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Mn-Salen Catalyzed Asymmetric Epoxidation of (±)-3-Alkylindene: Reagent-Dependent Stereoselectivity

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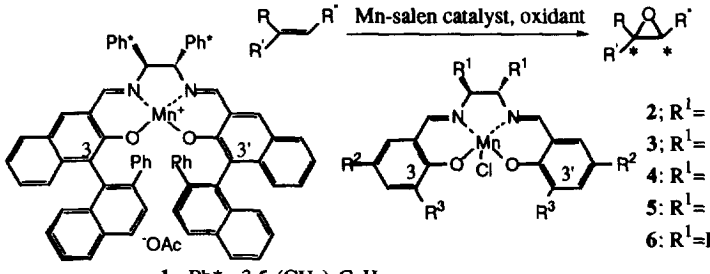
Abstract: Epoxidation of (±)-3-alkylindenes was examined with various (salen)manganese(III) complexes as catalysts and, from the analysis of the obtained data, it was found that the location and nature of C3- and C3'-substituents of the Mn-catalysts strongly influenced the stereochemistry of the epoxidation. Copyright © 1996 Elsevier Science Ltd

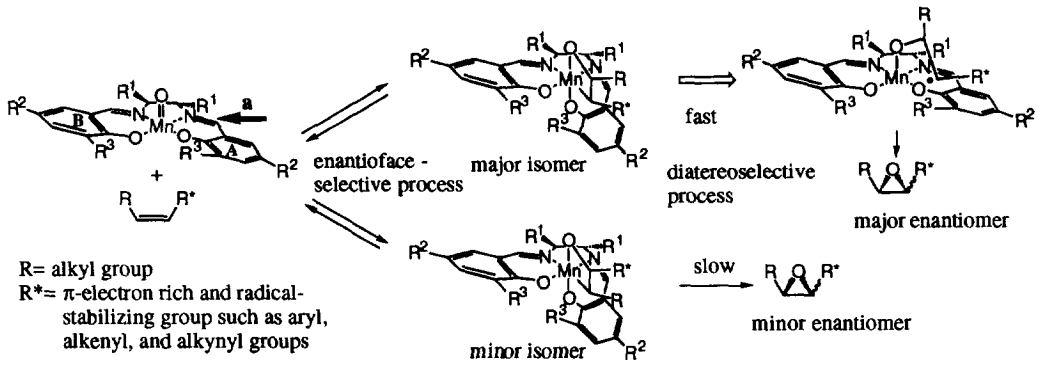
Many excellent metal-catalyzed asymmetric reactions have been developed in the past decade. In these reactions, the asymmetric coordination atmosphere around the metal center of the catalyst differentiates the enantiomeric faces or enantiotopic groups in achiral substrates and the enantiomers in racemic substrates. Naturally, the catalyst which is effective for the enantioface-differentiating reaction of achiral substrates, is often effective for the enantiomer-differentiating reaction of racemic substrates of a similar class, as exemplified by the asymmetric epoxidation of primary allylic alcohols and kinetic resolution of racemic secondary allylic alcohols using titanium-tartrate complex as a catalyst.[1] Recently, (salen)manganese(III) complexes (hereafter referred to as Mn-salen complex) were found to be effective catalysts for asymmetric epoxidation of achiral conjugated olefins.[2] Thus, we examined the kinetic resolution of racemic conjugated olefins with Mn-salen catalyst **1**. Contrary to our expectation, efficiency of the kinetic resolution was low. For example, the relative rate (k_{fast}/k_{slow}) was only modest (ca. 7.5) when (±)-3-isopropylindene was epoxidized with the catalyst **1** which showed high enantioselectivity of 98% ee in the epoxidation of indene.[2a]

We recently proposed that oxo Mn-salen complexes have non-planar structures as depicted in Scheme 1 and that olefins approach the metal-oxo bond along the pathway (**a**) beyond the downward benzene ring (**A**).[3] We also proposed that the oxygen atom transfer from oxo Mn-salen species to olefins proceeds through metallaoxetane and radical intermediates in tandem, on the basis of a non-linear relationship between enantioselectivity and reaction temperature and that enantioselectivity of the reaction is determined by enantioface selectivity in the metallaoxetane formation and diastereoselectivity in the decomposition of the



