CHAPTER 1
INTRODUCTION AND BACKGROUND

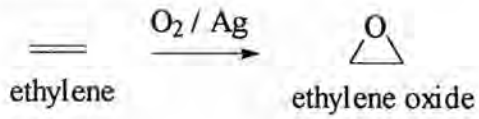
1.1 Problem Definition

Hydrocarbons are well-known to be the largest group chemicals of organic in pretroleum products and generally are not expensive. Hydrocarbon derivatives containing oxygen or other hetero-atoms are important intermediates in organic synthesis and in the petrochemical industry, and the future promised further substantial increases in demand. These compounds are much more expensive than the parent hydrocarbons, particularly in the case of oxygen containing compounds. A great deal of effort has been expended in attempts to develop a new process based upon catalytic epoxidation which will produce such products selectively. Unfortunately, the epoxidations using peracids or peroxides are generally unselective, giving a complex mixture of potentially valuable products which would require an elaborate refinery for separation[1] and low percent yield in the case of electron poor alkenes[2] In addition, the reactions were required to use vigorous conditions invariably such as high temperature, high pressure, acid-base conditions or the expensive catalysts were needed.

Nevertheless, several biological systems were reported to be able to oxidize hydrocarbons under mild conditions and gave selective products. The hydroxylation of alkanes and epoxidation of alkenes by Cytochrome P-450[3], the oxidation of alkenes by enzyme peroxidase[4] or the epoxidation of alkenes by enzyme chloroperoxidase[5] are among those remarkable instances. Those enzymes are of metal as a catalytic site in their molecules. Thus, extentive efforts have been devoted to mimic these remarkable abilities of biological systems.

1.2 Epoxidation of Alkenes

Oxygen is added to carbon-carbon double bonds to form epoxides (named as oxiranes in the IUPAC nomenclature). The important organic reactant ethylene oxide is prepared industrially by direct air oxidation of ethylene over a hot silver catalyst.[6]



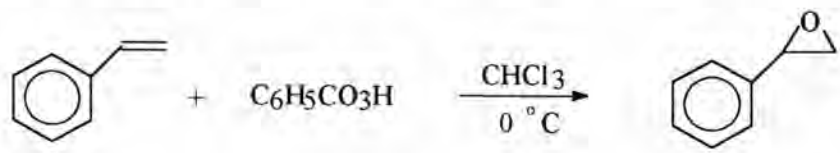
On the other hand, the laboratory preparation of epoxide is usually accomplished by using a peracid (also called a peroxy acid) or peroxide.

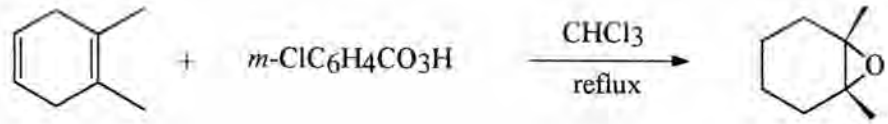
1.2.1 Epoxidation of Alkenes with Peroxy Acids

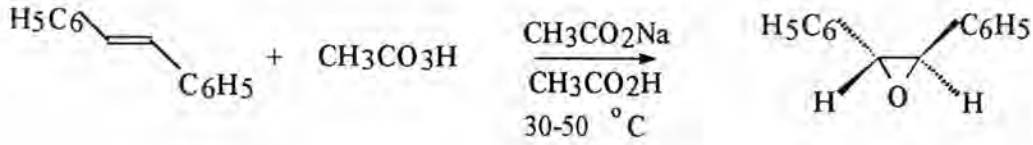
The reaction of alkenes with peroxy acids to produce epoxides has been known for almost 90 years.[7] It provides the most convenient method for the preparation of one of the most important intermediates in organic chemistry.

The choice of the preferred peroxy acid for epoxidation depends on the reactivity of olefins and the stability of epoxides. Carboxylic acids, which are formed in the reaction, can react with the epoxide to form monoester of 1,2-diols especially lower aliphatic acids. This type of the reaction may not be expected.

