## Asymmetric Oxidation of Sulfides with H<sub>2</sub>O<sub>2</sub> Catalyzed by (salen)Mn(III) Complexes

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Abstract: Optically active (salen)Mn(III)Cl complexes are effective catalysts for the oxidation of sulfides to sulfoxides with modest enantioselectivity. An optimal reaction system consisting of unbuffered hydrogen peroxide as the stoichiometric oxidant, acetonitrile as solvent, and 2-3 mol% of complex 1 effects conversion of aryl sufides to sulfoxides in 84-95% isolated yield, and 34-68% ee.

Sulfide oxidation and olefin epoxidation are fundamentally different reaction classes, yet both transformations generally can be effected with similar catalysts or reagents. Thus, mCPBA is the classical reagent for effecting both reactions in a non-enantioselective manner. Asymmetric stoichiometric epoxidation and sulfide oxidation strategies utilizing chiral oxaziridine derivatives have been developed with good-to-excellent success by Davis and coworkers.<sup>1</sup> Enantioselective catalysis of these reactions constitutes among the most interesting challenges in modern synthetic chemistry, and to date the only well-established and broadly successful methods for both processes employ closely related Ti-tartrate-based catalysts with alkyl hydroperoxides as the terminal oxidant.<sup>2</sup> In addition, several chiral porphyrin complexes have been reported to catalyze both types of oxidation processes with modest selectivity using iodosylarenes as terminal oxidants.<sup>3</sup> Given the clear homology between epoxidation and sulfide oxidation and the recent successful development of chiral (salen)Mn complexes as catalysts for the epoxidation of conjugated olefins,<sup>4,5</sup> we became interested in the potential of these catalysts for enantioselective sulfide oxidation. We report herein the preliminary results of these studies.

The protocol for enantioselective epoxidation by (salen)Mn catalysts developed in our laboratories employs aqueous sodium hypochlorite as the stoichiometric oxidant,<sup>6</sup> but the uncatalyzed reaction between sulfides and bleach proved too rapid for this oxidant to be of value for enantioselective sulfide oxidation reactions. Iodosylarenes react very slowly with sulfides, and therefore they have been employed in the majority of processes involving oxo transfer from a transition metal. Indeed, we found that iodosylbenzene served as an effective oxygen atom source in sulfide oxidations mediated by (salen)Mn complexes. Unfortunately, iodosylarenes are impractical stoichiometric oxidants for either small or large scale reactions due to their instability in the solid state, their lack of solubility, their relatively high cost, and the high molecular weight of the byproduct of oxygen transfer, an iodoarene. In screening other oxidants, we were pleased therefore to discover that unbuffered hydrogen peroxide also could be employed with good success.<sup>7</sup> Dialkyl sulfides underwent competitive uncatalyzed oxidation by H<sub>2</sub>O<sub>2</sub>, but aryl alkyl sulfides were oxidized slowly relative to the catalyzed pathway. Compared with iodosylbenzene, hydrogen peroxide afforded higher yields of sulfoxide, minimal overoxidation to sulfone, and identical enantioselectivities to those observed with iodosylbenzene. The latter result suggests that both oxidants generate a common Mn(V) oxo reactive intermediate. Catalase-like decomposition of hydrogen peroxide by the (salen)Mn(III) catalysts was minimized with acetonitrile as cosolvent, and complete conversion of sulfide was accomplished with less than 6 equivalents of oxidant.

In general, catalysts derived from 1,2-diaminocyclohexane and 1,2-diphenylethylene diamine were more selective than those prepared from other, synthetically less accessible diamines. Representative catalysts based on these auxiliaries that were screened for asymmetric sulfide oxidation are listed in Table 1. It is significant, although perhaps not surprising, that those ligand properties that have proven to be important for optimal enantioselectivity in epoxidation also improved selectivity in sulfide oxidation. Thus, the presence of bulky substituents on the 3,3' and 5,5' positions of the salen ligands has a marked effect on selectivity, indicating that these groups improve stereochemical communication in the transition state leading to oxo transfer by inducing substrate approach near the dissymmetric diimine bridge.<sup>4b</sup> An electronic effect on enantioselectivity was also very pronounced in sulfide oxidation with (salen)Mn catalysts.<sup>8</sup> As exhibited with in the epoxidation reaction, catalysts bearing electron withdrawing substituents are less enantioselective than electron rich analogs (entries 1, 3, and 4). This effect may be attributed to the greater reactivity, and concomitant lower selectivity, of the high valent intermediates bearing electron withdrawing groups.



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Table 1. Asymmetric Oxidation of Thioanisole with Catalysts 1-8.

