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Asymmetric oxidation of sulfides catalyzed by chiral (salen)Mn(III) complexes with a pyrrolidine backbone

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Catalytic properties of a series of chiral (pyrrolidine salen)Mn(III) complexes for asymmetric oxidation of aryl methyl sulfides were evaluated. Moderate activity, good chemical selectivity and low enantioselectivity were attained with iodosylbenzene as a terminal oxidant. Enantioselectivity of sulfide oxidation was affected slightly by polar solvent and the sulfoxidation carried out in THF for thioanisole and in CH_3CO_2Et for electron-deficient sulfides gave better enatioselctivities. The addition of the donor ligand PPNO (4-phenylpyridine *N*-oxide) or MNO (trimethylamine *N*-oxide) only has a minor positive effect on the enantioselectivity. Also explored was the steric effect of the N_{aza}-substituent in the backbone of (pyrrolidine salen)Mn(III) complexes on the enantioselectivity of sulfide oxidation. The sulfides' access pathway is discussed based on the catalytic results. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: asymmetric oxidation; pyrrolidine; (salen)Mn complexes; sulfides; sulfoxides

INTRODUCTION

Enantioselective oxidation of prochiral sulfides is an attractive subject in organic synthesis as optically pure sulfoxides are effective chiral auxiliaries and synthons in asymmetric synthesis,[1–3] and important bioactive ingredients in the pharmaceutical industry,[4,5] as well as being useful ligands in enantioselective catalysis.[1,3] The stoichiometric oxidation of sulfides based on chiral oxaziridines and Ti(O-*i*-Pr)$_4$-chiral tartrate systems afforded high enantioselectivities.[6–8] In the past two decades, catalytic asymmetric oxidation of sulfides has been extensively investigated using transition metal complexes of various chiral ligands as catalysts,[9,10] such as iron-porphyrins,[11–14] manganese-salens,[15–18] titanium-BINOL,[19] -C_2-symmetric diols[20,21] and -trialkanol amines,[22,23] vanadium-tridentate Schiff bases,[24–27] and very recently reported iron-tridentate Schiff base catalyst systems.[28–30] To date the development of highly efficient and practical catalysts for this type of reaction is still an interesting challenge in modern synthetic chemistry.

It has been proved that some transition metal-based catalyst systems that are efficient for asymmetric epoxidation of alkenes are also capable of catalytic asymmetric oxidation of sulfides, although the two types of the reactions are fundamentally different. The application of transition metal catalysts bearing chiral salen ligands in asymmetric oxidation of sulfides was initially reported by Fujita and co-workers.[31] After that salen-type complexes of manganese,[15–18] titanium[32] and niobium[33] were successively used in enantioselective sulfide oxidation. Recently we found that N_{aza}-substituted chiral (pyrrolidine salen)Mn(III) complexes (*R*,*R*)-**1**–**4** (Fig. 1) are highly active for asymmetric epoxidation of styrene and substituted chromenes, affording comparable enantioselectivity relative to Jacobsen's catalyst.[34] The advantage of the chiral salen ligand with a pyrrolidine

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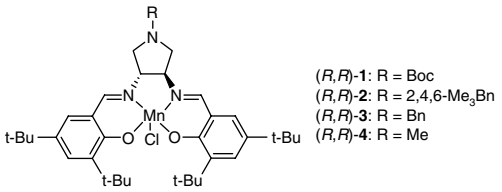


Figure 1. The catalysts used in the present study.

backbone is the fact that different groups and fragments, such as polymeric and inorganic supports, can be readily tethered to the backbone of the ligand through the N atom of pyrrolidine. To extend the scope of catalytic asymmetric reactions by this type of chiral salen ligands with a pyrrolidine backbone, we scrutinized the catalytic properties of chiral (pyrrolidine salen)Mn(III) complexes (*R*,*R*)-**1**–**4** in asymmetric oxidation of prochiral sulfides. Since the use of H_2O_2 led to quick decomposition of the catalyst and the reaction afforded sulfones as major products with *m*-CPBA as oxidant, PhIO was used as a terminal oxidant in sulfide oxidation catalyzed by chiral (pyrrolidine salen)Mn(III) complexes. In this paper we describe the preliminary results on the catalytic properties of (*R*,*R*)-**1**–**4** with PhIO for asymmetric oxidation of aryl methyl sulfide (Ar = C_6H_5, *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$) and the influences of the solvents, the third-components (PPNO, MNO) and the backbone R groups of (pyrrolidine salen)Mn(III) complexes on the catalytic activity and enantioselectivity.