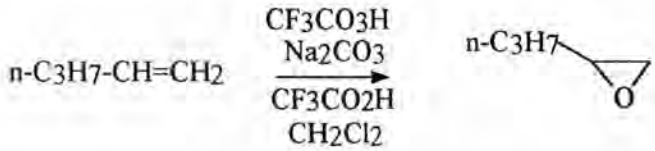
Some typical epoxidations with peroxy acids are shown bolow.[8]



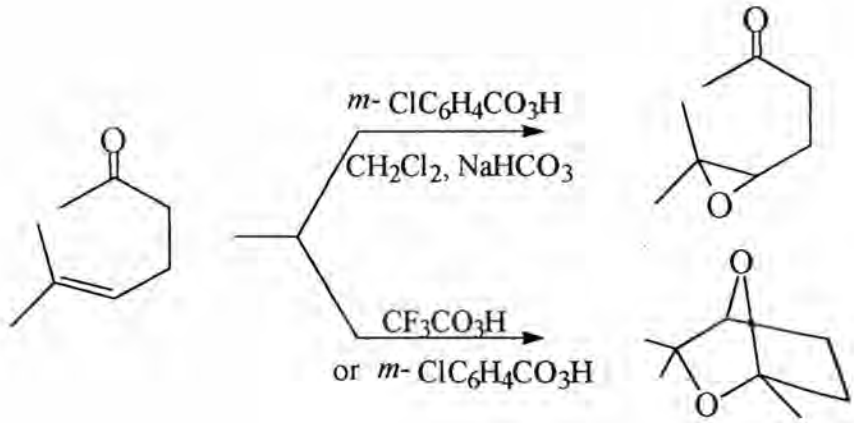




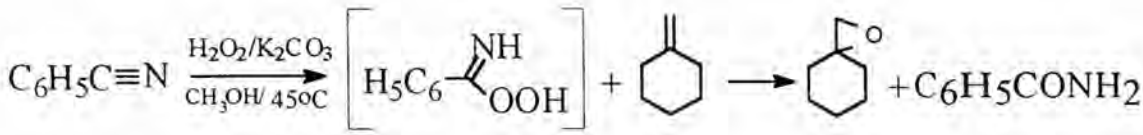
The reaction time is normally short depending largely on the number and nature of the group bonded to the unsaturated linkage. Tri- and tetra-substituted alkenes are epoxidized rather quickly even with relatively weak peroxyacetic acid while mono-substituted alkenes require stronger peroxy acid.[9] Relatively unreactive monosubstituted olefins can be converted to epoxides with peroxy trifluoroacetic acid. In the latter case, anhydrous sodium carbonate or disodiumhydrogen phosphate must be added to the reaction mixture to neutralize the trifluoroacetic acid produced.[10]



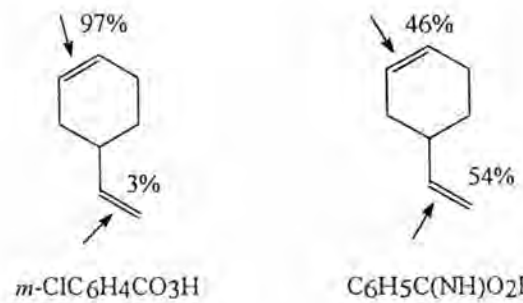
For acid sensitive olefins, which usually form rearranged products with aliphatic and aromatic peroxy acids, can conveniently be epoxidized with *m*-chloroperoxybenzoic acid in a dichloromethane-aqueous sodium bicarbonate two-phase system.[11]



Epoxides which are unstable under acidic conditions can also be prepared by oxidation with peroxybenzimidic acid, derived from benzonitrile and hydrogen peroxide in a buffer solution at pH 8.[12]

