CHAPTER I

INTRODUCTION

The epoxidation of alkenes is the most fundamental oxygen functionalization of carbon-carbon double bonds. The importance of this transformation is a direct consequence of the utility of the product epoxides as synthetic intermediates. Accordingly, the ability to carry out enantioselective oxygen atom transfer to alkenes has served as the vanguard for advances in asymmetric catalysis over the past two decades. The first practical asymmetric epoxidation reported by Sharpless *et al* for allylic alcohols was a watershed event in the exploration for more selective and general methods for epoxidation. In this reaction, the allylic hydroxy group plays a fundamental role, in coordination of the substrate to the chiral titanium complex. As a result, a favorable asymmetric environment can be crafted between reactant and substrate by virtue of the strong coordination of the alcohol to titanium metal center.

The next important advance in enantioselective oxygen atom transfer was the asymmmetric epoxidation of unfunctionalized alkenes. In this case, the enantioselectivity must be controlled by nonbonding, which are much weaker and less directional than coordination bonds between reactant and substrate. The Jacobsen epoxidation system employing the now-familiar manganese-salen complexes is the archetypal example of this reaction and one that has been extensively developed and applied over the past 10 years.³

1.1 Epoxidation of alkenes

Oxygen atom is analogous to a carbene. It has six electrons in its valance shell. It might be expected to act both an electrophile and a nucleophile in its reaction with an alkene, resulting in the formation of a three-membered ring containing an oxygen – an epoxide.

Epoxide ring (oxirane ring)

An epoxide is a three-membered cyclic ether, sometimes called an oxirane. Epoxides are valuable synthetic intermediates for organic chemistry, used to convert alkenes to a variety of other functional groups. Oxygen is added to carbon-carbon double bonds to form epoxides. The most important epoxide is the simplest one, ethylene oxide. It is prepared industrially by direct air oxidation of ethylene by silver catalyst.⁴

1.1.1 Epoxidation of unfunctionalized alkenes

Alkenes are versatile building blocks in the (enantio)selective production of organic compounds. The double bond is a handle for a variety of reactions. The prochiral nature of numerous olefins makes it possible to create in a single reaction an enantiomerically or diastereomerically enriched compound.

Sharpless epoxidation

Allylic alcohols can be converted in a single reaction into the corresponding epoxide with high stereoselectivity. The efficient procedure for the epoxidation of allylic alcohols was developed by Sharpless *et al.*⁵ The catalyst is a complex prepared from titanium-*iso* propoxide and an enantiomerically pure tartaric acid ester. In general 5-10 % of the titaniumalkoxide is necessary and 10-20 % excess of the tartrate with respect to titanium-*iso* propoxide. Molecular sieves are required when performing this reaction catalytically. Since both enantiomers of the tartaric acid derivatives are readily available, both enantiomers of the desired epoxide can be obtained with high enantiomeric excess. The catalyst employs the hydroxyl function of the allylic alcohol as a handle to accomplish the high enantioselectivity. Most functionalities, except the strongly coordinating protic ones are compatible with this reaction. *t*-Butyl hydroperoxide (TBHP) is used as the oxidant and is converted into *t*-butanol. A

variety of allylic alcohols can be epoxidized using this catalyst and enantiomeric excess (ee) usually exceed 90 % and yields are generally above 80%.

D-(-) dialkyl tartrate

$$R_1$$
 R_2
 CH_2Cl_2 , -20 C
 R_3
 R_1
 R_2
 CH_2Cl_2 , -20 C
 R_3
 R_1
 R_2
 CH_2Cl_2 , -20 C
 R_3

This reaction is used industrially on a modest scale by Sipsy to produce optically active glycidol. This was only possible after the oxidant had been changed to cumyl hydroperoxide for safety reasons.⁶

Epoxides are an important and very versatile class of organic compounds. The chemistry of epoxides is particularly attractive since various functionalized compounds can easily be prepared from them.

Oxidants

Epoxidation of alkenes can be achieved by a variety of oxidants. These include perbenzoic acids, which are among the most widely used reagents for this purpose in the laboratory, dioxiranes, alkylhydroperoxides, hydrogen peroxide, bleach, iodosylbenzene and molecular oxygen. Most of them suffer from the disadvantage that besides oxygenated products stoichiometric amounts of waste products are formed which have to be separated from the epoxides.

