Accounts

Recent Advances in Aerobic Oxygenation

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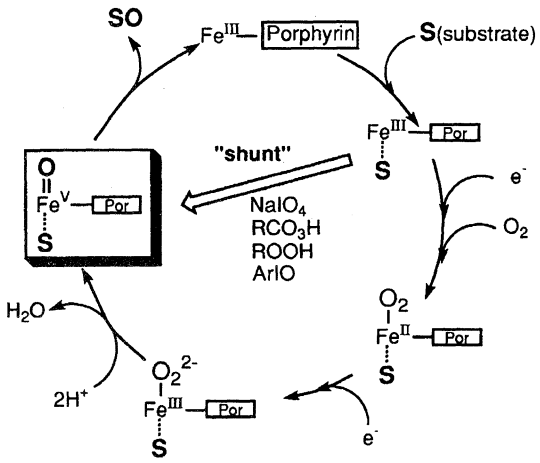
Recent advances in the aerobic oxygenations of olefins using transition-metal complex catalysts are reviewed. The main topics focused on are the cobalt(II)-complex-catalyzed oxygenation of olefins, nickel-(II)-complex-catalyzed aerobic epoxidation, enantioselective, aerobic epoxidation using chiral manganese(III) complex catalysts, aerobic Baeyer–Villiger oxidation and direct oxygenation of aromatic compounds.

Molecular oxygen is vital to almost all animals on earth, including man, for metabolism and to provide energy for life. In the chemical industry as well, much has been expected of molecular oxygen as the most available oxidant for mass production: for example, ethylene oxide has been obtained by the aerobic oxidation of ethylene catalyzed by silver salts,[1] and phenol has been produced by the cumene process, which involves an aerobic auto-oxidation of cumene into "cumene hydroperoxide" (1-methyl-1-phenyl hydroperoxide) in a key reaction step.[2] The aerobic oxidation of *p*-xylene into terephthalic acid by using manganese and cobalt salts as catalysts has also been used in industrial processes.[3] Palladium-and-copper-catalyzed oxidation of olefins, the Wacker reaction, has been employed in the production of aldehydes and ketones.[4] These successful processes, however, have some limitations, because they are operated under severe conditions of temperature and/or pressure. Hence, the development of efficient oxygenation reactions, which can be performed under mild conditions, has been eagerly pursued.

The ground state of molecular oxygen is a triplet with two unpaired electrons having parallel spins. Therefore, the direct reaction of molecular oxygen with a singlet organic molecule is a spin-forbidden process.[5] On the other hand, the radical chain reaction is one practical process by which organic compounds may be oxidized with molecular oxygen using transition-metal salt catalysts.

As oxygenation by biogenetic systems is performed under very mild conditions, biomimetic investigation has focused on modifying the structure of ligands in order to simulate the functions of hemocyanin[6,7] and hemoglobin, which are known to transport molecular oxygen *in vivo* and to incorporate the oxygen atom into organic substrates. Hemocyanin and tyrosigenase, which are found in invertebrates such as arthropods or mollusks, are copper-containing proteins, whereas hemoglobin, which is found in all vertebrates including mammals, contains a "heme" group. Iron-porphyrin, an iron complex of a macrocyclic tetrapyrrole, is considered to be the active site for oxygenation reactions. The mechanism of oxygenation by cytochrome P-450, a typical iron-complex containing heme-proteins, has been studied in detail; in this case, an oxo-iron complex is considered to be the reactive intermediate (Scheme 1).[8] It was reported during the 1970's that several oxygen donors, such as periodate, peroxy acid,[9] peroxide,[10] or iodosylarene,[11] completed a short-circuited catalytic cycle "shunt"[12] in accord with the proposed mechanism,[13] and cytochrome P-450 catalyzed oxidations such as the epoxidation of olefins were demonstrated. Following the publication of these results, many chemical studies have been done using such biomimetic approaches.

With regard to aerobic oxidation catalyzed by transition-metal complexes, several reactions involving the combined use of molecular oxygen with reducing agents have been studied: for example, (tetraphenylporphyrinato)manganese(III) complex/$NaBH_4$ (or colloidal Pt-H_2).[14] The combination of three components, that is, a transition-metal, organic ligands, and a re-



Scheme 1. "Shunt" pass mechanism for P450 model.

ductant, is considered to create an effective oxygenation system for such aerobic reactions.

Salicylideneamine derivatives, abbreviated as salen derivatives, have been studied for their catalytic activities as models of porphyrins. Although β-diketone derivatives also form coordinated complexes with transition-metals, few have been studied as model compounds of the porphyrin ligands except for the most simple acetylacetonato complex. It should be possible using conventional methods to prepare analogues containing a wide variety of electron-withdrawing or donating or sterically hindered substituents which would be expected to regulate the catalytic properties.

In this account, we would like to review the recent dramatic advances in aerobic oxygenation reactions catalyzed by transition-metal complexes, mainly concerning the exploration of new possibilities in the bis(β-diketonato)metal-complex-catalyzed aerobic oxygenation, which have led to new synthetic methodologies.[15]

1. Cobalt(II)-Complex-Catalyzed Oxygenation of Olefins

1-1. Catalytic Oxidation-Reduction Hydration. Cobalt(II) complexes are some of the most promising catalysts for aerobic oxidation reactions because they readily transfer to-and-fro between the oxidation states of Co^{2+} and Co^{3+}, and because, as has been reported,[16] bis(acetylacetonato)cobalt(II) readily absorbs molecular oxygen in the presence of pyridine.

Salen derivatives are easily prepared from the corresponding diamines and salicylaldehyde, and are one of the ligands most often used in models of porphyrins. Recently, it was reported that {*N*,*N*-bis[3-(salicylideneamino)propyl]methylaminato}cobalt(II) (CoSMDPT, Fig. 1), a salen-cobalt(II) complex, can be employed as an effective catalyst for the oxygenation of styrene into phenethyl alcohol and/or acetophenone in a primary or secondary alcohol solvent.[17] The ratio of hydrated product (alcohol) to oxidized product (ketone) was influenced by the concentration of ethanol in the solvent, although the ketone was produced as the major product in all cases (Table 1). Phenethyl alcohol was formed when a porphyrinato cobalt(II) complex such as (tetraphenylporphyrinato)cobalt(II) (Co(TPP)) and a hydride reductant such as Et_4NBH_4[18] or $NaBH_4$[19] were employed in the aerobic oxygenation of styrene derivatives (Scheme 2).

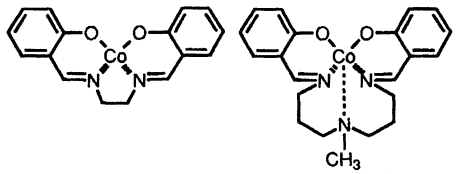
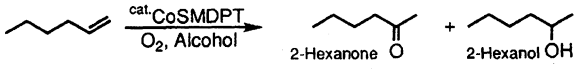


Fig. 1. Cobalt-salen deriv. complexes.

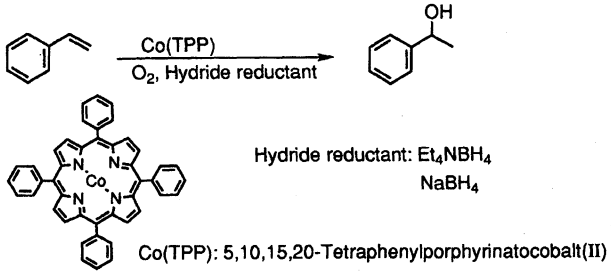
β-Diketone derivatives are widely employed as a fundamental organic ligand forming stable complexes with a wide variety of transition metals. Many kinds of 1,3-diketone derivatives have been used for the separation of metal ions in analytical chemistry, or as ligands for metal-complex catalysts in organic synthesis.[20] Many varied 1,3-diketone derivatives are easily prepared by common synthetic methods, and are able to regulate the stereochemical and/or electrochemical properties of the coordinated complexes.

Our research started by making use of the above properties of 1,3-diketones in cobalt(II) complex catalysts for the aerobic oxygenation of olefins with molecular oxygen. During the course of the above experiments, 4-phenyl-2-butanol, an oxygenated product, was formed as a major product along with 1-phenylbutane

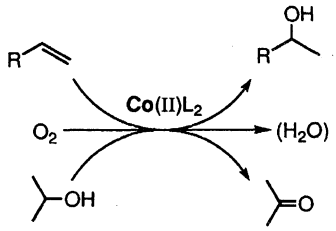
Table 1. CoSMDPT-Catalyzed Oxygenation in Alcoholic Solvent



Alcoholic solvent EtOH : ⟩-OH	Turnovers (24 h)	2-Hexanone : 2-Henanol
100 : 0	12.1	52 : 48
50 : 50	6.8	55 : 45
30 : 70	5.1	60 : 40
10 : 90	2.7	67 : 33
2 : 98	0.94	73 : 27



Scheme 2. Cobalt-catalyzed oxygenation in the presence of hydride reductant.



Scheme 3. Oxidation-reduction hydration.

and 4-phenyl-2-butanone when 4-phenyl-1-butene was treated with an atmospheric pressure of molecular oxygen in 2-propanol using a catalytic amount of bis(acetylacetonato)cobalt(II) (Table 2). The reaction proceeded smoothly in secondary alcohols such as 2-propanol or cyclopentanol,[21] whereas primary or tertiary alcohol solvents did not afford the hydrated product. Those results indicated that the (β-diketonato)cobalt(II)-catalyzed oxygenation reaction affords the corresponding hydrated product as a major product directly from the olefin via concomitant transfer of oxygen and hydrogen atoms, even under the neutral and mild oxidation conditions. In this hydration reaction therefore, both oxidation (oxygenation) and reduction (hydrogenation) occur together, thus it was named the "Oxidation-Reduction Hydration" (Scheme 3).