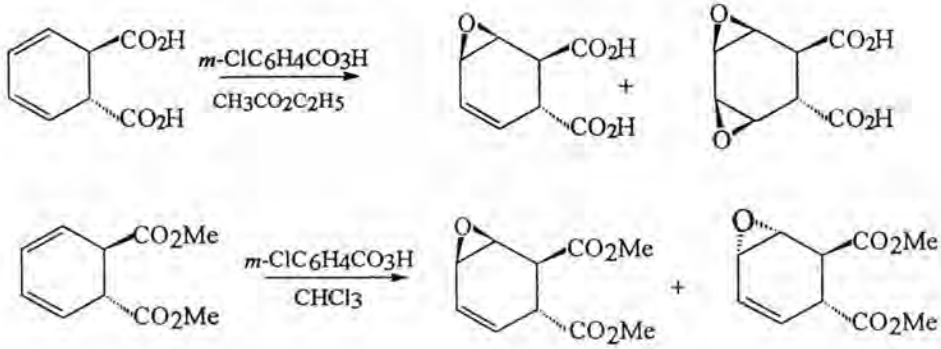


Peroxybenzimidic acid appears to be less selective than other peroxy acids for the epoxidation of olefins. 4-Vinylcyclohexene reacts with *m*-chloroperoxybenzoic acid to give predominantly 1, 2-epoxide, while peroxybenzimidic acid epoxidizes both double bonds to almost the same degree.[13]

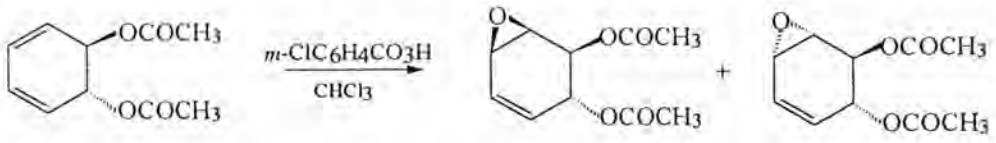


Additional stereochemical features of epoxidation with peroxy acids have been obtained by studying the oxidation of cyclic system. It has clearly been demonstrated that neighboring functional groups may influence the direction of the attack of the peroxy acid. For example, epoxidation of allylic compounds with a bulky group as a neighboring substituent proceeds with a preferential anti attack. Epoxidation of 3-*tert*-butylcyclohexene approximately yields a 9:1 ratio of *trans*- to *cis*-epoxide when it is epoxidized with *m*-chloroperoxybenzoic acid in dichloromethane.[14] Remote groups can also influence the direction of the approach of the peroxy acid molecule. 4-Methylcyclopentene reacts with peroxylauric acid to give 73:27 ratio for *trans*- to *cis*-epoxide. This ratio does not change significantly on going from nonpolar to polar solvents. This indicates that the alkyl group exerts a steric effect rather than polar effect. Generally, steric influence is important only in cases where there are not more than two carbon atoms between the substituent and the reaction center.

On the other hand, a 9:91 ratio for *trans*- to *cis*-epoxide has been reported for the epoxidation of the allylic alcohol, 2-cyclohexene-1-ol with little dependence on the solvent used.[15] Similar results were reported for unsaturated steroids having a free hydroxyl substituent in the allylic position.[16] Allylic carboxylic acids and carboxylates are also effective *syn*-directing groups. For example, epoxidation of *trans*-1,2-dihydrophthalic acid gives only the *cis*-monoepoxide[17] while epoxidation of dimethyl *trans*-1,2-dihydrophthalate yields a 9:1 mixture of *cis*- and *trans*-epoxide.[18]



Epoxidation of allylic acetates are considerably less stereospecific as an example shown below. A 2:1 mixture of *cis*- and *trans*-epoxide has been obtained.



The relative order of *syn*-directing ability of substituents in allylic epoxidation is believed to be $OH > CO_2H > CO_2R > OCOR$.[18]

Epoxidation with peroxy acids is a second-order reaction; it is first order in olefin and first-order in peroxy acid.

