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Mn-Salen Catalyzed Asymmetric Oxidation of Enol Derivatives

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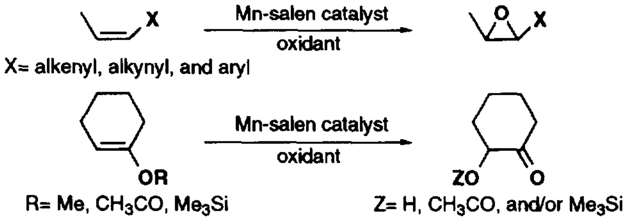
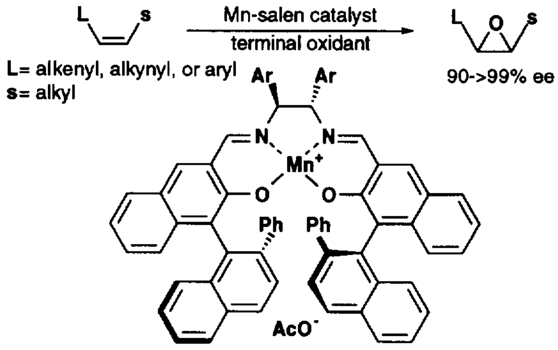
Abstract: Mn-salen complex **1** was found to catalyze highly enantioselective oxidation of enol ethers with iodosylbenzene as a terminal oxidant giving the corresponding hydroxy acetals, when the reaction was carried out in an alcoholic solvent. The reactions in the usual solvents such as dichloromethane and acetonitrile showed irregular and lower enantioselectivity, partly due to racemization of the resulting α-hydroxy ketones. Copyright © 1996 Elsevier Science Ltd

Optically active (salen)manganese(III) complexes (hereafter referred to as Mn-salen complexes) have been found to be effective catalysts of asymmetric epoxidation of simple conjugated olefins.[1,2] Recently, Norrby and Åkermark[3] and we[4] independently proposed that Mn-salen catalyzed epoxidation proceeds through a metallaoxetane intermediate and we attributed the high enantioselectivity observed in this reaction to twofold stereodifferentiation, enantioselective metallaoxetane formation and diastereoselective decomposition of the metallaoxetane.[4] This proposal suggested that olefins bearing a radical stabilizing group as a substituent could be good substrates for Mn-salen catalyzed epoxidation. It is well known that a radical on the carbon α to the hetero atom is stabilized by its interaction with lone pair electrons. Accordingly, olefins such as enol ether and its derivatives are expected to be good substrates for Mn-salen catalyzed oxidation (Scheme 1). However, oxidation of simple enol ethers with Mn-salen catalyst had showed only moderate enantioselectivity of up to 61%.[5] Only the oxidation of dienol acetates, 2-acetoxycyclopentadiene and 2-acetoxy-5,5-dimethyl-cyclohexa-1,3-diene, showed moderate to good enantioselectivity, giving 5-acetoxy-2-cyclopentenone of 71% ee and 6-acetoxy-4,4-dimethyl-2-cyclohexenone of 85% ee, respectively, but these substrates are a kind of conjugated olefins.[6] Thus, the issue of asymmetric oxidation of simple enol ethers and esters remained unresolved. Recently, we found that Mn-salen complex **1** is an efficient catalyst for asymmetric epoxidation of simple conjugated olefins (Scheme 2).[2] We, therefore, further examined oxidation of enol ethers with **1** as a catalyst.