Molecular oxygen, is the most attractive oxidant and used on large scale in industry. Besides the direct conversion of alkenes to the olefins, many epoxides are produced via the corresponding halohydrins. Molecular oxygen does not react with alkenes spontaneously but has to be activated with a suitable catalyst. For instance, in the case of the industrial conversion of ethene to ethylene oxide, one oxygen atom is transferred by a silver catalyst to ethene to form the desired product. The other oxygen atom cannot produce more of the epoxide but it oxidizes ethylene to CO and water. This process is only applicable with alkenes without α -hydrogen atoms

present. Propene is converted to the epoxide with the aids of percarboxylic acids or alkylhydroperoxides. The hydroperoxides or percarboxylic acids are produced from, for instance, isobutane or ethylbenzene in a reaction by autooxidation with molecular oxygen. In this process, secondary oxidation products arise from the hydroperoxides or percarboxylic acids as only one oxygen atom is transferred to the olefin to form the epoxide and the other one is left in stoichiometric 'waste products'. The 'waste products' are converted into a variety of industrially important products like acetic acid and styrene.

Epoxidation of olefins in the laboratory is usually accomplished with peracids. *Meta*-chloroperbenzoic acid (*m*-CPBA) is most commonly used as the oxidant and most olefins react readily with this compound to give the desired epoxide in good yields. Alternatives for *m*-CPBA include various peracids with higher or lesser reactivity⁷. *m*-CPBA is not safe for use on industrial scale.

Bleach is a very cheap and easy to use oxidant but suffers from the facts that stoichiometric amounts of salt are formed during reactions and the oxidant is highly diluted. Also the basicity of the reaction medium (pH > 10) can be a problem.

The oxidant of choice is hydrogen peroxide, which can be handled easily and leaves only water as the byproduct. Separation of water from the products is almost never a problem. Hydrogen peroxide, however, is often partially destroyed by catalase type activity⁹, a common side-reaction caused by several epoxidation catalysts. In this reaction, two molecules of H₂O₂ are converted into two molecules of water and molecular oxygen.

$$2H_2O_2$$
 Catalyst $2H_2O$ + O_2

1.2 Epoxidation of alkenes with peroxy acids

The reaction of alkenes with peroxy acid (peracid) to produce epoxides has been known for almost 90 years. It used to convert alkenes to epoxides. If the peroxy acid is strongly acidic, the epoxide opens to a glycol. Therefore, to make an epoxide, uses a weak peroxyacid such as peroxybenzoic acid. *m*-CPBA is often used for these epoxidations, reacts directly with alkenes to afford the corresponding epoxide. A large amount of data show that the reaction rate is increased by electron-donating groups on the peracids but that it is insensitive to the steric environment. Many epoxidation

reactions have been observed in biological systems and practical syntheses, including catalyst processes.

The mechanism¹⁰ of peracid epoxidation is believed to include a cyclic, concerted transition state, in which oxygen is transferred to the alkene at the same time that the carbon-carbon bond is broken and the proton is transferred to the carbonyl oxygen.

Examination of this mechanism suggests that nature of R group should not make much difference in the reaction. In fact, a number of different percarboxylic acid can be used to epoxidize alkenes, as is illustrated in the following examples. As expected, the additions occur with *syn* stereochemistry.¹¹

In addition, 4-vinylcyclohexene and *d*-limonene¹² were epoxidized with *m*-CPBA and peroxybenzimidic acid (see below). It is clear from these results that peroxybenzimidic acid is a far less selective reagent for the epoxidation of double bonds than are peracids. Although the reaction of peracids with alkenes is very markedly accelarated by the presence of electron-donating alkyl groups and a trisubstituted double bond is epoxidized approximately 275-300 times as fast as a monosubstituted double bond, the relative rates are greatly attenuated with peroxybenzimidic¹³ acid and the trisubstituted double bond is only five times as reactive as a monosubstituted olefin. As in peracid oxidations,⁶ however, the *cis* isomer of a *cis-trans* pair is oxidized more rapidly. In contrast to a number of other addition reactions,¹⁴ cyclopentene is oxidized less readily than both cyclohexene and cycloheptene.

1.3 Epoxidation of alkenes with peroxides

The epoxidation of *trans*-cyclooctene¹⁵ (*trans*-1) with the MTO/H₂O₂, MTO/UHP, and NaY/MTO/H₂O₂ oxidants leads to a mixture of *trans/cis*-olefins 1, *trans/cis*-epoxides 2, and the *cis*-diol 3. While the oxygen transfer proceeds stereoselectively, the monoperoxo rhenium complex A, which is generated *in situ* during the catalytic cycle, is responsible for the facile deoxygenation, isomerization, and hydrolysis of the *trans*-epoxide. In the case of the homogeneous MTO/H₂O₂ system, rapid decomposition of the catalytically active rhenium species into HReO₄

circumvents the formation of such side products. In contrast, for the heterogeneous oxidants MTO/UHP and NaY/MTO/H₂O₂, the catalytically active rhenium species are sufficiently stabilized and survive long enough to promote the observed side reactions.