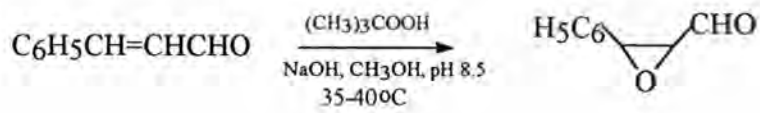
$$R = k\,[RCO_3H][\text{alkene}]$$

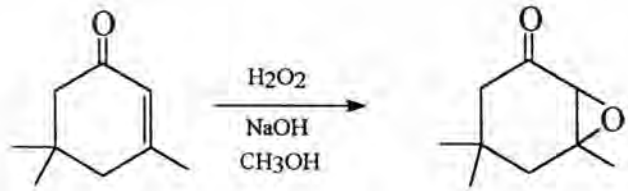
Electron releasing groups in alkenes accelerate the rate of epoxidation. The reaction is particularly rapid with tetraalkyl olefins, conditions are mild and yields are generally high.[19] Electron-withdrawing groups in peroxy acids also facilitate the rate of epoxidation. The order of reactivity (electrophilicity) approximates the pK values of peroxy acids, *i.e.*, peroxytrifluoroacetic > monoperoxymalic > peroxyformic > peroxybenzoic > peroxyacetic acid.

Epoxidation with peracids is stereospecific even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate. However, where there is an OH group in the allylic or homoallylic position, the stereospecificity diminishes or disappears, with both *cis*- and *trans*-isomers giving predominantly or exclusively the product which the incoming oxygen is *syn* to the OH group. This probably indicates a transition state in which there is hydrogen bonding between the OH group and the peroxy acid.

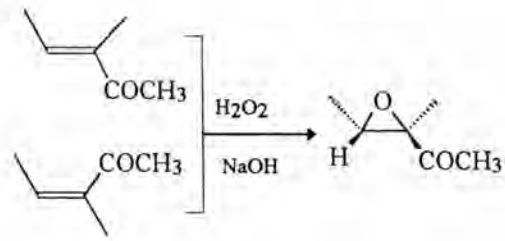
1.2.2 Epoxidation of Alkenes with Peroxides

Selective epoxidation of α, β-unsaturated ketones and aldehydes may be accomplished by oxidation with sodium salts of hydrogen peroxides or sodium salts of *tert*-butylhydroperoxides rather than peroxy acids.[20]





In contrast to epoxidation with peroxy acids, these reactions are stereoselective rather than stereospecific. For example, only one isomer is obtained by the epoxidation of either isomer of the unsaturated ketone.[21]



α, β-Unsaturated ketones (including quinones), aldehydes, and sulfones can be epoxidized with alkaline H_2O_2 (Weitz-Scheffer Reaction). This is a nucleophilic addition by Michael-type mechanism, involving attack by HO_2^-.[22] α, β-Unsaturated carboxylic acids can be epoxidized with H_2O_2 and heteropoly acid and α, β-unsaturated esters, amides and sulfones with *t*-BuOOH and alkyllithium in THF.[23] A new stereospecific epoxidation with α-azohydroperoxides in basic media is reported. For example, *cis*- and *trans*-

stilbene gave the corresponding epoxides stereospecifically in the reaction with α-azohydroperoxides catalyzed by pyridine or sodium hydroxide.[24]

Some epoxidation reactions of alkenes with peroxides as discussed earlier gave stereoselective products in basic media. A moderate yield of epoxide is obtained under high-reaction conditions. As a result of unconvenient condition, there are several attempt to search for milder and more selective epoxidation conditions.

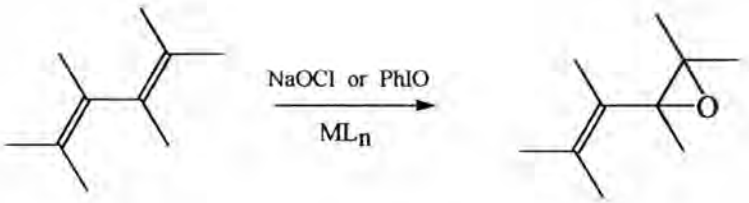
1.2.3 Epoxidation of Alkenes Catalyzed by Metal Complexes

The development of new strategies for the selective oxidation of hydrocarbons continues to be an important goal for both academic and industrial point of view. Whereas whole cells and coupled enzymes system have been employed for some recent applications, synthetic catalysts based on biological models represent an area of considerable untapped potential. During the last 15 years, metalloporphinates have been shown to be excellent models for Cytochrome P-450 and peroxidase enzymes, particularly to be very effective catalysts for the epoxidation of olefins,[25] C-H hydroxylation,[25] and O-demethylation.[26] Since these reactions usually proceed at very different rates, the epoxidation is, by far, more efficient than the others.

