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Enthalpy- and/or entropy-controlled asymmetric oxidation: stereocontrolling factors in Mn–salen-catalyzed oxidation

Tomohiro Nishida, Akio Miyafuji, Yoshio N. Ito and Tsutomu Katsuki*

Department of Chemistry, Graduate School of Science, Kyushu University 33, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

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Abstract

The degree of enantioselection by second-generation Mn–salen complexes was found to depend upon the conformation of their ligand and substrate nucleophilicity. Oxidation of usual olefins was better effected by using (*R*,*S*)-Mn–salen complexes as catalysts, while that of more nucleophilic ones was achieved by using (*R*,*R*)-Mn–salen complexes. This phenomenon was explained by analyzing the enthalpy and entropy factors of the reactions. © 2000 Elsevier Science Ltd. All rights reserved.

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Optically active (salen)manganese(III) complexes (hereafter referred to as Mn–salen complexes) are potent catalysts for enantioselective oxidation.[1] Mn–salen complexes which carry chiral units at both the ethylenediamine and salicylaldehyde parts, especially second-generation Mn–salen complexes bearing a binaphthyl unit as the chiral auxiliary at the salicylaldehyde part, exhibit versatile and efficient asymmetric catalysis:[2] epoxidation, oxidation of enol ethers, sulfoxidation, sulfimidation,[3] aziridination, kinetic resolution (KR) of racemic allenes, benzylic oxidation, desymmetrization of *meso*-heterocycles, etc. were effectively performed in a highly enantioselective manner. Since second-generation Mn–salen complexes have two different chiral units, they are classified into two diastereomeric complexes, (*R*,*S*)- and (*R*,*R*)-complexes. Among the above reactions, epoxidation, oxidation of enol ethers,[4] and KR of racemic allenes were efficiently effected by (*R*,*S*)-complexes in the presence of a donor ligand like 4-phenylpyridine *N*-oxide, while sulfoxidation and desymmetrization of *meso*-heterocycles are effected by (*R*,*R*)-complexes in the absence of a donor ligand. The role of the donor ligand was clarified by X-ray diffraction analysis of the diastereomeric Mn–salen complexes (**1** and **2**).[5] However, the question why the best catalyst for each oxidation varies with the substrate has remained unanswered.

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* Corresponding author. Fax: +81-92-642-2607; e-mail: katsuscc@mbox.nc.kyushu-u.ac.jp