Oxidant

$$CH_2Cl_2$$
, ca.20°C

 $trans-1$
 $trans-2$
 $trans-2$
 $trans-3$

monoperoxo rhenium complex A

 $trans-2$
 $trans-3$

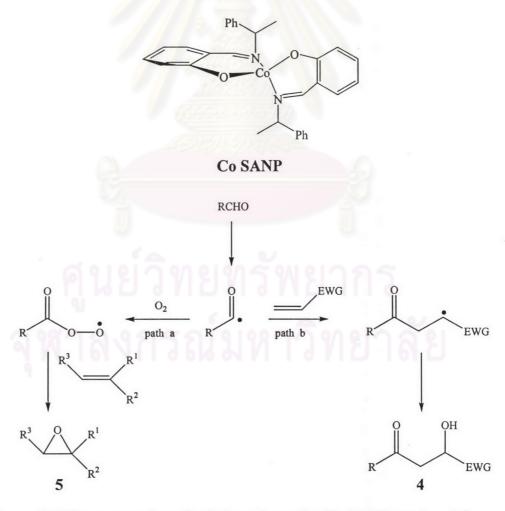
The epoxidation of alkenes with 30% aqueous hydrogen peroxide is catalyzed efficiently by methyltrioxorhenium (MTO) in the presence of pyridine additives. The addition of 1-10 mol % of 3-cyanopyridine increases the efficiency of the system for terminal and *trans*-disubstituted alkenes resulting in high isolated yields of the corresponding epoxides. The system allows for epoxidation of alkenes with various functional groups. Alkenes leading to acid-sensitive products are efficiently epoxidized using a mixture of pyridine and 3-cyanopyridine as additives. This method is operationally very simple and uses an environmentally benign oxidant.

1.4 Literature review on the epoxidation of alkenes catalyzed by metal complexes

Biomimetic oxygenations of organic substrates using soluble metal coordination complexes as catalysts ideally should use dioxygen, ¹⁷ O₂, as the source of oxygen atoms, since O₂ is used directly by oxygenase enzymes. ¹⁸ In most cases, however, the successful catalysts that have been developed for such reactions, *i.e.* metalloporphyrins and metal complexes of non-porphyrin ligands, require alternative oxidants, ¹⁹ *e.g.* hydrogen peroxide, organic peroxides, or iodosylbenzene, since reactions using dioxygen itself either give no reaction or give predominantly the undersirable side products of free-radical autoxidation. An apparent exception to this rule occurs when an aldehyde is added to the reaction mixture. In this case, it has been observed that olefins are epoxidized by dioxygen, in the presence of aldehydes and transition metal-containing catalysts, to give epoxides in high yield (eq 1).²⁰

$$C = C \qquad \underbrace{\frac{\text{Metal complex}}{\text{O_2}}}_{\text{RCHO} \qquad \text{RCOOH}} \qquad (eq 1)$$

Complex [bis(salicylidene-N-phenethyl)]cobalt(II) (Co SANP) catalyzed reaction of enolizable aliphatic aldehyde with an electron-deficient alkene leads to the formation of 4, whereas reaction with unactivated alkene affords the corresponding epoxides 5 in good yields. This process seems to be proceeding via a common pathway involving an acyl radical²¹ which reacts preferentially with electron-deficient alkenes to give an adduct radical, and the latter terminates by incorporation of dioxygen followed by reduction to afford 4. On the other hand unactivated alkenes do not undergo addition of acyl radical as the later perferentially reacts with dioxygen to give a peroxy carbonyl species which readily affords the epoxides 5 on interaction with carbon-carbon double bond. (Scheme 1.1)



Scheme 1.1 The proposed mechanistic pathway for Co SANP catalyzed the reaction of alkenes

Interestingly, the reaction with unactivated alkenes favors the formation of the epoxides 5 exclusively. Thus, styrene and 1-dodecene afforded the corresponding epoxides in excellent yields (88% and 62%, respectively). Similarly, the disubstituted olefins like (E)-stilbene and (Z)-2-octene gave the corresponding *trans* and *cis* epoxide 90% and 45%, respectively.