The hydroxylation of norbornane, aliphatic hydrocarbons, with oxidants such as iodosobenzene can be effectively catalyzed by iron(III) tetrakis(2,6-dichlorophenyl) octabromoporphyrin afforded good yields of a mixture of products which consisted of 86: 13: <1 ratios of *exo*-norbornan-2-ol, *endo*-norbornan-2-ol and 2-norbornanone, respectively.[27] The epoxidation of olefins with iodosylbenzene is catalyzed by (chloro-5, 10, 15, 20-tetraphenylporphyrinato) iron(III) (FeTPPCl). Cyclohexadiene oxide 93 % yield, cyclooctene oxide 84 %, *cis*-stilbene oxide 77 % were attained, but *trans*-stilbene was found to be unreactive under these conditions.[28] The iron(III) complex of β-hexanitro-TDCPPH$_2$, Fe(TDCPN$_6$P)Cl, was proved to be a good catalyst for the hydroxylation of heptane by PhIO (66 % yield of mixture products: heptanol and

heptanone) and was a remarkable catalyst for the epoxidation of cyclooctene with dilute H_2O_2 (complete conversion and 97 % yield in 0.5 h).[29] The reaction of hydrogen peroxide or *tert*-butyl hydroperoxide with cyclooctene and norbornene, catalyzed by iron(III) tetrakis (pentafluorophenyl) porphyrin chloride and other electronegatively-substituted porphyrins, produced 60-100 % epoxide yields.[30]

Manganese porphyrins have been shown to be very versatile catalyst for the epoxidation of a wide variety of alkenes. Efficient biomimetic system for epoxidation of alkenes and hydroxylation of alkanes by dioxygen and Zn as a reducing agent, were achieved by using manganese porphyrin catalysts in the presence of 1-methylimidazole and acetic acid.[31] The epoxidation of various alkenes by magnesium monoperoxyphthalate, like with other oxygen donors, catalyzed by tetra-2, 6-dichlorophenylporphinatomanganese(III) acetate, alkene conversion is nearly complete within 0.5-5 minutes at 0°C and good epoxide yields (60-93 %) are obtained.[32] The threitol-strapped manganese porphyrins is the most effective asymmetric catalyst in the epoxidation of simple, monosubstituted olefins and gives optical yields up to 88 % ee in the epoxidation of *cis*-disubstituted olefins when iodosylbenzene is the oxidant.[33] Moreover, the epoxidation of alkenes catalyzed by other manganese porphyrins has recently been reported. These high reactivity catalytic systems utilizing oxidants such as iodosylarenes, peracids, hypochlorites, alkylhydroperoxides, hydrogen peroxide, amine *N*-oxides, oxaziridines, monopersulfate and perchlorate have been described. In most cases, their behaviors were believed to derive from a hypervalent manganese(V)-oxo porphyrin species, which has been suggested as the viable oxidant in the catalytic systems.[34] The ML_n ($M=Mn^{III}$, Fe^{III} ; L_n = salens, porphyrins) can act as effective catalysts with sodium hypochlorite as well as iodosylbenzene as oxygen donor for the regioselective monoepoxidation of a variety of conjugated 1, 3-dienes.



The present method gives high yields of the corresponding monoepoxide and generally shows a high regioselectivity for epoxidation of the less substituted double bond of the 1, 3-diene system.[35]

Metalloporphyrins are the metal complexes that were synthesized with the aim to mimic enzymes in biological systems, being capable of catalyzing oxygen transfer from oxidizing agent to saturated and unsaturated hydrocarbons.

