Trapping of the Dichlorocarbonyl Oxide Using a Chiral (Salen)Mn(III) Complex

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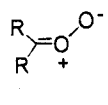
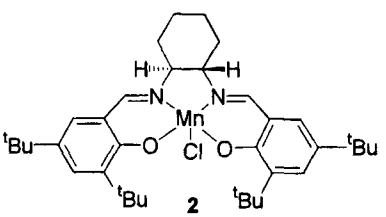
Carbonyl oxides **1** have long been established as key intermediates in the ozonolysis of olefins.[1] These oxides are also known to be generated by treatment of oxygen to the carbene species.[2] The intermediacy of **1** has been extensively characterized in terms of direct spectroscopic observation[3] as well as theoretical calculation.[4] Much attention has been devoted to study the reaction of the elusive intermediate **1**, including the cycloaddition with carbonyl compounds to give trioxolane adducts.[5] In addition, they may transfer an oxygen atom to organic substrates such as alkanes,[6] alkenes,[7] arenes,[8] and sulfoxides.[9]



1

1a: R = Cl

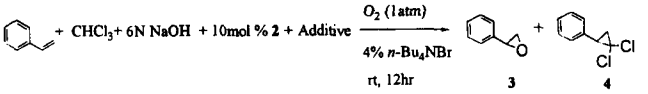


2

In view of the oxides' abilility of oxygen transfer, transition metal is another potential substrate which can accept an oxygen atom to form metal-oxo species. However, transition metal has been little explored in this oxo-transfer process of carbonyl oxides. For that sense, Groves and Stern's report[10] is notable, where they have described that aerobic reaction of dichlorocarbene and manganese porphyrine complex can lead to epoxidation of olefins. They proposed that manganese-oxo (Mn=O) complex generated *via* oxygen-transfer from dichlorocarbonyl oxide **1a**[11] was involved as the active intermediate in the epoxidation process. Recently, chiral (salen)Mn(III) complexes such as Jacobsen's catalyst **2** have attracted much attention as the catalysts for the enantioselective epoxidation of simple olefins.[12] In the presence of various stoichiometric oxidants,[13] the salen-manganese complex is well documented to effect epoxidations through Mn=O intermediate.[14] It is reasonable to assume that if dichlorocarbonyl oxide can generate common Mn=O species from chiral complex **2**, the chirality can be transfered to olefins to give optically active epoxides. To further elucidate the identity of dichlorocarbonyl oxide and metal-oxo intermediate, therefore, we decided to examine a chiral (salen) Mn(III) complex **2** as the mechanistic probe in the dichlorocarbene/oxygen-mediated oxidations.

It is well known that dichlorocarbene can be readily generated by the reaction of chloroform and aq. sodium hydroxide under phase transfer catalyst.[15] Styrene was examined to determine whether epoxide **3** is generated under the aerobic reaction conditions using this proctocol (Table 1). When the control reaction was run by bubbling oxygen gas in the absence of Mn catalyst **2**, all of the styrene was transformed to cyclopropane **4** as expected. Only a trace amount of epoxide was observed by careful analysis of GC-MS spectrum (entry 1). When the reaction was conducted in the presence of the catalyst **2**, we were able to obtain a small amount of epoxide along with cyclopropane as a major product (entry 2). We tried various reaction conditions to improve the yield of the epoxide, no better result was obtained. Imidazole derivatives were reported to facilitate the formation of metal-oxo (M=O) intermediate in metalloporphyrine[16] and metallosalen complex[13e] *via* electron-push effect. We, therefore, examined the imidazole effect in this reaction, and observed that the yields of epoxide were increased (entry 3). Different types of imidazoles were also found to give the similar results (entries 4, 5).