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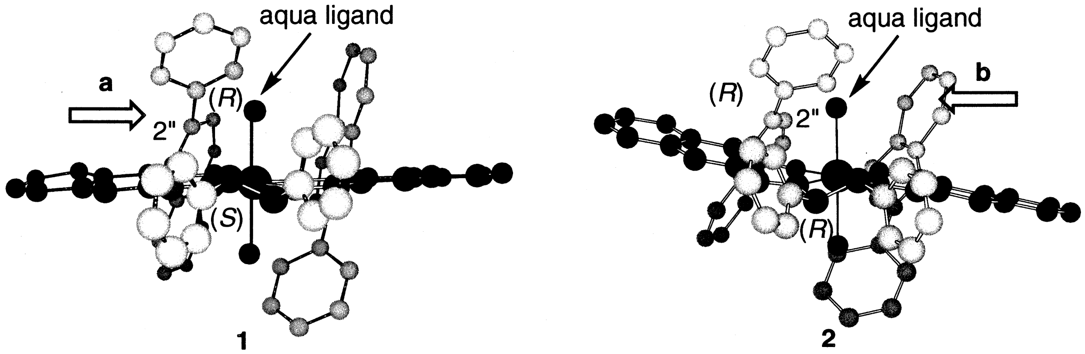
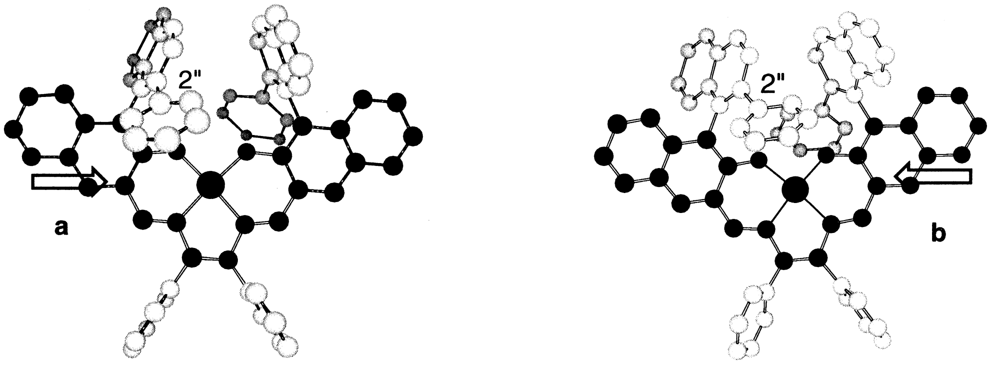
Although (*R*,*S*)- and (*R*,*R*)-complexes (**1** and **2**) bearing two aqua ligands at their apical positions are diastereomeric, their ligand conformations are considerably different (Fig. 1).[5] The basal salen ligand of **1** takes a slightly folded stepped conformation, while the ligand of **2** takes a much folded stepped conformation. The oxo Mn(V) species, which is the active intermediate in Mn(III)–salen-catalyzed oxidation, is also considered to possess a ligand conformation similar to that of the parent Mn(III)-complexes, respectively.[5] Substrates are expected to approach the oxo Mn(V) species beyond the downward naphthalene ring of the basal salen ligand. As indicated by arrows in Fig. 1, therefore, substrates approach the oxo Mn(V) species from the left side along path **a** in the reaction with complex **1** as the catalyst, and from the right side along path **b** in the reaction with complex **2** as the catalyst, if the oxene atom of the oxo species is delivered on the top side of the complexes.[6] As also shown in Fig. 1, the top apical aqua ligand, which is replaced with an oxene atom upon oxidation to the corresponding oxo species, exists in a concavity surrounded by the four gray-colored substituents on the ligand. However, in path **a**, the 2″-phenyl group, which is located closest to the oxene atom and causes the strongest steric repulsion and π–π anti-bonding interactions with the incoming olefins, protrudes in front of the oxene atom, while, in path **b**, it exists in the innermost position of the path. The critical distance for formation of a charge transfer complex between olefins and an oxo metal species has been reported to be ca. 3.5 Å or less.[7] The tip of the arrow in Fig. 1 is placed at a distance of 3.5 Å from the corresponding aqua ligand. Thus, the incoming olefin along path **a** interacts with the 2″-phenyl group at an early stage of the reaction and the repulsion between them plays an important role in the determination



The back views of complexes **1** and **2**. Counter anions are omitted for clarity. The substituents existing above the mean salen plane are colored gray.



The top views of complexes **1** and **2**.

Figure 1.

of the orientation of the incoming olefin and, in turn, the sense of enantioselection by the complex. Accordingly, the oxidation with complex **1** is expected to be enthalpy dependent. On the other hand, the olefin along path **b** should interact with the 2″-phenyl group at a late stage of the reaction and the enantioselectivity of the reaction should be influenced not only by the weak interaction between the salen ligand and the incoming olefin but also by the difference in the frequency factor in respect of the transit of the olefins of different orientations through the area surrounded by the four groups, disordering the solvent arrangement around the concavity. This latter effect is related to the entropy factor, and the reaction with **2** is considered to be more entropy dependent than that with **1**. From these analyses, it was expected that epoxidation of usual olefins would be better effected by using complex **1** as the catalyst, but that complex **2** might be a superior catalyst for the reaction of a more nucleophilic olefin in which the distance between the olefin and oxene atom at the transition state should be elongated, and the repulsion between the substrate and the 2″-phenyl group becomes smaller and the contribution of the enthalpy factor to enantioselectivity is reduced.