At first, we examined the oxidation of 1-methoxycyclohexene with **1** as a catalyst and iodosylbenzene as a terminal oxidant in the presence of 4-phenylpyridine *N*-oxide in various solvents at 0 °C and found that the



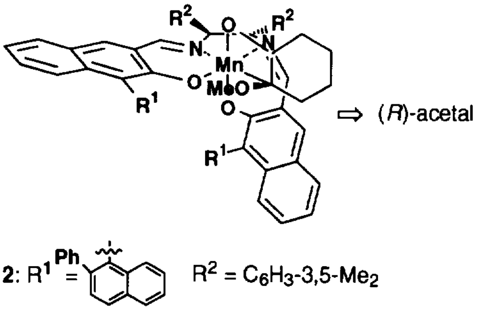
Scheme 1



1: Ar= 3,5-$(CH_3)_2C_6H_3$

Scheme 2

observed enantioselectivity is dependent upon reaction conditions. For example, oxidation with **1** in ethyl acetate, acetonitrile, or dichloromethane gave 2-hydroxycyclohexanone of 60, 58, 47% ee, respectively. Although the solvent used has been known to affect the enantioselectivity of epoxidation of simple olefins to some extent, the observed variation in enantioselectivity was considered to be partly attributable to racemization of the resulting α-hydroxy ketone which readily enolizes under basic or acidic conditions.[7] Since 2-hydroxycyclohexanone was considered to be produced by nucleophilic attack of water to the intermediary 1-methoxy-1,2-epoxycyclohexane, it was expected that an α-hydroxy acetal which is stable to neutral and basic conditions, would be obtained as a product, if the reaction is carried out in an alcoholic solvent. Actually, we found that the oxidation in methanol gave (*R*)-2-hydroxy-1,1-dimethoxycyclohexane and that enantioselectivity was improved up to 84% ee (Table 1, entry 1). The sense of asymmetric induction could be explained by our proposal on the reaction mechanism of Mn-salen catalyzed epoxidation:[4] The metallaoxetane intermediate **2** bearing a radical-stabilizing methoxy group at the carbon proximal to the manganese ion is converted faster to epoxide (and, in turn, to acetal) than the diastereomeric intermediate **3** bearing the methoxy group at the distal carbon. Thus, (*R*)-hydroxy acetal is obtained preferentially by way of the intermediate **2**. On the other hand, we have already reported that addition of a donor ligand such as pyridine *N*-oxide usually improves enantioselectivity in Mn-salen catalyzed epoxidation.[8] However, it was considered that coordination of the donor ligand was in equilibrium with that of alcohol and that the equilibrium was shifted toward coordination of the alcohol under the present reaction conditions using alcohol as a solvent. We then examined the reaction in the absence of 4-phenylpyridine *N*-oxide and found that the absence of a donor ligand did not affect enantioselectivity of the reaction (entry 2). Oxidation of 1-ethoxycyclohexene also showed a similar level of enantioselectivity (89% ee) to that of 1-methoxycyclohexene (entry 3). Oxidation of 1-ethoxycycloheptene, and 1-methoxy- and 1-ethoxy-cyclooctenes also showed good enantioselectivities, respectively (entries 4-6). On the other hand, conjugated enol derivatives such as 1-acetoxy-1,3-cyclohexadiene and 2-acetoxy-1,3-



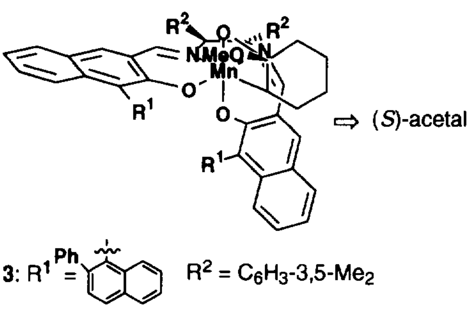
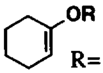
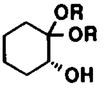
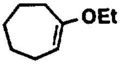
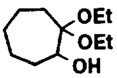
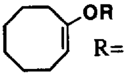
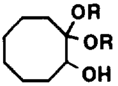
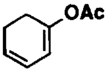
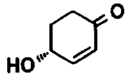
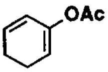
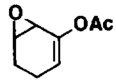


Table 1. Asymmetric Oxidation of Enol Derivatives using Mn-Salen Catalyst **1** as a Catalyst[a]

