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Asymmetric epoxidation using aqueous hydrogen peroxide as oxidant: bio-inspired construction of pentacoordinated Mn–salen complexes and their catalysis

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Abstract—Pentacoordinated Mn–salen complexes **1** and **5** possessing an internal pyridine or *N*-methylimidazole ligand, respectively, were found to be efficient catalysts for asymmetric epoxidation of conjugated *Z*-olefins using aqueous hydrogen peroxide. In particular, the epoxidation of chromene derivatives proceeded with high enantioselectivity greater than or equal to 97% ee.

Asymmetric epoxidation using aqueous hydrogen peroxide is a topic of current interest and much effort has been directed to this field of chemistry.[1] Since Juliá and co-workers reported chiral phase transfer-mediated asymmetric epoxidation using aqueous hydrogen peroxide,[2] many methodologies have been reported to date[3] but only a few methods have attained high enantioselectivity. Shi and co-workers reported that a fructose-derived ketone catalyzed epoxidation using aqueous hydrogen peroxide in acetonitrile in a highly enantioselective manner, albeit with moderate turnover number (TON).[4] Jørgensen and co-workers reported highly enantioselective epoxidation of α,β-unsaturated aldehydes using an organocatalyst in the presence of aqueous hydrogen peroxide.[5] We have recently disclosed that a di-μ-oxo Ti(salalen = half-reduced salen) complex serves as the catalyst for highly enantioselective epoxidation using 1 equiv of aqueous hydrogen peroxide with high TON (up to 4500).[6] On the other hand, the catalysis of a typical oxidizing enzyme, cytochrome P-450, that carries an ironporphyrin complex as its active site has been well studied. As a part of the studies of P-450's catalysis with modeling porphyrin complexes, it has been found that hydrogen peroxide or peracid serves as the terminal oxidant and that the ironporphyrin complex is oxidized with the oxidant to the corresponding oxo metal species through a synergetic push–pull mechanism:[7] the cleavage of the O–O bond of intermediary iron-hydroperoxo or -acylperoxo species is promoted by coordination of an imidazole group and protonation of the distal oxygen (in the case of acylperoxo species, protonation is not necessarily needed due to high dissociating ability of the acyloxy group)[7c,d,8] and generates the active iron-oxo species which undergoes oxidation. In 1993, Berkessel et al. reported biomimetic asymmetric epoxidation using a manganese(salalen) complex bearing an imidazole substituent at the C7 carbon in the presence of aqueous 1% hydrogen peroxide, albeit with moderate enantioselectivity,[9] wherein the imidazole group has been considered to coordinate at the apical position of the complex. Subsequently to this, Pietikäinen reported an intermolecular biomimetic version using a Mn–salen complex, aqueous hydrogen peroxide, *N*-methylimidazole, and ammonium acetate system.[10,11] We independently disclosed Mn–salen catalyzed asymmetric epoxidation using hydrogen peroxide under almost identical conditions.[12] During this study, we also found that the epoxidation using hydrogen peroxide proceeded even in the absence of a protonic substance, if an excess amount of *N*-methylimidazole was used. On the other hand, in the course of our study on asymmetric catalysis of Mn–salen complexes, we had found that asymmetry-inducing ability of a Mn–salen complex is strongly related to its conformation[13] and that introduction of a coordinating substituent such as a carboxylate group at the ethylenediamine unit causes inversion

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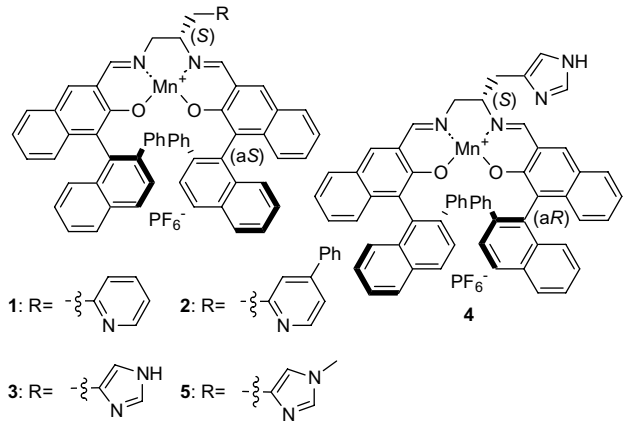
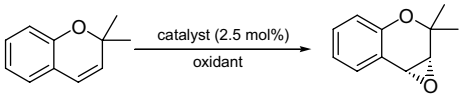


Figure 1.