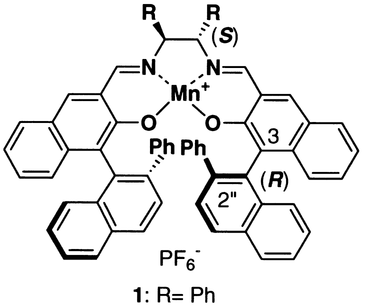
To explore this possibility, we examined oxidation of *cis*-olefins, indene **5** and more nucleophilic olefins like *N*-toluenesulfonyl-1,2,3,4-tetrahydropyridine (NTTP) **6** and 3,4-dihydro-2*H*-pyrane (DHP) **7**, with complexes **1**–**4** (Table 1).[8] Reaction was carried out in ethanol, with iodosylbenzene as the oxidant in the absence of a donor ligand.[9] The reaction of **6** gave the corresponding mixture of *cis*- and *trans*-β-hydroxy-α-ethoxypyrrolidines, and that of **7** gave *trans*-2-hydroxy-1-ethoxytetrahydrofurans. Oxidation of indene gave the corresponding epoxide when the reaction was carried out at a temperature lower than 20°C, while a mixture of 2-hydroxy-1-ethoxyindane and indeneoxide was obtained by the reaction at the temperature above 40°C. The enantiomeric excesses of the respective *cis*- and *trans*-products were found to be identical. As we expected, (*R*,*S*)-complex **1** or **3** was a superior catalyst to (*R*,*R*)-complex **2** or **4**, respectively, when the substrate was **5** (entries 1 and 2), while (*R*,*R*)-complex **2** or **4** was a superior catalyst for oxidation of more nucleophilic substrates, **6** and **7** (entries 3–6).[10]

Table 1
Asymmetric oxidation with complexes **1**–**4** as the catalysts[a]

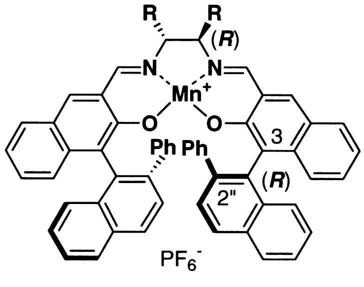
Entry	Substrate	Catalyst	Yield (%) [b]	ee (%)	Catalyst	Yield (%) [b]	ee (%)	Confign[c]
1	indene (**5**)	(*R*,*S*)-**1**	84	91.0[d]	(*R*,*S*)-**3**	57	96.0[d]	1*S*,2*R*[e]
2	"	(*R*,*R*)-**2**	80	89.0	(*R*,*R*)-**4**	44	89.4	1*R*,2*S*
3	DHP (**7**)	(*R*,*S*)-**1**	59	65.2[f]	(*R*,*S*)-**3**	39	58.7[f]	2*R*,3*R*
4	"	(*R*,*R*)-**2**	67	74.4	(*R*,*R*)-**4**	28	64.3	2*S*,3*S*[g]
5	NTTP (**6**)	(*R*,*S*)-**1**	51[i]	64.2[h]	(*R*,*S*)-**3**	42[i]	82.4[h]	3*R*[j]
6	"	(*R*,*R*)-**2**	78	88.1	(*R*,*R*)-**4**	61	93.9	3*S*

a) The reaction was carried out at 0 °C. For other reaction conditions, see the typical experimental procedure.
b) Determined by NMR analysis using 2-bromonaphthalene as an internal standard.
c) (*R*,*S*)-**1** and -**2** and (*R*,*R*)-**3** and -**4** showed the same sense of enantioselectivity, respectively.
d) Determined by HPLC analysis using DAICEL CHIRALCEL OJ (hexane/*i*-propanol=4/1).
e) Determined by comparison of elution order of HPLC analysis.
f) Determined by HPLC analysis using DAICEL CHIRALCEL OD-H (hexane/*i*-propanol=9/1) after converted to the corresponding *p*-nitrobenzoate.
g) Determined by chirotopic comparision $[\alpha]_D^{25}$=+65.3 [*c*=1.0, chloroform, 61% ee (obtained at rt)] [Lit.$[\alpha]_D^{20}$=+17.8 (*c*=1.1, chloroform, 18% ee) for (2*S*,3*S*)-isomer: Sugai, T. *et al. Tetrahedron*. **1996**, *52*, 8123-8134.]
h) Determined by HPLC analysis using DAICEL CHIRALCEL OD-H (x 2) (hexane/*i*-propanol=10/1).
i) Isolated yield.
j) Determined by comparison of elution order of HPLC analysis using DAICEL CHIRALCEL OJ (hexane/*i*-propanol=4/1) after converted into (*R*)-*N*-toluenesulfonyl-3-hydroxypiperidine [i) BSA, ii) Et_3SiH, TMSOTf, iii) H_2O] which was also prepared from commercial (*R*)-3-hydroxypiperidine hydrochloride.