Examination of the catalytic activity of several cobalt(II) complexes having different 1,3-diketone-type ligands (Table 3) indicated that the ratio of the three products: i.e. hydrated product (alcohol), oxidized product (ketone), and reduced product (alkane), was influenced by the structure of the ligand.[22] The selectivity towards hydration was increased when cobalt(II) complexes coordinated by a ligand containing an electron-withdrawing group were employed as the catalyst. Finally, the yield of alcohol was improved to 81% by using bis(trifluoroacetylacetonato)cobalt(II) as the catalyst.

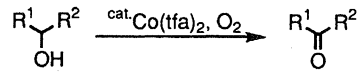
To elucidate the effect of ligands on catalytic activity, the redox potentials of the above cobalt(II) complexes were measured (Fig. 2).[23] Catalytically active complexes were characterized by having redox potentials between those of Co^{2+} and Co^{3+}. It was found that complexes whose redox potentials were in the range 0.0 to +0.5 V were effective catalysts of this hydration reaction. These complexes having higher or lower redox potentials, outside the above-mentioned range, showed no catalytic activity at all. This relationship between the structure of ligand and the catalytic activity of its cobalt(II) complex can be explained as follows: in the case of cobalt(II) complexes containing ligands with electron-donating groups, such as 3-phenyl-2,4-pentanedione (Entry 1 in Table 3), the complex is readily oxidized itself, both electrically and by molecular oxygen, and the oxidized complex no longer shows any catalytic activities in the hydration reaction. On the other hand, molecular oxygen can not be captured by cobalt(II) complexes containing ligands with strongly electron-withdrawing groups such as hexafluoroacetylacetone and hence they show no catalytic activity (Entry 9 in Table 3).

As mentioned above, one oxygen atom of molecular oxygen (Oxidant) was introduced into the olefin to form the corresponding alcohol, while the other accepted two hydrogen atoms from the secondary alcohol (Reductant) to form water (Scheme 3). Thus, it was assumed that removal of water from the reaction system would increase the yield based on catalyst. Addition of 4A Molecular Sieves into the reaction mixture or azeotropic removal of water was found to be effective, and the desired alcohol was formed in 8500 and 9140% yield, respectively.

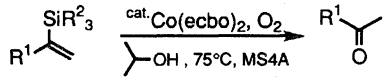
This Oxidation-Reduction Hydration was successfully applied to various olefins. Both acyclic and cyclic olefins were hydrated in high yields. Trisubstituted and 1,1-disubstituted ethenes were converted into the corresponding tertiary alcohols in more than 10000% yield (Table 4). Since the conventional method for hydration of olefin is performed under strongly acidic conditions,[24] functionalized olefins having ester, amide or acetal groups cannot usually be employed. On the other hand, even olefins containing an acetal group can be hydrated to give the desired product in high yield using this new reaction, because it proceeds under neutral conditions.

The present procedure using a cobalt(II) complex catalyst together with molecular oxygen (Oxidant) and 2-propanol (Reductant) was also applied to the direct oxidation of secondary alcohols into the corresponding ketones (Scheme 4),[25] to the direct preparation of ketones from vinylsilane (Scheme 5),[26] and to the stereoselective oxidative cyclization of 5-hydroxyalkenes into tetrahydrofuran derivatives (Scheme 6).[27]

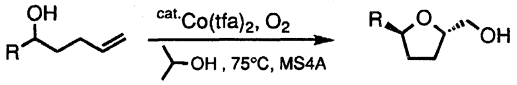
Concerning the mechanism and reactive intermediates of the cobalt(II)-catalyzed oxygenation of olefins, Nishinaga has proposed cobalt(I) hydride to be the key intermediate, from the deuterium labelling experiments. When $PhCD_2OH$ was used in place of $PhCH_2OH$ as hydrogen-donor (Reductant), the olefin (styrene) was oxygenated to the corresponding mixture of mono- and



Scheme 4. Aerobic oxidation of *s*-alcohol into ketone.

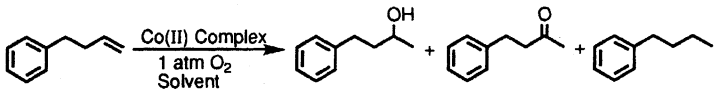


Scheme 5. Aerobic oxidation of vinylsilane into ketone.



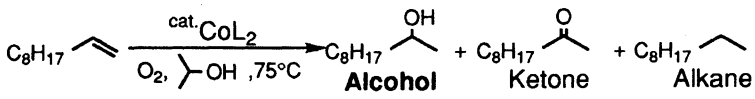
Scheme 6. Oxidative cyclization of 1-alken-5-ol.

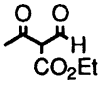
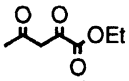
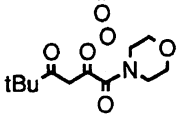
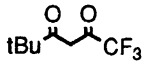
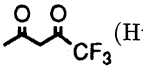
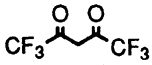
Table 2. Solvents for Oxidation-Reduction Hydration Catalyzed by (β-Diketonato)cobalt(II) Complexes



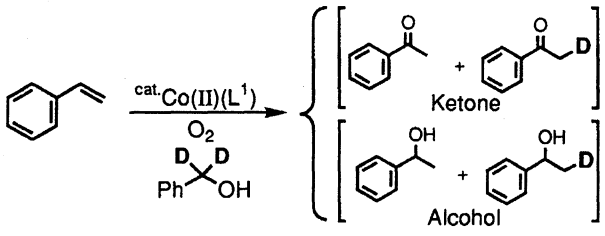
Entry	Co(II) complex	Solvent	Yields/%		
			Alcohol	Ketone	Alkane
1	$Co(acac)_2$		**46**	8	17
2	$Co(acac)_2$		**45**	9	16
3	$Co(acac)_2$	EtOH	No Reaction		
4	$Co(acac)_2$		No Reaction		
5	Co(salen)		No Reaction		

Table 3. Efect of Ligands for (β-Diketonato)cobalt(II) Complexes



Entry	Ligand (LH)	Conversion/%	Yields/%		
			Alcohol	Ketone	Alkane
1		No Reaction			
2	 (Hacac)	100	**45**	7	22
3	 (Hecbo)	100	**72**	14	2
4		100	**59**	17	15
5		87	**65**	10	2
6	 (Hmodp)	94	**74**	7	5
7		100	**81**	9	4
8	 (Htfa)	100	**81**	13	2
9	 (Hhfa)	No Reaction			

non-deuterated ketones (acetophenones) and alcohols (1-phenylethanols) (Scheme 7).[28] The results suggested that hydrogen transfer from the α-position of the alcohol ($PhCD_2OH$, reductant) to the terminal methylene carbon of olefin takes place during the oxygenation: that is, the key step is the addition of cobalt hydride to the olefin, which is followed by insertion of molecular oxygen to afford a peroxy intermediate, and this then is converted into the alcohol or ketone (Scheme 8). Contrary to this, Drago[4] proposed that cobalt hydroperoxide is a reactive intermediate (Scheme 9), based



Scheme 7. Cobalt-catalyzed oxygenation in deutrated alcohol.

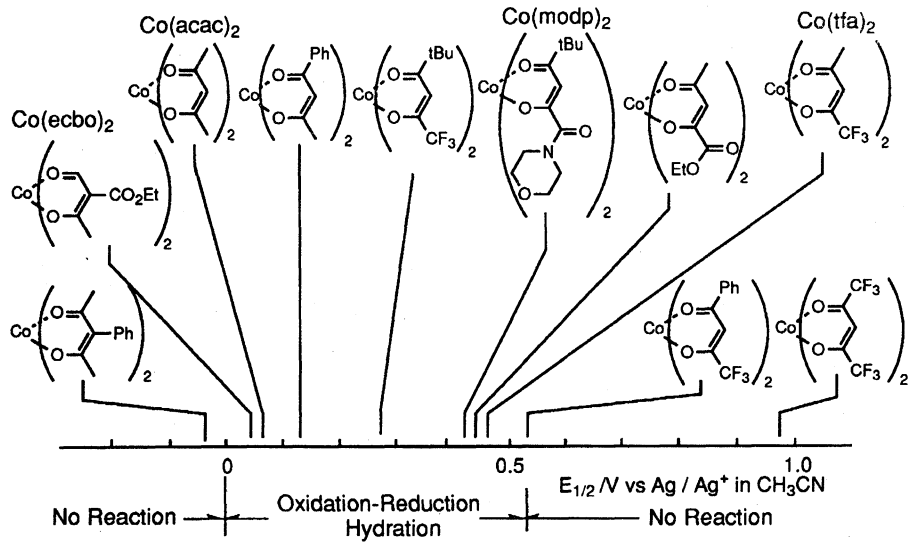
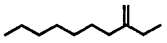
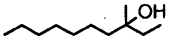
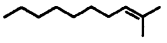
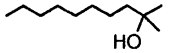
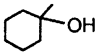
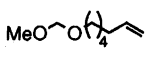
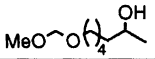
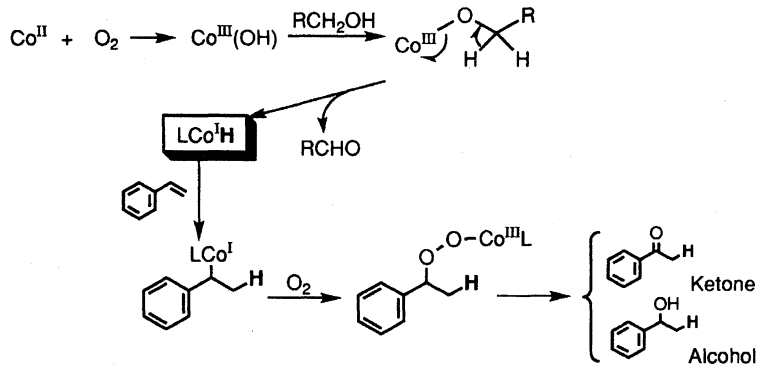


