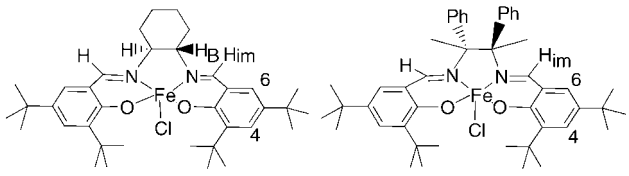

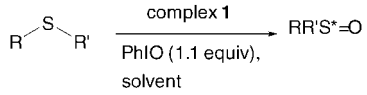

Scheme 1. Iron-catalyzed asymmetric oxidation of sulfides.

Asymmetric Catalysis

Evidence for the Formation of an Iodosylbenzene(salen)iron Active Intermediate in a (Salen)iron(III)-Catalyzed Asymmetric Sulfide Oxidation**

Konstantin P. Bryliakov and Evgenii P. Talsi*

Asymmetric sulfoxides are finding increasing use in the pharmaceutical industry.[1] Most methodologies for catalytic asymmetric sulfide oxygenation involve a transition metal (titanium, vanadium, or manganese) and a chiral ligand, such as bidentate diethyl tartrate,[2a] diols,[2b] binaphthol (binol),[2c,d] tridentate Schiff base ligands,[2e–h] or tetradentate salen-type ligands (salen = (salicylidene)ethylenediamine).[2i–l] Recently, inexpensive active systems based on hydrogen peroxide as the oxidant and nontoxic chiral iron(III) complexes as catalysts were reported.[3] Rajagopal and coworkers published a mechanistic study of the nonenantioselective [Fe^{III}Cl(salen)]-catalyzed oxidation of sulfides with iodosylbenzene.[4,5] Herein, we present asymmetric [Fe^{III}Cl(salen*)] catalytic systems (complexes **1a** and **1b**, where salen* = the corresponding chiral Schiff base ligand; Scheme 1) and report the NMR spectroscopic investigation of the [Fe^{III}(salen*)(OIPh)] active intermediates.

Complexes **1a** and **1b** were synthesized either according to the known procedure[6] or an original one (see Supporting Information). The electron paramagnetic resonance (EPR) and ^{1}H NMR spectra for **1a** and **1b** are typical of those for high-spin $S = 5/2$ iron(III) complexes with $E/D \approx 0.15$, assuming that the zero-field splitting parameter $D \leq h\nu$ and $g_x = 2.0$, $g_y = 2.0$, and $g_z = 2.0$ (Figure 1).[7] Assignment of the NMR spectra was achieved on the basis of the relative intensities and linewidths of the resonances (the latter correlates with the proximity to the paramagnetic metal center), and by comparison of the spectra of **1a** and **1b**.

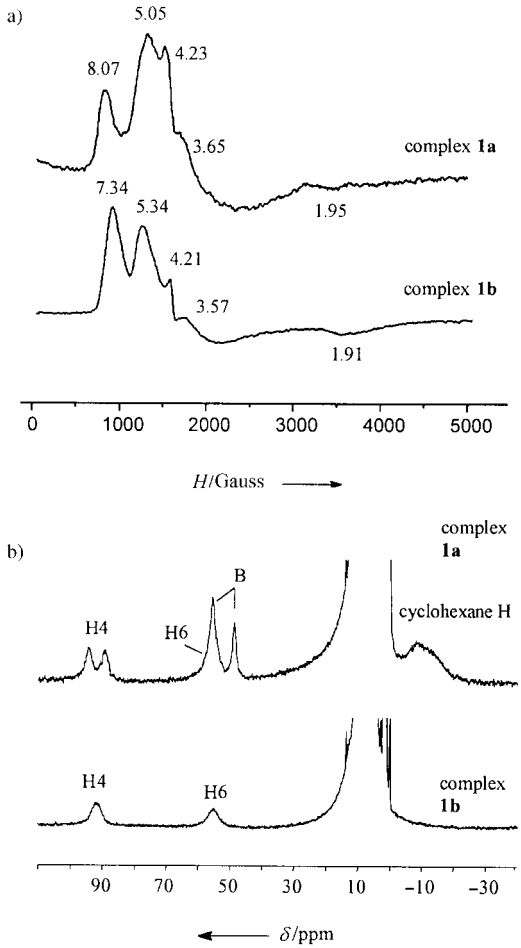

Figure 1. a) EPR spectra (−196 °C) of 0.015 M solutions of complexes **1a** and **1b** in CH_2Cl_2. b) ^{1}H NMR spectra (0.02 M in $CDCl_3$, +20 °C) of complexes **1a** and **1b**. Admixtures at $g = 4.2$ were observed in the EPR spectra.