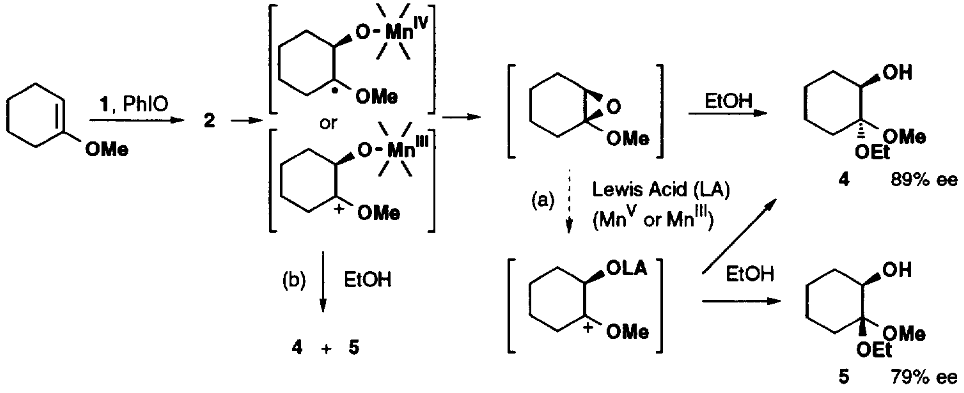
entry	substrate	solvent	oxidant (eq)	time (h)	product	yield (%)[b]	% ee	$[\alpha]_D(CHCl_3)$[c]	Confign
1	 R= Me	MeOH	PhIO (1 eq)	4	 R= Me	31	84[d,e]	-0.2 (c 0.68)	*R*[f]
2	"	MeOH	PhIO (1 eq)	4	"	38	85[d]	-0.2 (c 0.68)	*R*[f]
3	", R= Et	EtOH	PhIO (2 eq)	8	", R= Et	58	89[g]	-8.1 (c 0.87)	*R*[f]
4		EtOH	PhIO (2 eq)	8		55	81[g]	+2.5 (c 0.67)	-[h]
5	 R= Me	MeOH	PhIO (1 eq)	4	 R= Me	60	83[d]	+7.1 (c 0.77)	-[h]
6	", R= Et	EtOH	PhIO (2 eq)	8	", R= Et	68	88[g]	+1.4 (c 0.68)	-[h]
7		AcOEt	NaOCl (1 eq)	1		45	86[e,i]	+46.3 (c 0.42)	*R*[j]
8		AcOEt	NaOCl (1 eq)	1		34	94[d,e]	-16.6 (c 0.26)	-[h]
9	"	MeOH	PhIO (1 eq)	4	"	6	84[d]		-[h]

[a] All the reactions were carried out at 0 °C.
[b] Isolated yield.
[c] Optical rotation was measured in chloroform.
[d] Determined by ^1H NMR (270 MHz) analysis using chiral shift reagent $[Eu(hfc)_3]$.
[e] The reaction was carried out in the presence of 4-phenylpyridine *N*-oxide.
[f] Determined by chiroptical comparison after the acetal was converted into 2-hydroxycyclohexanone $[\alpha]_D$ +9.4 (c 0.05, $CHCl_3$), (Lit., $[\alpha]_D$ +13.4 (c 0.01, $CHCl_3$) for *R*iisomer. D'Accolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993**, 58, 3600-3601. Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, 33, 7823-7826.)
[g] Determined by HPLC analysis using DAICEL CHIRALCEL OF (hexane/*i*-PrOH = 400/1).
[h] Configuration has not been determined.
[i] Determined by HPLC analysis using DAICEL CHIRALCEL OB-H (hexane/*i*-PrOH = 2/1).
[j] Determined by chiroptical comparison (Lit., $[\alpha]_D$ -95 (c 0.06, $CHCl_3$) for 4*S*-isomer. Brünjes, R.; Tilstam, U.; Winterfeldt. E. *Chem. Ber.* **1991**, 124, 1677-1678.)

cyclohexadiene, showed higher asymmetric induction, when the oxidation was carried out in the presence of a donor ligand in a non-alcoholic solvent such as ethyl acetate using aqueous sodium hypochlorite as a terminal oxidant (entries 7-9).