EXPERIMENTAL

Materials and instruments

4-Nitrothioanisole, 4-bromothioanisole, 4-methoxythioanisole, iodosobenzene diacetate, PPNO and MNO · $2H_2O$ were purchased from Aldrich and Acros. Thioanisole (analytically pure reagent), $Mn(OAc)_2 \cdot 4H_2O$ and other commercially available chemicals were laboratory-grade reagents from local suppliers. All solvents used were purified by standard procedures. Iodosylbenzene was prepared from iodosobenzene diacetate by literature procedure.[35] (Pyrrolidine salen)Mn(III) complexes (*R*,*R*)-**1**–**4** were synthesized by the previously reported protocols.[34]

Optical rotations at 589 nm were measured with a Jasco P-1010 digital polarimeter. The chemical selectivities of sulfoxides to sulfones were analyzed on an HP 6890 gas chromatograph using a capillary column (HP-5) and their mass spectra were performed by electrospray ionization (ESI) on an HP1100 MSD instrument. The ee values of sulfoxides were determined by HPLC (Waters 2487) analysis using chiral columns (Daicel Chiracel OD-H, 0.46 cm i.d. × 25 cm and Daicel Chiracel OB-H, 0.46 cm i.d. × 25 cm).

A general procedure for asymmetric oxidation of sulfides

Thioanisole (24.8 mg, 0.2 mmol) was added to a solution of complex (*R*,*R*)-**3** (4.2 mg, 6 μmol) in CH_3CN (1.0 ml) and the mixture was cooled to 0 °C. To this solution was added iodosylbenzene (48.4 mg, 0.22 mmol) at once and the mixture was stirred for 3 h at 0 °C. The resulting solution was detected by GC analysis to determine the ratio of sulfoxide and sulfone in the products. The solution was then concentrated *in vacuo* and the residue was purified by column chromatography on silica gel with ethyl acetate as eluent. The corresponding sulfoxide (18.7 mg, 67%) was obtained after removal of the solvent by rotary evaporation. The enantiomeric excess of the sulfoxide was determined by HPLC analysis (Daicel chiracel OD-H, hexane/*i*-PrOH 9 : 1).

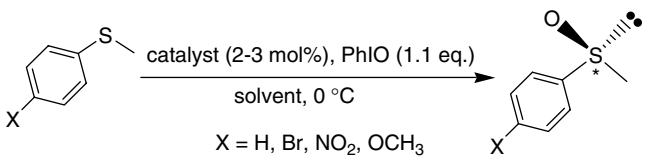
RESULTS AND DISCUSSION

Catalytic oxidation of aryl methyl sulfides by complex (*R*,*R*)-3

In the initial experiments, the ratio of oxidant to sulfide was optimized with thioanisole as model substrate using 2 mol% of (*R*,*R*)-**3** in CH_3CN at 0 °C. When an equivalent of PhIO was used, satisfied chemical selectivity to sulfoxide (82%) was obtained, but the conversion of thioanisole was relatively low (56%). The conversion (95%) was apparently improved as 1.3 equiv. of PhIO were used with a considerable sacrifice of chemical selectivity (60%). A compromise of these two aspects was worked out by using 1.1 equiv. of PhIO and 3 mol% of (pyrrolidine salen)Mn(III) complexes (*R*,*R*)-**1**–**4** in the catalytic experiments.

The results on the catalytic activities and enantioselectivities of complex (*R*,*R*)-**3** with PhIO as oxidant for asymmetric oxidation of aryl methyl sulfides (Scheme 1) are summarized in Table 1. As reported for the (salen)Mn- and (porphyrin)Fe-based catalysts,[11–18] the (pyrrolidine salen)Mn(III) complex exhibited moderate activity, good chemical selectivity and low enantioselectivity in sulfide oxidation. The *S*-configuration sulfoxide is the major product, suggesting that the predominant face selectivity in the asymmetric oxidation of sulfides is similar to that in asymmetric epoxidation of *cis*-alkenes.[34]

The influence of solvents on asymmetric oxidation of sulfides was explored using 3 mol% of (*R*,*R*)-**3** as catalyst. Different polar solvents display a slight influence on the catalytic activity and enantioselectivity. The better yield



Scheme 1.

