Communications

Efficient Asymmetric Sulfoxidation of Prochiral Sulfides Catalyzed by Chiral Salen-Mn(III) Complexes

Ji Yun Choi, Geum-Sook Hwang,† Bidyut Kumar Senapati, and Do Hyun Ryu*

*Department of Chemistry, Sungkyunkwan University, Suwon, Gyeonggi 440-746, Korea. *E-mail: dhryu@skku.edu*
†Korea Basic Science Institute, 5 St, Anam-Dong, Seongbuk-Gu, Seoul 136-713, Korea
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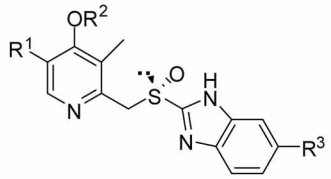
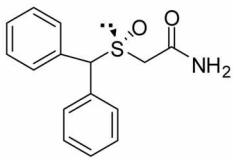
The asymmetric synthesis of sulfoxides has received particular attention in recent years due to their excellent stereochemical control as chiral auxiliaries in a variety of highly diastereoselective carbon-carbon bond forming reactions, including the synthesis of chiral amines, amino acids, aziridines, and amino phosphoric acids.[1] Moreover, enantiomerically pure sulfoxides are widely used as drug intermediates, such as esomeprazole and eslansoprazole (strong proton pump inhibitors used as antiulcer drugs), and modafinil (used in the treatment of sleep disorders).[2]



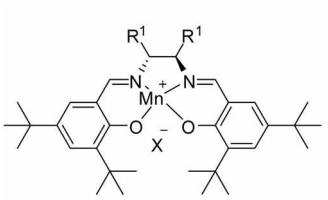
Esomeprazole (R^1, R^2 = Me, R^3 = OMe)
Eslansoprazole (R^1 = H, R^2 = CH_2CF_3, R^3 = H)



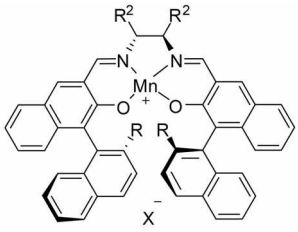
Modafinil

Chiral complexes of transition metals such as titanium, manganese, iron, and vanadium have attracted much attention for the development of efficient catalysts in the synthesis of enantiopure sulfoxides. A metal-free asymmetric sulfur oxidation has also been described by using oxaziridines and hydroperoxides.[3,4] One of the most efficient and prominent enantioselective sulfoxidations was discovered independently by Kagan and Modena using a modified Sharpless catalytic system (ROOH/Ti(O^iPr)$_4$/DET), although the amount of water present in those reactions must be carefully controlled.[5] Later, Umura *et al.* reported the titanium/BINOL complex in asymmetric sulfoxidations.[6] Bolm and Bienewald reported a vanadium-based vigorous sulfoxidation where hydrogen peroxide was used as an oxygen source.[7] A polymer-supported modification of these vanadium Schiff base complexes has also been reported in recent years; however, the catalyst concentration was 50 mol%.[8] Salen-Mn(III) complexes have been described for the asymmetric oxidation of thioethers, yet enantioselectivity remains moderate.[9]

Despite the high yields and enantioselectivities previously reported, most of the systems were mainly assessed with unfunctionalized thioethers with limited scope and applicability due to the restricted availability of suitable chiral precursors of the catalysts. With the synthesis of esomeprazole as the primary focus, we herein report the asymmetric sulfoxidation of aryl alkyl thioethers using Salen-Mn complexes (**1-4**) with moderate to high yields and enantioselectivities.



1, R^1 = -$(CH_2)_4$-
2, R^1 = Ph

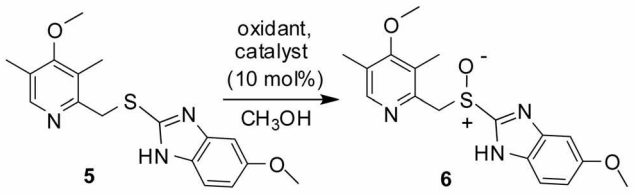


R= *t*-$BuCO_2$
3, R^2 = -$(CH_2)_4$-
4, R^2 = Ph

Our first study involved various chiral Salen-Mn(III) complexes and iodosylbenzene as oxidant to serve as a useful method for the synthesis. Salen-Mn complexes (**1-4**) were prepared using known methods.[10] We first examined the activity of Salen-Mn(III) complex **1** under various conditions as shown in Table 1. When catalyst **1** (10 mol%, 0 °C, 14 h), activated by a tetrafluoroborate anion, was used, the reaction proceeded slowly with the formation of esomeprazole **6** at 58% yield with 69% ee (entry 1) in the presence of iodosylbenzene as the oxidant. When *ortho*-nitro-iodosylbenzene was used as an oxidant, the same sequences of reaction with catalyst **1** provided sulfoxide **6** in 59% yield and 70% ee, only after 72 h at –40 °C in methanol (entry 2). Methanol afforded the best results in terms of yield and enantioselectivity of product compared to dichloromethane, acetonitrile or THF. We then investigated the efficiency of the same catalyst in the presence of different anions, but none proved suitable to serve our purpose. Further modifications of the catalytic systems (**2**, **3**, or **4**), complex anions, or oxidizing agents did not provide any significant results.