The epoxidation of olefins by iodosylbenzene is catalyzed by synthetic iron porphyrins.²² With (chloro-5,10,15,20-tetraphenylporphyrinato)iron(III) (FeTPPCl), cyclohexadiene oxide was produced in 93% yield and with (chloro-5,10,15,20-tetra-O-tolyporphyrinato)iron(III) (FeTTPCl), cyclooctene oxide was produced in 84% yield. Cis-olefins were found to be more reactive than trans olefins. Thus, whereas cis-stilbene was epoxidized by FeTPPCl/iodosylbenzene in 77% yield, trans-stilbene was unreactive under these conditions. The degree of cis/trans selectivity was a sensitive function of substitution of the porphyrin periphery. With (chloro-5,10,15,20tetramesitylporphyrinato)ion(III), the relative reactivity of cis- and transcyclododecene was 8.92:1. Similarly, the less reactive cis double bond of trans, trans, cis-cyclododecatriene could be selectively epoxidized by this catalyst. Trans-1,2-disubstituted double bond and 1,1-disubstituted double bonds showed similar reactivities. These results suggest an approach of the double bond from the side of the iron-bound oxygen and parallel to the porphyrin plane. A mechanism involving formation of and oxygen transfer from a reactive iron-oxo intermediate is proposed for this reaction. The preference for side-on approach of the olefin to the iron-bound oxygen has been attributed to a stereoelectronic effect involving partially filled oxygen-iron $p\pi$, $d\pi$ antibonding orbitals.

Epoxidation of oleic acid with oxygen in the presence of benzaldehyde using cobalt(II)tetraphenylporphyrin²³ (Co²⁺-TPP) as catalyst was studied. The results show that high yield of epoxidized oleic acid is obtained by the liquid phase epoxidation of oleic acid in the presence of benzaldehyde using Co²⁺-TPP as catalyst, which does not catalyze the decomposition of perbenzoic acid, which is one of the oxidation reagents for epoxidation and is formed by the oxidation of benzaldehyde. The oleic acid can be easily epoxidized in this system. The reaction mechanism was proposed. The experimental and theoretical results indicate that the epoxidized oleic acid was formed by a series of free-radical reaction steps. The rate-determining steps were experimentally identified, and the rate equation of epoxidation was obtained. The factors affecting the rate of epoxidation of oleic acid were also obtained.

A ruthenium complex of meso-tetrakis (2,6-dichlorophenyl)porphyrin,²⁴ (Ru^{II}(TDCPP)(CO)(EtOH)], is immobilized into mesoporous MCM-41 molecular sieves; the supported Ru catalyst can affect highly selective heterogeneous alkene epoxidations using 2,6-dichloropyridine N-oxide as terminal oxidant. Aromatic and aliphatic alkenes can be efficiently converted to their epoxides in good yields and selectivities, and cis-alkenes such as cis-stilbene, cis-β-methylstyrene, and cis-βdeuteriostyrene are epoxidized stereospecifically. Oxidation of cycloalkenes, e.g., norbornene and cyclooctene, can be carried out effectively using the heterogeneous Ru-catalyzed reaction while these alkenes are unreactive in the zeolite-based titanium silicate (TS-1)-catalyzed conditions. On the other hand, the Ru/M-41(m) catalyst displays size selectivity in the (+)-limonene oxidation where the terminal C=C bond (vs internal trisubstituted C=C bond) becomes more readily oxidized. Bulky 3,4,6-tri-O-benzyl-D-glucal has falled to react under the heterogeneous Ru-catalyzed conditions, whereas the smaller acetyl derivative is converted to a 3:1 mixture of α and β-glycal epoxides. The Ru/M-41(m) catalyst can be used repeatedly, and 67% of its initial activity is retained after 11 691 turnovers (three runs). The loss of activity is attributed to catalyst leaching and/or deactivation. On the basic of Hammett correlation ($\rho^+ = -0.72$, R = 0.997) and product studies (cyclohexene and *cis*-alkenes as the substrates), a reactive dioxoruthenium(IV)porphyrin intermediate is not favored. An oxoruthenium(V) complex or oxoruthenium(IV) porphyrin cation radical could be the key intermediate for this highly selective epoxidation reaction.

