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Unusual Solvent-Effect in Stereochemistry of Asymmetric Epoxidation Using a (Salen)chromium(III) Complex as a Catalyst

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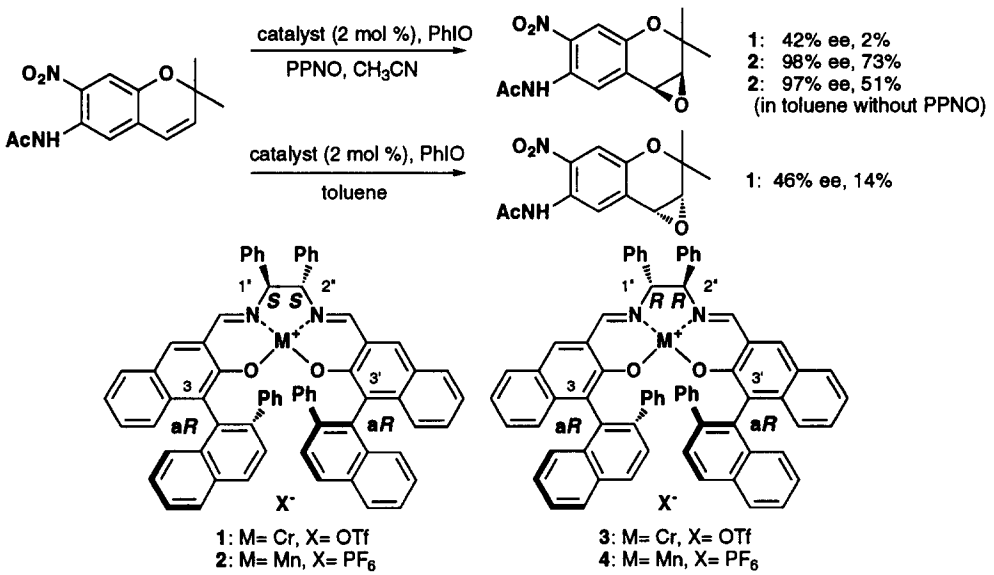
Abstract: Epoxidation of conjugated olefins has been examined with (salen)chromium(III) complexes as catalysts. Although (salen)chromium(III) complexes were catalytically less active than the corresponding (salen)manganese(III) complexes, the reactions with the chromium complexes were found to exhibit interesting solvent-dependent stereochemistry. Copyright © 1996 Elsevier Science Ltd

Many metallosalen complexes catalyze oxidation reactions such as epoxidation and oxidation of sulfides. Among them, optically active (salen)manganese(III) complexes have attracted the attention of chemists due to their high catalytic activity as well as high asymmetry-inducing ability in epoxidation of conjugated olefins and oxidation of alkyl aryl sulfides.[1] However, asymmetric oxidation using other metallosalen complexes as catalysts has not been fully examined. Recently, Gilheany *et al.* reported that an optically active (salen)chromium(III) complex (hereafter referred to as Cr-salen complex) bearing a chloro-substituent at C3, C3', C5, and C5' showed high asymmetric induction of 83% ee in the epoxidation of *trans*-β-methylstyrene, when triphenylphosphine oxide was added to the reaction medium.[2] However, their study is limited to epoxidation of *trans*- and *cis*-β-methylstyrenes and the scope of Cr-salen catalyzed epoxidation is still unclear. We had also studied epoxidation with Cr-salen complexes bearing the ligand identical with chiral Mn-salen complexes which were proven to be good catalysts for asymmetric epoxidation, but problems of low catalytic activity and low asymmetric induction were always encountered. For example, epoxidation of

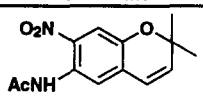
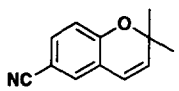


