CHAPTER I

INTRODUCTION

1.1 Importance of epoxide and products from epoxide ring opening

Epoxides have become highly popular building blocks in organic synthesis in recent years. To a great extent, the development was influenced by the discovery of enantioselective protocols for the formation of functionalized epoxides such as Sharpless epoxidation and the products from the diastereoselective ring opening of epoxide with organometallic reagents. The products from epoxide ring opening are indeed important in pharmaceutical industries, organic synthesis, and other chemical fields. For example, β-amino alcohols, a product of epoxide ring opening with amine, are widely recognized as building blocks in organic synthesis and in medicinal chemistry. They have recently been used for the synthesis of 1-phenyl-2-[(2-phenyl-1-alkylethyl)amino]ethanol derivatives, a new important class of antidiabetic agents. Another instance 3-azido-1,2-diol (I) constitutes the most critical elements in biologically active natural products including certain aminoglycoside antibiotics and antitumor agents.

\[ \text{I} \]

In recent years, the pharmaceutical industry had relied greatly on solution phase parallel synthesis as a mean of production for lead generation libraries of small molecules. The 1,2-phenethyldiamine substructure (II) provided an excellent core for a drug-like lead generation library. Furthermore, substituted 1,2-phenethyldiamines have proven to possess biological activities.
(2S,3R)-3-Hydroxy-2-methyldecanoic acid was a component of hapalosin, a cyclic depsipeptide exhibiting an anti-multidrug resistance (MDR), a phenomenon encountered in cancer chemotherapy.

Ring opening of epoxide by thiol was a widely used reaction for the synthesis of β-hydroxythio derivatives which were useful intermediates in natural product synthesis. For example, 2-hydroxyethyl thiocyanate (III) was drawn much attention in medicinal chemistry, because it could be developed a straightforward method for the preparation of β-hydroxyethyl thiocyanate. This class of compounds was considered as a key intermediate in agricultural and pharmaceutical chemistry.

Moreover, the epoxide ring and products derived from ring opening are useful in various polymer processes and petrochemical industries.

1.2 Methods for epoxide ring opening

An epoxide ring could be opened by common reagents such as acid, base and metal salt. Sometime the reaction could take place without any catalyst.

1.2.1 By common catalysts

By acid

In the reaction with nucleophiles at pH less than about 4, acid catalysis took over and the initial was attacked on oxygen. The oxygen could leave with the bonding pair of electrons determining which bond was broken. The chief product from a monoalkyl oxide was the primary alcohol.
It was reported that acid could be exploited as a catalyst for the epoxide ring opening under milder conditions. A well known example involving the steroidal skeleton rearrangement, 16α,17α-epoxy-20-one system which had proven to be quite resistant to nucleophilic/ Lewis acid catalyzed ring opening. The only reported opening of the epoxide ring was the conversion by HBr-AcOH, of (IV) to bromohydrin (V).

By Lewis acid

Iqbal and co-worker reported the reaction of cinnamoyl epoxide with N-substituted aniline in the presence of cobalt (II) chloride afforded the corresponding amino alcohol in good yields. The stereochemistry of the amino alcohol was depended upon the para substituent on the aromatic ring. The opening reaction of cinnamoyl epoxide with N-substituted aniline having a para methoxy group gave the corresponding anti amino alcohol as the major product in high yield and only a trace of syn diasteromer was observed. The reaction of secondary amines with anti epoxide of ethyl cinnamate in the presence of catalytic cobalt (II) chloride afforded the anti amino alcohol as the major product in good isolated yield.
Another metal salt catalyst reported by Salehi and co-worker\textsuperscript{10} involved the ring opening of different classes of epoxides in primary, secondary and tertiary aliphatic alcohols in the presence of 0.01 - 0.1 molar equivalents of ferric perchlorates to the corresponding \(\beta\)-alkoxy alcohol in excellent yields with high degree of regio- and chemo-selectivity.

\[ R_1 \overset{\text{Fe(ClO}_4\text{)}_3}{\longrightarrow} R_1\text{CH} = \text{CH}_2\text{CH}_2\text{OH} + R_1\text{CH} = \text{CH}_2\text{OR}_2 \]

