Enantiotopic-Place Selective C-H Oxidation Using a (Salen)manganese(III) Complex as a Catalyst

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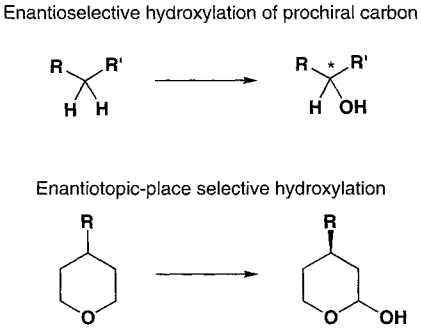
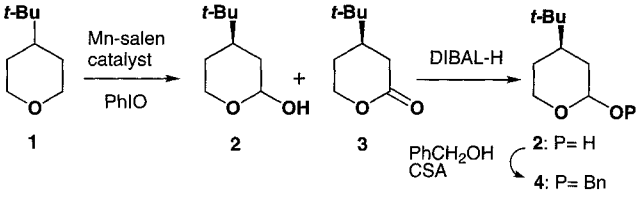
Abstract: A highly enantiotopic-place selective C-H oxidation of cyclic ether (up to 82% ee) was first achieved by using (*R,R*)-(salen)manganese(III) complex **8** as a catalyst.

Recent development of asymmetric metal catalysis has realized highly enantioface-selective oxidation of carbon-carbon double bonds.[1] However, highly enantioselective C-H bond oxidation except for the oxidation of activated benzylic[2] and allylic C-H bonds,[3] remained unsettled mainly due to the high stability of C-H σ-bond, which compels vigorous reaction conditions or use of highly reactive oxidants for the oxidation of C-H bond and makes realization of high enantioselectivity in this type of reaction difficult. However, there are many biological C-H bond oxidations which proceed with high stereo- and regioselectivity. These oxidations are catalyzed by oxidizing enzymes which carry metallocomplex(es) as their active site. For example, an iron-porphyrin complex exists in cytochrome•P-450 and a dinuclear non-heme iron complex does in methane monooxygenase. This suggests that a well-designed metal catalyst can be a good catalyst for enantioselective oxidation of C-H bond. Recently, we and others have demonstrated that (salen)manganese(III) complexes (hereafter referred to as Mn-salen complexes) are excellent catalysts for asymmetric epoxidation of simple olefins.[4] We have also disclosed that (salen)manganese(III) complexes are effective catalysts for enantioselective hydroxylation of a prochiral benzylic carbon.[2b] To further expand the scope of enantioselective C-H oxidation, we examined the enantiotopic-place selective hydroxylation of cyclic ethers (Scheme 1).



Scheme 1

Since the α-hydroxylation of non-substituted cyclic ethers provides lactols which readily undergo racemization, we used 4-(*t*-butyl)tetrahydropyran (**1**)[5] as a test material and examined its oxidation in chlorobenzene[6] using various (salen)manganese(III) complexes as catalysts and iodosylbenzene as a terminal oxidant (Scheme 2). These reactions afforded a mixture of the corresponding lactol **2** and lactone **3** as the products. To determine enantiotopic-place selectivity of the reaction, the mixture was directly treated with diisobutylaluminum hydride (DIBAL-H) to give the lactol which was in turn converted into the corresponding benzyl acetal **4**.[7] Enantiomeric excess of the benzyl acetal was determined by HPLC analysis. The results are summarized in Table 1. In asymmetric oxidations using (salen)manganese(III) catalyst, the relationship between the relative configuration of the catalyst and the degree of enantioselectivity varies with the substrate used.[4a,b] For example, (*R,S*)-complexes like **5-7** generally show higher enantioselectivity in epoxidation of olefins and benzylic hydroxylation than the corresponding (*R,R*)-complexes like **8-10**, while (*R,R*)-complexes show higher enantioselectivity in oxidation of sulfides than (*R,S*)-complexes. Thus, we examined oxidation of **1** with both (*R,S*)- and (*R,R*)-complexes and found that (*R,S*)-complexes **5-7** showed very poor enantioselectivity (entries 1-3). However, (*R,R*)-complex **8** showed modest enantioselectivity of 22% ee (entry 4). Enantioselectivity was enhanced up to 48% ee by lowering the reaction temperature (entries 5 and 6).