Dioxiranes are highly clean and powerful oxidants and have been applied to a variety of oxidations. Recently Shi and co-workers reported a new method for epoxidation using trifluoroacetone in aqueous acetonitrile as solvent and hydrogenperoxide²⁵ in place of Oxone²⁶ (potassium peroxomonosulfate) generally used as dioxiranes generator. Though this method is practical and does not need large amounts of potassium carbonate to neutralize the consequently formed potassium hydrogen sulfate, several problematic features are still evident from the standpoint of large scale manufacturability. For example, aqueous acetonitrile generally does not readily dissolve aromatic olefins due to their poor solubilities. A more fundamental problem is that toxic and rather expensive acetonitrile is unavoidable as an oxidizing mediator²⁵ to ensure high conversion. Recycling of acetonitrile is also difficult mainly due to boiling point which is almost the same as that of water. In the last two dacades, two-phase systems have been investigated in order to overcome these problems.²⁷

These procedures in general used *n*-Bu₄NHSO₄ as the phase transfer catalyst (PTC).²⁸, ²⁹ As a result, a tedious dropwise addition of base solution over a long time period under strict pH control was needed to avoid the oxidation of the PTC.

The singlet-oxygen ene reaction and the epoxidation by dimethyldioxirane (DMD) of chiral oxazolidine-substituted alkenes, equipped with a free urea NH functionality³⁰ and a conformationally fixed double bond, proceed in high *like* diastereoselectivity (up to >95:5); also a high regioselectivity was found for the ¹O₂ ene reaction. Capping of the free NH functionality by methylation erases this *like* selectivity for both oxidants and significantly reduces the regioselectivity in the ene reaction. These data demonstrate effective hydrogen bonding between the remote urea NH functionality and the oxidant that favors the *like* attack on the C-C double bond. For ¹O₂, the hydrogen bonding in the exciplex results in preferred hydrogen abstraction from the alkyl group *cis* to the directing urea functionality.

$$R^{1}$$
 R^{2}
 R^{3}
 R^{4}
 R^{4

The highly substituted dioxoruthenium(VI) porphyrins³¹ [Ru^{VI}(DPP)O₂] (6a; H₂DPP = 2,3,5,7,8,10,12,13,15,17,18,20-dodecaphenylporphyrin), [Ru^{VI}(TDCPP)O₂] (6b; H₂TDCPP = meso-tetrakis(2,6-dichlorophenyl)porphyrin), and [Ru^{VI}(TMOPP)O₂] (6c; H₂TMOPP = meso-tetrakis(2,4,6-trimethoxyphenyl)porphyrin) are competent oxidants for alkene epoxidation. The oxidations were carried out in a CH₂Cl₂/Hpz solution, and a paramagnetic bis(pyrazolato)ruthenium(IV)porphyrin, [Ru^{IV}(Por)(pz)₂] (7; H₂Por) H₂DPP, H₂TDCPP, H₂TMOPP), was isolated and characterized. For the oxidation of cis-alkenes, stereoselectivity is dependent upon both the alkenes and the ruthenium oxidants, and it decreases in the order: cis-stilbene > cis- β -methylstyrene > cis- β -deuteriostyrene. The observation of inverse secondary KIE for the oxidation of β -d₂-styrene [kH/kD = 0.87 (6a); 0.86 (6b)] but not for the R-deuteriostyrene oxidations suggests that the C-O bond formation is more advanced at the C(β) atom than at the C(α) atom of styrene, consistent with a nonconcerted mechanism. By consideration of spin delocalization and polar effects, the second-

order rate constants for the oxidation of *para*-substituted styrenes by ruthenium complexes of **6a-c** can linearly correlate with the carboradical substituent constants σ_{mb} and σ_{JJ} . This implies that the styrene oxidation by the dioxoruthenium(VI) porphyrins should involve rate-limiting generation of a benzylic radical intermediate, and the magnitude of $|\rho_{JJ}/\rho_{mb}| > 1$ suggests that the spin delocalization effect is more important than the polar effect in the epoxidation reactions. The spontaneous epoxidation of *trans-\beta*-methylstyrene by the sterically encumbered [Ru^{VI}(TDCPP)O₂] and [Ru^{VI}(TMOPP)O₂] complexes and the comparable ΔS values for their reactions with *trans-\beta*-methylstyrene and styrene are incompatible with the "side-on approach" model; a "head-on approach" model is implicated.

