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Recent Development of Mn(III)-Mediated Oxidations in Organic Synthesis

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요 약. 천이 금속인 망간은 다양한 산화상태로 존재하기 때문에, 고배위 망간 착물은 오래 전부터 산화제로 애용되어 왔다. 그러나, 망간 3가 이온(Mn^{+3})은 착물의 형성이 혼하지 않기 때문에, 산화반응에 이용되기 시작한 것은 최근의 일이다. 그 중에서, 키랄 (살렌)망간(III) 착물은 올레핀의 비대칭 에폭시화 반응의 촉매로 개발되어 주목받고 있다. 또한 아세트망간(III)은 일전자 전이 산화제로서, 탄소-탄소 결합의 형성에 이용되고 있다. 본고에서는 최근에 개발된 이러한 산화반응의 반응성및 작용기전에 관해 서술하였다.

I. Introduction

Transition metal organometallic chemistry has been one of the most active areas of chemical research. A significant part of this academic and industrial research has been concerned with the use of transition metals in organic synthesis.[1] Thus, metals such as Ni, Ti, Pd and Rh have been widely utilized as catalysts in modern synthetic chemistry.

Manganese(Mn), also, has been used as one of the most valuable transition metals in organic synthesis. Its electron configuration is $[Ar]3d^5 4s^2$. By employing first two 4s electrons and then, consecutively, up to all five of its unpaired 3d electrons, manganese exhibits all oxidation states from +2 to +7. Thus, much efforts have been made to utilize its oxidation-reduction cycle in the synthetic process. High valent manganese complexes such as $KMnO_4$ and MnO_2 have long been used as important oxidants.[2] Since the most common oxidation states of manganese are +2, +4 and +7, Mn(+3) complexes have not been explored until recently. In this paper, recent synthetic development in the oxidation process employing Mn(III) complexes will be discussed. The discussion will be devided into the following two subjects; i) Mn(III)-catalyzed asymmetric epoxidation and ii) Mn(III)-mediated oxidation process. Although the above two topics are in common in using Mn(III) as the reaction mediator, the applied redox cycle is very different. In the epoxidation process, Mn(III) and Mn(V) are related in the reaction cycle. On the other hand, Mn(III) is transformed to Mn(II) in the reaction discussed in chapter III in this article.

II. Mn(III)-catalyzed asymmetric epoxidation

Nature sometimes provides us an impetus for the creation of novel chemical reactions which mimic the biological systems. Cytochrome P-450, heme enzyme, performs a biological epoxidation with high enantioselectivity.[3] This biological reaction led chemists to study an effective oxidation process enploying metalloporphyrins as the artificial catalyst. Various iron or manganese porphyrins have been developed for the catalysts of enantioselective epoxidations of simple olefins in organic synthesis. Even though lots of efforts have been made to use metalloporphyrins as selective oxidation catalysts, their application in organic synthesis has not yet been achieved yet. The major problem is its low selectivity. Furthermore, the difficulties for the synthesis of the chiral porphyrin ligand make this process impractical. Nevertheless, this subject is one of the most active research areas in terms of synthetic and more importantly mechanistic point of views.[4]

Recently, the synthetic breakthrough on the enantioselective olefin epoxidations has been made by Jacobsen's research group, where chiral Mn(III)salen complexes were employed as catalysts.[5] Even though Mn(III)salen complexes are structurally different from the Mn(III)porphyrines, their reaction mechanism is very similar. Because Mn(III)salen is the only catalyst which is applicable in organic synthesis thus far, most of the discussions in this chapter will be concentrated on the Mn(III)salen-catalyzed epoxidations. The comprehensive review of this topic has been published in 1993.[6] However, rather important experimental results have been reported more recently. This paper will discuss the chemistry focusing on those results.