The application of NbCl\(_3\) as a catalyst for epoxide ring opening was addressed.\textsuperscript{11} Rearrangement products, chlorohydrins, and 1,2-diols were noticed as a main product depending on both substrate structure and reaction conditions.
Tributylphosphine was found to be another effective promoting reagent for the ring opening reaction of various epoxides with nucleophile to produce the corresponding anti-bifunctional products in moderate to excellent yields in water.\textsuperscript{11}

\[ \begin{align*}
R_1 & \quad R_2 \\
\text{NuH, } \text{PBU}_3 \text{ 10 mol\%} \\
\text{H}_2\text{O, 25-40 °C} \\
\end{align*} \]

**By Lewis base**

Lowden and Mendoza\textsuperscript{4} reported that chiral styrene oxide could be opened with secondary amines to yield amino alcohol regioisomers. The alcohol products were then mesylated to form a relatively stable aziridinium intermediate which was opened regiospecifically with primary amines at the benzylic carbon to form the 1,2-phenethylidiamine products.
Coote and co-worker\textsuperscript{13} documented the reaction of homochiral (-)-(R)-styrene oxide with methylamine in ethanol at reflux. The reaction produced homochiral (-)-(R)-halostachine and 2-methylamino-2-phenylethanol. Similar treatment of a racemic styrene oxide gave a racemic halostachine. Treatment of (-)-(R)-halostachine or (R,S)-halostachine with 3,4-dimethoxybenzyl bromide in acetonitrile at reflux in the presence of potassium carbonate yielded pure (-)-(R)-N-3,4-dimethoxy benzylstachine and (R,S)-N-3,4-dimethoxybenzylstachine, respectively.

Racemic secondary alcohols with an $N$-protected oxyamine function at $\beta$-position were prepared by a base-catalyzed epoxide ring opening with $N$-hydroxyphthalimide or acetone oxime. The starting $N$-(2-substituted-2-hydroxyethoxy)-phthalimides were prepared from styrene oxide and $N$-hydroxy phthalimide yielding a primary alcohol, $N$-(2-hydroxy-1-phenylethoxy)phthalide.

Azidolysis of 1,2-epoxide was widely investigated in organic reaction since 1,2-azidoalcohols were precursors of vicinal amino alcohols and building blocks for carbohydrates and nucleosides. The classical protocol used NaN\textsubscript{3} (5 mol/eq) as a reagent in the presence of NH\textsubscript{4}Cl (2.3 mol/eq) as a coordinating salt in alcohol–water at 70-80 °C.\textsuperscript{15}
1.2.2 By metal complexes

By metal Schiff's base

The development of a new process for the opening of epoxide ring has been continued to be an important goal for both academic and industrial point of views. Metal Schiff's base complexes have been reported to be employed as a catalyst in the epoxide ring opening obviously seen from the work contributed by Jacosen and co-workers.\textsuperscript{16-19}

Some instances were described below. The screening of first-row transition metal complexes derived from the commercially available salen ligand was came out and revealed that several of them could catalyze the epoxide decomposition, but only the chromium (III) and cobalt (II) complexes mediated clean transformation to the ring-opening product. This was in fact later the preferred catalyst for asymmetric epoxide ring opening reaction with TMSN\textsubscript{3}.

The reaction of various meso epoxides with TMSN\textsubscript{3} was screened utilizing 2 mol\% of metal Schiff's base as a catalyst. Epoxides fused to five-membered ring underwent ring opening with very high levels of enantioselectivity, while six membered ring and acyclic substrates were slightly less effective.

Fluorine substituted organic compounds have gained a growing interest because of their unique properties due to the influence of the eletronegative fluorine substituent on the acidity of neighboring position and dipole moment of the molecule. The reaction of cyclohexene oxide with KHF\textsubscript{2}/18-crown-6 was trans-diastereoselective and was proceeded with 55\%ee to form (R,R)-(+)2-fluoro cyclohexanol in the presence of Jacobsen's (S,S)-(+-)(salen)chromium chloride.
complex. From racemic epoxides such as styrene oxide or phenyl glycidyl ether, mainly or exclusively products with fluorine in primary position were formed with 90 or 62 %ee, respectively. In all cases, minor amounts of the corresponding chlorohydrins were formed.\textsuperscript{20}