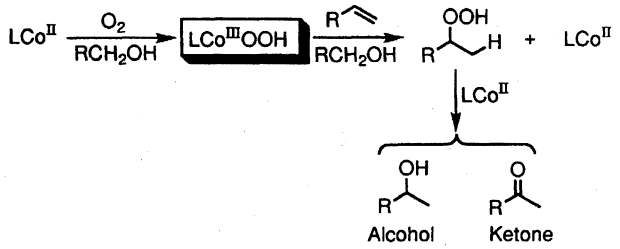
Fig. 2. Relationship of redox potentials and catalytic activities for Co(II) complexes.

Table 4. Oxidation-Reduction Hydration of Various Olefins Catalyzed by $Co(ecbo)_2$

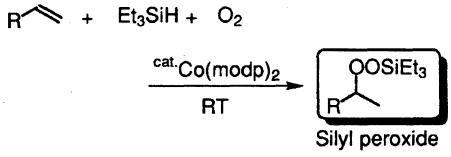
Entry	Olefin	Alcohol	Yield based on catalyst/%
1			10110
2			9780
3			10370
4			9340



Scheme 8. Cobalt-hydride mechanism proposed by Nishinaga.

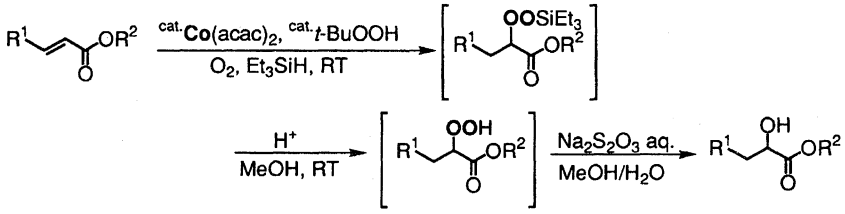


Scheme 9. Cobalt-hydroperoxide mechanism proposed by Drago.



Scheme 10. Direct peroxygenation of olefins.

on experiments using hydrogen peroxide as oxidant in place of molecular oxygen. The oxygenation reaction of olefin occurred not only with the latter but also with the former. In the latter case, were the cobalt hydride species, proposed by Nishinaga, to be formed when hydrogen peroxide is added to the cobalt complex in the presence of the olefin, the dioxygen species generated by



Scheme 11. Hydration of α,β-unsaturated carboxylic acid ester.

decomposition of hydrogen peroxide would be required to insert into the resulting alkyl-cobalt bond. Therefore, it seems likely that cobalt hydroperoxide should be considered as a key intermediate, although the detailed mechanism is not yet completely clear.

1-2. Catalytic Peroxygenation of Olefins. Silane is known as one of the most reliable reductants in organic synthesis.[29] To try to find a new effective reductant (a hydrogen donor) for the bis(1,3-diketonato)-cobalt(II) catalyzed hydration, triethylsilane was employed in place of 2-propanol.[30] As a result, an unexpected peroxygenated product, the triethylsilylperoxy derivative, was obtained when the above reaction was carried out at room temperature in dichloroethane.[31] For example, 4-phenyl-1-butene reacted with molecular oxygen and triethylsilane at room temperature in the presence of a catalytic amount of bis(acetylacetonato)cobalt(II) complex to give the corresponding 1-phenyl-3-(triethylsilylperoxy)butane in good yield. After screening various cobalt(II) complexes, $Co(modp)_2$ was found to be most effective (Scheme 10). The silylperoxy group was introduced into olefins with complete regioselectivity according to the Markownikov rule (Table 5). The resulting triethylsilyl peroxide is purified without any decomposition by thin layer chromatography on silica gel or vacuum distillation.[32] The present peroxygenation reaction provides a simple and efficient method for the direct introduction of dioxygen functionality into the carbon–carbon double bond of olefinic compounds under mild conditions.

Besides peroxygenation of simple olefins, several α,β-unsaturated esters were also peroxygenated according to the above procedure, producing the corresponding triethylsilylperoxy derivatives.[33] This peroxygenation with molecular oxygen catalyzed by cobalt(II) complex was achieved by adding a catalytic amount of *t*-butyl hydroperoxide, and the corresponding triethylsilylperoxy derivatives were formed in high yields. The triethylsilylperoxy group was introduced into the α-position of such esters with complete regioselectivity, and the initial product was transformed into the corresponding α-hydroxy ester in high yield via reductive treatment (Scheme 11).

An efficient method for the direct preparation of α-hydroxy carboxylic ester from α,β-unsaturated esters was also established. When phenylsilane[34] was employed as reductant in place of triethylsilane, direct reduction of silylperoxy intermediates, derived from peroxygenation of α,β-unsaturated ester, proceeded in one-pot, affording the corresponding α-hydroxy carboxylic acid esters in high yields. Also, it was shown that a manganese(II) complex, bis(dipivaloylmethanato)-manganese(II) ($Mn(dpm)_2$), is more effective than cobalt(II) complexes for the direct hydration of α,β-unsaturated esters.[35] The reaction proceeded smoothly, and the corresponding α-hydroxy carboxylic esters were obtained regioselectively in high yields (Table 6).

The reactive intermediates generated in this system of using phenylsilane and cobalt(II) complex in the absence of molecular oxygen also accepted several aldehydes as well as molecular oxygen.[36] In the presence of phenylsilane and a catalytic amount of cobalt(II) complex under argon atmosphere, the coupling reaction of α,β-unsaturated carbonitrile and carboxamide with aldehydes afforded aldol-type adducts in good to high

Table 5. Peroxygenation of Various Olefins with Molecular Oxygen and Triethylsilane Catalyzed by $Co(modp)_2$

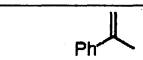
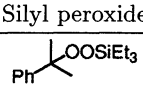
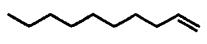
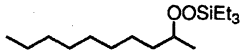
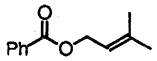
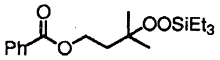
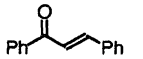
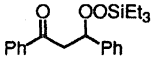
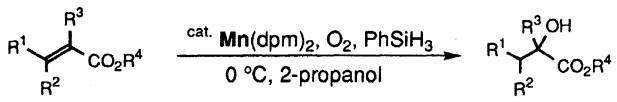
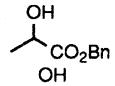
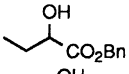
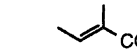
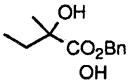
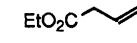
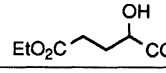
Entry	Olefin	Silyl peroxide	Yield/%
1			95
2			80
3			99
4			75

Table 6. Manganese(II) Catalyzed Hydration of Various α,β-Unsaturated Esters



Entry	α,β-Unsaturated ester	α-Hydroxy ester	Yield/%
1			91
2			91
3			94
4			82

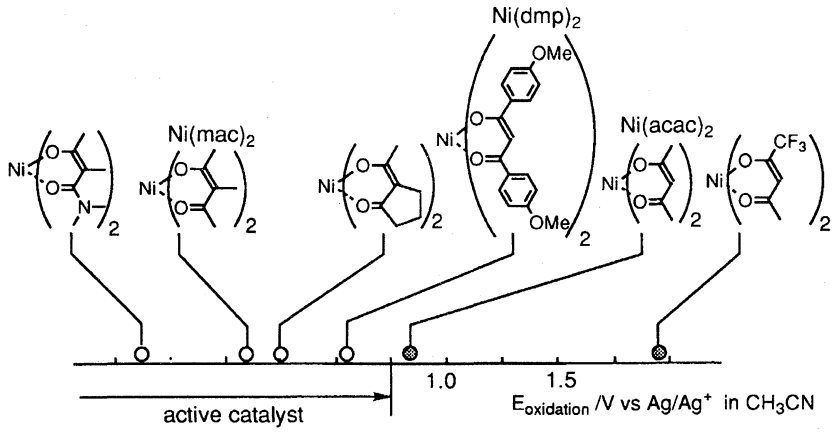
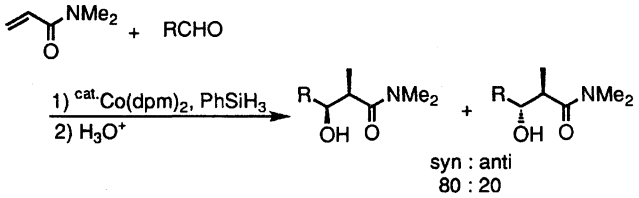


Fig. 3. Oxidation potentials and catalytic activities of nickel(II) complexes.