Anions play essential roles in biological processes; indeed, it is believed that they participate in 70% of all enzymatic reactions. There is, therefore, intense effort being devoted to the problem of anion complexation and recognition. In the molecular recognition arena, a number of research groups have followed nature's lead and have designed and synthesized receptors that use hydrogen bonds alone,³² or in concert with electrostatic interactions,³³ to coordinate to anions. Nonetheless, there remains at present a critical need for additional anion complexing agents that are either easy to make or inherently selective in their substrate-binding properties.

Porphyrinogens are macrocyclic species composed of four pyrrole rings linked in the α -position via sp³-hybridized carbon atoms. Porphyrinogens which carry *meso*-hydrogen atoms are prone to oxidation to the corresponding porphyrin. On the other hand, fully *meso*-substituted porphyrinogens are generally not only stable crystalline materials but also readily obtainable.³⁴ In fact, the first such species, an octamethyl derivative, was obtained over a century ago by Baeyer³⁴ as the result of an acid catalyzed condensation between acetone and pyrrole. Subsequently, this synthesis was

refined by a number of research groups.³⁴ In 1971 Brown and co-workers condensed cyclohexanone with pyrrole in a 1:1 ratio in the precence of acid to produce tetraspirocyclohexylporphyrinogen 9. Recently Floriani and co-workers have made an extensive study of the chemistry of metal complexes of various deprotonated octaalkylporphyrinogens.³⁵

While the term porphyrinogen is now widely accepted in the literature, octaalkylporphyrinogens are not *bona fide* precursors of the porphyrins and might, therefore, be better considered as being *calixpyrroles*. Such a renaming, which has precedent in the chemistry of other heterocyclic ring systems, would allow the analogy to calixarenes³⁶ to be more fully stressed. Interestingly, while functionalized calixarenes have been shown to be capable of binding anions,³⁷ unmodified calixarene frameworks show no affinity for anionic guests.

Ligands 8 and 9 were prepared in one step using known literature procedures.³⁴ Single crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of acetone and acetone/dichloromethane (1:1) solutions of macrocycles 8 and 9, respectively. As illustrated in Figure 1.1, the molecules adopt a 1,3-alternate conformation in the solid state where in adjacent rings are oriented in opposite directions just as is ture in the case of the previously reported octaethyl analogue.³⁵ This is a less common conformation for calixarenes, only a few structurally characterized examples having been reported.³⁶

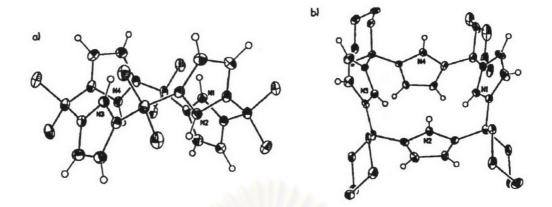


Figure 1.1 View of the molecular structures of (a) 8 and (b) 9 Thermal ellipsoids are scaled to the 30% probability level. Both compounds adopt a 1,3-alternate conformation in the solid state

The production of new receptors for anions and neutral species which are easy to synthesize and yet effective and selective in their guest binding properties is an area of supramolecular chemistry. Calix[4]pyrroles(meso-octaalkylporphyrinogens) are stable tetrapyrrolic macrocycles first synthesized in the 19th century by Baeyer via acid-catalyzed condensation of pyrrole with acetone to produce meso-octamethylcalix[4]pyrrole 8. The discovery that these species act as receptors for anions and neutral molecules³⁸ has been used in the production of fluorescent, colorimetric, and electrochemical sensors for anions, in addition to new solid supports capable of separating mixtures of anions (including oligonucleotides).

Encouraged by the facile synthesis of both calix[4]pyrrole and thiophen-o-phen ligands in high yield, together with there was no report cited in chemical literature to utilize these cobalt(II) calix[4]pyrrole and cobalt(II) thiophen-o-phen complexes in the epoxidation reaction, the selectively catalytic epoxidation of alkenes under mild condition will be thoroughly investigated in this research. Cyclohexene was employed as a chemical model. The outcome of this work will certainly expand the use of these two catalysis in the catalytic epoxidation.

1.5 The goal of this research

The aim of this research can be summarized as follows:

 To synthesize calix[4]pyrrole and thiophen-o-phen ligands and their complexes

- 2. To study the optimum conditions for alkene epoxidation reaction using cobalt(II) thiophen-o-phen, cobalt(II) salophen, cobalt(II) saloa and cobalt(II) calix[4]pyrrole as catalyst
- 3. To study the stereoselectivity and regioselectivity of the developed system using those mentioned catalysts
- 4. To apply the optimum conditions for the epoxidation of various selected alkenes