We next examined the oxidation of 1-methoxycyclohexene in ethanol in the expectation of obtaining a diastereomerically pure mixed acetal. However, the reaction gave a 9:1 mixture of two diastereomers (**4** and **5**).[9,10,11] These results apparently can be explained by two possible pathways (Scheme 3). One possibility is that the intermediary epoxide undergoes ring opening to give the cationic intermediate (route a). The other is that the C-M bond of the metallaoxetane intermediate undergoes heterolytic cleavage to give another cationic intermediate (route b).[12,13,14] More study is required to draw a conclusion on the reaction mechanism.

A typical experimental procedure is exemplified with oxidation of 1-ethoxycyclooctene with **1** as a catalyst: To a 5 ml round-bottomed flask were added 1-ethoxycyclooctene (77.1 mg, 0.50 mmol), **1** (14.1 mg, 12.5 μmol) and ethanol (6.3 ml). After cooling the mixture to 0 °C, iodosylbenzene (110.0 mg, 0.50 mmol) was added at the same temperature and the whole mixture was stirred. After 4 h, another equivalent of iodosylbenzene (110.0 mg, 0.50 mmol) was added and the mixture was stirred for an additional 4 h. Then dimethyl sulfide was added to the mixture and stirred for another 20 min. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate= 9/1) to give 2-hydroxy-1,1-diethoxycyclooctane (73.8 mg, 68%). The enantiomeric excess of this sample was determined to be 88% by HPLC analysis using DAICEL CHIRALCEL OF (hexane/*i*-PrOH = 400/1) after benzoylation. ^1H



Scheme 3

NMR (270 MHz) of 2-hydroxy-1,1-diethoxycyclooctane: δ 3.95 (br d, 1H), 3.59-3.27 (m, 4H), 2.55 (br d, 1H), 2.16-1.38 (m, 12H), 1.05 (t, $J = 7.1$ Hz, 3H), 1.04 (t, $J = 7.1$ Hz, 3H).

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† Research Fellow of the Japan Society for the Promotion of Science.

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6. Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, 35, 669-672.
7. For example, the optical purity of 2-hydroxytetralone decreased on standing under the reaction conditions.
8. Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1991**, 265-266.
9. Relative configurations of **4** and **5** are tentatively assigned by ^{1}H NMR analysis of the corresponding acetates. The signal of the methoxy group of **4** appears at lower field than that of **5** due to the anisotropic effect of the vicinal C-O bond.
10. This mixture is not a thermodynamic but a kinetic product. This is supported by the result that oxidation of 1-ethoxy-1-cyclohexane in methanol gave a 1: 9 mixture of **4** and **5**.
11. The enantiomeric excesses of **4** and **5** were determined as described in Scheme 3 by HPLC analysis using DAICEL CHIRALCEL OF (hexane/*i*-PrOH = 600/1 and 400/1, respectively) after chromatographic separation (SiO2, hexane/ethyl acetate =19/1). Configuration of the carbinol carbon in **4** and **5** was determined as described in the footnote f to Table 1.
12. Involvement of the cationic rearrangement has been proposed for metalloporphyrin and Cr-salen catalyzed epoxidation. Meunier, B.*Chem. Rev.* **1992**, 92, 1411-1456.
13. Although we have proposed that the diastereoselective homolytic cleavage of the Mn-C bond of the metallaoxetane intermediate explains the stereochemistry observed in the epoxidation of simple olefins (ref. 4), the diastereoselective heterolytic cleavage of the Mn-C bond equally explains the stereochemistry of the epoxidation and it is well known that the cation at the carbon bearing an alkoxy group is strongly stabilized by the lone pair electrons of the oxygen atom.
14. Heterolysis of the O-M bond has been proposed by Norrby et al. (ref. 3).

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