Other transition-metal complexes have also been reported to have the same properties for catalytic epoxidation as that of metalloporphyrins. For example, the reaction of covalent molybdenum(VI) peroxy-complexes $[Mo(O_2)_2O]L_1L_2$ (L_1L_2 = organic ligands such as DMA, HMPT, DMF) with olefins, epoxides are formed in high yield.[36] Epoxidation of olefins by sodium periodate is effected by the catalysis of $RuCl_3.(H_2O)_n$ associated with bipyridyl. Olefins leads to epoxides rather than to ketones or carboxylic acids. The reaction is stereospecific for both *cis*- and *trans*- alkenes.[37] Nickel complexes of bidentate heterocyclic amines such as 2, 2′-bipyridine and 1, 10-phenanthroline have been found to be active catalysts for the epoxidation of olefins with hypochlorite as terminal oxidant. Epoxides are obtained as the major products.[38] Ru^{III} (hedta) and Ru^{III} $((CH_3)_2$ edda$)^+$ (hedta^{3-} = *N*-hydroxyethylethylenediaminetri acetate; $(CH_3)_2$ edda^{2-} = *N, N′*-dimethethylethylenediamine-*N, N′*-diacetate) catalyze the epoxidation of *cis*-stilbene and *trans*-stilbene using *tert*-butylhydroperoxide as the oxygen source. Yields as high as 63.5 % *cis*-stilbene oxide plus 11.0 % *trans*-stilbene oxide from *cis*-stilbene and 65.1 % *cis*-stilbene oxide from *trans*-stilbene (with no *trans*-stilbene oxide) are formed in the epoxidation reactions.[39] Olefins were epoxidized with dioxygen in the presence of 2 equivalent of 2-methylpropanal under the influence of a catalytic amount of the mixed

heteropolyoxometalate $(NH_4)_5H_4PV_6Mo_6O_{40}.6H_2O$ to give the corresponding oxides in moderate to good yields.[40] An efficient synthesis of acid sensitive epoxides, such as chromene oxide or epoxide of γ, δ-unsaturated alcohol, was successfully achieved by the oxygenation of corresponding olefins with the combined use of an atmospheric pressure of molecular oxygen and aldoacetal catalyzed by a cobalt(II) complex coordinated with the 1, 3-diketone ligand. The reaction proceeded under mild and neutral conditions, and the desired epoxides were obtained in good yields.[41]

In steroid series, nuclear β-epoxides have been difficult to prepare due to steric hindrance resulting from the angular methyl groups at C-10 and C-13 (the C-18 and C-19 methyl groups) which dominate the β-face of the molecule. A methodology employing a mixture of $KMnO_4$-$CuSO_4$ in refluxing methylene chloride in the presence of a small amout of water and *tert*-butanol, however, has been found to be a highly β-selective high-yield epoxidation reagent for Δ^4, Δ^5 and Δ^7 unsaturated steroids.[42]

From literature reviews described above, metalloporphyrins (biomimetic enzymes in biological system) and metal complexes could catalyze the conversion of alkenes to epoxides selectively. These have been an impetus in developing methods for the facile epoxidation. For several methods, metal Schiff's base complexes catalyzed epoxidation of alkenes to epoxides selectively under mild conditions, such as the catalytic epoxidation of various olefins with iodosylbenzene is efficiently carried out by a series of chromium(III) cations (Cr^{III} (salen)$^+$) which are promoted by pyridine *N*-oxide (pyO) and related oxygen donors as the cocatalysts. The donor adduct O=Cr(salen)(pyO)$^+$ was believed to be the reactive intermediates in the catalytic cycle. The *exo* product of norbornene oxide could be isolated in 70% yield.[43] A system for catalytic epoxidation of alkenes, in which an aqueous solution of the cationic complex $[Cr(salen)(H_2O)_2]Cl$ was treated with an alkene dissolved in CH_2Cl_2 using iodosylbenzene as an oxidant and β-cyclodextrin as a phase-transfer agent, to solubilize the alkene in water. Norbornene gave norbornene oxide as the only

product whereas styrene gave a mixture of styrene oxide and phenylacetaldehyde. Styrene oxide is known to undergo thermal rearrangement to phenylacetaldehyde in the g. c. injection port.[44]