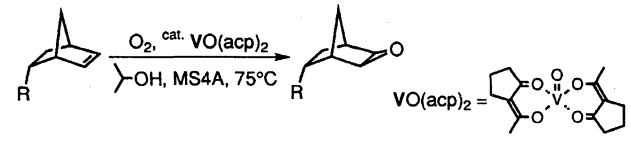


Scheme 12. Coupling reaction of α,β-unsaturated compounds with aldehyde.

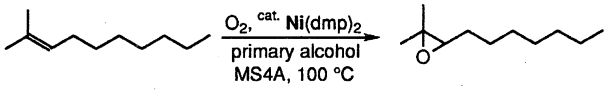
yields (Scheme 12).[37]

2. Nickel(II)-Complex-Catalyzed Aerobic Epoxidation of Olefins

Epoxides are one of the most useful synthetic intermediates for the preparation of oxygen-containing natural products or the production of epoxy resins. Peroxy acids[38] are often employed as convenient oxidants for the synthesis of epoxides; i.e. *m*-chloroperbenzoic acid in small scale preparations, and peracetic acid in industrial production. Hydroperoxides are also useful oxidants in the preparation of allyl alcohols using vanadium(IV) complex catalysts.[39] Since peroxy compounds have potentially explosive properties, careful handling is always required when using them, whereas molecular oxygen, abundant in the atmosphere, is a fairly safe and clean oxidant. Thus, much effort has been made to develop direct and selective epoxidations of olefins with molecular oxygen. Ethylene oxide is produced industrially by aerobic epoxidation of ethylene catalyzed by silver compounds. However, it is difficult to control the reaction of substituted olefins such as propylene, because of side-reactions under the usually severe reaction conditions of high pressure of oxygen or



Scheme 13. Vanadium-catalyzed aerobic epoxidation.



Scheme 14. Nickel(II)-complex-catalyzed aerobic epoxidation.

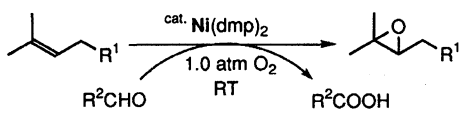
high temperature. Here the search for mild reaction conditions has been persued to eliminate side-reactions and to lead to more efficient epoxidation method.

2-1. Nickel(II)-Catalyzed Epoxidation. The "Oxidation-Reduction Hydration"[23] of olefins into the corresponding hydrated compounds by using molecular oxygen (Oxidant) and a secondary alcohol (Reductant) catalyzed by bis(1,3-diketonato)cobalt(II) was described in Chapter 1. The results indicated that one oxygen atom from molecular oxygen and two hydrogen atoms from 2-propanol were introduced together into the olefin, affording the hydrated product, the secondary alcohol behaving as an effective reductant. It was postulated that secondary alcohols would also behave as reliable reductants to bring about a catalytic cycle in the epoxidation of olefins with molecular oxygen.

As expected, norbornene analogues are monooxygenated to the corresponding epoxides in good yields by the combined use of molecular oxygen and 2-propanol in the presence of a catalytic amount of bis(2-alkyl-1,3-diketonato)oxovanadium(IV) (Scheme 13).[40]

Nickel(II) complexes have been reported to be efficient catalysts for the epoxidation of olefins when terminal oxidants such as iodosylbenzene[41] or sodium hypochlorite are used.[42]

The aerobic epoxidation of olefins in an alcohol solvent (a reductant) was attempted by using such com-



Scheme 15. Aerobic epoxidation by nickel(II)-aldehyde procedure.

plexes having 1,3-diketone ligands. Contrary to our expectations, epoxide was formed in higher yield using a primary rather than secondary alcohol (2-propanol), or in the absence of alcohols (Scheme 14).[43]

Several 1,3-diketone ligands were examined in the epoxidation of 2-methyl-2-decene with molecular oxygen in primary alcohols such as 1-butanol, and nickel(II) complexes having electron-donating ligands were found to be more effective (Fig. 3). For example, using bis[1,3-bis(*p*-methoxyphenyl)-1,3-propanedionato]-nickel(II) ($Ni(dmp)_2$) epoxidation proceeded smoothly even under lower oxygen pressure.

During a continued study to find reductants other than alcohols in the above aerobic epoxidation of olefins, the use of an aldehyde as reductant together with molecular oxygen at room temperature was found to give excellent results (Scheme 15).[44] Similar combinations have already been reported in patents and the chemical literature; for example, propylene was monooxygenated into propylene oxide with molecular oxygen in the presence of several metal complex catalysts and an aldehyde, such as acetaldehyde[45] or crotonaldehyde.[46] However in these cases, the conversion of olefin and the selectivity of epoxide formation never reached satisfactory levels. Recently, praseodymium(III) acetate was also shown to be an effective catalyst for the aerobic epoxidation of olefins in the presence of an aldehyde.[47]

In the above-mentioned nickel(II)-complex-catalyzed epoxidation, the yield of epoxide was influenced by the structure of the aldehyde (reductant); for example, for epoxidation of 2-methyl-2-decene catalyzed by bis(β-diketonato)nickel(II), both conversion of the olefin and yield of the epoxide were low when butyraldehyde was used, while the corresponding epoxides were obtained in quantitative yields when aldehydes having secondary or tertiary carbon next to the carbonyl carbon, such as isobutyraldehyde, cyclohexanecarbaldehyde, or pivalaldehyde, were employed (Table 7). Various trisubstituted or 1,1-disubstituted ethenes and norbornene analogues were smoothly monooxygenated according to the above procedure to the corresponding epoxides in high to quantitative yields under an atmospheric pressure of oxygen at room temperature. It should be pointed out here that in no case did over-oxidation at the allylic position, or cleavage of carbon–carbon double bonds, take place to any extent. Styrene derivatives were also monooxygenated to the corresponding epoxides in high yields. In the case of trisubstituted ethenes, the corresponding epoxides were obtained in quantitative yields even under air. For the aerobic epoxidation of 1,2-disubstituted ethenes, the use of a smaller amount of nickel(II) complex was sufficient to give good yield of the corresponding epoxide. Isovaleraldehyde was remarkably effective in the epoxidation of terminal olefins (1-alkenes), and the corresponding 1,2-epoxyalkanes were obtained in good to high yields (Table 8).[48] The following results show the efficiency of nickel(II) complexes in this epoxidation: even using only 0.0096 molar amount of $Ni(dmp)_2$, the epoxidation proceeded smoothly and the yield of produced epoxide based on catalyst was 1020000%.

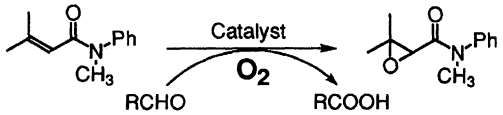
Table 7. Aldehydes as Reductant in Aerobic Epoxidation of 2-Methyl-2-decene

Entry	Aldehyde	Conversion/%	Yield/%
1		10	7
2		100	Quant.
3		100	Quant.

The nickel(II)-catalyzed epoxidation was also applied to the oxidation of enolates, and α-silyloxy carbonyl compounds were obtained, probably via rearrangement of the initially formed silyloxy epoxides.[49] α-Hydroxy carbonyl compounds were obtained in good yields by subsequent desilylation with potassium fluoride. By using an iron(III) complex catalyst, epoxy alcohol was obtained in quantitative yield without any over-oxidation of the hydroxyl group of alkyl alcohols, whereas nickel(II) complex-catalyzed epoxidation of citronellol stopped half-way, and the yield of epoxy alcohol was moderate.[50]

Bis(acetylacetonato)nickel(II) and tris(acetylacetonato)iron(III), both of which exhibited excellent catalytic activity in the epoxidation of aliphatic or aromatic olefins, were not effective for the oxygenation of α,β-unsaturated carboxamides, and the corresponding epoxide was formed in low yield. On the other hand, bis(dipivaloylmethanato)oxovanadium(IV) ($VO(dpm)_2$) was an effective catalyst, and an α,β-unsaturated carboxamide was oxygenated by the combined use of molecular oxygen and isovaleraldehyde, affording the corresponding epoxide in 87% yield.[51] It was suggested that the above epoxidation is promoted by the possible interaction with the amide group of the α,β-unsaturated carboxamide (Scheme 16).

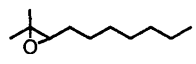
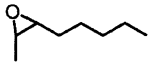
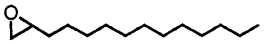
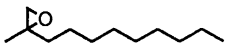
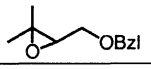
Recently, aerobic epoxidations catalyzed by (tetramesitylporphyrinato)ruthenium(II) (Ru(TMP), Fig. 4),[52] or ethoxooxo(tetra-*p*-tolylporphyrinato)-molybdenum(V)[53] has been reported by Groves and Murakami et al. Studies on the mechanism of aerobic oxidation catalyzed by the ruthenium complex (Ru(TMP)) showed that the catalytic system was achieved by the interconversion of ruthenium between its Ru^{2+},



Catalyst	Conversion / %	Yield / %
$Ni(acac)_2$	—	trace
$Fe(acac)_3$	33	26
$VO(dpm)_2$	92	87

Scheme 16. Epoxidation of α,β-unsaturated carboxamide.