Table 1. Imidazole effect on the dichlorocarbene-mediated aerobic epoxidations

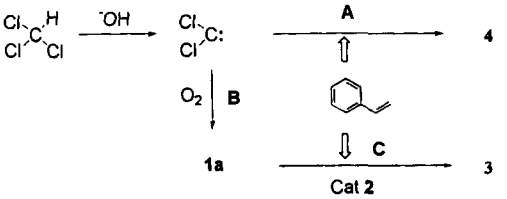


Entry	Additive	Conversion (%)[a]	Product ratio 3 : 4
1[b]	None	100	<1 : >99
2	None	95	2 : 98
3	imidazole	58	33 : 67
4	N-methylimidazole	58	29 : 71
5	N-octylimidazole	41	24 : 76

[a] Determined by GC analysis using capillary column. [b] Reaction was run without the catalyst **2**.

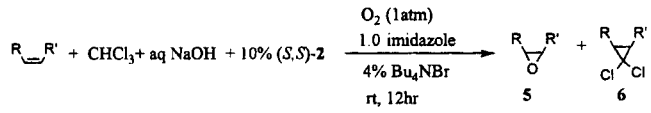
The competetion process between the formation of dichlorocyclopropane **3**[17] and the epoxide **4** was proposed in Scheme 1. The epoxide formation was reasonably explained by proposing the (salen)Mn-mediated oxidation pathway *via* dichlorocarbonyl oxide.[18] Even though the role of imidazole in this process is not clealy defined yet, it is conceivable that the process C in scheme 1 is accelerated by the aid of imidazole to provide increased epoxide/cyclopropane product ratio.

We further examined the hypothesis asserted above by screening the enantioselectivities of the resulting epoxides. The results are summarized in Table 2.[19] The styrene oxide



Scheme 1.

Table 2. Asymmetric aerobic epoxidation of olefins mediated by dichlorocarbene using (S,S)-**2** as the catalyst



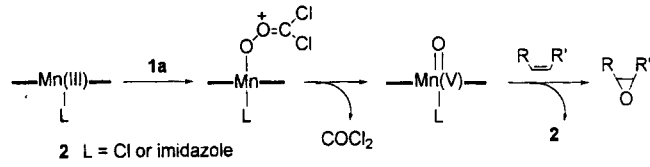
Entry	Substrate	Epoxide	Conversion (%)	5 (ee%)[a]	5/6
1			58	23	0.49
2			22	53	1.3
3			21	81[b]	2.5
4			18	58	0.86
5			14	80	0.75
6			38	43	0.36
7			45	18	0.21

[a] Enantioselectivities were determined by capillary GC using a commercial chiral column (Alletech Chiraldex G-TA). [b] Determined by GC using J&W Scientific Cyclodex-B capillary column.

was obtained in 23% ee (entry 1). Dihydronaphthalene and dimethylchromene were converted to the epoxides in 53% and 81% ee respectively (entries 3, 4). Trisubstituted olefin was also converted to the epoxides in 58% selectivity (entry 4). Acyclic *cis*-olefins gave *cis*-epoxide as major product in good selectivity (entry 5). *Trans*-β-methylstyrene gave the *trans*-epoxide exclusively in 43% ee (entry 6). It is noteworthy that this selectivity is comparable or better than that observed with other oxidant.[12a] Cyclic diene was also examined as the substrate for this epoxidation process (entry 7).

All of the reactions examined above showed low reactivities, and provided both epoxides and dichlorocyclopropanes through the competetion process. The observed optical purities were a little lower than those obtained using NaOCl as an oxidant. This may be attributed to the involvement of decomposed Mn species or the other nonselective reaction pathway for the oxidations. On the other hand, the sense of the asymmetric induction was clearly consistant with that expected *via* common manganese-oxo intermediate generated by other oxidant. The absolute configuration of the epoxides was identified by comparing to the authentic sample prepared by Jacobsen's procedure using chiral GC column. Therefore, it is reasonable to assume that manganese-oxo intermediate is involved, at least as the major pathway, in this enantioselective epoxidation process. The probable process of oxygen-transfer from carbonyl oxide to Mn(III) complexes is depicted in Scheme 2.[20]

We demonstrated that chiral (salen)Mn(III) complex can be used as the reagent which can trap the short-lived intermediate such as **1a**. This technique could be extended to



Scheme 2.

identify other carbonyl oxides which are of importance in chemical and biological[21] point of view. Coupled with a unique property of the catalyst **2** which provides high selectivities to the olefin epoxidations, this method will find useful in the study of other carbonyl oxides. In addition, this procedure has a potential for the chiral aerobic epoxidations in organic synthesis.