of the conformation of the parent Mn–salen complex and reverses the sense of asymmetric induction, together with improvement of the TON of the catalyst.[14] Although biomimetic approaches to asymmetric epoxidation using hydrogen peroxide have hitherto achieved moderate success, we considered that it should be a promising one: based on the above-mentioned results, a Mn–salen complex bearing a nucleophilic substituent at its ethylenediamine unit would promote epoxidation using hydrogen peroxide in a highly asymmetric atmosphere without adding any external nucleophile, showing high enantioselectivity. Another advantage of this type of Mn–salen complex is that the coordination of the internal nucleophile always keeps one of the two apical sites available for coordination of hydrogen peroxide. Thus, we synthesized complexes **1**–**5**[15] bearing a (2-pyridyl)methyl, (4-phenyl-2-pyridyl)methyl, (1*H*-imidazol-4-yl)methyl or (*N*-methylimidazol-4-yl)methyl group as the nucleophilic substituent (Fig. 1) and first examined the epoxidation of 2,2-dimethylchromene in the presence of 3 equiv of aqueous hydrogen peroxide as the terminal oxidant, because some of the epoxy compounds derived from 2,2-disubstituted epoxychromane derivatives show unique physiological activity such as potent hypertensive activity of Cromakalim (Table 1).[16,17]

As expected, the reaction with **1** in dichloromethane proceeded at room temperature with high enantioselectivity of 95%, irrespective of the concentration of hydrogen peroxide, albeit with modest chemical yields (entry 1). The use of urea · hydrogen peroxide adduct instead of using aqueous hydrogen peroxide slightly reduced enantioselectivity (entry 2). On the other hand, lowering the reaction temperature to 0 °C somewhat improved both enantioselectivity (up to 97% ee) and the chemical yield (entry 3). Use of acetonitrile as solvent not only reduced chemical yield but also diminished enantioselectivity (entry 4).[18] It is noteworthy that the observed sense of asymmetric induction by complex **1** is opposite to that observed in the epoxidation with the (a*R*,*S*)-Mn–salen complexes bearing a cyclohexanediamine unit. This supports that the pyridyl substituent is coordinated

Table 1. Asymmetric epoxidation of 2,2-dimethylchromene catalyzed by **1**–**5**[a]

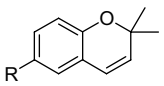
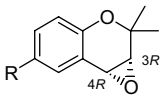
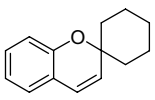
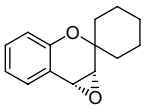
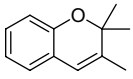
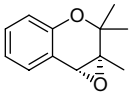
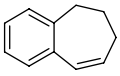
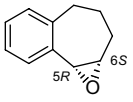
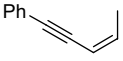
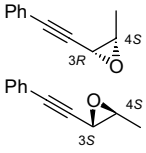
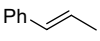


Entry	Catalyst	Oxidant	*T* (°C)	Yield (%)[b]	ee (%)[c]
1	**1**	30% H_2O_2 aq	rt	27	95
2	**1**	UHP[d]	rt	22	92
3	**1**	30% H_2O_2 aq	0	49–60	97
4[e]	**1**	30% H_2O_2 aq	0	28	90
5	**2**	30% H_2O_2 aq	0	67	96
6	**3**	30% H_2O_2 aq	0	26	95
7	**4**	30% H_2O_2 aq	0	12	83
8	**5**	30% H_2O_2 aq	0	63	97
9	**5**[f]	30% H_2O_2 aq	0	85	98
10	**5**[f]	30% H_2O_2 aq[g]	0	48	98
11	**5**[f]	30% H_2O_2 aq[g,h]	0	56	98
12	**5**[f]	30% H_2O_2 aq.[i]	0	67	98
13	**5**[f]	30% H_2O_2 aq[j]	0	80	98

[a] All the reactions were carried out for 24 h with 2.5 mol % of catalyst in the presence of 3 equiv of oxidant in dichloromethane, unless otherwise mentioned.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpack OB-H; hexane/*i*-PrOH 9:1). Absolute configuration was determined to be 3*R*,4*R* by chiroptical comparison (Ref. 19).
[d] 1 equiv of UHP was used as oxidant.
[e] Acetonitrile was used as a solvent.
[f] 5 mol % of **5** was used.
[g] 1 equiv of H_2O_2 was used.
[h] The reaction was carried out for 48 h.
[i] 1 equiv of H_2O_2 was added over the period of 8 h and the mixture was stirred for another 62 h.
[j] After the reaction was carried out with 1 equiv of H_2O_2 for 24 h, 2 equiv of H_2O_2 were added and the reaction mixture was stirred for another 24 h.