Scheme 1

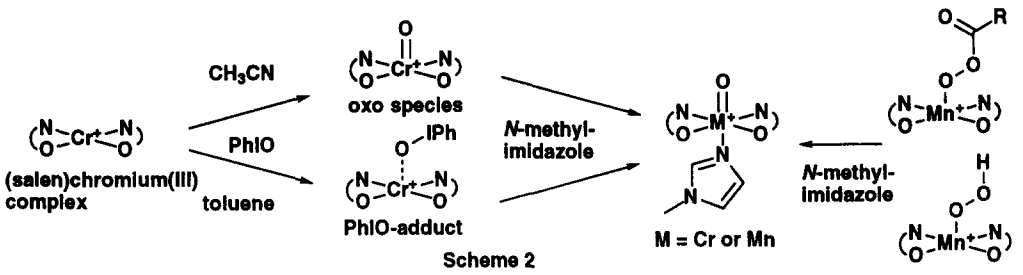
6-acetamido-7-nitro-2,2-dimethylchromene with Cr-complex **1**[3] in the presence of 4-phenylpyridine *N*-oxide (PPNO) in acetonitrile gave the corresponding (3*S*,4*S*)-epoxide of 42% ee in 2% yield, while that with Mn-complex **2** gave the same epoxide of 98% ee in 73% yield (Scheme 1). Recently, however, we found that the stereochemistry of Cr-catalyzed epoxidation was strongly dependent upon the solvent and the donor ligand used, differing from that of Mn-catalyzed epoxidation. For example, epoxidation of the same substrate with **1** in toluene without PPNO gave the (3*R*,4*R*)-epoxide of 46% ee, while epoxidation with **2** in toluene gave the (3*S*,4*S*)-epoxide of 97% ee (Scheme 1). We also found that complex **3**, the diastereomer of **1**, exhibited stereochemical behavior similar to **1** but showed higher enantioselectivity than **1**.[4] In this paper, we describe the unusual stereochemistry of Cr-salen catalyzed epoxidation.

We first examined the epoxidation of 6-acetamido-7-nitro-2,2-dimethylchromene with Cr-complex **3** (Table 1). A rough tendency was seen in that the reaction in a less polar solvent gave the (3*S*,4*S*)-epoxide and the reaction in a polar solvent gave the (3*R*,4*R*)-epoxide preferentially (entries 1-10) [dipole moment (D): CH_3CN, 3.94; C_6H_5Cl, 1.70; CH_2Cl_2, 1.62, $C_6H_5CH_3$, 0.37].[5] It was also observed that addition of PPNO was advantageous for the formation of the (3*R*,4*R*)-isomer, though the yields of epoxides were decreased. A similar trend was also observed in epoxidation of 6-cyano-2,2-dimethylchromene (entries 11-14). There seemed to be two possible explanations for these interesting stereochemistries observed in Cr-catalyzed epoxidation: i) Cr-complex **1** gives different active species in toluene and acetonitrile, respectively, and ii) Cr-catalyzed epoxidations in toluene and acetonitrile proceeds through different intermediates. It has already been established that treatment of Cr-salen complexes with iodosylbenzene in acetonitrile gives the corresponding oxo Cr-salen species (Scheme 2).[6] On the other hand, an iron(III)-porphyrin complex has been reported to form a complex with iodosylbenzene (PhIO) in dichloromethane, which epoxidizes olefins.[7] This suggested that treatment of a Cr-salen complex with PhIO in toluene might form a Cr-salen complex-

Table 1. Asymmetric epoxidation of conjugated olefins using Cr-salen complex **3** as a catalyst.[a)]

Entry	Substrate	Solvent	Donor ligand[b)]	Yield	% ee[c)]	Configuration[d)]
1		CH_3CN	PPNO	10	78	3*R*,4*R*
2	"	CH_3CN	-[e)]	32	52	3*R*,4*R*
3	"	CH_3CN	*N*-methylimidazole	5	23	3*R*,4*R*
4	"	C_6H_5Cl	PPNO	17	4	3*R*,4*R*
5	"	C_6H_5Cl	-[e)]	60	40	3*S*,4*S*
6	"	CH_2Cl_2	PPNO	11	1	3*S*,4*S*
7	"	CH_2Cl_2	-[e)]	26	19	3*S*,4*S*
8	"	toluene	PPNO	23	23	3*S*,4*S*
9	"	toluene	*N*-methylimidazole	6	41	3*S*,4*S*
10	"	toluene	-[e)]	56	65	3*S*,4*S*
11		CH_3CN	PPNO	24	76	3*R*,4*R*
12	"	CH_3CN	-[e)]	25	38	3*R*,4*R*
13	"	toluene	PPNO	12	14	3*S*,4*S*
14	"	toluene	-[e)]	39	51	3*S*,4*S*