In conclusion, chiral (salen)Mn(III) complex can be employed as the traping agent of the dichlorocarbonyl oxide, prepared in situ from the reaction of chloroform and hydroxide under aerobic condition. The observed enantioselectivity and the mode of stereochemistry of epoxides strongly suggests the intermediacy of manganese-oxo, the common intermediate as proposed in the other oxidant mediated process. Further study on the chiral Mn(III) complex **2** as the mechanistic probe for the detection of the other elusive intermediate **1** will be warranted.

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17. The enantiomeric excess of the compound **4** was determined to be zero, which implies that the catalyst **2** was not involved in cyclopropanation process. For the reference of the related metalloporphyrin-mediated cyclopropanation reaction, see Ziegler, C. J.; Suslick, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 5306.
18. We could not exclude the possibility of dichlorodioxirane, the cyclic isomer of **1a**, involving as the active oxidant. However, the isomerization of carbonyl oxide to the corresponding dioxirane was reporeted to have relatively high activation energy barrier. For the reference, see Hull, L. A. *J. Org. Chem.* **1978**, *43*, 2780.
19. Typical experimental procedure is as follows; To the solution of the olefin (1 mmol), chloroform (20 mL), *n*-Bu_4NBr (0.04 mmol), imidazole (1 mmol) and sodium hydroxide (6 M, 10 mL) in the presence of the catalyst (*S,S*)-**2** (0.1 mmol) was bubbled the oxygen gas for 12 h at room temperature. After the phases were separated, the organic layer was washed with brine solution and dried with anhydrous sodium sulfate. After being concentrated, the mixture was analyzed by GC and GC-MSD spectroscopy or purified by flash column chromatography.
20. There is a possibility of generation of hydrogen peroxide during the reaction as depicted in equation 1.
We have examined the possible involvement of H_2O_2 as

(1)

the active oxidant in this process. Pretreatment of dichlorocarbene and oxygen for 1 hr followed by addition of cat **2** and olefin provided no epoxide at all, which indicates no participation of free H_2O_2 as the oxidant.
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The Role of Highly Conserved Tetrapeptide Sequence of C-Peptide in the Folding of Proinsulin

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Proinsulin, a single chain insulin precursor, comprises the B-chain, a Arg-Arg sequence, the connecting C-peptide of 31 amino acids, a Lys-Arg sequence, and the A-chain. After folding and the formation of disulfide bridges, insulin is released by a proteolytic cleavage of proinsulin at the two dibasic sites. The presence of a pair of basic residues is considered to be a minimum requirement for conversion.[1]

The role of C-peptide in the folding of proinsulin was speculated to bring the two distant parts of the polypeptide, A and B chains, into proximity for efficient formation of disulfide bridges between the two chains,[2] but the exact role has not been elucidated.

C-peptide is the most variable portion of the proinsulin molecule except the highly acidic region which occurs in the first four positions of the C-peptide. This acidic region is highly conserved in various animal species with the sequence Glu/Asp-X-Glu/Asp, where X is alanine, valine or leucine.[3] The presence of highly conserved acidic residues immediately following dibasic residues may suggest some functional role of this region in the formation of proinsulin structure.

In the present work, we have examined the role of the highly conserved tetrapeptide sequence of C-peptide in the folding of proinsulin. For this purpose, we have produced two analogue forms of proinsulin, in which either the tetrapeptide sequence, Glu-Ala-Glu-Asp, was deleted (D4PI) or replaced with Gly-Gly-Gly-Gly sequence (G4PI) (see Figure 1 for the sequence).

The proinsulin and analogues were produced as fusion proteins which form inclusion bodies in *E. coli* cells. The gene for the fusion protein was placed under the control of the T7 promoter in the expression plasmid pET-3a[4] and the fusion protein was expressed in *E. coli* BL21(DE3) by IPTG induction. N-terminal portion of human tumor necrosis factor-alpha (hTNF-α) was used as a fusion partner, a fusion system described by our group previously.[5] After