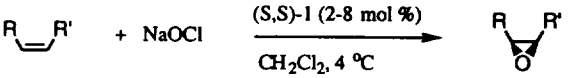
1) Development of chiral Mn(III)salen catalysts

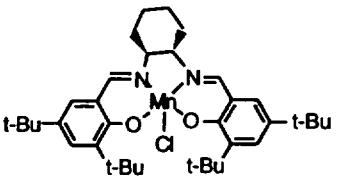
Kochi and co-workers showed that achiral Mn(III)salen complexes catalyze the epoxidation of olefins in the presence of a stoichiometric oxidant. Jacobsen did a pioneering work on the enantioselective epoxidation with chiral Mn(III)salen complexes. His research group prepared more than 120 chiral Mn(III)salen derivatives as catalysts for the enantioselective epoxidation of unfunctionalized olefins using iodosylarenes and sodium hypochlorite as the oxidant.[7] The reactive species in metallosalen oxidations is probably a high-valence metallo-oxo complex, just like those in metalloporphyrin systems[8] However, asymmetric metallosalen has shown greater selectivity over chiral porphyrin systems, probably because the salen ligand has two chiral sp^3-hybridized carbon atoms at its periphery. Because these chiral carbon atoms are just two bond lengths away from the metal, their proximity to the reactive site can yield a high degree of stereoselectivity. Facile and relatively inexpensive ligand synthesis, coupled with high enantioselectivities and the

ability to use a cheap stoichiometric oxidant, make these the best practical catalysts currently available for epoxidizing unfunctionalized olefins.

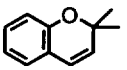
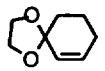
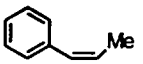
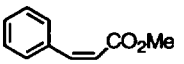
The most optimized catalyst in terms of selectivity and availability turned out to be the compound **1**,[9] which is named as 'Jacobsen's catalyst' and now commercially available from Aldrich and Fluka Company. With catalyst **1**, greater than 90 % ee can be obtained in the epoxidation of various *cis*-disubstituted olfins (Table 1).

Table 1 Enantioselective epoxidation of *cis*-olefins using **1** as the catalyst





(S,S)-1

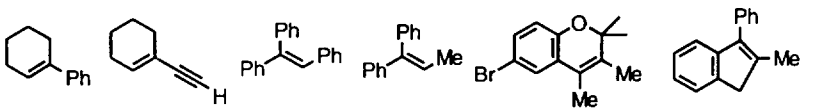
Olefins	Epoxides Yield (%)	ee (%)
	72	98
	63	94
	84	92
	65	89

2) NaOCl as an oxidant

Jacobsen originally employed iodosylarene, relatively unstable and expensive reagent, as the stoichiometric oxidant.[5] But, he has shown that aqueous NaOCl, inexpensive household bleach, can be used as the oxidant in the two phase system without phase transfer catalyst for the olefin epoxidation process.[8] Thus, most of his epoxidation has been conducted using NaOCl as an oxidant.

It was reported that the best substrates for the Jacobsen's enantioselective epoxidation were the *cis*-olefins such as b-methyl styrene, dienes and enynes.[10] The obtained selectivities are simply explained by proposing that the substrate approaches to the Mn=O species through 'side-on' manner. More recently, trisubstituted[11] and even tetrasubstituted[12] olefins were also reported as excellent substrates to give the chiral epoxide in high selectivities (Scheme 1).

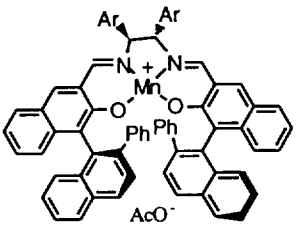
Scheme 1



93% ee 92% ee 86% ee 93% ee 92% ee 86% ee

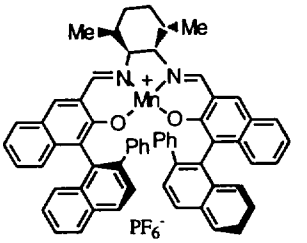
This looks unusual considering the proposed epoxidation mechanism. At this point, it is quite clear that side-on approach is not enough to explain the enantioselectivities we have observed. Top-on or other specific non-bonding interaction seems to be incoorporated to address the chirality transfer. Synthetically, the above results expand the substrate pool for the chiral epoxidation. Thus, further work on this area is definately warranted.