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The asymmetric sulfide oxidation results are summarized in Table 1. Typically, the reaction was complete in 2 hours at 0 °C, with the catalyst performing 100–200 turnovers. However, at least 500 turnovers can be made without loss of enantioselectivity (Table 1, entries 10 and 11; in these cases, the reaction was carried out at room temperature to shorten the reaction time). The corresponding sulfoxides, sulfones, and residual sulfides were found in the reaction mixtures. Both complexes demonstrated similar enantioselectivities, (*R*,*R*)-**1a** and (*S*,*S*)-**2a** affording *S* and *R* sulfoxides, respectively. The highest *ee* values were achieved in acetonitrile as solvent (see entries 4–6 and 9); donor additives did not lead to an increase in enantioselectivity (entries 7 and 8). Increasing the temperature led to lower enantioselectivity (entry 10). Further ligand adjustment seems to be possible to improve the *ee* value.

Table 1: Catalytic enantioselective oxidation of sulfides with PhIO catalyzed by iron complexes **1a** and **1b**.

Entry	Sulfide **2**	Catalyst	Solvent	Conversion [%]	Selectivity [%][a]	*ee* [%][b]	Config.[c]
1	PhSMe	**1a**	CH_2Cl_2	74	99	20	(*S*)-(−)
2	PhSMe	**1a**	CH_3CN	96	83	22	(*S*)-(−)
3	*p*-BrPhSMe	**1a**	CH_2Cl_2	95	96	41	(*S*)-(−)
4	$PhCH_2SPh$	**1a**	CH_2Cl_2	94	92	58	(*S*)-(−)
5	$PhCH_2SPh$	**1a**	C_6H_6[d]	90	69	57	(*S*)-(−)
6	$PhCH_2SPh$	**1a**	C_6H_5CN	no reaction	–	–	–
7	$PhCH_2SPh$	**1a**	CH_2Cl_2[e]	96	89	55	(*S*)-(−)
8	$PhCH_2SPh$	**1a**	CH_2Cl_2[f]	96	86	55	(*S*)-(−)
9	$PhCH_2SPh$	**1a**	CH_3CN	95	91	62	(*S*)-(−)
10	$PhCH_2SPh$	**1a**	CH_3CN[d]	92	91	55	(*S*)-(−)
11	$PhCH_2SPh$	**1a**	CH_3CN[d,g]	96	72	55	(*S*)-(−)
12	*p*-BrPhSMe	**1b**	CH_3CN	90	90	43	(*R*)-(−)
13	$PhCH_2SPh$	**1b**	CH_3CN	91	85	62	(*R*)-(−)

Reaction conditions (unless otherwise stated): Fe complex (0.001 mmol), solvent (1 mL), sulfide (0.1 mmol), PhIO (0.11 mmol), 0 °C, 150 rpm stirring for 2 h. [a] Selectivity = [RSOR']/([RSOR'] + [RSO_2R']). [b] Determined by ^{1}H NMR spectroscopy with a [Eu(hfc)$_3$] chiral shift reagent in CCl_4 (Hfc = 3-(heptafluoropropylhydroxymethylene)-D-camphorate). [c] Determined by comparing [Eu(hfc)$_3$]-shifted NMR patterns of sulfoxides with those of the sulfoxides with known absolute configuration. [d] At room temperature. [e] DMF was added, [DMF]:[Fe] = 5:1. [f] *N*-methylmorpholine-*N*-oxide was added, [NMO]:[Fe] = 10:1. [g] Fe (0.0001 mmol), solvent (0.4 mL), substrate (0.05 mmol), thus substrate/catalyst ratio of 500; reaction time 7 h.

Interestingly, catalysts **1** can oxidize sulfides using terminal oxidants other than PhIO with remarkable chemical selectivity (Table 2). However, in all these cases the reaction gave racemic products, which implies that it is PhIO that is responsible for the formation of the specific active sites of oxidation. Recently, the active sites were proposed to be $[Fe^{IV}{=}O(salen)]^{+\bullet}$ species;[4] however, the characterization was unreliable. Our spectroscopic observations provide evidence in favor of other active species.

Oxoferryl π-cation radicals are expected to have typical $S = 3/2$ spectra with resonances at $g^{eff} \approx 4$ and $g^{eff} \approx 2$.[8] However, treatment of complexes **1a** and **1b** with PhIO and *m*-chloroperoxybenzoic acid (*m*-CPBA, which was reported to generate (oxoferryl)porphyrin π-cation radicals[8,9a]) did not lead to formation of $S = 3/2$-type spectra, only a sharp peak at $g = 4.2$ belonging to an unidentified $S = 5/2$ species (see Supporting Information). The latter species would not contribute to the catalytic cycle, as it is stable for hours even in the presence of the substrate, and its concentration estimated by EPR spectroscopy does not exceed 10% of the total Fe concentration.[10] Thus, this species must be interpreted as a minor inactive high-spin Fe^{III} admixture.

