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Asymmetric Benzylic Oxidation Using a Mn-Salen Complex as Catalyst

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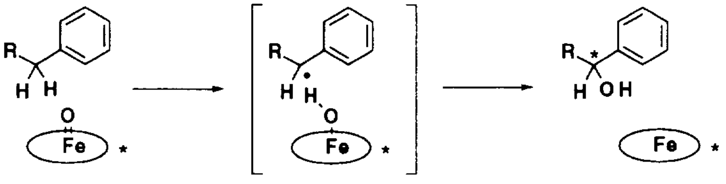
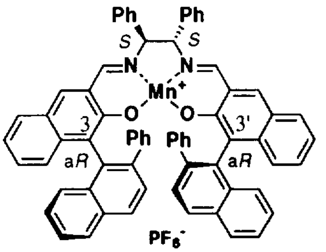
Abstract: Benzylic oxidation using a Mn-salen complex **3** as catalyst and iodosylbenzene as oxidant was found to proceed with moderate enantioselectivity to give the corresponding benzylic alcohol in solvents of high viscosity such as chlorobenzene and fluorobenzene. For example, the oxidation of 1,1-dimethylindane with **3** gave 3-hydroxy-1,1-dimethylindane of 64% ee. Copyright © 1996 Elsevier Science Ltd

Oxidizing enzyme, cytochrome P-450 which has an iron-porphyrin complex as an active site, catalyzes stereoselective oxidation of C=C and C-H bonds and many optically active metalloporphyrin complexes have been synthesized as model compounds of cytochrome P-450 to effect these oxidations stereoselectively in a flask.[1] While asymmetric oxidation of the C=C bond with metalloporphyrin complexes as catalysts has achieved considerable success, asymmetric oxidation of the C-H bond still remains at a preliminary stage.[2] In 1990, Groves *et al.* reported asymmetric benzylic oxidation of moderate to good enantioselectivity (up to 72% ee) by using a very sophisticated, optically active iron-porphyrin complex as a catalyst (Scheme 1).[3] This reaction has been proposed to proceed via a radical intermediate and enantioselectivity has been considered to depend both on the selectivity of the hydrogen abstraction step and on the relative rate of radical cage collapse, since the enantiomeric radical intermediates escape from the chiral ligand cage at different rates. On the other hand, (salen)manganese(III) complexes (hereafter referred to as Mn-salen complexes) have been found to be excellent catalysts for asymmetric epoxidation of simple olefins.[4] Mn-salen complexes have been known to catalyze oxidation of the C-H bond giving a hydroxy group[5], and optically active Mn-salen catalyst has been used for kinetic resolution of racemic 1,2-epoxy-3,4-dihydronaphthalene by effecting diastereomeric oxidation of the benzylic C-H bond.[6] However, enantioselective oxidation of the benzylic C-H bond has not been reported. Herein we describe our preliminary study on enantioselective benzylic oxidation using Mn-salen complexes (**1-4**) as catalysts.



Scheme 1 ⬭* = optically active porphyrin



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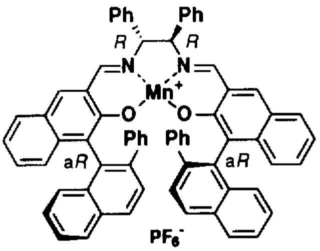

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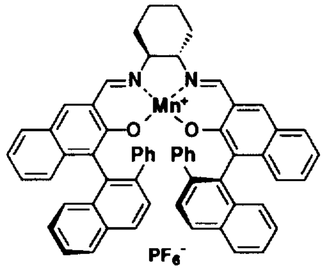

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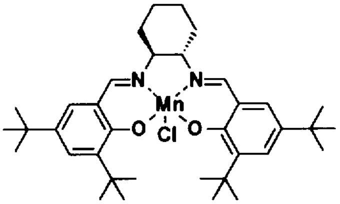

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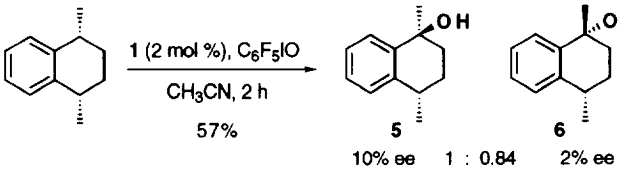

Scheme 2

To investigate whether Mn-salen catalyzed benzylic oxidation proceeds through a radical intermediate as proposed in the porphyrin-catalyzed oxidation,[3] we first examined the oxidation of *cis*-1,2,3,4-tetrahydro-1,4-dimethylnaphthalene using complex **1** as a catalyst and pentafluoroiodosylbenzene as a terminal oxidant in acetonitrile (Scheme 2). Reaction proceeded smoothly at room temperature to give a mixture of diastereomeric isomers (**5** and **6**)[7] in a ratio of 1:0.84, suggesting the participation of a radical intermediate.

We next examined oxidation of 1,1-dimethylindane with various catalysts (Table 1). (a*R*,*S*)-Complex **1** showed higher asymmetric induction than (a*R*,*R*)-complex **2** (entries 1 and 2). While the structure of the ethylenediamine moiety did not affect enantioselectivity, the chemical yield was influenced to a considerable extent (c.f. entries 1 and 3). Presence of the chirality at C3- and C3'-substituents seemed to be essential for asymmetric induction by the catalyst. Jacobsen's catalyst **4** which has no chirality at C3- and C3'-substituents showed almost no enantioselectivity (entry 4).