Katsuki, who has also been studying the chiral Mn(III)salen complexes as the epoxidation catalysts, has observed the similar results using his own chiral catalyst such as binaphthol-based Mn(III)salen **2**.[13] Interestingly, they proposed slightly different approach from the Jacobsen's on the basis of the result obtained with the catalyst **3**, which bears dimethyl at the chiral cyclohexane moiety.[14] They also have shown that this process is applicable to the asymmetric synthesis of some natural products.[15]



Ar = 3,5-$(CH_3)_2C_6H_3$

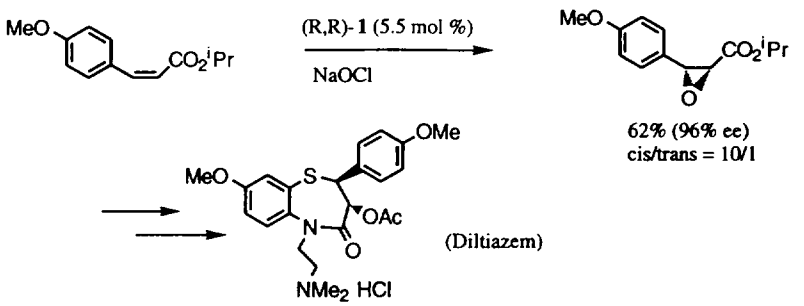
2



3

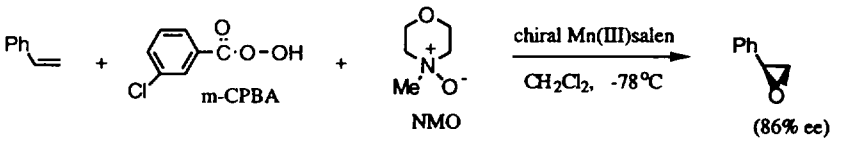
Jacobsen has employed his procedure in the asymmetric synthesis of biologically active compounds such as Lemakalim,[16] Leukotrienes,[17] side chain of Taxol,[18] and recently Diltiazem[19] (Scheme 2). All of these examples demonstrated that chiral (salen)Mn(III) was a powerful catalyst to introduce chirality onto the prochiral olefins in organic synthesis.

Scheme 2



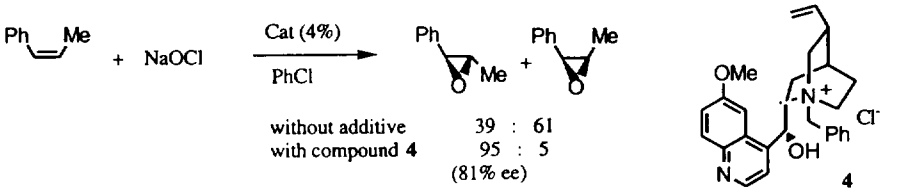
One of the problems associated with Mn(III)salen-catalyzed epoxidation of the acyclic olefins is the production of epoxide in the mixture of *cis* and *trans* isomers. These results are originated from the fact that the reaction proceeds through step-wise radical addition process.[20] In the case of styrene, rotation of the radical adduct results in the partial racemization. Recently, it was observed that lowering the reaction temperature could prevent the rotation of the radical intermediate, i.e. *cis/trans* ratio increased from 16 (23 °C) to 31 (-78 °C). Furthermore, facial selectivity also increased by lowering the reaction temperature. This technique improved the enantioselectivity of the styrene up to 91 %, when the reaction was conducted under -78 °C. The combination of *m*-CPBA and NMO was used as the oxidant in the organic solvent such as dichloromethane (Scheme 3).[21] The active oxidation component in this system is not clear yet. From this observation, we can imagine that more room is hidden to be explored for this catalysis.

Scheme 3



With regard to the production of *cis/trans* isomer, the method which led to the *trans*-epoxide as the far major product in high selectivity was reported.[22] Addition of the salt of cinchona alkaloid derivative such as N-benzylquininium chloride(4) mysteriously improved the *trans/cis* selectivity dramatically. Even though the exact process is not clear yet, this procedure will make Jacobsen's epoxidation process more useful in organic synthesis (Scheme 4).