Asymmetric olefin epoxidation with sodium hypochlorite catalyzed by easily prepared chiral salen (*N, N'-bis* (salicylideneamino)ethane) Mn(III) complexes, *cis*-stilbene gave *cis*-stilbene oxide 85% at pH 11.3. Good isolated yields of epoxide are achievable with inexpensive reagents under mild conditions. No phase transfer catalyst is required, purification of solvents is unnecessary; the reaction is run in air, and the workup protocol is simple.[45] Iron(III) Schiff's base chelates $[Fe_2(PA_2ppd)_2Cl_4)Cl_2$, $[Fe_2(PA_2mpd)_2Cl_4]Cl_2$, and $[Fe(PA_2opd)Cl_2]Cl$ catalyzed the epoxidation of alkenes with iodosylbenzene as an oxidant, norbornene oxide was obtained 6%, 8% and 2% respectively.[46] The epoxidation of cyclohexene using various Mn^{III} (Schiff's base)NCS complexes (Schiff's base = SALEN, ANAC, AACEN, ANAAN, ACDAP, SALPA, ACEN) as catalyst and PhIO as oxidant gives cyclohexene oxide, cyclohexenol and cyclohexenone as the products. The effect of catalyst concentration shows that, on increasing the concentration of catalyst the yield of the epoxide decreases. The relative rate of the reaction towards cyclic alkenes follows the order; norbornene > cyclooctene > cycloheptene > cyclohexene > cyclopentene.[47] Manganese complex bearing the optically active salen ligand [*N, N'-bis*(*S*)-3-(1-phenylpropyl)salicylidene]-(1*R*, 2*R*)-1, 2-diphenylethylenediaminato] was found to be an effective catalyst for the enantioselectivity of 50% ee for the epoxidation reaction of (*E*)-1-phenyl-1-propene.[48a] The highest enantioselectivity of 48% ee of (*E*)-stilbene was disclosed by using another chiral (salen) manganese(III) complexes, [(8*S*, 8'*S*)-3,3'-*bis*[(1R)-1-phenylpropyl]-4, 4'-dimethyl-8, 8'-diphenylsalen] manganese (III) complex.[48b] Chiral manganese salen complexes substitued in the 3 position with bulky silyl group (TMS, TBDMS) catalyzed the epoxidation of unfunctionalized olefins in moderate to high ee's. Styrene gave styrene oxide 18%(R) ee, 33%(R) ee followed the substituent in the 3 position, respectively.[49] A variety of oxidants are effective oxygen donors for olefin

epoxidation in the presence of chiral (salen) Mn(III) complexes. The combination of *m*-CPBA and NMO was found to be particularly effective for low temperature reactions. Epoxidation of a wide array of unfunctionalized olefins proceeded with an increase in enantioselectivity under anhydrous low temperature conditions relative to biphasic reactions employing bleach. Other olefins which are either water-soluble or which decompose in the presence of aqueous bleach are also now viable substrates for the epoxidation reaction.[50]

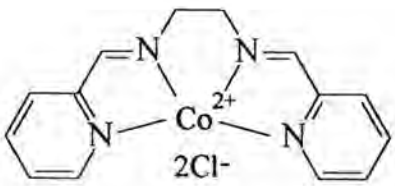
Enantioselective epoxidation of unfunctionalized olefins is achieved by the combined use of molecular oxygen and pivalaldehyde in the presence of a catalytic amount of optically active Mn(III) salen complexes. *N*-alkylimidazoles are effective axial ligands to produce optically active epoxides with high enantioselectivities; *i.e.*, 1, 2-dihydronaphthalene derivatives and 2, 2-dialkyl-2H-chromene derivatives are converted into the corresponding optically active epoxides with 60-92% enantiomeric excess.[51]