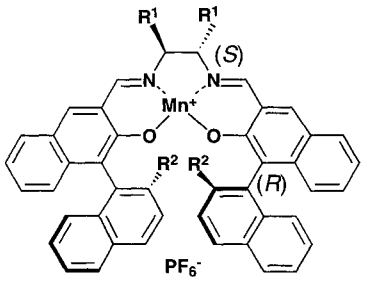


Scheme 2

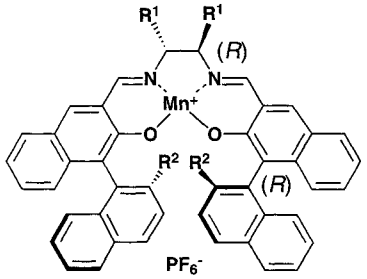
Table 1. Enantiotopic-place selective hydroxylation of **1** using (salen)manganese(III) complexes as catalysts[a)]

entry	catalyst	temp. (°C)	time (h)	yield(%)[b)]	% ee[c)]
1	**5**	10	2	12	3
2	**6**	10	1	12	3
3	**7**	10	2	2	3
4	**8**	10	2	12	22
5	"	-10	4	14	36
6	"	-40	71	13	48

a) The reaction was carried out in chlorobenzene by using 1 equivalent of iodosylbenzene as an oxidant.
b) Isolated yield of the lactol after DIBAL-H reduction.
c) Determined by HPLC using optically active column (DAICEL CHIRALCEL OD, hexane/*i*-PrOH 100:1).

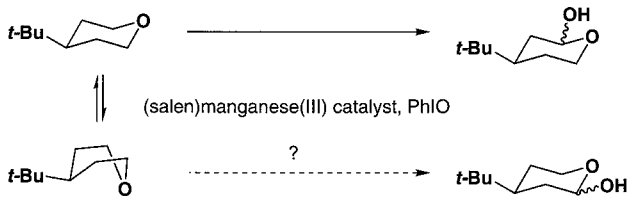


5: R^1= -$(CH_2)_4$-
R^2= Ph
6: R^1= -$(CH_2)_4$-
R^2= 4-TBDPSPh
7: R^1= Ph
R^2= 4-TBDPSPh



8: R^1= -$(CH_2)_4$-
R^2= Ph
9: R^1= -$(CH_2)_4$-
R^2= 4-TBDPSPh
10: R^1= Ph
R^2= 4-TBDPSPh

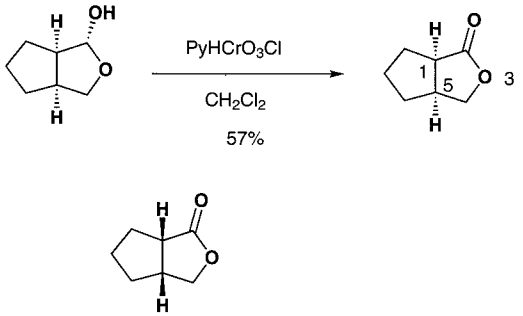
Recently, Koga and the co-worker have reported highly enantiotopic-place selective proton abstraction.[8] In this study, they reported that enantioselectivity of the reactions using cyclohexanone derivatives as substrates was affected by the participation of a boat conformation. In the present reaction, 4-(*t*-butyl)tetrahydropyran was considered to exist in a chair form preferentially but we could not exclude the possibility of the participation of its boat conformer which might show enantioselectivity opposite to the chair conformer (Scheme 3).



Scheme 3

Thus, we synthesized conformationally fixed 3-oxa-bicyclo[3.3.0]-octane (**11**)[9] and subjected to oxidation. Differing from the oxidation of 4-(*t*-butyl)tetrahydropyran, oxidation of **11** gave the corresponding lactol **12** as a single isomer and the formation of the lactone was not detected. This is probably because the hydroxy group of lactols takes sterically less hindered *exo*-orientation and oxidation of the *endo*-oriented C-H bond is strongly inhibited by steric hindrance. The enantiomeric excess of the lactol was determined by HPLC analysis after the lactol was converted into the corresponding benzyl acetal. The results are summarized in Table 2. (*R,S*)-Complexes **5-7** again showed poor enantioselectivity (entries 1-3), while (*R,R*)-complexes **8-10** showed moderate to good enantioselectivity. Especially oxidation with **8** gave the corresponding lactol of 77% ee (entry 4). We also examined oxidation of **11** with **8** in other solvents but the reaction in chlorobenzene gave the best result in terms of enantioselectivity and chemical yield (entries 5-8). The reaction at lower temperature (-30 °C) showed higher enantioselectivity of 82% ee together with better chemical yield (entry 9). The reaction at -40°C exhibited the same level of enantioselectivity (82% ee) but the yield of **12** decreased.