Scheme 4



One of the potential applications of the Jacobsen's process is the kinetic resolution. More recently,utilizing selective C-H hydroxylation, this process has been testified.[23] Even though it is premature to set up the precise procedure, this paper shows the feasibility to obtain the enantioselectivities through the kinetic resolution.

Further application of chiral (salen)Mn(III) catalysis will be anticipated using practical oxidant, NaOCl, in organic synthesis. There need to be further efforts to elucidate the exact reaction profile and to apply it to the asymmetric synthesis of important chiral compounds.

3) Other oxidants

Recently hydrogen peroxide has attracted attention as an oxidant, because it is inexpensive and environmentally more friendly. Use of hydrogen peroxide in the Mn(III)salen-catalyzed oxidation has been first reported in the asymmetric oxidation of sulfides.[24] Later, hydrogen peroxide was also used as the oxidant in the enantioselective epoxidation in the presence of Jacobsen's catalyst.[25] In this case, employment of imidazole ligand seems to be crucial for the success of this process (Scheme 5).

Scheme 5

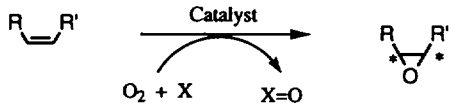
53% (52% ee)

Molecular oxygen has been incorporated as the valuable oxidant in the biological system as well as in the chemical industry. To achieve the monooxygenase-like activity, it is necessary to use one-oxygen reductant. Nature is doing it electronically by employing 2 equivalents of electron and a proton to generate a water. Mukaiyama and co-workers have been working on this oxygenation

reaction using transition metals such as Ni(II), Co(II) and Mn(III) complexes.[26] The reductant commonly employed involves $NaBH_4$, alcohol, aldehyde and acetals. The course of the oxidation depends largely on the nature of the metal complexes and appropriate reducing agent.

Using Jacobsen's catalyst and trimethylacetaldehyde, they reported that aerobic enantioselective epoxidation could be achieved.[27] In the presence of imidazole as an axial ligand, it seems that the intermediate, Mn(V)=O species are active oxidizing species like Jacobsen's (Scheme 6).

Scheme 6

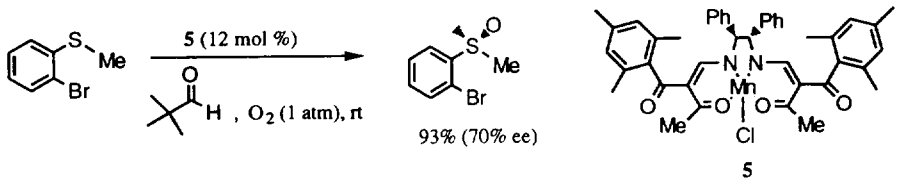


System	Catalyst	X	X=O
Biological (Monooxygenase)	Fe(II)-Porphyrin	$2H^+$, 2e	H_2O
Artificial (Mukaiyama's)	Mn(III)-salen		

Mukaiyama's system can be an artificial model of the biological oxidations where molecular oxygen is consumed as the real oxidant. However, this system is far from the practical process. It has limitations associated with relatively low selectivities, low chemical yields, and the employment of expensive co-reductant (trimethylacetaldehyde). There needs to be further study to improve the whole process.

Very recently, Mukaiyama and co-workers applied their aerobic oxidation system to the synthesis of chiral sulfoxides.[28] By screening the chiral catalysts, they found that b-oxo aldiminato manganese(III) complex **5** is better than the Jacobsen's (salen)Mn(III) complex for the enantioselective oxidation of sulfides. Their result is comparable to the Jacobsen's system[24] in terms of the enantioselectivities and chemical yields.

Scheme 7



5

This work shows that chiral salen is not the only ligand we can rely on to reach the desired selectivities in the epoxidation reaction. Considering the importance of the aerobic oxidation in the biological and chemical process, further efforts should be focused to elucidate the mechanistic and synthetic pathways in this field.