The ^{1}H NMR spectra (−20 °C) showed the formation of a new Fe^{III} complex after interaction of **1a** with PhIO (Figure 2a). This new species has a *t*Bu peak at $\delta =$ 4.75 ppm (the *t*Bu peak of **1a** is at $\delta = 5.44$ ppm) and its concentration is up to 40% of the total observable Fe^{III} concentration. We particularly emphasize that at this stage no PhI signals are observed in the spectrum (Figure 2a). Thus, it is natural to conclude that this new species is **1a**(PhIO), similar to the iodosylbenzene–iron(III) porphyrin intermediates recently discussed in the literature.[9a–c] Indeed, after addition of an excess of the substrate (*p*-BrPhSMe) and warming the sample to 0 °C, the PhI ^{1}H NMR signal appeared at $\delta = 7.71$ ppm and the *p*-BrPhSOCH_3 signal at $\delta = 2.73$ ppm (Figure 2c). At the same time, the intensity of the **1a**(PhIO) signal decreased. After consumption of the **1a**(PhIO) intermediate, shaking with additional PhIO (Figure 2d,e) restored its concentration. Thus, the reaction cycle for the reported catalytic system could be represented as given in Scheme 2, which includes the Lewis acid activation of iodosylbenzene,[9d] the oxygen-transfer step proceeding probably by precoordination of the sulfide to the **1a**(PhIO) active species.[4]

In summary, we have proposed a new catalytic system for the asymmetric oxidation of sulfides by PhIO, based on an asymmetric (salen)iron(III) complex, and performed the catalytic oxidation of several aryl sulfides. The active species

Table 2: Catalytic oxidation of sulfides catalyzed by iron complexes **1a** and **1b**.

Entry	Sulfide **2**	Complex (mol%)	Solvent	Oxidant	Conversion [%] (after)	Selectivity [%]	*ee* [%]
1	PhSMe	**1a** (4)	CH_3CN	H_2O_2 (2.5 equiv)	71 (16 h)	75	0
2	PhSMe	**1a** (3)	CH_3CN	TBHP (1.4 equiv)	59 (40 h)	98	0
3	$PhCH_2SPh$	**1b** (2)	CH_2Cl_2	NaOCl (1.0 equiv)	no reaction	–	–
4	$PhCH_2SPh$	**1b** (1)	CH_2Cl_2	H_2O_2 (2.0 equiv)	4 (36 h)	not measured	0
5	$PhCH_2SPh$	**1b** (1)	CH_3CN	*m*-CPBA (1.2 equiv)	100 (2 h)	78	0

Reaction conditions (unless otherwise stated): Fe complex, solvent (1 mL), sulfide (0.1 mmol), room temperature, 150 rpm stirring. TBHP = *tert*-butylhydroperoxide.

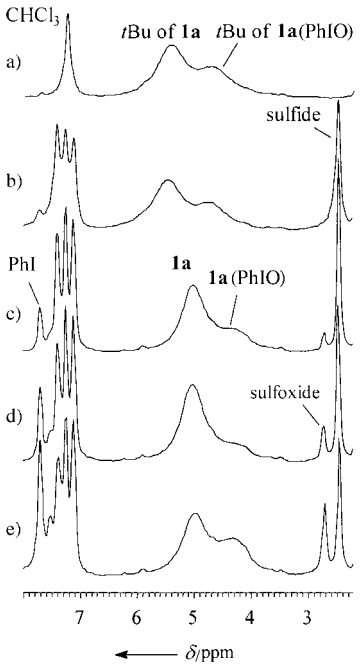
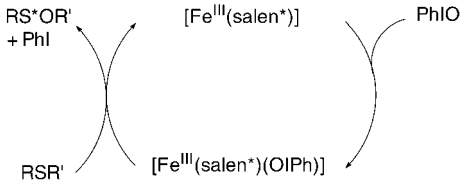


Figure 2. ^{1}H NMR spectra (in the range 8 to 2 ppm) of a) complex **1a** (0.02 M in $CDCl_3$) shaken for 5 min with PhIO (2 equiv) on cooling, −20 °C; b) after addition of *p*-BrPhSMe (5 equiv); c) after warming to 0 °C; d) after storing for 5 min at 0 °C; e) after shaking with additional PhIO (1 equiv) without cooling, recorded at 0 °C.



Scheme 2. Proposed catalytic cycle for iron-catalyzed asymmetric oxidation of sulfides.

was detected and shown to be an iodosylbenzene(salen)-iron(III)complex. We hope this new knowledge will be of interest to those scientists who deal with metal–salen catalytic systems and asymmetric oxidation of sulfides, and foresee further ligand designs to improve the enantioselectivity.

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