Table 8. Nickel-Catalyzed Aerobic Epoxidation of Various Olefins

	Quant.		97% yield (*cis* : *trans*=51 : 49)
	Quant.		89% yield
	93% yield		97% yield

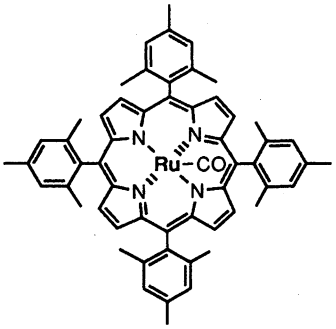
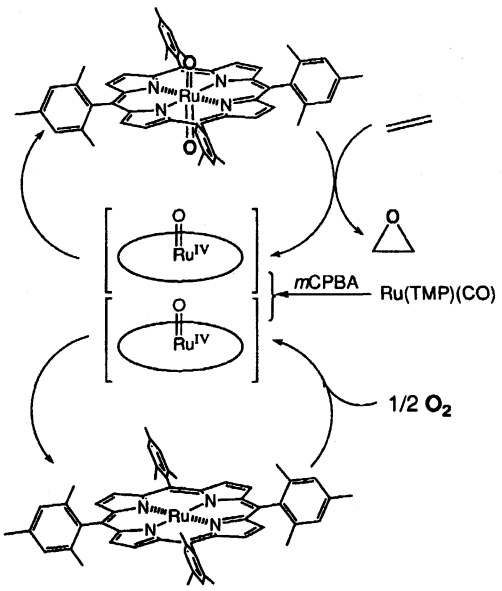


Fig. 4. Ru(TMP)(CO).



Scheme 17. Ru(TMP)-catalyzed aerobic epoxidation.

Ru^{4+}, and Ru^{6+} oxidation states (Scheme 17): that is, initially an oxoruthenium(IV) complex is formed by treating the ruthenium carbonyl complex with *m*CPBA. Then, the former complex behaves as a co-reductant, disproportionating[54] rapidly into $Ru^{VI}(TMP)(O_2)$ and $Ru^{II}TMP$. The resulting $Ru^{VI}(TMP)(O_2)$, the active oxidant, reacts with olefins to afford epoxides and molecular oxygen is captured by a transient ruthenium(II) complex. Furthermore, the stereochemistry of the aerobic epoxidation of the 5,6-double bond in cholesteryl benzoate catalyzed by ruthenium complex was studied.[55] When peroxy acids such as *m*CPBA or MMPP (magnesium monoperoxyphthalate hexahydrate)[56] were used, cholesteryl benzoate was converted into the corresponding mixture of 5,6-α- and 5,6-β-epoxides in the ratio of 71 to 29 (*m*CPBA, Entry 1 in Table 9),[57] or of 85 to 15 (MMPP), respectively. This was explained as due to steric hindrance of the β-face by the axial methyl group at C-10 and C-13, causing α-stereoselection in the epoxidation of cholesterol with peroxy acids.[58] On the other hand, β-stereoselectivity was observed in the epoxidation catalyzed by $Ru(TMP)(O_2)$ (Entry 2). This was explained by assuming a mechanism in which the alkene approaches the metal–oxo bond via side-on manner.

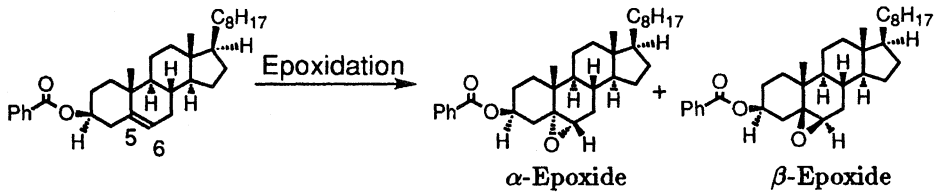
Similarly, the epoxidation with molecular oxygen and isobutyraldehyde in the presence of a catalytic amount of metal ion (nickel(II), iron(III), or manganese(II)) coordinated by 1,3-diketones led to the formation of the *hindered* 5,6-β-epoxide as the major product,[59] whereas the *less hindered* 5,6-α-epoxide was obtained as the major product when a peroxy acid was used as an oxidant (Entries 3 and 4 in Table 9). This remarkable reversal of stereoselectivity in the epoxidation of cholesteryl benzoate obviously indicates that the active oxidant in the above-mentioned epoxidation is not a simple peroxy carboxylic acid generated from an aldehyde in an autooxidative manner.

Interesting behavior concerning the reactive intermediate of this aerobic epoxidation is reported in the reaction with a singlet-oxygen scavenger:[60] that is, the reaction mixture of bis(β-diketonato)nickel(II) and various aldehydes exhibits high reactivity toward tetraphenylcyclopentanedione (singlet-oxygen scavenger). This observation suggests that a nickel(II) complex coordinated by aldehyde and molecular oxygen is formed in the first step and the latter is then converted into a singlet oxygen-like active oxygen species. It is this which is tentatively considered to be the reactive intermediate.

The stereochemistry of the epoxidation of cholesterol derivatives suggests that the manganese complex participates directly in the oxidation step. An enantioselective aerobic epoxidation should be achievable, were optically active manganese complexes to be used as catalysts (see next Section; 2-2.).

2-2. Enantioselective Aerobic Epoxidation of Unfunctionalized Olefins Catalyzed by Chiral Manganese(III) Complexes. Optically active epoxides have attracted much attention as versatile intermediates[61] for the synthesis of a wide variety of chiral compounds, including biologically active compounds[62] such as precocene II derivatives, cyto-

Table 9. β-Stereoselective Epoxidation of Cholesteryl Benzoate

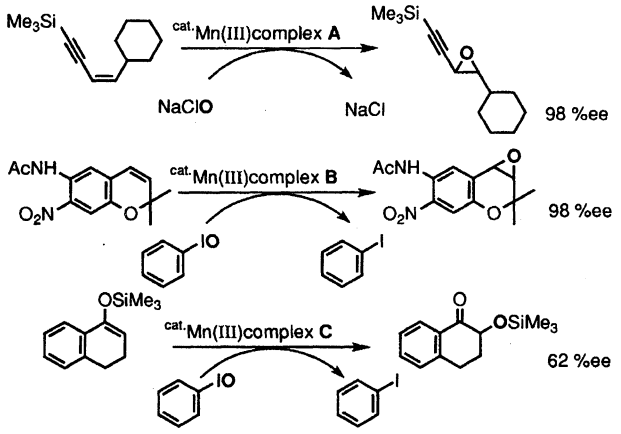


Entry	Epoxidation reagent	α-Epoxide : β-Epoxide
1	*m*CPBA	71 : 29
2	$^{cat.}$**Ru**(TMP)(O_2), O_2	>99
3	$^{cat.}$**Ni**(dmp)$_2$, O_2, ⟩CHO	31 : 69
4	$^{cat.}$**Mn**(dpm)$_2$	20 : 80

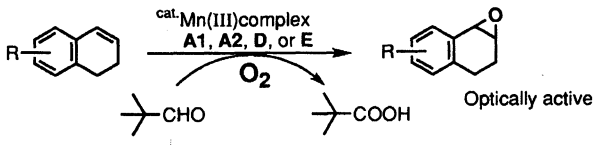
toxic agent selectively to insects,[63] and medicinal compounds for the remedy of hypertension and asthma,[64] as well as functional organic materials such as ferroelectric liquid crystals.[65] The reliable enantioselective titanium(IV)-catalyzed epoxidation of allylic alcohols developed by Sharpless and Katsuki uses *t*-butyl hydroperoxide as an oxidant, affording optically active 2,3-epoxy alcohols with very high enantiomeric excesses.[66] Such epoxidation has been widely applied to the synthesis of a number of natural products.

Many approaches have been tried to develop efficient, enantioselective epoxidation of unfunctionalized olefins; for example, several biological systems have been employed in the enantioselective epoxidation of terminal alkenes using an enzymatic catalyst such as *Pseudomonas oleovorans*,[67] hydrocarbon-assimilating microorganisms such as *Nocardia corallia* B-276,[68] or *Corynebacterium equi* (IFO 3730).[69] With regard to nonenzymatic systems, artificial metal-porphyrins (Fig. 5) have been designed as cytochrome P-450 modeling systems which catalyze the enantioselective epoxidation of styrene analogues.[70] Recently, Jacobsen[71] and Katsuki[72] independently reported that manganese(III)-salen complexes, (**A** and **B**[73] in Fig. 6), are effective catalysts for the enantioselective epoxidation of unfunctionalized olefins (Scheme 18) using terminal oxidants such as iodosylbenzene,[71] sodium hypochlorite,[74] or hydrogen peroxide.[75] The manganese(III)-catalyzed system was also applied to the oxidation of silyl enol-ethers into the corresponding α-hydroxy carbonyl compound[76] (catalyst **C** in Fig. 6). However except for the case of artificial-bleomycin catalyzed epoxidations,[77] few scientists have reported on the utilization of molecular oxygen for the enantioselective epoxidation of simple olefins.