a) The reaction was carried out at 0 °C for 3 h in the presence of 2 mol% of **3** by using iodosylbenzene as a terminal oxidant.
b) Twenty mol% of the donor ligand was added.
c) Determined by HPLC using DAICEL CHIRALCEL OJ (hexane:2-propanol=1:1)
d) Determined by comparison of the elution order of enantiomers with the authentic sample in HPLC analysis.
e) No donor ligand was added.

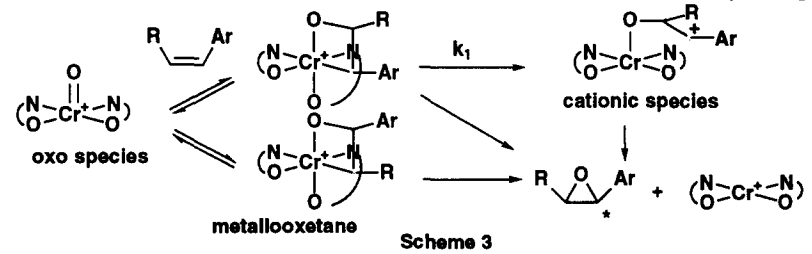


Scheme 2

PhIO adduct as an active species (Scheme 2). In parallel with this, it has been reported that *N*-alkylimidazole remarkably accelerates the conversion of acylperoxy- or hydroperoxy(salen)manganese species to the corresponding oxo species.[8] Thus, we expected that, even if the PhIO-adduct is formed in toluene, it would be converted to the oxo species by adding *N*-methylimidazole and reactions both in toluene and acetonitrile would proceed through a common intermediate to give the same product. Contrary to our expectation, the two reactions gave opposite enantiomers to each other (entries 3 and 9). This result did not seem compatible with the reaction mechanism described in Scheme 2, though it can not be excluded completely.[9] So, we explored another possibility.

Epoxidation with Mn-salen complexes as a catalyst has been proposed to proceed through metallaoxetane and radical intermediates in tandem.[10,11] In contrast, epoxidation with a Cr-salen complex in acetonitrile has been proposed to proceed through a cationic intermediate.[6] It is well known that the stereochemistry of radical reactions is not very strongly affected by polarity of the solvent used. As described above (Scheme 1), Mn-catalyzed epoxidation gave the same enantiomer, regardless of the solvents used. On the other hand, the stereochemistry of ionic reactions is affected by polarity of the solvent. Accordingly, we considered that epoxidation in acetonitrile proceeded mainly by way of metallaoxetane and cationic intermediates in tandem, while epoxidation in toluene preferentially follows the pathway only through a metallaoxetane intermediate (Scheme 3). If our speculation is correct, epoxidation of styrene derivatives (R= H), especially the derivative bearing an electron-withdrawing group, in toluene could avoid epimerization by the participation of the cationic species and show better enantioselectivity than the Mn-salen catalyzed epoxidation.[12,13] As expected, epoxidation of *p*-nitrostyrene in toluene showed good enantioselectivity of 70% ee and this enantioselectivity was better than that observed in the epoxidation of styrene (Table 2, entries 1 and 8). In contrast, the enantioselectivity of the epoxidation in acetonitrile was highly dependent on the substrate used. For example, epoxidation of *p*-nitrostyrene and styrene exhibited low enantioselectivity of 28 and <1% ee, respectively (entries 2 and 9), but that of *p*-chlorostyrenes showed enantioselectivity of 72% ee (entry 7), though the yields of the epoxides were poor. This is probably attributed to the fact that the conformation of the extended carbon chain in the cationic species is affected by the electronic nature and steric demand of the aryl moiety of the substrate and that the rate of the opening of metallaoxetane (k_1) is also affected by the electronic nature of the aryl substituent.