1 Ph*= 3,5-$(CH_3)_2C_6H_4$

2; R^1= $(CH_2)_4$, R^2=OSi-*i*-Pr_3, R^3= *t*-Bu
3; R^1= $(CH_2)_4$, R^2=R^3= *t*-Bu
4: R^1= H, R^2=R^3= *t*-Bu
5: R^1= H, R^2=H, R^3= *t*-Bu
6: R^1=R^2=R^3= H



Scheme 1

metallaoxetane.[3,4] Furthermore, we had proposed that efficiency of enantioface differentiation in the first step is determined by steric and electronic repulsions between the salen ligand and the substituent of the incoming olefin; that is, the incoming olefin orientates its bulky and/or π-electron rich substituent away from C3-substituent (R^3).[5] To understand the above unexpected results obtained in the epoxidation of (±)-3-alkylindene with **1**, we further examined the reaction with various types of Mn-salen catalysts (**1**, **3**-**6**). The analysis of the obtained data provided useful information on which factors contribute to the stereocontrol by Mn-salen catalyst. Concurrent with our study, Jacobsen et al. independently reported the kinetic resolution of racemic 2,2-dialkylated chromene derivatives with their catalyst **2** but the relative rate was also modest (4.5~9.3).[6]

We first examined *trans-cis* selectivity of the epoxidation of (±)-3-methylindene with achiral oxidant or catalysts (Table 1). *Trans-cis* selectivity is mainly controlled by the steric factor (*vide infra*). Thus, epoxidation with a sterically less bulky oxidizing agent or catalyst shows lower selectivity. For example, epoxidation of (±)-3-methylindene with *m*-chloroperbenzoic acid (MCPBA) showed no selectivity, while epoxidation with sterically bulky TMPMnCl [TMP= 5,10,15,20-tetrakis(2,4,6-trimethylphenyl)-21*H*,23*H*-porphine] showed moderate *trans*-selectivity (entries 1 and 2). Complexes **4** and **5** also showed moderate but higher *trans*-selectivity than complex **6**, suggesting that the incoming olefin approaches along the pathway (**a**) passing nearby the C3 (or C3')-*t*-butyl group. That complexes **4** and **5** show an equal level of *trans*-selectivity can be explained by considering that salen ligands have a non-planar structure as described in Scheme 1 and, therefore, the C5'-*t*-butyl group (R^2 in Scheme 1) does not interact with the incoming olefin.[3] Similar trends were observed in the epoxidation of (±)-3-isopropylindene (entries 11-13).

We next examined the epoxidation with optically active Mn-salen catalysts and found that seemingly bulky **1** showed lower *trans*-selectivity (entries 6-8 and 14-16) than **3** which exhibited a similar level of *trans*-selectivity to **4** (entries 9, 10 and 17), while complex **1** showed considerably higher enantioselectivity than **3**. Both the kinetic resolutions using complex **1** or **3** showed poor results [k_{rel}= 2.6 and 4-5[7,8] for 3-methylindene and 7.5 and 4-5[7] for 3-isopropylindene, respectively (entries 6, 9, 14 and 17)]. Differing from the epoxidation with an achiral catalyst, reaction of *R*- and *S*-isomers of (±)-3-alkylindenes with optically active catalysts proceeds with different selectivity (If the catalyst is achiral, olefins can approach it from both C5- and C5'-sides equally so that *R*- and *S*-isomers show the same selectivity. However, in the case that the catalyst is chiral, olefins can approach it only from one side and *R*- and *S*-isomers behave differently.). *Trans-cis* selectivity, enantioselectivity, and efficiency of kinetic resolution now depend upon steric and electronic repulsions between the salen ligand and the olefinic substituent and upon the radical-stabilizing ability[3] of the olefinic substituent. Although there are two stereoselective steps in Mn-salen catalyzed epoxidation (Scheme 1), diastereoselectivity in the metallaoxetane cleavage step is considered to be mainly affected not by the structure of the Mn-salen catalyst used but by the nature of the olefinic substituent.[3] Thus, the difference in the stereochemistry of the reactions using **1** and **3** should be attributed to the difference in stereochemistry of the first step, which is mainly dictated by steric and electronic factors (*vide infra*).[5] Therefore, the selectivity