Nickel complex, [*N, N'-bis* [*o*-(*p*-toluenesulfonylamino) benzylidene]ethylenediaminato]nickel(II), was found to be a good catalyst for the epoxidation of olefins with molecular oxygen in the presence of 2-methylpropanal (Mukaiyama's conditions). *Trans*-stilbene gave *trans*-stilbene oxide up to 79% yield.[52]

In the asymmetric epoxidation of styrene by the chiral Ru(II) Schiff's base complexes of the type $[RuL(PPh_3)(H_2O)_2]$ (where L= chiral Schiff's bases derived from salicylaldehyde and L-amino acids) and iodosylbenzene, the R form of the catalyst resulted in the formation of (*S*)-styrene oxide as dominant enantiomer.[53] Ruthenium(III) Schiff's base (bidentate ligand) catalyzed epoxidation efficiently and provided better yield of epoxide compared to tridentate, tetradentrate or macrocyclic ligands. Norbornene gave *exo*- and *endo*-epoxides. The relative rates of epoxidation follow the order : norbornene > cycloheptene > cyclohexene.[54] $[Ru(Me_3tacn)O_2(CF_3CO_2)]^+$, *cis*-dioxoruthenium(VI) complex of *N, N', N''*-trimethyl-1, 4, 7-triazacyclononane have been reported to catalyze alkene epoxidation by PhIO. Cyclohexene gave cyclohexene oxide as a dominant

product under this particular conditions.[55]

CoSANP, [*bis*(salicylidene-*N*-phenethyl)] cobalt (II), catalyzed the reaction of aliphatic aldehydes and dioxygen with unactivated alkenes leads to the corresponding epoxides, whereas the reaction with an electron deficient alkenes afforded the adducts between aldehyde and alkene. These reactions were proposed to proceed *via* a common pathway involving acyl radicals.[56] Cobalt(II) Schiff's base complex **1** and **2** exhibited a remarkable chemoselectivity during oxidation of cyclic alkenes with molecular oxygen in the presence of 2-methylpropanal. Catalyst **1** enhanced the oxidation of double bond to give epoxide as the major product whereas catalyst **2** promoted mainly the allylic oxidation leading to allylic alcohols or enones. The difference in the chemoselectivity in these oxidations was apparently due to the effect of ligand around cobalt in catalysts **1** and **2**. The diverse nature of catalyst **1** (charged) and catalyst **2** (neutral) was believed to be responsible for the formation of various reactive species (*i.e.*, $O_2^{\bullet}$, O_2^{-}, O_2^{2-} *etc.*), thereby resulting in different chemoselectivity.[57]



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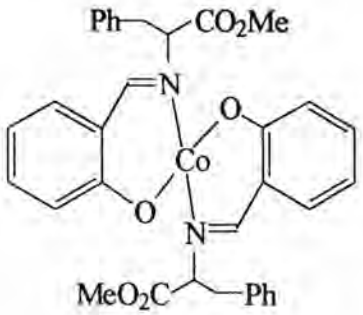

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In this research, the selectively catalytic epoxidation by metal Schiff's base complexes under mild conditions will be investigated and the epoxidation of cyclohexene to cyclohexene oxide was chosen as a model reaction to examine. The interested metal Schiff's bases were Cr(III), Co(II) and Mn(II) Schiff's base complexes. Among them, the most interest metal was Cr(III) Schiff's base since not many of them have been reported to utilize in

epoxidation reactions. The outcome of this work will certainly expand the use of Cr(III) Schiff's base complexes in the catalytic epoxidation.

1.3 The Goal of This Research

The purpose of this research can be summarized as follows:

1. To synthesize Schiff's base ligands and metal Schiff's base complexes

2. To study the optimum conditions for alkene epoxidation by using metal Schiff's base complexes as catalyst at room temperature or slightly higher

3. To apply the optimum conditions for the epoxidation of some selected alkenes and some natural products bearing a double bond in order to observe the chemoselectivity of the reaction