CHEMISTRY LETTERS, pp. 527-530, 1994.

N-Alkyl Imidazoles as Effective Axial Ligands in the Aerobic Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by Optically Active Manganese(III)-salen-type Complex

Kiyomi IMAGAWA, Takushi NAGATA, Tohru YAMADA, and Teruaki MUKAIYAMA†
Basic Research Laboratories for Organic Synthesis, Mitsui Petrochemical Industries, Ltd.,
Nagaura, Sodegaura-shi, Chiba 299-02

N-Alkyl imidazoles are effective axial ligands to achieve highly enantioselective epoxidation of unfunctionalized olefins by combined use of molecular oxygen and pivalaldehyde with optically active Mn(III)-salen-type complex catalysts. In the presence of *N*-alkyl imidazole, the epoxidation of 2,2-dimethylchromene proceeded smoothly to afford the corresponding optically active epoxide in 92% enantiomeric excess.

In our previous communications, an aerobic asymmetric epoxidation of unfunctionalized olefins by using optically active manganese(III) complex was described.[1] In the present experiment, it was found that the absolute configuration of the obtained epoxide is completely reversed when a catalytic amount of *N*-methylimidazole was added to the above oxidation. As shown in Table 1, when 1,2-dihydronaphthalene was oxidized by molecular oxygen with (*R,R*)- manganese(III)-salen-type complex catalyst **1** or **2** alone (Shown in Fig. 1)[2], the formed epoxide had (*1S,2R*)-(-) configuration. On the contrary, the epoxide of (*1R,2S*)-(+) configuration was afforded by the addition of a catalytic amount of *N*-methylimidazole to the same reaction system.[3] The result clearly indicates that imidazole derivatives play important roles in controlling the enantioselection of the present epoxidation. Concerning the similar effect of imidazole derivatives in oxidation reaction, it has been revealed that bonito ferrocytochrome *c* consists of a heme group and a polypeptide chain, and that the imidazole ring of histidine 18 coordinates the heme iron atom as the 5th ligand, which is supposed to activate molecular oxygen.[4] Myeloperoxidase also contains histidine

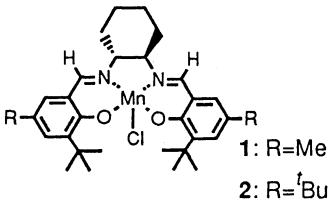
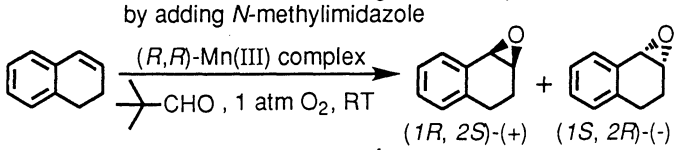


Fig. 1. (*R,R*)-Mn(III) complex.

Table 1. Reversion of absolute configuration of epoxide by adding *N*-methylimidazole



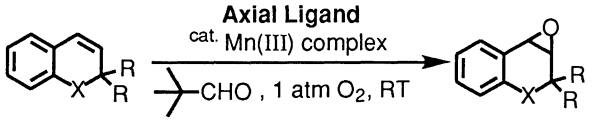
Additive	Absolute configuration
None	(*1S, 2R*)-(-)
N-methylimidazole	(*1R, 2S*)-(+)

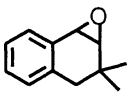
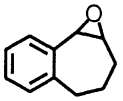
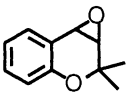
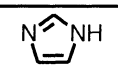
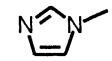
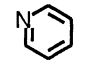
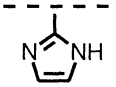
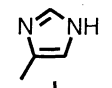
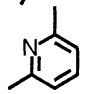
† Address: Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162.

coordinating the heme iron atom with the imidazole ring.[5] Bleomycin includes imidazole moiety as the ligand of the central iron atom.[6] Although the effects of imidazole derivatives as donar ligands have been studied in cytochrome P-450 model reactions by several groups,[7] few were reported on the stereochemistry of olefin-epoxidation.[8] In this communication, we would like to describe the effect of *N*-alkyl imidazoles, axial ligands, in achieving highly enantioselective epoxidation of unfunctionalized olefins by combined use of molecular oxygen and pivalaldehyde with optically active manganese(III)-salen-type complex catalysts.