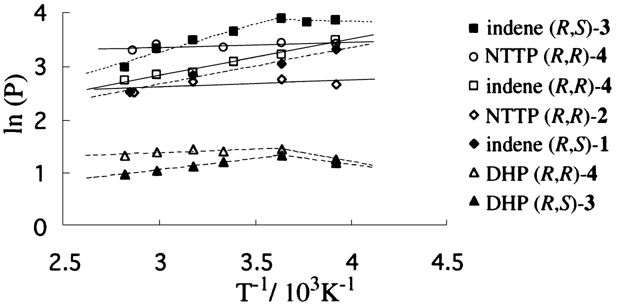
Enantioselectivity of the asymmetric reaction is given by the Eyring equation: $\ln(k_R/k_S) = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}$. As discussed above, the enantioselectivity observed with complex **3** as the catalyst should be enthalpy dependent, and that with complex **4** should be affected by both enthalpy and entropy factors. Therefore, the value of the enthalpy fragment of the Eyring equation obtained with complex **3** is expected to be larger than that obtained with complex **4**. It is also expected that oxidation of more nucleophilic olefins would show smaller dependence on the enthalpy fragment. Based on these analyses, we examined the reactions of **5** and **7** at various temperatures. The results are shown in Fig. 2: $\ln(k_R/k_S)$ was plotted against $1/T$. The Eyring plots for the oxidation of **5** with both complexes **3** and **4** sloped more steeply than the plots for the oxidation of **7** and, of the plots for the reaction of indene, the plot obtained with complex **3** was steeper than that obtained with complex **4**. On the other hand, the plot for the reaction of **7** with complex **4** sloped slightly less than the plot obtained with complex **3**, but the enantioselectivity of the former reaction was slightly better than that of the latter reaction. These results are all compatible with the above discussions and suggest that the entropy factor plays an important role in enantioselection by (*R*,*R*)-complex **4**, especially when the substrate nucleophilicity is high. In accord with these results, the enantioselectivity observed in the oxidation of **5** with (*R*,*S*)-complex **1** also showed the same temperature dependence as that with (*R*,*S*)-complex **3**. On the other hand, the enantioselectivity of the oxidation of **6** with (*R*,*R*)-complex **2** as the catalyst was much less temperature dependent. It is noteworthy that some Eyring plots showed non-linear relationship.[11]



1: R= Ph
3: R= -(CH$_2$)$_4$-



2: R= Ph
4: R= -(CH$_2$)$_4$-



$$\ln(P) = -\frac{\Delta\Delta H^{\neq}}{RT} + \frac{\Delta\Delta S^{\neq}}{R}$$

$$P = \frac{I\text{ (major enantiomer of product)}}{I'\text{ (minor enantiomer of product)}}$$

Figure 2.

In connection with this study, we have reported that complex **4** is a better catalyst for desymmetrization of *meso*-tetrahydrofurans via enantiotopic selective C–H oxidation than complex **3**.[12] The C–H bonding orbital is, however, less nucleophilic than the π-bonding orbital. Thus, we examined the kinetic isotopic effect (k_H/k_D) in the desymmetrization to clarify the reaction mechanism of the desymmetrization. The kinetic isotopic effect in hydrogen atom abstraction by oxo metal species falls in the range of ca. 5–12.[13] However, the kinetic isotopic effect in the oxidation of 8-oxa-bicyclo[4.3.0]nonane and its 7,7,9,9-d_4 derivative was 2.3. This low value indicates that the desymmetrization does not proceed through hydrogen atom abstraction, but probably through an electron transfer process. It has been reported that an electron transfer reaction can occur at longer distance than formation of a charge transfer complex.[7b] These results may explain why (*R*,*R*)-complexes are suitable catalysts for desymmetrization of *meso*-hetrocycles.[12]