to the manganese ion and the conformation of the salen ligand is reversed.[14] Under the optimized conditions, we next examined the epoxidation with complexes **2**–**5** as catalyst (entries 5–8). It is noteworthy that all the a*S*,*S*-complexes showed high enantioselectivity (entries 5, 6, and 8), while the a*R*,*S*-complex **4** showed considerably inferior enantioselectivity (entry 7): in general, the (a*R*,*S*)-Mn–salen complex bearing a cyclohexanediamine unit is a superior catalyst for asymmetric epoxidation to the corresponding (a*S*,*S*)-Mn–salen complex and this fact also supports our hypothesis on the effect of the nucleophilic substituent.[14] Of the a*S*,*S*-complexes (**1**–**3**, and **5**), complex **5** was found to be the catalyst of choice in terms of yield and enantioselectivity. The reaction using 5 mol % of complex **5** and 3 equiv of aqueous hydrogen peroxide at 0 °C gave the desired epoxide of

Table 2. Asymmetric epoxidation using aqueous hydrogen peroxide[a]

Entry	Substrate	Product	Yield (%)	ee (%)
				
1	**6**; R = CN	R = CN	95[b]	99[c,d]
2	**7**; R = Br	R = Br	98[b]	98[e]
3	**8**; R = NO_2	R = NO_2	85[b]	99[c,d]
4	**9**; R = Me	R = Me	80[b]	97[e]
5	**10**; R = OMe	R = OMe	78[b]	98[f]
6	**11** 		84[b]	98[e]
7	**12** 		84[b]	97[g]
8	**13** 		95[h]	88[i,j]
9[k]			92[h]	90[i,j]
10[k]	**14** 		94 (4:1)[h,l]	88[m,n]
11	**15** 		58[h]	31[o,j]

[a] All the reactions were carried out for 24 h with 5 mol % of **5** and 3 equiv of aq 30% H_2O_2 in dichloromethane at 0 °C, unless otherwise mentioned.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpack OJ-H; hexane/*i*-PrOH 7:3).
[d] Determined by chiroptical comparison (Ref. 19).
[e] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpack OJ-H; hexane/*i*-PrOH 9:1).
[f] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpack OB-H; hexane/*i*-PrOH 7:3).
[g] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpack OB-H; hexane/*i*-PrOH 99:1).
[h] Determined by 1H NMR (400 MHz) spectroscopic analysis.
[i] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpack OB-H; hexane/*i*-PrOH 99.9:0.1).
[j] Determined by chiroptical comparison (Ref. 20).
[k] Complex **1** was used as catalyst.
[l] Product is a mixture of cis- and trans-epoxides. Numbers in parentheses are a ratio of cis- and trans-epoxides.
[m] Face selectivity. The face selectivity was calculated by the equation, face selectivity = [% ee(cis) × %(cis) + % ee(trans) × %(trans)]/100. % ee of cis-isomer (3*R*,4*S*) = 83 and that of trans-isomer (3*S*,4*S*) = 96. Ees were determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpack OJ-H; hexane/*i*-PrOH 99.9:0.1).
[n] Determined by chiroptical comparison (Refs. 6 and 11b).
[o] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpack IA; hexane/*i*-PrOH 99.9:0.1).

98% ee in 85% yield (entry 9). The reaction with 1 equiv of aqueous hydrogen peroxide was much slow and the yield of the epoxide was reduced (entry 10). The elongated reaction slightly increased the chemical yield (entry 11). Slow addition of 1 equiv of aqueous hydrogen peroxide also slightly but significantly improved the yield to 67% with the same enantioselectivity of 98% ee (entry 12). However, when 2 equiv of aqueous hydrogen peroxide were further added after 24 h to the reaction mixture including 1 equiv of aqueous hydrogen peroxide, the yield amounted to 80% (entry 13). These results suggest that hydrogen peroxide is slowly decomposed during the reaction, but the catalyst is proof against the conditions.

Under the optimized conditions, the asymmetric epoxidation of various 2,2-disubstituted chromene derivatives was examined with 3 equiv of aqueous hydrogen peroxide, because the reaction with stoichiometric one was slow, and the results are shown in Table 2. All the reactions of 2,2-disubstituted chromene derivatives showed high enantioselectivity greater than or equal to 97% ee, irrespective of the electronic nature of the C6-substituent (entries 1–6). The epoxidation of trisubstituted olefin **12** also proceeded with good chemical yield and high enantioselectivity (entry 7). The scope of the present reaction is not limited to the epoxidation of chromene derivatives. The epoxidation of 1,2-benzo-1,3-cycloheptadiene and (*Z*)-1-phenyl-3-penten-1-yne also proceeded with high enantioselectivity. However, complex **1** showed better enantioselectivity in these reactions than complex **5** (cf. entries 8 and 9). The epoxidation of 1,2-benzo-1,3-cycloheptadiene and (*Z*)-1-phenyl-3-penten-1-yne with **1** showed 90 and 86% ees, respectively (entries 9 and 10). As in the epoxidation using usual Mn–salen complex as catalyst, the epoxidation of acyclic *cis*-enyne with **1** or **5** gave a mixture of cis- and trans-epoxides (entry 10).[11] In agreement with the epoxidation with usual Mn–salen complex, epoxidation of *trans*-β-methylstyrene was low enantioselective (entry 11).