III. Mn(III)-mediated oxidation process

As discussed above, Mn(III) can be oxidized to Mn(V) with the aid of appropriate oxidizing agents. The resulting Mn(V)=O intermediate is considered to be the actual oxygen-transfer component in the olefin epoxidation. In this section, we will discuss that Mn(III) complex which can be utilized in the different type of reaction, i.e. carbon-carbon formation reactions. The reaction mechanism is very different from that described in chapter II. For the most part, the role of Mn(III) is the one-electron oxidant for the chemistry in this chapter. We will devide this topic into the following two catagories. 1) free-radical process and 2) other related process.

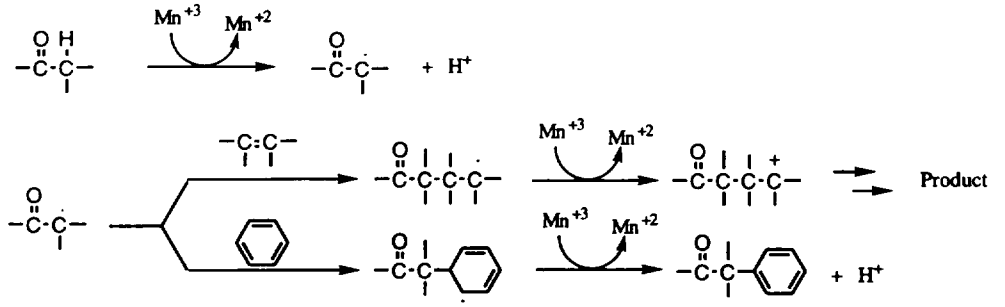
1) Free-radical process

The formation of carbon-carbon bond is of prime importance in the organic synthesis. Free-radical process has been emerged as the strong tool for the carbon-carbon couplings.[29] Some transition metals including Mn(III) complex are well studied as the mediator of the radical chain reactions. The extensive review of this chemistry appeared, and the literature was covered up to 1993.[30b] Thus, this article will discuss the chemistry developed thereafter.

Mn(III) is easily reduced to Mn(II) species in the presence of oxidizable substrates. Synthetic application of this properties involves the Mn(III)-mediated oxidative cleavage of the C-H bond, which is at the a-position of the carbonyl groups. The resultant carbon radical intermediate adds to other unsaturated compounds such as olefins and arenes. The second radical intermediate, thus formed, usually undergo another oxidation to give the carbocation, which is transformed to the product (Scheme 8). Experimentally, most of this type of chemistry has been studied using

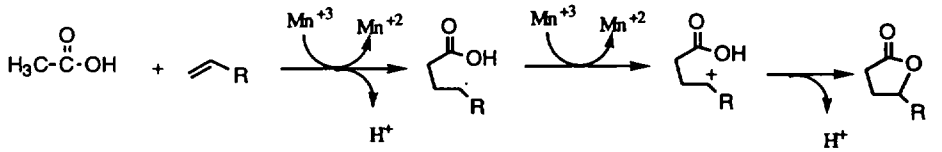
$Mn(OAc)_3 \cdot 2H_2O$ as the Mn(III) source, and acetic acid as the solvent. This is because $Mn(OAc)_3 \cdot 2H_2O$ is the most readily available Mn(III) salt, and acetic acid is one of the few compounds which can dissolve the salt. Technically, the reaction can be monitored by the disappearance of the characteristic brown color of the Mn(III) species.

Scheme 8



One of the pioneering works in this field involves the synthesis of g-lacotnes developed by Heiba and co-workers, where they treated the olefins with acetic acid in the presence of 2 equivalents of $Mn(OAc)_3 \cdot 2H_2O$ under the refluxing conditions.[31] This reaction has been extensively studied and proven to be very useful in organic synthesis.[30] The reaction proceeds through the following process i) direct generation of carboxymethyl radical by Mn(III)-mediated oxidation ii) rapid addition of the carboxymethyl radical to the olefin iii) rapid oxidation of the intermediate adduct radical to the carbonium ion by another equivalent of Mn(III) complex iv) electrophilic cyclization to form the lactones (Scheme 9).