$\bigcirc$	∕ <sup>s</sup> _сн₃ + ноон	Catalyst CH	(2-3 mol %) I <sub>3</sub> CN	- CH3
Entry	Catalyst	Yield,% <sup>a</sup>	ee,%b	Sulfoxide confgn <sup>C</sup>
1	(R,R)-1	90	47	<u>S-(-)</u>
2	(R,R)-2	72	24	S-()
3	(R.R)-3	82	0	_
4	(R,R)-4	74	14	S-()
5	(R,R)-5	86	36	S-()
6	(R,R)-6	64	34	S-(-)
7	(R.R)-7	84	7	S-()
8	(S,S)-8	79	0	<u> </u>

<sup>a</sup>All yields correspond to pure products isolated by flash chromatography. <sup>b</sup>Ee's were determined by HPLC using a Chiralcel OD column. <sup>c</sup>Absolute configuration assigned by comparison of the sign of  $[\alpha]_D$  to the literature value.

			1 (2-3 mol %)		O U	
		CH <sub>3</sub> CN		Ar R		
Entry	Sulfide	Catalyst	Yield (%) <sup>a</sup>	<del>ee</del> (%)b	Sulfoxide confgn <sup>C</sup>	
1	C <sub>6</sub> H <sub>5</sub> S CH <sub>3</sub>	<i>(R,R)</i> -1	90	47	S-()	
2	o-Br-C <sub>6</sub> H₄ S_CH₃	<i>(R,R)</i> -1	80	68	<i>S</i> -(-)	
3	<i>р</i> -СН <sub>3</sub> -С <sub>6</sub> Н <sub>4</sub> <sup>S</sup> СН <sub>3</sub>	(R,R)-1	95	42	S-()	
4	C <sub>6</sub> H <sub>5</sub> S	<i>(R,R)-</i> 1	84	40	S-()	
5	C <sub>6</sub> H <sub>5</sub> S ⊢C₄H <sub>9</sub>	<i>(R,R)-</i> 1	94	43	S-()	
6	2-napthyl SCH <sub>3</sub>	(R,R)-1	84	46	<b>S-(</b> -)	
7	<i>₀</i> -MeO-C <sub>6</sub> H₄∕ <sup>S</sup> ∕CH₃	<i>(S,S)</i> -1	94	34	<i>R</i> -(+) <sup>d</sup>	
8	<i>р</i> •NO <sub>2</sub> -С <sub>6</sub> Н <sub>4</sub> <sup>S</sup> СН <sub>3</sub>	<i>(R,R-</i> 1	86	66	S-()d	
9	m-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> S CH <sub>3</sub>	<i>(S,S)-</i> 1	84	63	<i>R</i> -(+) <sup>d</sup>	
10	p-Br-C <sub>6</sub> H₄ S_CH <sub>3</sub>	<i>(S,S</i> )-1	93	56	<i>R</i> -(+) <sup>d</sup>	
11	o-I-C <sub>B</sub> H	<i>(S,S</i> )-1	95	65	<i>R</i> -(+) <sup>d</sup>	

Table 2. Asymmetric Oxidation of Prochiral Sulfides Using Catalyst (R,R)-1 or (S,S)-1.

<sup>a</sup>Isolated yields based on sulfide. Pure sulfoxides (>99% by GC analysis) were isolated by flash chromatography. <sup>b</sup>Ee's were determined by HPLC using a Chiralcel OD column except for entries 8,9,10 which were determined by <sup>1</sup>H NMR in the presence of (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. <sup>c</sup>Absolute configurations were established by comparison of the sign of [ $\alpha$ ]<sub>D</sub> to literature values unless otherwise indicated. <sup>d</sup>Absolute configurations assigned by analogy (sign of [ $\alpha$ ]<sub>D</sub>) to entries 1-6.

Complex 1 emerged as the most selective of the catalysts that were screened, and the asymmetric oxidation of a variety of alkyl aryl sulfides was examined with this system (Table 2). Selectivities in all cases were moderate, although a significant electronic effect on substrate could also be discerned. More reactive, electron rich sulfides were oxidized with lower selectivity (e.g. entry 7), while selectivities above 60% ee were obtained with substrates bearing halide or nitro groups (entries 2, 8-11). The face selectivity in the sulfide oxidation reactions is analogous to that in alkene epoxidation (Figure 1), suggesting that the nature of the transition states in the two processes may indeed be similar. The observation of lower selectivities in sulfide oxidation relative to alkene epoxidation with given catalysts has precedent in porphyrin-based catalysts,<sup>3</sup> and may also be interpreted on the basis of more reactive systems being less selective.

(Salen)Mn (III) catalysts are generally accessible on large scale from readily available precursors, catalysis in sulfide oxidation is efficient, and the stoichiometric oxidant  $H_2O_2$  is inexpensive and amenable to both small and large scale reactions. Although synthetically useful enantioselectivities have not yet been attained in sulfide oxidation with the systems developed thus far, it is likely that significant improvements will result from further modification of the steric and electronic properties of these and related catalysts.

Figure 1



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