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Table 1. The results of asymmetric oxidation of sulfides catalyzed by complex (*R*,*R*)-**3**[a]

Entry	Sulfide	Solvent	Additive	Yield[c] (%)	Ee[d] (%)	Configuration[e]
1	$PhSCH_3$	THF	—	54	22	*S*
2	$PhSCH_3$	THF	PPNO[b]	46	28	*S*
3	$PhSCH_3$	C_6H_5Cl	—	71	16	*S*
4	$PhSCH_3$	C_6H_5Cl	PPNO[b]	55	25	*S*
5	$PhSCH_3$	CH_3CN	—	67	14	*S*
6	$PhSCH_3$	CH_3CN	$MNO \cdot 2H_2O$[b]	65	18	*S*
7	$PhSCH_3$	$CHCl_3$	—	65	17	*S*
8	$PhSCH_3$	CH_3CO_2Et	—	53	17	*S*
9	*p*-$BrC_6H_4SCH_3$	THF	—	44	25	*S*
10	*p*-$BrC_6H_4SCH_3$	CH_3CN	—	64	18	*S*
11	*p*-$BrC_6H_4SCH_3$	CH_3CO_2Et	—	57	31	*S*
12	*p*-$O_2NC_6H_4SCH_3$	THF	—	48	34	*S*
13	*p*-$O_2NC_6H_4SCH_3$	CH_3CN	—	54	31	*S*
14	*p*-$O_2NC_6H_4SCH_3$	CH_3CO_2Et	—	53	42	*S*
15	*p*-$CH_3OC_6H_4SCH_3$	CH_3CN	—	68	3	*S*
16	*p*-$CH_3OC_6H_4SCH_3$	CH_3CO_2Et	—	30	6	*S*

[a] Reaction conditions: 3 mol% of catalyst (*R*,*R*)-**3**, 1.1 equiv. of PhIO, 0 °C, 3 h.
[b] With 0.1 equiv. of PPNO or $MNO \cdot 2H_2O$.
[c] Isolated yield based on sulfide.
[d] The ee values of entries 1–8 and 15, 16 were determined by HPLC analysis with a Daicel Chiracel OD-H column, hexane–*i*-PrOH = 9 : 1, and that of entries 9–14 with a Daicel Chiracel OB-H column, hexane–*i*-PrOH = 8 : 2 for entries 9–11 and 4 : 6 for entries 12–14.
[e] Absolute configuration of the major product was determined by comparison of its sign of optical rotation with literature data.[36]

(71%) of sulfoxide was obtained when C_6H_5Cl was used as solvent (entry 3), and the oxidation of thioanisole in THF afforded a better enantioselectivity (ee 22%, entry 1) to the corresponding *S*-configuration sulfoxide as compared with the results obtained in other solvents.

With addition of a donor ligand PPNO, the yield of sulfoxide was decreased from 71 to 55% for catalytic oxidation of thioanisole by (*R*,*R*)-**3** and the ee value was improved from 16 to 25% in the case of C_6H_5Cl as solvent (entry 4), while with THF as solvent the yield of methyl phenyl sulfoxide was reduced from 54 to 46% and the ee value went up from 22 to 28%. Another donor ligand MNO exhibited an immaterial effect on the catalytic activity and enantioselectivity (entries 5 and 6).

The electronic effect of the substituent on the benzene ring of aryl methyl sulfides was also tested in CH_3CN with 3 mol% (*R*,*R*)-**3** and 1.1 equiv of PhIO as catalyst system. As found for Jacobsen's catalyst,[15] under the same condition, the oxidation of the electron deficient sulfides afforded higher ee value of sulfoxides (entries 9–14) as compared with that observed from the electron rich sulfide, *p*-$CH_3OC_6H_4SCH_3$ (entries 15 and 16). As the methoxy is replaced by the nitro substituent in aryl methyl sulfides the ee values increased from 3 and 6 to 31 and 42 for the reactions in CH_3CN and CH_3CO_2Et, respectively. For substrates bearing a bromo or a nitro substituent on the *para* position of the aryl group, better ee values were obtained in CH_3CO_2Et than in THF and CH_3CN solvents (entries 9–14).

The steric effect of the backbone R group on enantioselectivity of sulfide oxidation

We prepared (pyrrolidine salen)Mn(III) complexes (*R*,*R*)-**1**–**4** with different backbone R groups in attempt to gain insight into the steric effect of the R group on the enantioselectivity of sulfide oxidation. Under the same reaction condition, an increase in the size of the R group on the N atom of the (pyrrolidine salen)Mn(III) complex, from methyl [(*R*,*R*)-**4**], benzyl [(*R*,*R*)-**3**], 2,4,6-trimethylbenzyl [(*R*,*R*)-**2**] and Boc [(*R*,*R*)-**1**], led to an observable increase in the enantioselectivity, from 7 to 31% ee, for asymmetric oxidation of thioanisole (Table 2). This incremental tendency of enantioselectivity with the increase in the volume of the backbone R groups is consistent with but more apparent than that observed for catalytic epoxidation of alkenes by the same series of chiral (pyrrolidine salen)Mn(III) complexes.[34] The mechanism proposed for asymmetric epoxidation of alkenes catalyzed by chiral (pyrrolidine salen)Mn(III) complexes also provides a reasonable explanation for asymmetric oxidation of sulfide under similar conditions.