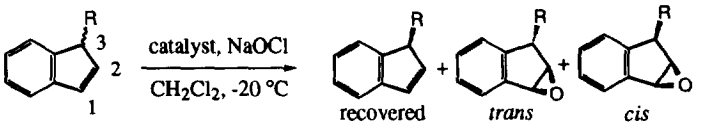


Table 1. Epoxidation of 3-Alkylindene under Various Conditions[a)]

entry	substrate (R)	catalyst or oxidizing agent	conversion (%)	*trans*/*cis*[b)]	% ee[c)] recovered	%ee[d)] (*cis*)	%ee[d)] (*trans*)	relative rate	confign (*cis*)	confign (*trans*)
1	Me	MCPBA	50	1	-	-	-	-	-	-
2	"	TMPMnCl[e)]	57	6.5	-	-	-	-	-	-
3	"	**4**[e)]	40	6.2	-	-	-	-	-	-
4	"	**5**[e)]	100	5.7	-	-	-	-	-	-
5	"	**6**[e)]	23	3	-	-	-	-	-	-
6	"	**1**[e)]	11	2.7	5.5	>99	95	2.6	1*S*,2*R*,3*R*[f)]	1*S*,2*R*,3*S*[g)]
7	"	"[e)]	87	1.7	82	98	93	-	-	-
8	"	"[e)]	100	1.2	-	93	91	-	-	-
9	"	**3**[e)]	8	6.3	6.5	82	87	4-5	1*S*,2*R*,3*R*	1*S*,2*R*,3*S*
10	"	"[e)]	25	6	22	84	85	-	-	-
11	*i*-Pr	**4**[e)]	64	55	-	-	-	-	-	-
12	"	**5**[e)]	58	83	-	-	-	-	-	-
13	"	**6**[e)]	15	20	-	-	-	-	-	-
14	"	**1**[e)]	11	10	7.0	>99	92	7.5	1*S*,2*R*,3*R*[f)]	1*S*,2*R*,3*S*[g)]
15	"	"[e)]	51	6.4	61	>99	87	-	-	-
16	"	"[e)]	90	2.5	100	>99	67	-	-	-
17	"	**3**[e)]	5.6	60	5.7	35	64	4-5	1*S*,2*R*,3*R*	1*S*,2*R*,3*S*

a) Reaction was carried out with a Mn-salen catalyst (0.02 eq) using NaOCl as a terminal oxidant or with MCPBA (1 eq) in dichloromethane at -20 °C.
b) Determined by ^{1}H NMR analysis (400 MHz).
c) Determined by GC analysis using chiral fused silica capillary column (SPELCO α-DEX 120 for alkyl= methyl and SPELCO β-DEX 120 for alkyl= isopropyl, respectively).
d) Determined by ^{1}H NMR analysis (400 MHz) using chiral shift reagent [Eu(hfc)$_3$].
e) Reaction was carried out in the presence of 4-phenylpyridine *N*-oxide.
f) Determined by chemical correlation: *Cis*-epoxide was converted to the corresponding (1*R*,2*S*)-1-alkyl-2-acetoxyindane (alkyl= methyl or isopropyl) which was derived from (1*S*,2*R*)-1,2-epoxyindane in a stereochemically established manner.
g) Determined by chemical correlation: *Trans*-epoxide was converted to the corresponding (1*R*,2*R*)-1-alkyl-2-acetoxyindane which was derived from (1*S*,2*R*)-1,2-epoxyindane in a stereochemically established manner.

observed should be rationally explained by considering the spatial location of C3- and C3'-substituents and their steric and electronic natures. The C3(C3')-*t*-butyl group in oxo-**3** (hereafter, the oxo Mn-salen species derived from **1** and **3** are referred to as oxo-**1** and oxo-**3**, respectively) is displaced closer to the oxo ligand than the phenyl group in oxo-**1**, as described in Fig. 1. The C3'-*t*-butyl group in **3** causes steric repulsion with an olefinic substituent but the phenyl group in **1** causes mainly π-electronic repulsions when the substituent is an unsaturated group, since the range of van der Waals repulsion is short but that of coulombic repulsion is relatively long. Accordingly, the orientation of the olefin approaching **3** is mainly controlled by the steric factor and high *trans*-selectivity equal to that observed with **4** is realized at the beginning of the reaction. However, *trans*-selectivity gradually drops as the reaction proceeds, because the slow-reacting isomer shows lower *trans*-selectivity than the fast-reacting isomer (e.g., entries 9 and 10). The sense of enantioselection in the epoxidation of (*R*)- or (*S*)-3-alkylindene is the same as that of indene, because the metallaoxetane derived from the orientation (**A** or **C**) decomposes faster to epoxide by way of radical intermediate than the