At first, the influence of the position of an alkyl group attached to an imidazole ring and a pyridine ring upon the optical yields of the obtained epoxides was examined. In all cases of epoxidation of 3,3-dimethyl-3,4-dihydronaphthalene, 1,2-benzo-1,3-cycloheptadiene, and 2,2-dimethylchromene, the optically active epoxides were afforded in good to high enantioselectivities by the addition of imidazole or *N*-methylimidazole (55-91% ee, Entries 1 and 2 in Table 2). While, the optical yields of the epoxides were much lower when 2-methylimidazole[8a] or 4-methylimidazole was added (26-51% ee, Entries 4 and 5). Similar results were observed in the cases of using pyridine or 2,6-lutidine as an axial ligand; that is, when pyridine was added, the optically active epoxide was obtained with better enantioselection compared with the reaction by adding 2,6-lutidine, 51 vs. 7% ee, 27 vs. 1% ee, and 76 vs. 22% ee, respectively (Entries 3 and 6). The results suggested that alkyl groups attached to the carbon next to nitrogen would prevent the coordination to the central manganese atom because of their steric hindrance, and that manganese(III) complex molecules could not be always coordinated by imidazole derivatives. Reactive catalysts for the epoxidation would include both the manganese complex coordinated by imidazole derivatives and the imidazole-free complex, which afforded the epoxide with the reversed absolute-configuration. Therefore, the total optical yield was offset and lowered.[9]

Table 2. Effect of axial ligands on optical yield of epoxides



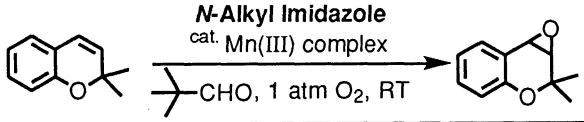
Entry[a]	Axial ligand	Optical yield / %ee[b]		
				
1		55	63	91[c]
2		71	83	91[c]
3		51	27	76[c]
4		45	32	26[c]
5		48	30	51[c]
6		7	1	22[c]

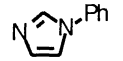
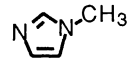
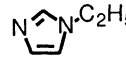
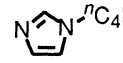
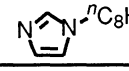
a) Reaction conditions; olefin 1.15 mmol, pivalaldehyde 3.5 mmol, axial ligand 0.55 mmol, Mn(III) complex **1** 0.138 mmol (12 mol%) in fluorobenzene 4 ml, RT, 1 atm O_2. b) Determined by GC analysis (Chiraldex B-DA, ASTEC Co.). c) Mn(III) complex **2** was used as catalyst, and benzene as solvent.

Since the optical yields of the obtained epoxides were the highest in all cases when *N*-methylimidazole was added, a variety of *N*-alkyl imidazoles[10] was screened by taking 2,2-dimethylchromene as a model olefin. It was found that the optical yields of the corresponding epoxides were improved up to more than 90% ee by the addition of imidazole derivatives having *N*-alkyl groups (see Table 3), while 71% ee in case of

N-phenylimidazole. It was also shown that the longer alkyl groups are attached to the imidazole rings, the higher the chemical yield of the epoxide attained, and that *N*-octylimidazole was the most suitable axial ligand with respect to both chemical and optical yields (Entry 5).

Table 3. *N*-Alkyl imidazoles as effective axial ligands



Entry [a]	Imidazole	Yield / %[b]	Optical yield / %ee[c]
1		23	71
2		12	91
3		31	91
4		26	92
5		37	92

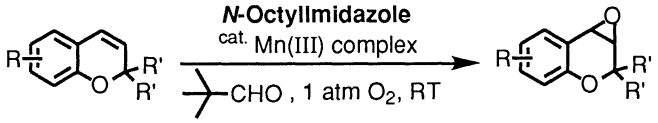
a) Reaction conditions; olefin 1.15 mmol, pivalaldehyde 3.5 mmol, imidazole 0.55 mmol, Mn(III) complex **2** 0.138 mmol (12 mol%) in benzene 4 ml, RT, 1 atm O_2. b) Isolated yield. c) Determined by GC analysis (Chiraldex B-DA, ASTEC Co.).

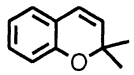
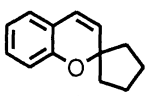
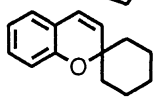
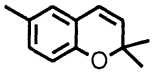
Optically active chromene oxides have attracted much attention as intermediates for biologically active compounds, such as precocene II derivatives[11] and medicines of hypertension and asthma.[12] Jacobsen[13] and Katsuki[14] recently reported enantioselective epoxidation of chromene derivatives by using optically active manganese(III)-salen-type complex catalysts and sodium hypochlorite or iodosylbenzene. Then, the present system was applied to the enantioselective epoxidation of various chromene derivatives[15] (see Table 4). In all cases of chromene derivatives, the corresponding optically active epoxides were obtained in more than 90% enantiomeric excess.

A typical procedure is described for the asymmetric epoxidation of 2,2-dimethylchromene (Entry 1 in Table 4): To a mixture of (*R,R*)-Mn(III)-salen-type complex (**2**) (87.7 mg, 0.138 mmol, 12 mol%) and *N*-octylimidazole (99.5 mg, 0.552 mmol) in benzene (3.0 ml) was added a solution of 2,2-dimethylchromene (184 mg, 1.15 mmol) and pivalaldehyde (300 mg, 3.5 mmol) in benzene (1.0 ml). After stirred at room temperature under an oxygen atmosphere for 8 h, the reaction mixture was extracted with ethyl ether, washed with saturated solution of sodium hydrogen carbonate and brine, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica-gel (hexane / ethyl acetate) to afford the corresponding optically active epoxide in 37% yield (65.4 mg). The enantiomeric excess was determined by GC analysis (Chiraldex B-DA, ASTEC Co.) to be 92% ee.