Typical experimental procedure: to a solution of complex (**1**, **2**, **3** or **4**; 2.0 mg, 2.0 μmol) and olefin (**5**, **6** or **7**; 0.1 mmol) in ethanol was added iodosylbenzene (22.0 mg, 0.1 mmol) at appropriate temperature under nitrogen atmosphere and the whole mixture was stirred for 1 h (for **5**), 6 h (for **6**) and 1 h (for **7**), respectively, and filtered through a pad of Celite and silica gel. The filtrate was concentrated and the residue was chromatographed on silica gel to give the corresponding epoxide or hydroxy acetal. The enantiomeric excesses of the products were determined by HPLC analysis (see the footnote to Table 1). Each reaction was repeated five times. All the ee's obtained at the same temperature were within ±1% ee (±2% ee only for the reaction of **7** with **4**).

In conclusion, we were able to demonstrate that the enthalpy factor plays an important role in stereocontrol of the oxidation with (*R*,*S*)-Mn–salen complexes, while the role of the entropy factor becomes more pronounced in the oxidation with (*R*,*R*)-Mn–salen complexes. It is noteworthy that second-generation Mn–salen catalysts are endowed with wide applicability to a variety of reactions due to the fact that the reactions with diastereomeric (*R*,*S*)- and (*R*,*R*)-Mn–salen complexes depend on enthalpy and entropy factors to different degrees.

Acknowledgements

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References

1. (a) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189–214. (b) Katsuki, T. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 940–951. (c) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp. 159–202.
2. Ito, Y. N.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603–619.
3. Nishikori, H.; Ohta, C.; Oberlin, E.; Irie, R.; Katsuki, T. *Tetrahedron* **1999**, *55*, 13937–13946.
4. Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4389–4392.
5. (a) Hashihayata, T.; Punniyamurthy, T.; Irie, R.; Katsuki, T.; Akita, M.; Moro-oka, Y. *Tetrahedron* **1999**, *55*, 14599–14610. (b) Punniyamurthy, T.; Irie, R.; Katsuki, T.; Akita, M.; Moro-oka, Y. *Synlett* **1999**, 1049–1052.
6. For olefin's approach to oxo Mn–salen species, see also: Kuroki, T.; Hamada, T.; Katsuki, T. *Chem. Lett.* **1995**, 339–340.
7. (a) Shimada, K.; Szwarc, M. *J. Am. Chem. Soc.* **1975**, *97*, 3321–3323. (b) He, G.-X.; Mei, H.-Y.; Bruice, T. C. *Ibid.* **1991**, *113*, 5644–5650.
8. Second-generation Mn–salen complexes bearing a cyclohexanediamine unit also have a basal ligand conformation similar to the complexes bearing a diphenylethylenediamine unit: (a) Ref. 3; (b) Ohta, C.; Irie, R.; Katsuki, T. Unpublished result.
9. Oxidation of enol ethers under usual conditions gives α-hydroxy carbonyl compounds which racemize slowly under the conditions. However, the reactions in ethanol provide the corresponding α-hydroxy acetal and aminal, respectively, which tolerate the reaction conditions.[4]

10. (*R*,*S*)-Complex **2** was a catalyst of choice for oxidation of 1-alkoxycycloalkenes which are as nucleophilic as **7**.[4] However, they approach an oxo species, directing the alkoxy group downward, which suffers steric and n–π antibonding interactions. Thus, the reaction is expected to be enthalpy dependent and efficiently effected by complex **2**.
11. (a) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515–530. (b) Norrby, P.-O.; Linde, C.; Åkermark, B. *J. Am. Chem. Soc.* **1995**, *117*, 11035. We and others have proposed the participation of metallaoxetane intermediate in Mn–salen-catalyzed epoxidation based on the non-linear relationship and calculation, respectively. However, a recent study did not support its participation: Delmonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907–9908. At this moment, it is unclear what factor causes the non-linear relationship at lower reaction temperatures.
12. (a) Miyafuji, A.; Katsuki, T. *Synlett* **1997**, 836–838. (b) *Idem*, *Tetrahedron* **1998**, *54*, 10339–10348.
13. (a) Groves, J. T.; Viski, P. *J. Am. Chem. Soc.* **1989**, *111*, 8537–8538. (b) *Idem*, *J. Org. Chem.* **1990**, *55*, 3628–3634. (c) Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10017–10028.