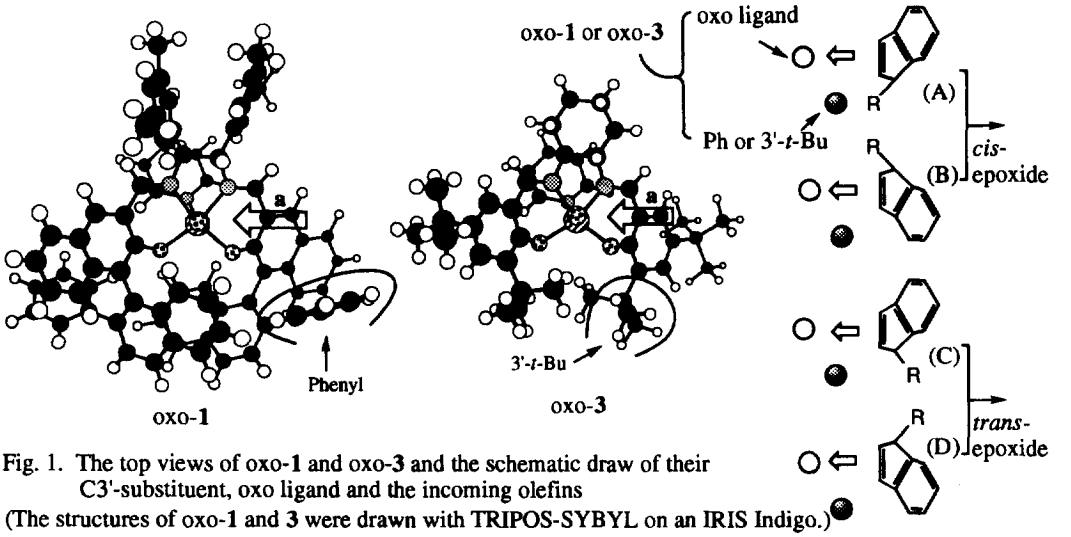


Fig. 1. The top views of oxo-**1** and oxo-**3** and the schematic draw of their C3'-substituent, oxo ligand and the incoming olefins
(The structures of oxo-**1** and **3** were drawn with TRIPOS-SYBYL on an IRIS Indigo.)

metallaoxetane from **B** or **D** (Fig. 1 and Scheme 1).[3] However, π-electronic repulsion between the olefinic substituent and the salen ligand is weak and the orientations (**B** and **D**) are not strongly disfavored. Accordingly, the enantioselectivity by **3** is moderate to good (entries 9, 17). On the other hand, higher enantio- and lower *trans*-selectivities were observed in the epoxidation with **1**. The phenyl group of **1** is located apart from the incoming olefin so that even the (*S*)-olefin of orientation (**A**) can approach without severe steric repulsion, but the phenyl group causes electronic repulsion with unsaturated olefinic substituent making the orientation (**B** or **D**) unfavorable. The (*R*)-olefin of orientation (**C**) can approach very easily. Accordingly, **1** shows high enantioselectivity and low *trans*-selectivity (entries 6 and 14).

In this study, we were able to disclose the factor controlling the stereochemistry of Mn-salen catalyzed epoxidation. This new knowledge will be the basis for the construction of more effective Mn-salen catalyst for kinetic resolution of racemic simple olefins.

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7. Precise values could not be determined because the oxidation with **3** gave unidentified side products.
8. Complex **2** also showed the modest relative rate (k_{rel}≈ 3) in the epoxidation of 3-methylindene. The ratio of *trans*- and *cis*-epoxides was 4:1 and their enantiomeric excesses were 87 and 92%, respectively, when 19% of the starting material were consumed.

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