Thus, it is noted that *N*-alkyl imidazoles behave as effective axial ligands in the aerobic asymmetric epoxidation of unfunctionalized olefins catalyzed by optically active manganese(III)-salen-type complex.

Table 4. Aerobic asymmetric epoxidation of various chromenes



Entry	Chromene	Yield / %	Optical yield / %ee
1		37	92
2		32	90
3		34	91
4		24	91

a) Reaction conditions; olefin 1.15 mmol, pivalaldehyde 3.5 mmol, *N*-octylimidazole 0.55 mmol, Mn(III) complex **2** 0.138 mmol (12 mol%) in benzene 4 ml, RT, 1 atm O_2. b) Isolated yield. c) Determined by GC analysis (Chiraldex B-DA, ASTEC Co.). d) Determined by ^{1}H-NMR analysis. Eu(hfc)$_3$ was used as a chiral shift reagent in $CDCl_3$. e) Determined by GC analysis (Chiraldex G-TA, ASTEC Co.).

References

1) T. Yamada, K. Imagawa, T. Nagata, and T. Mukaiyama, *Chem. Lett.*, **1992**, 2231; T. Mukaiyama, T. Yamada, T. Nagata, and K. Imagawa, *ibid.*, **1993**, 327.

2) Optically active Mn(III)-salen-type complexes (**1** and **2**) were prepared by Jacobsen's method (W. Zhang and E. N. Jacobsen, *J. Org. Chem.*, **56**, 2296 (1991).), and purified by washing the benzene solution of crude complex with aqueous lithium chloride solution.

3) The absolute configuration was determined by comparing the sign of optical rotation with the reported value. D. R. Boyd, D. M. Jerina, and J. W. Daly, *J. Org. Chem.*, **35**, 3170 (1970).

4) T. Ashida, N. Tanaka, T. Yamane, T. Tsukihara, and M. Kakudo, *J. Biochem.*, **73**, 463 (1973).

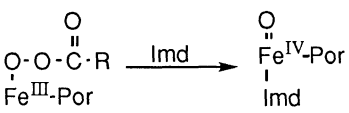
5) J. Zeng and R. E. Fenna, *J. Mol. Biol.*, **226**, 185 (1992).

6) Y. Kaku, M. Otsuka, and M. Ohno, *Chem. Lett.*, **1989**, 611.

7) For example; D. Mansuy, P. Battioni, and J.-P. Renaud, *J. Chem. Soc., Chem. Commun.*, **1984**, 1255; E. G. Samsel, K. Srinivasan, and J. K. Kochi, *J. Am. Chem. Soc.*, **107**, 7606 (1985).

8) It was reported that 2-alkyl imidazole was effective as a donor ligand in the asymmetric epoxidation by using manganese(III)-salen-type catalyst and iodosylbenzene as terminal oxidant. a) R. Irie, Y. Ito, and T. Katsuki, *Synlett.*, **1991**, 265; b) T. Schwenkries and A. Berkessel, *Tetrahedron Lett.*, **34**, 4785 (1993).

9) It was recently reported that acylperoxo-iron porphyrin complexes were converted into the corresponding oxo-iron complexes by coordination of imidazole derivatives (K. Yamaguchi, Y. Watanabe, and I. Morishima, *J. Am. Chem. Soc.*, **115**, 4058 (1993)). Reversal of the absolute configurations of the epoxides suggested that the similar conversion would take place in the present epoxidation with combined use of molecular oxygen and aldehyde, and determination of the reactive intermediates and further investigation of the detailed mechanism are now under way.



10) Each *N*-alkyl imidazole was prepared by the literature method. O. A. El Seoud and V. Aldrigue, *An. Acad. Brasil. Cienc.*, **50**, 87 (1978).

11) D. M. Soderlund, A. Messeguer, and W. S. Bowers, *J. Agric. Food Chem.*, **28**, 724 (1980).

12) Nissan Chemical Industries, Ltd., JP Patent Tokkaihei 5-301878 (1993).

13) N. H. Lee, A. R. Muci, and E. N. Jacobsen, *Tetrahedron Lett.*, **32**, 5055 (1991).

14) A. Hatayama, N. Hosoya, R. Irie, Y. Ito, and T. Katsuki, *Synlett.*, **1992**, 407; N. Hosoya, R. Irie, and T. Katsuki, *ibid.*, **1993**, 261.

15) Chromene derivatives were prepared by the literature methods. Entries 1 and 4: R. Bergmann and R. Gericke, *J. Med. Chem.*, **33**, 492 (1990). Entries 2 and 3: H. J. Kabbe, *Synthesis*, **1987**, 886. The racemic chromene oxides were prepared from the corresponding chromene derivatives by using dimethyl dioxirane as epoxidation reagent. R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, **50**, 2847 (1985); J. Bujons, F. Camps, and A. Messeguer, *Tetrahedron Lett.*, **31**, 5235 (1990).

(Received November 25, 1993)