Encouraged by the above results, we examined the catalytic activity of bulky Salen-Mn(III) complexes **3** and **4** in the asymmetric oxidation of simple aryl alkyl thioethers.

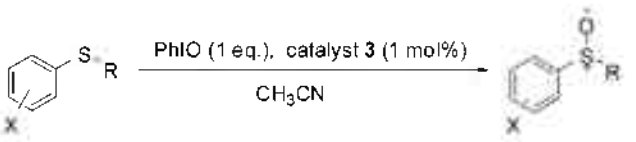
Table 1. Asymmetric sulfoxidation of **5** for the synthesis of esomeprazole **6**

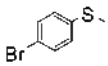
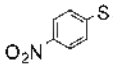


Entry	Catalyst	X	Oxidant (eq.)	Temp. (°C)	Time (h)	Yield %[a]	%ee[b]
1	**1**	BF_4^-	PhIO (2.0)	0	14	58	69
2	**1**	BF_4^-	*o*-PhIONO$_2$ (1.5)	−40	72	59	70
3	**1**	Cl^-	PhIO (2.0)	0	11	38	70
4	**1**	AcO^-	PhIO (2.0)	0	11	47	66
5	**2**	Cl^-	PhIO (2.0)	0	12	52	54
6	**2**	Cl^-	*o*-PhIONO$_2$ (1.5)	0	4	46	67
7	**3**	Cl^-	PhIO (3.0)	r.t.	24	21	24
8	**4**	Cl^-	PhIO (3.0)	r.t.	16	14	40

[a]Yields of isolated product. [b]Determined by HPLC analysis (Daicel Chiralcel OD-H, Hexane:*i*-PrOH = 9:1, flow rate 0.5 mL min^{-1}).

Table 2. Asymmetric oxidation of alkyl aryl sulfides catalyzed by Salen-Mn(III) complex **3**



Entry	Sulfide	Temp. (°C)	Time (h)	Yield %[a]	%ee[b]	Config.[c]
1		25	3	74	60	(*S*)
2		25	0.3	76	60	(*S*)
3		0	5	86	70	(−)
4		−20	5	82	60	(*S*)
5		−20	4	90	50	(*S*)
6		−20	4	88	31	(*S*)
7		−20	4	76	80	(*S*)
8		−20	4	68	30	(*S*)
9		0	2	77	76	

[a]Yield of isolated product. [b]Determined by HPLC analysis (Daicel Chiralcel OD-H for entries 1, 2 and 8. Daicel Chiralcel OB-H for entries 3, 4, 5 and 6. Daicel Chiralcel OJ-H for entry 7). Determined by GC analysis (Cyclosil B for entry 9). [c]Determined by comparison of HPLC analysis data.[10]

To our surprise, it has been revealed that although these bulkier ligands were not suitable for the synthesis of esomeprazole (entries 7 and 8, Table 1), they were more efficient for the oxidation of simple sulfides (Table 2).[11] Treatment of phenyl methyl thioether with catalyst **3** (only 1 mol%, complexed with chloride ion) produced the desired chiral sulfoxide in 74% yield and 60% ee in the presence of iodosylbenzene as the oxidant (entry 1). Catalyst **4** provided poor results (64% yield, 35% ee) compared to **3** under the same conditions. Having reaction conditions being established with catalyst **3** in acetonitrile, various aryl alkyl substituted sulfides were screened in order to investigate the reaction scope with representative results summarized in Table 2. It has been observed that the effect of the substituent's electronic nature on the aromatic ring plays a significant role in yield and enantioselectivity. The sulfide possessing electron-withdrawing bromo or nitro functionalities (entries 3, 4, and 7) provided better enantioselectivity than electron-donating methoxy or methyl groups (entries 5, 6, or 8). It is noteworthy that oxidation of methyl *tert*-butyl sulfide furnished the corresponding dialkyl sulfoxide in 77% yield with 76% ee (entry 9) after 2 h at 0 °C.

In summary, we have developed an efficient asymmetric oxidation of sulfides using chiral Salen-Mn(III) catalysts under mild conditions. Optically active sulfoxides were obtained in moderate to high yields and enantioselectivities in the presence of 1 mol% catalyst.

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11. Katsuki group also showed that Mn-salen complex bearing binaphthyl group provided better results compared to simple Mn-salen complex; see reference 10a.