In conclusion, we were able to disclose that manganese(III)–salen complexes bearing a nucleophilic substituent at the diamine unit, especially complexes **1** and **5**, serve as efficient catalysts for epoxidation of conjugated cis-olefins using aqueous 30% hydrogen peroxide as the terminal oxidant. The role of the nucleophilic substituent is considered to be twofold: regulation of the conformation of the manganese(III) complexes and acceleration of the conversion of the hydroperoxo intermediate to the oxo species. These results demonstrate that bio-inspired approach is a potential entry to asymmetric epoxidation using aqueous hydrogen peroxide.

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8. Although P-450 possesses a thiol group as the apical ligand, Watanabe et al. have reported that a myoglobin mutant that has a imidazole group as the apical ligand shows P-450's activity and they have proposed that an intermediary hydroperoxo species is converted to the corresponding oxo species due to synergetic push–pull effect by the apical imidazole and distal histidine groups (Ref. 7g).
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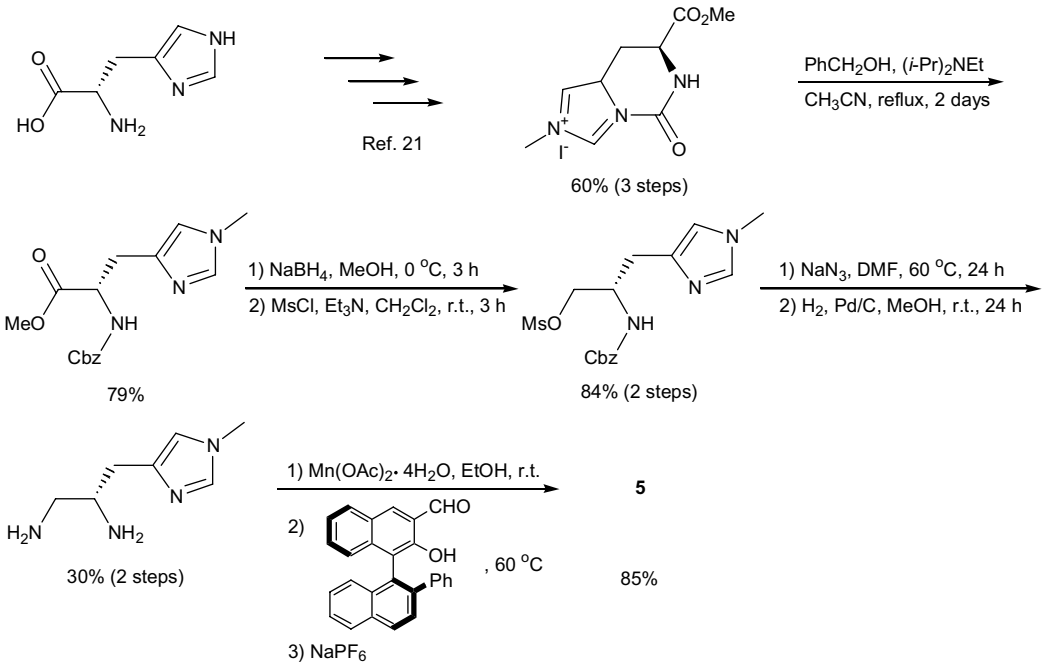
15. Diamine units bearing a nucleophilic substituent were synthesized from L-serine or L-histidine in conventional manner. The pathway for the synthesis of **5** is shown below.[21]



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17. General procedure for asymmetric epoxidation: Mn–salen complex **5** (2.7 mg, 2.5 μmol) and 2,2-dimethylchromene (0.1 mmol) were dissolved in dichloromethane (1 ml). After the addition of aqueous 30% hydrogen peroxide (0.3 mmol) at 0 °C, the resultant mixture was stirred for 24 h. The solvent was removed in vacuo and the residue was purified by chromatography on silica gel (pentane/Et_2O 20:1) to give the corresponding epoxide. The ee value of the epoxide was determined by HPLC analysis under the condition described in the footnote to Table 1.
18. The reaction in AcOEt was also slow and gave the corresponding epoxide of 95% ee in 9% yield after 24 h and the reaction in THF was sluggish.
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