It can be predicted that, if the molecule of sulfide approaches the (oxo)Mn(V) center along pathway **a** or **d** (Scheme 2) an increase in the size of the backbone R group should have no effect on the enantioselectivity of sulfide oxidation. The catalytic data exclude approach pathways **a** and **d** from the catalytic oxidation of sulfides by (*R*,*R*)-**1**–**4**. The presence of the bulky *tert*-butyl groups on the 3, 3′ and 5, 5′ positions of the pyrrolidine salen ligand strongly disfavors

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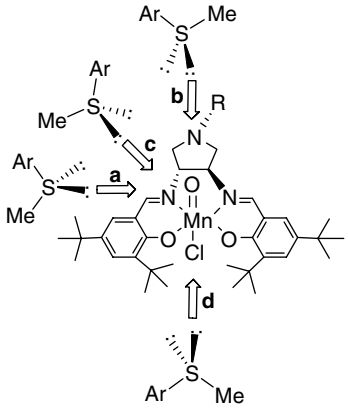
Table 2. The influence of the backbone R groups of the catalysts[a]

Entry	Catalyst	R Group	Yield[b] (%)	ee[c] (%)	Configuration
1	(*R*,*R*)-**1**	Boc	64	31	*S*
2	(*R*,*R*)-**2**	2,4,6-Me_3Bn	68	28	*S*
3	(*R*,*R*)-**3**	Bn	54	22	*S*
4	(*R*,*R*)-**4**	Me	68	7	*S*

[a] Reaction conditions: molar ratio $PhSCH_3$–PhIO–catalyst 1:1.1:0.03, solvent THF, 0 °C, 3 h.
[b] Isolated yield based on sulfide.
[c] Determined by HPLC analysis with a Daicel Chiracel OD-H column.



Scheme 2. Plausible side-on approach pathways for sulfide access.

the attacks through side-on approach pathway **a** and **d**. The experimental facts, low ee values and the substantial influence of the size of the backbone R group on the enantioselectivity, suggest that, besides the predominant approach pathway **c** along the direction of the N–Mn bond, the backside approach pathway **b** (Scheme 2) might also take place in sulfide oxidation catalyzed by (pyrrolidine salen)Mn(III) complexes. Pathway **b** is proposed to be one of the plausible approaches of the sulfide to the (oxo)Mn(V) center when two structural features of the catalyst and the sulfide are taken into account. First, the backbone R group on the N atom of sp^3-hybridization could direct somewhat downward, avoiding a face-to-face encounter with the oncoming sulfide molecules along approach pathway **b**. Second, two substituents on the S atom of sp^3-configuration could direct somewhat upward as the sulfide approaches the (oxo)Mn(V) center, to further reduce the steric hindrance for pathway **b**. In this context, the backside access to the (oxo)Mn(V) center is more facile for the sulfide than for the *cis*-alkene, which takes a side-on perpendicular approach to the (oxo)Mn(V) center.[37] On the basis of a nonplanar (pyrrolidine salen)Mn(III) catalyst, the large group of the sulfide should favor the orientation anti to the imine moiety in the backside approach. As shown in Scheme 2, pathway **b** gives *R*-configuration sulfoxides, while pathway **c** affords *S*-enantiomers. When the size of the backbone R group of the catalyst increases, the attack of the sulfide along approach pathway **b** becomes less favored, resulting in the increase of the enantioselectivity for sulfide oxidation.

In conclusion, the (pyrrolidine salen)Mn(III) complexes (*R*,*R*)-**1**–**4** exhibit moderate activity, good chemical selectivity and low enantioselectivity in asymmetric oxidation of aryl methyl sulfides, as found for (salen)Mn- and (porphyrin)Fe-based catalysts.[11,12,15,18] The volume of the N_{aza}-substituent in the pyrrolidine backbone of complexes (*R*,*R*)-**1**–**4** does have an apparent steric effect on the enantioselectivity of sulfide oxidation, suggesting that side-on approach **c** should be the predominant access of the sulfide to the (oxo)Mn(V) center and pathway **b** could not be excluded from the plausible approaches.

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