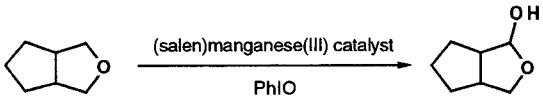
Absolute configuration of the lactol **12** obtained with **8** was determined to be 1*R*,5*S* by the comparison of the specific rotation after it was converted into the corresponding lactone (Scheme 4).



$[\alpha]_D^{23}$ −77° (*c* 0.29, $CHCl_3$)
Lit.[11] $[\alpha]_D^{20}$ +96.9° (*c* 1, $CHCl_3$)

Scheme 4

Typical experimental procedure is exemplified with the oxidation of **11** using **8** as a catalyst: In a 10 ml round-bottom flask were placed **11** (11.7 mg, 0.10 mmol), **8** (2.1 mg, 2 mol%), and chlorobenzene (1 ml) and the mixture was subjected to freeze-drying in nitrogen atmosphere. After the mixture was warmed to -30 °C, it was transferred to another flask containing iodosylbenzene (22 mg, 0.10 mmol) by using a cannula and stirred for 65 h at -30 °C. The reaction mixture was quenched by adding dimethyl sulfide (15 µl, 0.20 mmol) and directly subjected to column chromatography on silica gel (hexane-ethyl acetate= 7:3) to give the corresponding lactol (**12**, 7.9 mg) in 59% yield. The lactol was converted into the corresponding benzyl acetal by treatment with benzyl alcohol in the presence of catalytic amount of camphorsulfonic acid in dichloromethane and its optical purity was determined to be 82% ee by HPLC using optically active column (DAICEL CHIRALCEL OD, hexane/2-propanol 1000/1).



11 **12**

Table 2. Enantiotopic-place selective hydroxylation of **11** using (salen)manganese(III) complexes as catalysts[a)]

entry	catalyst	temp. (°C)	solvent	time (h)	yield (%)	% ee	Confign.
1	**5**	-10	C_6H_5Cl	1	26	3	(1*R*,5*S*)[b)]
2	**6**	-10	"	4	22	21	(1*R*,5*S*)[b)]
3	**7**	-10	"	2	28	19	(1*R*,5*S*)[b)]
4	**8**	-10	"	4	45	77	(1*R*,5*S*)[b)]
5	"	-10	C_6H_5F	4	29	73	(1*R*,5*S*)[b)]
6	"	-10	acetone	3.5	37	74	(1*R*,5*S*)[b)]
7	"	-10	CH_2Cl_2	4	9	69	(1*R*,5*S*)[b)]
8	"	-10	ethyl acetate	4	19	65	(1*R*,5*S*)[b)]
9	"	-30	C_6H_5Cl	65	59	82	(1*R*,5*S*)[c)]
10	**9**	-10	"	2	30	41	(1*R*,5*S*)[b)]
11	**10**	-10	"	3	27	42	(1*R*,5*S*)[b)]

a) The reaction was carried out by using 1 equivalent of iodosylbenzene as an oxidant.
b) Determined by the elution order of enantiomers in HPLC analysis using optically active column (DAICEL CHIRALCEL OD, hexane/2-propanol 1000/1).
c) For determination of the configuration, see the text.

In conclusion, we were able to disclose the first example of highly enantiotopic-place selective C-H oxidation. Further investigation is under way in our laboratory.

Acknowledgment Financial support from a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan, is gratefully acknowledged.

Reference and Notes

(1) For the recent review for asymmetric oxidation, see: a) In "Comprehensive Organic Synthesis" ed by Trost, B. M., Pergamon Press, Oxford, 1991, Vol. 7. b) In "Catalytic Asymmetric Synthesis" ed by Ojima, I., VCH, New York, 1993, Chapt. 4.

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(5) 4-(*t*-Butyl)tetrahydropyran was synthesized according to the reported procedure: Bailey, W. F.; Bischoff, J. J. *J. Org. Chem.* **1985**, *50*, 3009-3010.

(6) Chlorobenzene has been found to be the best solvent for asymmetric benzylic oxidation using (salen)manganese(III) complex as a catalyst (reference 2b).

(7) Although compound **4** was a mixture of *axial*- and *equatorial*-isomers, the values of enantiomeric excess of these two isomers were equal.

(8) Sobukawa, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 5101-5104.

(9) Compound **11** was synthesized from cyclopentene-1,2-dicarboxylic acid which was prepared according to the reported procedure (reference 10), by the sequence: i) Fisher's esterification, ii) catalytic hydrogenation with Pd-C, iii) LAH reduction of the resulting diethyl *cis*-cyclopentane-1,2-dicarboxylate, and iv) heating the resulting diol in DMSO.

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