Although enantioselective escape of radical intermediates from the ligand cage further enhanced the enantioselectivity acquired at a proton abstraction step in Grove's hydroxylation reaction,[3] we considered that participation of a free radical intermediate might lower the enantioselectivity in the case of Mn-salen catalyzed hydroxylation,[8] since the salen ligand did not have any efficient cage structure and both the enantiomeric radical intermediates could dissociate from the catalyst at similar and rapid rates. Accordingly, participation of the free radical intermediate should be suppressed by some means. To deal with this problem, we examined oxidation in a solvent of high viscosity considering that such solvent would form a stout solvent cage.

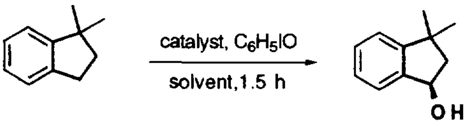

Table 1. Asymmetric Hydroxylation of 1,1-Dimethylindane using a Mn-Salen Complex as Catalyst[a]

Entry	Catalyst	Solvent	Temp.	% ee[b]	Yield (%)[c]	Confign[d]
1	**1**	CH_3CN	rt[e]	36	15	*R*
2	**2**	"	"	15	7	*R*
3	**3**	"	"	36	25	*R*
4	**4**	"	"	1	3	*R*
5	**3**	AcOEt	"	56	23	*R*
6	"	fluorobenzene	"	62	21	*R*
7	"	chlorobenzene	10 °C	64	29	*R*

a) Reaction was carried out with 2 mol % of a Mn-salen complex as catalyst and iodosylbenzene as terminal oxidant.

b) Determined by capillary GLC using optically active column (β-DEX™ 120).

c) Isolated yield.

d) Determined by modified Mosher's method; Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.

e) Room temperature was around 10 to 15 °C.

As expected, use of solvents of this kind considerably improved enantioselectivity and the highest ee of 64% was achieved when chlorobenzene was used (entries 5-7) [viscosity coefficient (25 °C): CH_3CN, 0.341; ethyl acetate, 0.426; fluorobenzene, 0.598; chlorobenzene, 0.799].[9] Under optimized conditions, we examined oxidation of various substrates (Table 2) and moderate enantioselectivity was observed in most cases.

Typical experimental procedure is exemplified with the hydroxylation of 1,1-dimethylindane using **3** as a catalyst: In a 5 ml round-bottom flask were placed 1,1-dimethylindane (14.6 mg, 0.1 mmol), **3** (2.2 mg, 2 μmol), and chlorobenzene (1 ml) and the mixture was subjected to freeze-drying. This solution was transferred

Table 2. Asymmetric Oxidation using **3** as a Catalyst[a]

Entry	Substrate	% ee	Yield (%)[b]	Confign	(% ee)[c]
1	ethylbenzene	53	22	*R*[d]	40
2	4-methoxyethylbenzene	53	19	*R*[e]	66
3	tetrahydronaphthalene	55	19	*R*[f]	72
4	1,2,3,4-tetrahydro-1,1-dimethylnaphthalene	56	28	-[g]	

a) Reaction was carried out in chlorobenzene at 10 °C for 1.5 h with 2 mol % of **3** as catalyst and iodosylbenzene as terminal oxidant.

b) Isolated yield.

c) Reported value with optically active iron-porphyrin complex as catalyst (ref. 3).

d) Determined by comparing the retention times of the enantiomers of the product (DAICEL CHIRALCEL OB-H, hexane-2-propanol= 9:1, flow rate= 0.5 ml/min) with that of commercially available (*R*)-1-phenylethanol.

e) Determined by chiroptical comparison; Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, 2, 601-612.

f) Determined by chiroptical comparison; Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880-2888.

g) Configuration has not been determined.

to a flask containing iodosylbenzene (22.0 mg, 0.1 mmol) by using a canula and stirred for 90 min at 10 °C. The reaction mixture was quenched by adding several drops of dimethylsulfide and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-ethyl acetate= 9:1) to give 3-hydroxy-1,1-dimethylindane (4.7 mg) in 29% yield. The optical purity of the product was determined to be 64% ee by capillary GLC using optically active column (β-DEX^{TM} 120).

Although there is ample room for improvement of this methodology, our study showed the potentiality of a Mn-salen complex as catalyst for asymmetric benzylic oxidation. Further investigation is under way in our laboratory.

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7. Racemic **6** was synthesized according to the reported procedure: Newman, M. S.; Dali, H. M.; Hung, W. M. *J. Org. Chem.* **1975**, *40*, 262-265. Absolute configurations of **5** and **6** are unknown. Enantiomeric excesses of **5** and **6** were determined by capillary GLC using optically active column (β-DEX^{TM} 120).
8. Since epoxidation of simple olefins and oxidation of sulfides with Mn-salen complexes proceed with high enantioselectivity (reference 4a), high enantioselectivity in the hydrogen abstraction step can very reasonably be expected.
9. Although the yield of the desired product was not very high under the present reaction conditions, prolongation of the reaction time did not improve the yield. This may suggest the decay of the catalyst during the reaction, but the enantioselectivity of the product did not change in the observed reaction time. The reaction with pentafluoroiodosylbenzene as oxidant also showed the same enantioselectivity.

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