Reversal of stereochemistry by changing solvent suggests that the rates of each step (formation of diastereomeric metallaoxetane and their conversion into respective enantiomeric epoxides and/or cationic species) in epoxidation are affected by polarity of the solvent used, but further study is required to draw



Scheme 3

Table 2. Asymmetric epoxidation of styrene derivatives using **3** as a catalyst.[a)]

Entry	Substrate	Solvent	Donor ligand[b)]	Yield (%)[c)]	% ee	Sign of $[\alpha]_D$[d)]
1	*p*-nitrostyrene	$C_6H_5CH_3$	-[e)]	48	70[f)]	(+)(+)
2	"	CH_3CN	PPNO	10	28	(-)(-)
3	*p*-bromostyrene	$C_6H_5CH_3$	-[e)]	20	59[g)]	(-)(+)
4	"	CH_3CN	PPNO	7	61	(+)(-)
5	*p*-chlorostyrene	$C_6H_5CH_3$	-[e)]	41	54[g)]	(-)(+)
6	"	CH_3CN	-[e)]	25	22	(+)(-)
7	"	"	PPNO	5	72	(+)(-)
8	styrene	$C_6H_5CH_3$	-[e)]	28	51[h)]	(-)[i)](+)
9	"	CH_3CN	PPNO	7	<1	-

a) The reaction was carried out at 0 °C for 3 h in the presence of 2 mol% of **3** by using iodosylbenzene as a terminal oxidant.
b) Twenty mol% of donor ligand was added.
c) A small amount of the corresponding arylaldehyde (<10%) was also formed.
d) Optical rotation was measured in benzene and chloroform and their signs are described in the first and the second parentheses, respectively.
e) No donor ligand was added.
f) Determined by HPLC using DAICEL CHIRALCEL OB-H (hexane:2-propanol=9:1).
g) Determined by HPLC using DAICEL CHIRALCEL OB-H (hexane:2-propanol=1000:1).
h) Determined by HPLC using DAICEL CHIRALCEL OF (hexane:2-propanol=1000:1).
i) Configuration of styrene oxide was determined to be *S* by the comparison of the sign of optical rotation (reference 14).

conclusion about the solvent effect on stereochemistry.

In conclusion, the stereochemistry of Cr-salen catalyzed epoxidation was found to be highly solvent-dependent and the possibility that a pathway other than through the cationic intermediate exists in this reaction suggests that highly enantioselective epoxidation of styrene derivatives will be achieved by further modification of the Cr-salen catalyst and optimization of the reaction conditions.

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2. Bousquet, C. ; Gilheany, D. G. *Tetrahedron Lett.* **1995**, *36*, 7739-7742.
3. (Salen)chromium(III) complex (**1**) was synthesized from the corresponding Schiff base (reference 15) according to Kochi's procedure (reference 6).
4. In the case of manganese catalysts, complex **2** shows higher enantioselectivity than **4**.
5. The reaction without PPNO in acetone at 0 °C also gave the (3*R*,4*R*)-epoxide of 52% ee, while that in benzene at rt gave the (3*S*,4*S*)-epoxide of 60% ee.
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9. Differing from PhIO, pentafluoroiodosylbenzene has been reported to oxidize an iron-porphyrin complex to the corresponding oxo species smoothly (reference 7). Therefore, we examined the epoxidation of *p*-chlorostyrene using these two oxidants but both reactions in toluene and acetonitrile showed the same sense and similar level of enantioselectivity, respectively, suggesting that these two oxidants gave the same active species.
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12. Epoxidation of *p*-nitrostyrene at 0 °C using complex **2** or the structurally related Mn-salen complex shows enantioselectivity lower than 30% ee due to the epimerization at the stage of the radical intermediate (reference 11a).
13. Mn-salen catalyzed epoxidation of styrene derivatives at -78 °C using *m*-CPBA as an oxidant has been reported to show high enantioselectivity: Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333-9334.
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