. [c] By $^1H$ NMR spectroscopy in the presence of (*R*)-1,1′-bi-2-naphthol (see: ref. 5). [d] The configurations in parentheses were estimated by analogy with the NMR spectral pattern of optically active methylphenyl sulfoxide. [e] By polarimetry in acetone (P. Pitchen and H. B. Kagan, *Tetrahedron Lett.*, 1984, 1049). [f] 1-Methylimidazole was used.

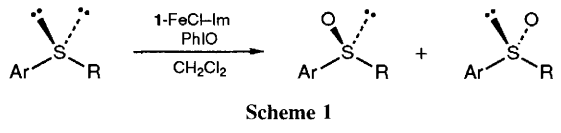



**1**

porphyrin II dimethyl ester {2,12-bis[2′-(methoxycarbonyl)-ethyl]-3,8,13,18-tetramethyl-7,17-dihexylporphine}, which is $C_{2h}$ symmetry and has enantiotopic faces. Upon introducing a strap on either side of the two faces, the porphyrin should be chiral. The antipodes of this chiral strapped porphyrin have been resolved by HPLC.[3]

In the present communication, we report results of the asymmetric oxidation of aryl sulfides by using the chloroiron complex of **1**(**1**-FeCl)† as chiral catalyst (Scheme 1).[4]

† The Dolphin's method (S. David, B. R. James and D. Dolphin, *J. Inorg. Biochem.*, 1988, **28**, 125) was partly modified to prepare **1**-FeCl. The crude product was recrystallized from $CH_2Cl_2$–hexane, affording **1**-FeCl as reddish-brown crystals in 52% yield. $\lambda_{max}$ ($CHCl_3$) 376, 503, 534 and 635 nm.




**Scheme 1**

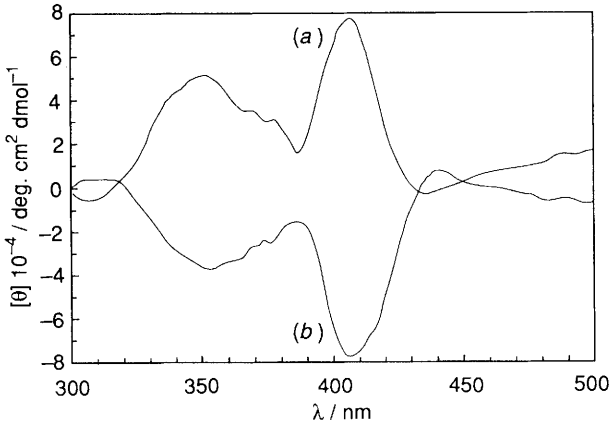



**Fig. 1** CD spectra of the antipodes of **1**-FeCl [(+)-**1**-FeCl (*a*) and (−)-**1**-FeCl (*b*)] in $CHCl_3$ at 25 °C

The antipodes of the catalyst showed perfect mirror-image circular dichroism (CD) spectra of each other [(*a*) and (*b*), Fig. 1], where positive and negative CD bands were clearly observed at 352 and 406 nm. Thus, the antipodes providing the spectra (*a*) and (*b*) are denoted as (+)-**1**-FeCl and (−)-**1**-FeCl, respectively.

Oxidation of aryl sulfides with the chiral catalyst proceeded enantioselectively under appropriate conditions, where the essential effect of imidazole was observed. A typical example is given below: To a 20 $cm^3$ Schlenk flask containing biphenyl (13 mg, GC standard) and imidazole (1080 μmol), under nitrogen were successively added thioanisole (900 μmol) and a $CH_2Cl_2$ solution of (+)-**1**-FeCl (1.8 μmol $cm^{-3}$), and the solution was degassed by freeze-to-thaw cycles. Then, iodosobenzene (PhIO) (360 μmol, oxidant) was added to the flask thermostated at −43 °C. The reaction proceeded to give the corresponding sulfoxide in the yields, as determined by GC

based on the amount of PhIO, of 24 and 71% [turnover number with respect to (+)-**1**-FeCl: 142] in 0.5 and 2.0 h, respectively (run 2, Table 1). After column chromatography, methyl phenyl sulfoxide with the enantiomeric excess (e.e.) of 43% (*S*), as determined by $^1$H NMR spectroscopy (see: footnote for Table 1),[5] was obtained in 68% yield, as determined by gravimetric analysis. When the catalyst with the opposite configuration [(−)-**1**-FeCl)] was used, the sulfoxide with the inverted configuration (*R*) was formed (runs 3 and 4). However, in the absence of imidazole, the enantioselectivity of the reaction virtually disappeared, giving the racemic sulfoxide in 34% yield (run 1).

Asymmetric oxidation of other aryl sulfides such as *p*-methyl-, *p*-bromo- and *p*-nitro-thioanisoles (runs 5, 7 and 8), and ethyl and methoxymethyl phenyl sulfides (runs 13, 15–17) also took place in the presence of imidazole, where the highest enantioselectivity was observed in the case of methoxymethyl phenyl sulfide. Use of (+)-**1**-FeCl as catalyst in the presence of 100 or 600 equiv. of imidazole resulted in the predominant formation of (*S*)-methoxymethyl phenyl sulfoxide in 70–71% e.e, while the sulfoxide with the (*R*)-configuration was obtained in a comparable e.e. (67%) when (−)-**1**-FeCl was the catalyst. In the absence of imidazole, such a high enantioselectivity disappeared completely (run 14), again indicating the important role of imidazole in asymmetric induction. In sharp contrast, the asymmetric oxidation occurred even in the absence of imidazole when the substrate carrying an electron-deficient phenyl ring (run 9) or an amide group with a hydrogen-bonding capability (run 11) was oxidized.

The spectral changes upon titration of a $CH_2Cl_2$ solution of racemic **1**-FeCl with imidazole were linear with the concentration of imidazole to the first power, indicating that only one imidazole molecule can bind to **1**-FeCl. The binding constant was $4.3 \times 10^2$ dm$^3$ mol$^{-1}$ at 25 °C.

The catalyst (**1**-FeCl) has two chemically inequivalent, diastereotopic faces with different steric requirements for the access of substrates and/or oxidants. In the absence of imidazole, the oxygen-transfer reaction is considered to occur predominantly on the unstrapped, open face because of low steric hindrance. However, when imidazole is present, the unstrapped face of the catalyst is possibly blocked by the coordination with imidazole, so that the oxygen-transfer reaction is considered to occur predominantly on the sterically hindered strapped face with a large steric requirement.

The protohaem, the active site of cytochrome P-450, is coordinated by a cysteine thiolate group of the haemoprotein, and has diastereotopic faces originating from the enantiotopic structure of the ligand protoporphyrin IX.[6] Thus, the chiral iron porphyrin catalyst (**1**-FeCl) provides a conceptually new stereochemical model of the P-450 active site.

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