In the presence of a catalytic amount of optically active manganese(III) complex of salen derivatives (**A1** and **A2** in Fig. 7) or (β-oxo aldiminato)manganese(III) complex (**D** and **E**), aerobic and enantioselective epoxidation of unfunctionalized olefins was performed by the combined use of molecular oxygen and pivalaldehyde (Scheme 19). Optically active salen-type manganese(III) complexes were prepared by the conventional method,[78] and purified by column chromatography on silica-gel, or by washing a benzene solution with aqueous lithium chloride solution (**A1** and **A2**).[79] In addition, various (β-oxo aldiminato)-manganese(III) complexes (type **D** and **E**) were synthesized from the corresponding alkyl(R) acetoacetate[80] and acetophenone derivatives in a few steps, and purified by the above procedures. After screening various aldehydes, it was found that use of pivalaldehyde resulted in good enantioselection and chemical yields. In the case of epoxidation using a salen-type complex catalyst, addition of a catalytic amount of *N*-methylimidazole was effective in improving[81] the optical yield of epoxide. Interestingly, the absolute configuration of the



Scheme 18. Mn(III)-catalyzed enantioselective epoxidation by using a terminal oxidant.



Scheme 19. Aerobic enatioselective epoxidation catalyzed by Mn(III) complexes.

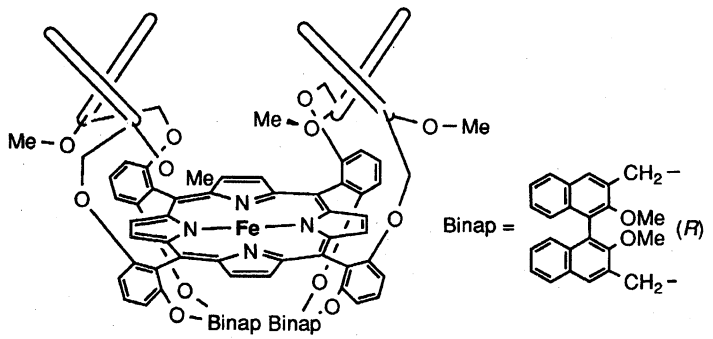


Fig. 5. "Twin-cornet" porphyrin complex catalyst.

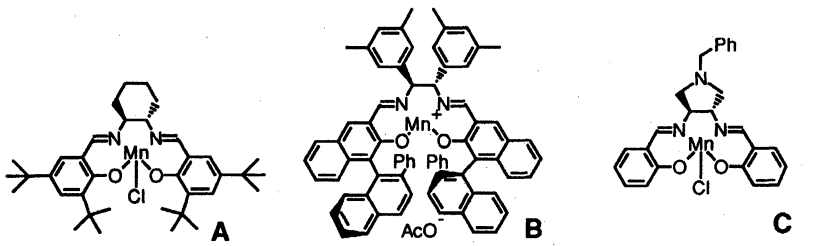


Fig. 6. Optically active manganese(III) catalyst with combined use of terminal oxidants.

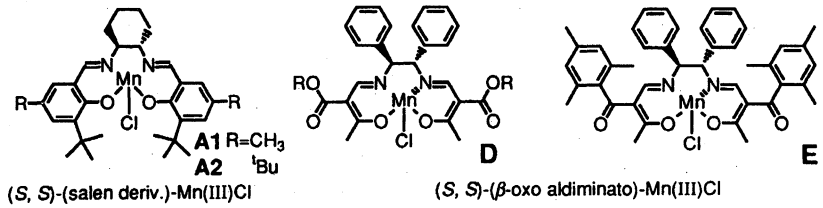


Fig. 7. Optically active manganese(III) catalyst for aerobic enantioselective epoxidation.

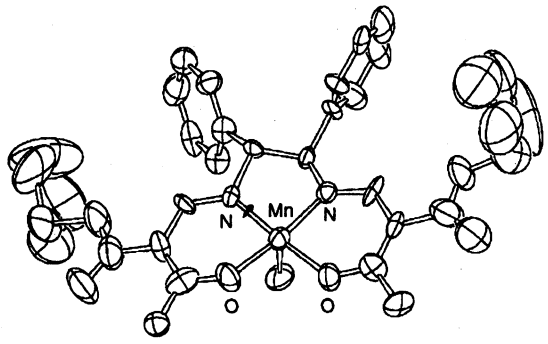
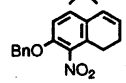
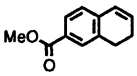
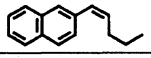


Fig. 8. X-Ray analysis of (α-aminomethylene-β-oxo ester)-Mn(III) **D** (**R**=cyclopentyl).

epoxide obtained was reversed by adding *N*-methylimidazole.

Effective ligands have been rationally designed from the prediction that bulkiness in the ester moiety of α-aminomethylene-β-oxo ester ligands would influence the optical yield, as deduced from an X-ray diffraction study (Fig. 8).[82] Thus, the (α-aminomethylene-β-oxo ester)-Mn(III)Cl containing the isoborneol moiety (**D**) and the (α-aminomethylene-β-diketone)-Mn(III)Cl containing the mesitoyl side-chain (**E**) were prepared.

Table 10. Aerobic Enantioselective Epoxidation of Various Olefins

Entry	Olefin	Optical yield/%ee (Yield/%)	Catalyst
1		64 (70)	**D**
2		72 (80)	**A1**
3		70 (43)	**D**
4		66 (38)	**A1**
5		59 (67)	**D**
6		84 (52)	**D**
7		92 (37)	**A2**
8		80 (40)	**E**

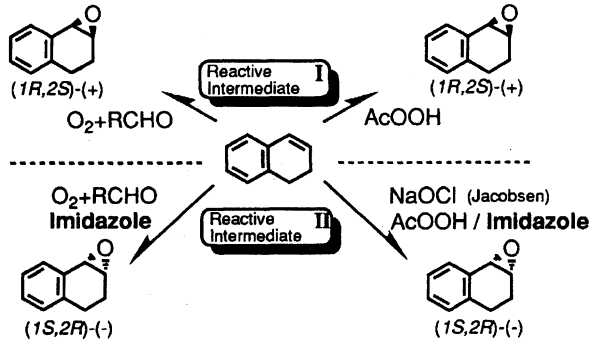
The present aerobic oxidation system was applied to the enantioselective epoxidations of various simple olefins (Table 10). Dihydronaphthalenes were con-

Table 11. Absolute Configuration of Epoxide Catalyzed by ((*S*,*S*)-salen deriv.)-Mn(III) Complex **A1**

Entry	Oxidant	Major product	
1	O_2, ⟩CHO		(1*R*,2*S*)-(+)
2	NaClO		(1*S*,2*R*)-(−)
3	PhIO		

verted into the corresponding optically active epoxides in good yields with moderate to good enantioselectivities. The enantioselective aerobic epoxidation of 7-membered cyclic olefins afforded the corresponding epoxides with high enantiomeric excess in the presence of Mn(III) complex (salen deriv.-Mn(III)Cl **A1**: 83%ee, (α-aminomethylene-β-oxo ester)-Mn(III)Cl **D**: 84%ee, Entry 6). Chromene derivatives[83] and simple acyclic olefins were also converted into the corresponding optically active epoxides with high enantioselectivities.

When the (*S*,*S*)-complex was employed as a catalyst in the aerobic epoxidation (Entry 1 in Table 11), the absolute configuration of the epoxide derived from dihydronaphthalene was determined to be (1*R*,2*S*) by comparison of the sign of its optical rotation with the reported value.[84] It should be noted here that this result, formation of the (1*R*,2*S*)-epoxide using the (*S*,*S*)-catalyst, is opposite to that reported by Jacobsen or Katsuki using iodosylbenzene or sodium hypochlorite as oxidant (Entries 2 and 3 in Table 11). Furthermore, in the presence of a catalytic amount of *N*-methylimidazole, the absolute configuration of the epoxide formed in the (*S*,*S*)-complex-catalyzed epoxidation is completely reversed, and the epoxide with the (1*S*,2*R*)-configuration is formed. These results suggested that the reactive intermediate affording the (1*R*,2*S*)-epoxide was different from that giving the (1*S*,2*R*)-epoxide in the presence of *N*-methylimidazole. Similarly, the (1*R*,2*S*)-(+)-epoxide resulted when the epoxidation was carried out in the presence of a catalytic amount of (*S*,*S*)-salen deriv.-Mn(III) complex **A1** with peracetic acid as oxidant instead of the combined system, molecular oxygen and pivalaldehyde. The absolute configuration of the epoxide formed were again reversed to (1*S*,2*R*)-(−),[85] by an addition of *N*-methylimidazole (Scheme 20). It was recently reported that [(acylperoxo)porphyrinato]iron complexes are converted into the corresponding (oxo)iron complexes by coordination of imidazole derivatives.[86] Thus, the reversal of absolute configuration of the epoxides may be explained as follows: (acylperoxo)manganese complex **I** is formed from molecular oxygen, pivalaldehyde, and the manganese-(III) complex in the first step. In the absence of *N*-methylimidazole, (acylperoxo)-(*S*,*S*)-salen deriv.-Mn-(III) complex **I**[87] reacts with olefin to afford the (1*R*,-2*S*)-(+)-epoxide. On the other hand, complex **I** is con-



Scheme 20. Reactive intermediates ((*S*,*S*)-salen deriv. complex).

verted into (oxo)manganese complex **II** in the presence of *N*-methylimidazole by coordination of the latter as an axial donor ligand (Fig. 9). The complex **II** is widely accepted[88] to be the reactive intermediate in epoxidation when terminal oxidants such as iodosylbenzene[89] and sodium hypochlorite are used.[90]

Also, in the aerobic enantioselective epoxidation of 1-propenylbenzene catalyzed by chloro(β-oxo aldiminato)manganese(III),[91] the enantiofacial selection is opposite to the results reported using oxidants other than molecular oxygen: that is, using a terminal oxidant such as sodium hypochlorite, (*S*,*S*)-(α-aminomethylene-β-diketone)Mn(III)Cl **E**, afforded (1*S*,2*R*)-(+)-*cis*-epoxide, while (1*R*,2*S*)-(−)-epoxide was obtained from the (*S*,*S*)-(α-aminomethylene-β-diketone)Mn(III)Cl **E** catalyzed epoxidation using the combination of molecular oxygen and pivalaldehyde (Fig. 10). These results clearly indicate that the reactive species in this aerobic, enantioselective epoxidation is different from the (oxo)-manganese complex intermediate generated from chiral manganese(III) catalyst and terminal oxidants such as sodium hypochlorite or iodosylbenzene. Since the combined use of (*S*,*S*)-(α-aminomethylene-β-diketone)-Mn(III)Cl **E** and peracetic acid also afforded (1*R*,2*S*)-epoxide, it is reasonable to assume that the (acylperoxo)manganese complex generated from optically active manganese catalyst, molecular oxygen and pivalaldehyde is the key intermediate in this reaction.