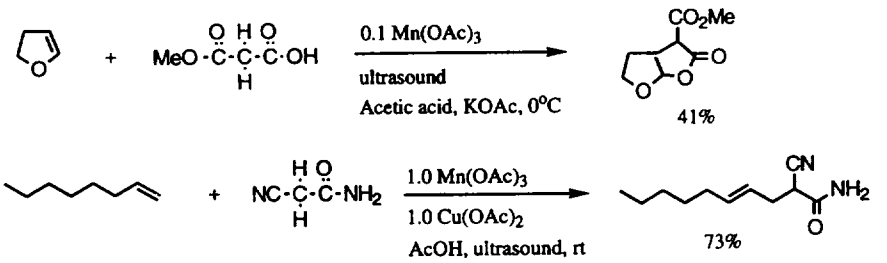
Scheme 9



1,3-dicarbonyl compound turned out to be the better precursor of the carbon radicals in the presence of Mn(III). Thus, lots of work have been conducted using the 1,3-dicarbonyl compounds as the starting material. Most of recent studies described that use of $Cu(OAc)_2$ as the second oxidant, because Cu(II) complex is known to oxidize the adduct radical more favorably than Mn(III) does. The carbocation thus formed seems to be coordinated to Cu complex, which undergoes facile transformation to the C-C double bond via hydride elimination or undergoes

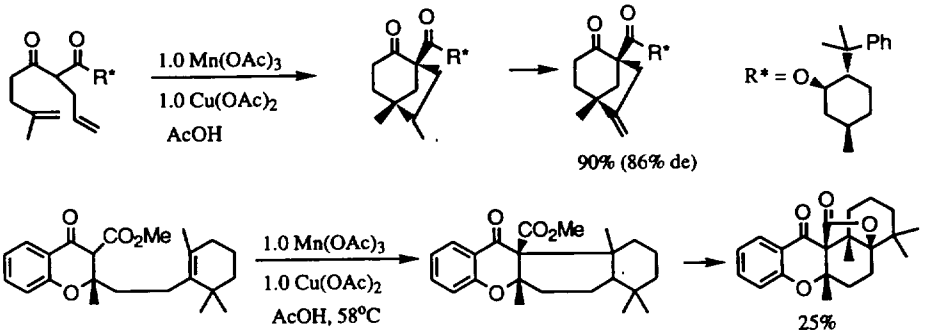
cyclizations. In addition, recent study has shown that the reaction proceeds under rather mild conditions using sonochemical method. Ultrasound irradiation caused a significantinhancement in yields and selectivitiesof the products[32]. More importantly, under these conditions, catalytic version of Mn(III)-mediated oxidation seems to be possible. Hydroxy radicals generated under solvolysis conditions were suggested as the species responsible for the reoxidation of the Mn(II) to Mn(III).[33] This observation is important, because it shows the possibility of the catalytic use of Mn(III) salt for the first time (Scheme 10).

Scheme 10



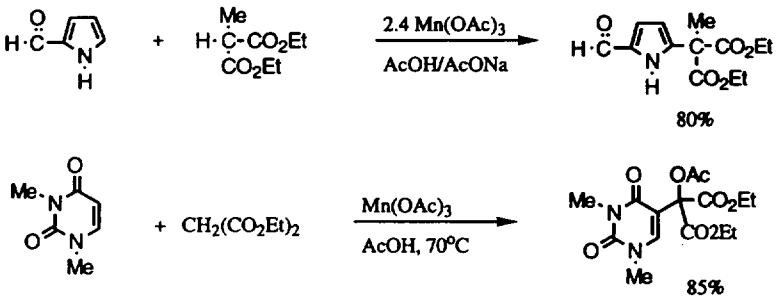
Intramolecular version of this radical process provide a valuable one-pot process for the construction of polycyclic compounds. Snider and co-workers extensively studied this process to effect tandem, triple cyclizations. Recently they have showed that employment of chiral auxiliary such as menthyl ester afforded the cyclic product with high selectivities.[34] Thus, this chemistry can be applied to the synthesis of homochiral polycyclic compounds. Recent paper also described the radical cyclization to obtain a rather complex sesquiterpene moiety[35] (Scheme 11).