Asymmetric hydrolysis of cyclohexene oxide was selected as a challenging test of the reactivity of oligomeric (salen)-Co catalysts, as this reaction had proven to be very difficult to catalyze with monomeric (salen)-Co complexes. At a catalyst loading of 1.5 mol\% with respect to Co, hydrolysis of cyclohexene oxide was completed within 11 h, providing the corresponding trans-1,2-diol in 94-96 %ee.\textsuperscript{21}
By metal carboxylate complexes

From the published data, it has been known that chromium (III) ethanoate could be used for epoxide ring opening. Reactivities have been compared with acetic, acrylic, and methacrylic acid in the reaction with epichlorohydrin, phenylglycidyl ether, glycidyl acetate and glycidyl methacrylate carried on in the presence of Cr(III) ethanolate. The acid reactivities changed greatly with respect to the oxirane series.
Iranpoor and Adibi\textsuperscript{23} reported that iron (III) trifluoroacetate was utilized as an efficient and nonhygroscopic catalyst for the alcoholysis, hydrolysis, and acetolysis of epoxides. The addition of chloride, bromide, iodide, and nitrate ions to epoxides to produce the corresponding 2-halo and 2-nitratoalkanols and also the conversion of epoxides to acetonides and thiiranes were also performed efficiently in the presence of this catalyst.

\[
\begin{array}{c}
\text{O} \\
\text{R}
\end{array} \xrightarrow{\text{Fe(TFA)}_3, \text{Nu}} \xrightarrow{\text{rt, or heat}} \text{RCH(Nu)CH}_2\text{OH} + \text{RCH(OH)CH}_2\text{Nu}
\]

By Organometallic catalysts

The mechanism of silver(I)-catalyzed reaction of organozirconocenes with epoxides was likely to involve an initial Cp\textsubscript{2}ZR\textsuperscript{+}-induced epoxide opening, followed by a [1,2]H shift and nucleophilic attack on the resulting aldehyde. The Lewis acid Cp\textsubscript{2}ZR\textsuperscript{+}, initially prepared by Ag(I)-induced chloride abstraction from Cp\textsubscript{2}RZrCl was regenerated by chloride ion transfer from Cp\textsubscript{2}RZrCl to alkoxyzirconocene cation.\textsuperscript{1}

Garrett and Fu\textsuperscript{24} reported that σ-bond phosphorus heterocycles, could function as a catalyst, especially phosphaferrocene catalyzed the ring opening of epoxide with TMSCl. Phosphines serve as a nucleophilic catalyst for a wide array of reaction. Thus treatment of an epoxide with 1.2 equivalents of TMSCl and 5 mol% of phosphaferrocene in CH\textsubscript{2}Cl\textsubscript{2} at room temperature, followed by deprotection of the resulting TMS ether with acid, cleanly afforded a chlorohydrin.
By supported catalysts

Alternatively, Iqbal and co-worker reported that novel synthesis of pyrrolidine containing α-hydroxyamide core structures as inhibitors for HIV protease was developed by employing polyaniline supported cobalt (II) salen to catalyze the formation of the epoxide from cinnamoylamides of L-proline followed by its opening with anilines at ambient conditions. The intermediate cinnamoyl epoxide underwent a stereoselective S_N2 type ring opening with several aromatic amines leading to a highly selective synthesis of the anti diasteromer of β-phenylisoserine derivatives.

Two series of solid catalysts in which a chiral chromium salen complex have been anchored on aminopropyl-functionalized SiO_2, ITQ-2 or MCM-41 have been prepared.
A model substrate shown below represented another epoxide ring opening reaction of cyclohexene oxide catalyzed by supported chromium catalyst.²⁷

Recent literature review has been revealed that main reactions of epoxide ring opening involved the use of Lewis acid or Lewis base. Several transition metal complexes have been developed to exploit for this kind of reaction. Since there was no record on the utilization of Fe(TCA)₃.1.5H₂O as a catalyst for epoxide ring opening, this research was accordingly focussed on the use of this catalyst for this type of organic transformation.

### 1.3 The goal of this research

The aims of this research can be summarized as follows:

1. To search for effective transition metal complexes catalysts for ring opening of styrene oxide.

2. To study of the optimum conditions for epoxide ring opening using styrene oxide as a model substrate.

3. To apply the optimum conditions for the ring opening of selected epoxides.