2-3. Cobalt(II)-Complex-Catalyzed Epoxidation of Olefins under Neutral Conditions. In the aerobic epoxidation mentioned above, aldehydes were converted into the corresponding carboxylic acids as a result of accepting one oxygen atom during the epoxidation process and also by autooxidation. When peroxy acids, conventional oxidants, are employed in the epoxidation of olefins, carboxylic acids are also produced together with the desired epoxides. In these reactions, acid-sensitive epoxides often undergo oxiran-opening or rearrangement caused by the carboxylic acids produced at the same time. Accordingly, much effort has been dedicated to the development of olefin epoxidation under neutral conditions. One solution to this problem for allylic alcohols has been the vanadium-catalyzed

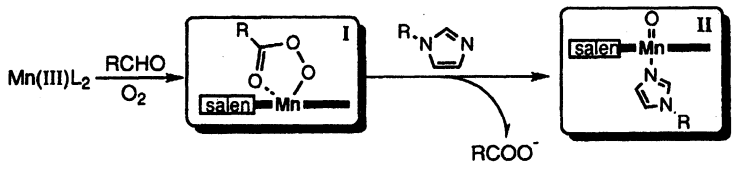


Fig. 9. Reactive intermediates **I** and **II**.

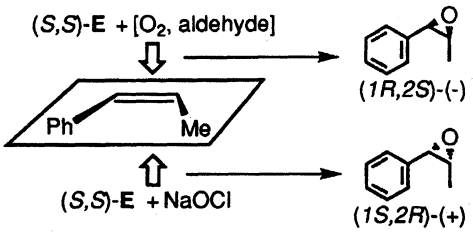
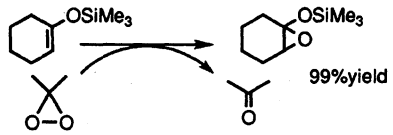
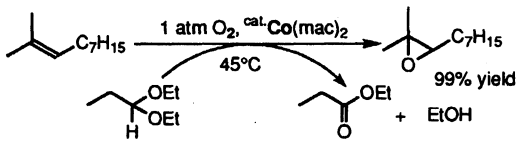


Fig. 10. Absolute configuration of epoxide formed by catalyst (*S,S*)-**E**.



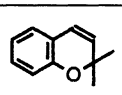
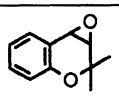
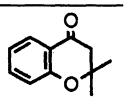
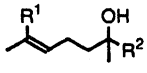
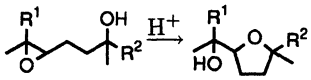
Scheme 21. Neutral oxidation with dioxirane.

epoxidation with *t*-butyl hydroperoxide, which is performed under acid-free conditions, since only *t*-butyl alcohol is co-produced.[92] Furthermore, it was recently reported that dimethyldioxirane and its derivatives, prepared from the corresponding ketones and potassium peroxomonosulfate,[93] are also useful and more general reagents for this purpose,[94] because nonacidic compounds are formed during the epoxidation reactions (Scheme 21).



Scheme 22. Aerobic epoxidation under neutral conditions.

Table 12. Cobalt(II)-Catalyzed Epoxidation in the Presence of Acetal

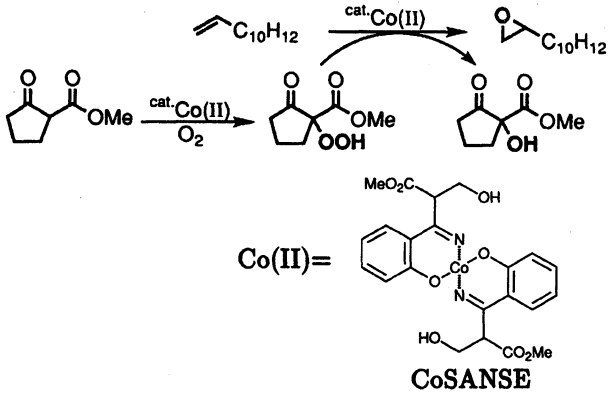
Olefin		Yield/%	
		Epoxide	By-product
	Epoxidation ⟶		
	cat. Co(II)L_2, O_2 EtCH$(OEt)_2$	77	0
	*m*CPBA	46	33
	⟶ 		
	cat. Co(II)L_2, O_2 EtCH$(OEt)_2$	82	0
	*m*CPBA	0	84

Recently, we have found cyclic ketones such as 2-methylcyclohexanone,[95] and acetals such as propionaldehyde diethyl acetal,[96] to be useful reductants in the aerobic epoxidation of olefins catalyzed by cobalt(II) complexes. In the latter case, ethyl propionate and ethanol co-products were detected in nearly stoichiometric amounts (Scheme 22), showing that the reaction system remained neutral throughout the epoxidation. Using this procedure, epoxidation of γ,δ-unsaturated alcohols and 2*H*-chromenes was achieved, affording the desired epoxides in good to high yields without any further reaction (Table 12). The cobalt(II)-catalyzed epoxidation was also applied to the oxygenation of acid-sensitive compounds, such as silyl enol ethers and silyl ketene acetals, to afford α-hydroxy carbonyl compounds in good yields.[97]

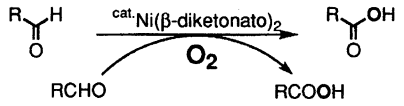
By the combined use of molecular oxygen with methyl 2-oxocyclopentanecarboxylate as co-reductant, a similar aerobic epoxidation system was recently reported to be achieved in the presence of a catalytic amount of cobalt complex prepared from cobalt(II) salt and Schiff base containing L-serine (CoSANSE) (Scheme 23).[98]

3. Miscellaneous

An efficient aerobic epoxidation of various olefins using molecular oxygen, aldehyde and a catalytic amount of metal complex, was described in the previous chapter. After our results were published, similar aerobic oxygenation systems using an aldehyde as oxygen acceptor were reported using either clay-impregnated nickel(II) acetylacetonate as a heterogeneous catalyst,[99] or tris(tetrazolyl enolate)iron(III) complex,[100] bis[*N*-(1-phenylethyl)-*N*-salicylideneaminato]cobalt(II) complex,[101] *N,N'*-bis[*o*-(*p*-tolylsulfonylamino)benzylidene]ethylenediami-



Scheme 23. Cobalt-catalyzed aerobic epoxidation.



Scheme 24. Aerobic oxidation of aldehyde catalyzed by nickel.

nonickel(II) complex,[102] or copper(II) hydroxide[103] as homogeneous catalyst, or without any catalyst at all.[104]

The observation that carboxylic acid is formed during the epoxidation led us to study the direct oxygenation of aldehydes into the corresponding carboxylic acids (Scheme 24).[105,106] A similar aerobic oxidation of a secondary alcohol into the corresponding ketone with a ruthenium[107]-cobalt bimetallic catalyst in the presence of aldehyde has been reported.[108]

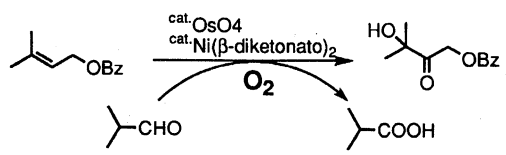
Since oxidation of olefins into 1,2-diols[109] or α-hydroxy ketones is a useful reaction for introducing two oxygen-containing functions in a one-step procedure, this kind of reaction has also been a focus of research, and oxidation of steroid derivatives with Milas' reagent (hydrogen peroxide in anhydrous *t*-butyl alcohol),[110] ruthenium-catalyzed oxidation with peracetic acid,[111] and stoichiometric manganese(VII) peroxide oxidation[112] have been reported.

We too have demonstrated an aerobic bifunctionalization reaction of various olefins into α-hydroxy ketones using catalytic amounts of osmium(IV) tetraoxide and bis(β-diketonato)nickel(II) (Scheme 25).[113]

3-1. Aerobic Baeyer–Villiger Oxidation. In the aerobic epoxidation reaction, one oxygen atom of molecular oxygen is added to a carbon–carbon double bond (substrate) to afford the corresponding epoxide, while the other is captured by an aldehyde (reductant) to form the corresponding carboxylic acid.