Scheme 11



Heiba first reported that carboxymethyl radical generated by acetic acid and Mn(III) can undergo addition to aromatic compounds, which provided substitution product via another Mn(III)-mediated oxidation followed by proton elimination.[36] The resulting carboxymethyl radical is electrophilic, thus coupling is more efficient with electron-rich substrates such as toluene, anisole and naphthalene than with benzene. Even though this reaction lacks general utility because of low yields and selectivities, valuable introduction of carbon functionalities is reported in some case[37] (Scheme 12).

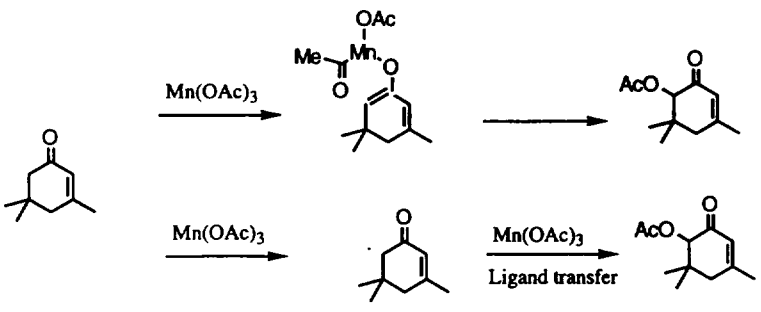
Scheme 12



3) Other related process

Mn(III) was also reported to mediate the a'-acetoxylation of the enones in good yields.[38] This process constitutes a mild procedure for the introduction of acetyl functionality at the complex compound. Two possible mechanisms are envisioned, i.e. acetate transfer via manganese enolate and a-keto radical formation followed by ligand transfer (Scheme 13).

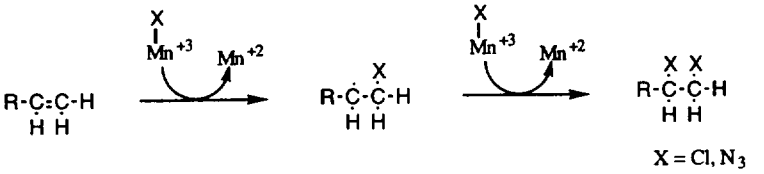
Scheme 13



During the study of Mn(III)-based lactonizations, Fristad and co-workers have found that

manganese chloride species were generated by the treatment of $Mn(OAc)_3$ and chloride salt (NaCl or $CaCl_2$). The $MnCl_3$, thus formed, was found to be an effective chlorinating agent of alkenes.[39] Mechanistically, the reaction proceeds through oxidative transfer of a Cl ligand directly to an alkene without the intimacy of free chloride radicals (Scheme 14). They also observed that employment of sodium azide and Mn(III) salt could effect the double azidation of alkenes.[40] Experimentally, the reaction was conducted by heating a brown solution of manganese(III) acetate, sodium azide, and the alkene in glacial acetic acid until the solution turned colorless, which indicated the reduction of Mn(III) to Mn(II). The desired 1,2-azides were prepared in 51-76 % yields.

Scheme 14



III. Conclusion

Manganese is an inexpensive and relatively non-toxic transition metal. Its use in the oxidation chemistry has been one of the oldest applications of transition metals in organic synthesis. However, Mn(III) has been little explored in organic synthesis, probably because the oxidation state of +3 in Mn is uncommon.

Mn(III)-salen complexes have attracted much attention after Jacobsen's sucessful application in the asymmetric olefin epoxidations. It is premature to evaluate the overall impact of Jacobsen's procedure in organic synthesis. We expect further important findings to be disclosed on the reaction mechanism and synthetic applications.

C-C bond forming reaction utilizing the oxidation power of Mn(III) salt has been useful procedure in organic synthesis. The reaction proceeds through radical intermediates. One of the major limitations of this procedure is the fact that more than one equivalent of Mn(III) is required. The process which can employ Mn(II) as a catalyst should be developed to make this reaction more practical.

IV. Acknowledgment

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Foundation (Grant No. 951-0301-020-2).

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