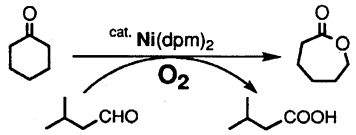
The Baeyer–Villiger reaction is one of the typical one-oxygen transfer reactions of organic synthesis; reagents like hydrogen peroxide or organic peroxy acids such as peracetic acid and *m*CPBA are generally employed. In addition to these, bis(trimethylsilyl) peroxide[114] and magnesium monoperoxyphthalate (MMPP)[115] have recently been shown to be effective oxidants. Several attempts to achieve an aerobic Baeyer–Villiger reaction, preparing ε-caprolactone from cyclohexanone by the combined use of aldehyde and transition-metal catalysts, have been reported.[116,117] However, the selectivities for ε-caprolactone formation are not satisfactory (70—86%), and conversions of cyclohexanone are generally low (3—30%).

On the other hand, in the presence of a catalytic amount of nickel(II) complexes coordinated by 1,3-diketones, cyclohexanone is effectively converted into ε-caprolactone by the combined use of molecular oxygen and isovaleraldehyde (Scheme 26).[118] The nickel(II)-catalyzed aerobic Baeyer–Villiger oxidation has successfully been applied to various ketones (Table 13). Cyclohexanone and its derivatives (2- or 4-substituted) were oxidized to the corresponding ε-caprolactones in high yields without any accompanying over-oxidation products. Oxidation of 2-methylcyclohexanone afforded ε-heptanoic lactone as a single isomer via regioselective migration of the more substituted carbon atom, whereas two isomers, ε-heptanoic lactone and 2-methylcaprolactone were obtained with *m*CPBA. Similar aerobic Baeyer–Villiger oxidations have recently been reported using iron powder[119] or copper(II)/nickel(II) salts[120] as catalyst in the presence of an aldehyde. The aerobic oxidation system has been applied to a "Tandem oxidation–Baeyer–Villiger sequence": That is, a cyclic secondary alcohol was converted into a ketone, which was in turn oxidized to the corresponding lactone via a Baeyer–Villiger reaction in a one-pot procedure catalyzed by using a cyclic chromium(VI) ester catalyst.[121] The aerobic Baeyer–Villiger reaction has also been applied to the oxidation of 2-alkoxycyclohexanones, subsequent acidic treatment affording acetal carboxylic acids[122] (Scheme 27).



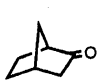
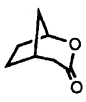
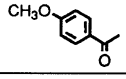
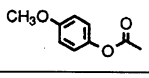
Scheme 25. Aerobic oxidation catalyzed by osmium and nickel.

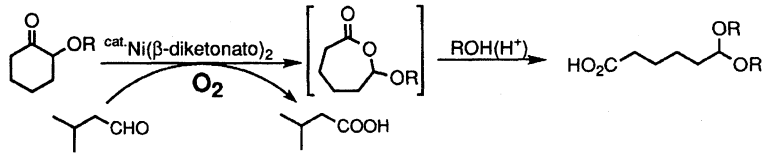
3-2. Direct Oxygenation of Aromatic Compounds. The direct oxygenation of aromatics into their hydroxylated derivatives is one of the most challenging problems in organic synthesis. Since the



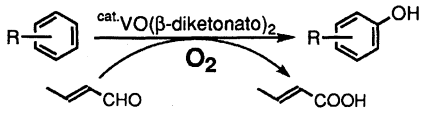
Scheme 26. Nickel(II)-catalyzed aerobic Baeyer–Villiger reaction.

Table 13. Nickel(II)-Catalyzed Aerobic Baeyer–Villiger Oxidation

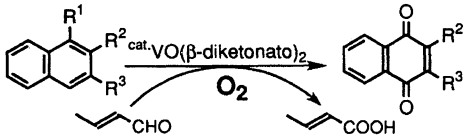
Entry	Ketone	Lactone (Ester)	Yield/%
1			91
2			93
3			R=CH_3 96
4			^{t}Bu 95
5			Ph 83
6			99
7			76



Scheme 27. Preparation of acetal carboxylic acid.



Scheme 28. Aerobic hydroxylation of aromatic compounds.



Scheme 29. Aerobic oxidation of naphthalene into 1,4-naphthoquinone.

aromatic nucleus is resistant to oxidation because of its resonance stabilization, oxygenation almost invariably requires a highly reactive oxidant and severe conditions.[123] Transition metal-catalyzed oxygenation by using an iron(III) compound with hydrogen peroxide (Fenton's reagent),[124] and stoichiometric hydroxylation by a vanadium(V) peroxo complex[125] have been reported. Direct oxygenation with molecular oxygen promoted by several oxygenases[126] has also been examined *in vivo*. Aerobic oxygenation of aromatics by using transition-metal catalysts have also been demonstrated, though phenolic compounds were only detected in low yields.[127]

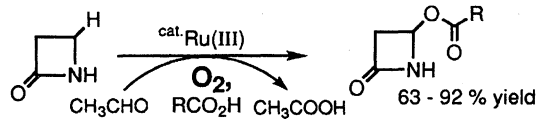
Based on the results we had obtained, it seemed that the direct aerobic oxygenation of benzene and its analogues into phenol derivatives should be possible. We have studied this reaction by using bis(β-diketonato)-oxovanadium(IV) catalyst in the presence of crotonaldehyde[128] (Scheme 28).

This oxovanadium(IV) catalyzed oxygenation was also applied to the transformation of naphthalene derivatives into the corresponding 1,4-naphthoquinones[129] (Scheme 29). It has previously been reported[130] that 2,3,6-trimethylphenol is effectively oxygenated to trimethyl-*p*-benzoquinone, a key compound for vitamin E synthesis, with molecular oxygen in the presence of copper(II) chloride–hydroxylamine in an alcoholic solvent.

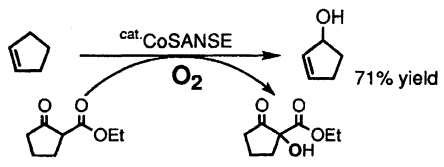
3-3. Aerobic Oxygenation of the Carbon-Hydrogen Bond. The functionalization of unactivated carbon–hydrogen bonds in hydrocarbons has been investigated for both its synthetic and its biological interest. A combination of molecular oxygen and nonporphyrinic iron catalysts has been examined for the oxygenation of saturated hydrocarbons ("Gif" and "Gif-Orsay" system).[131] Recently, the ruthenium-catalyzed transformation of the C–H bond into an acyloxy group was reported.[132] In the presence of an aldehyde, carboxylic acid and a catalytic amount of ruthenium(III) chloride, β-lactams were effectively converted into the corresponding 4-acyloxy-2-azetidinones with molecular oxygen in good to high yields (Scheme 30). A similar catalytic system was applicable to the oxidation of unactivated alkanes.[133] Cyclohexane was converted into cyclohexanone (66% selectivity at 11% conversion), and cyclohexanol (29% selectivity), and adamantane into 1-adamantanol (75% selectivity at 36% conversion).

Several new "reductants" other than alcohols and aldehydes have been reported for aerobic oxygenation reactions. For example, 2-oxocyclopentanecarboxylate[134] was reported to be an efficient reductant for aerobic epoxidation or allylic and benzylic oxidation catalyzed by cobalt(II) complexes (Scheme 31). Also, carbon monoxide (CO)[135] and α-diketone[136] have been reported to be useful reductants for the oxidation of benzyl ethers[137] and/or cyclic ether into the corresponding lactone (Scheme 32).

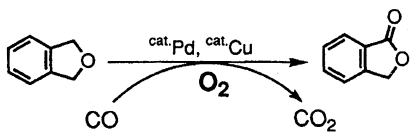
As mentioned above, one oxygen atom of molecular oxygen was captured by the "reductant", while the other was introduced to the substrate via a mono-oxygen transfer reaction. The substrates and "reductants" mentioned in this review are listed in Table 14. These aerobic oxygenation systems using a "reductant" and a metal-catalyst act as an "artificial-monooxygenase",[138]



Scheme 30. Ruthenium-catalyzed Oxidation of β-lactam.

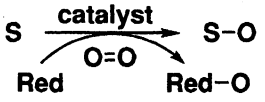


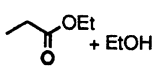
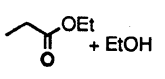
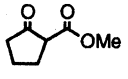
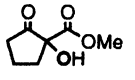
Scheme 31. Co(II)-catalyzed aerobic oxidation of allylic carbon.



Scheme 32. Pd–Cu catalyzed aerobic oxidation in the presence of CO.

Table 14. Monooxygenase-Like Oxidation in the Presence of Reductant



S (Substrate)	S–O	Red (Redutant)	Red–O
			
		RCHO	RCOOH
			
			
			
		CO	O=C=O
R–H	R–OH		

enabling various efficient, one-oxygen transfer reactions.

4. Conclusion

Through observation of an unexpected phenomenon, we were able to find and develop an oxidation–reduction hydration not so long after we started our research work on oxygenation of olefins. This gave us the important hint (combined use of molecular oxygen (oxidant) and an appropriate reductant) that proved essential to developing an aerobic oxygenation.

In chemical research, one topic leads to another through pursuit by experiment. Such knowledge, backed up by our daily accumulated experience of practical research, becomes the driving force for new advances. At present, it is important to dig out further interesting and useful possibilities from the limitless potential of O_2 chemistry hidden all around us.

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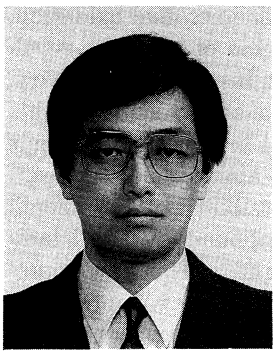

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