

# CHAPTER I

## INTRODUCTION

### 1.1 A chemical industry in overview [1]

There are many dealers and various product categories in fine chemical business in Thailand. This actually plays an important role in overall economic system. The chemicals are raw materials used in many industries where manufacture ready-made products. The production of chemicals causes a continuous process in other downstream industries. Though there are various product types of chemicals, it can be divided by the production process into three groups:

- An upper-stream chemical industry consisting of organic chemicals and inorganic chemicals
- An intermediate chemical industry such as petrochemical industry
- A downstream chemical industry which is color and co-products, pesticides and cosmetics

Approximately 10% of chemical industry is the upper-stream and intermediate chemical industries and the rest are downstream chemical industry which has the total product value more than 80%. The market structure of chemical industry is a monopolistic competition and has few traders. The fact is that the amount of the production is higher, the production cost then gets cheaper, or that the production is the continuous process. Domestic market is the main market and the competitive capability depends mostly on the production cost, raw materials, market size and energy usage.

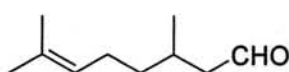
The chemical manufacture is commonly an additive process and uses simple technology. Most of the production is to replace import. There are some industries that can be developed to export, for example cosmetics and perfumery. However, the production cost of raw material is still high because Thailand has to import raw materials from foreign countries under an import duty rate higher than neighboring countries. It was thus a significant reason for the industrial development.

### 1.1.1 The cosmetics and perfumery industry

The cosmetics and perfumery industry growth in Thailand has highly expanded. After an economic crisis, the production for import replacement has increased. At the same time, small and medium drug factories have changed from drug production to cosmetics and perfumery. And it seems to be more popular among consumers. The consumers tend to use domestic products which are cheap and at the same quality as imported product. Therefore, in the future import will decline but export will expand. Nowadays Thailand can produce almost every kind of cosmetics with the same quality as those from foreign countries. There are 30 large manufacturers and 300 minor Thai manufacturers. They produce cosmetics and perfumery almost all kinds of product types. Mostly it supplies the needs of low and middle markets. Raw materials are mostly imported from EU, USA, Japan, Korea and China. Export market is Asian countries. Therefore, domestic manufacturers need to upgrade their working efficiency and reduce the cost of production.

The aims of this research are to search for a new methodology towards rearrangement of epoxides to more valuable products which could be used as raw materials for the cosmetics and perfumery industry. Aldehyde compounds are generally used at industrial scale in fine chemistry for the production of the cosmetics and perfumery.

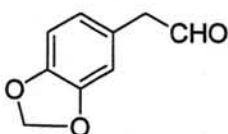
### 1.1.2 The raw materials of the cosmetics and perfumery industry [2]



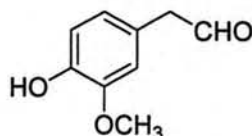
*Citronellal*: A powerfully odorous oil could be isolated from the oils of citronella and eucalyptus citriodora by means of sodium bisulphate.



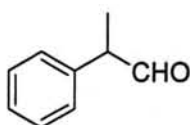
*n-Dodecanal*: A solid at normal temperatures, it possesses a rather objectionable fatty odor, but when much diluted this becomes comparatively pleasant and recalls the earthy odor associated with wood violets.



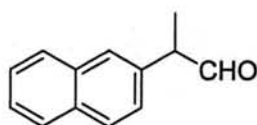
*Homoheliotropin*: A pale yellow liquid of heliotropin-like odor. Miscible with essential oils and synthetic aromatics, but on exposure is prone to resinify.



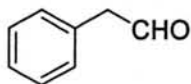
*Homovanillin*: A white crystalline substance having an agreeable floral odor which resembles vanilla more closely than vanillin.



*Hydratropic Aldehyde*: A colorless semi-viscous liquid of powerful, almost harsh, hyacinth type odor. It is remarkably stable and does not polymerize. Its principal use is in soaps of the type of hyacinth, lilac, and rose.



*Methyl-β-Naphthylacetaldehyde*: A chemical having a fine odor of orange blossom.



*Phenylacetaldehyde*: A viscous and highly odorous liquid widely used as the base of Hyacinth oils. This aldehyde may be employed in compounding numerous flower oils. In addition to being the base of most hyacinths, it is useful in narcissus, sweet-pea, lilac, lily, and jonquille and is recommended in traces for preparing special types of rose perfumes. On account of its intense floral odor it is used in small quantities in many compounds where price will not allow the inclusion of large proportions of natural absolutes. It is seldom used in soaps, being replaced by the more stable ω-bromstyrene.

## 1.2 Literature review on the rearrangement of epoxides

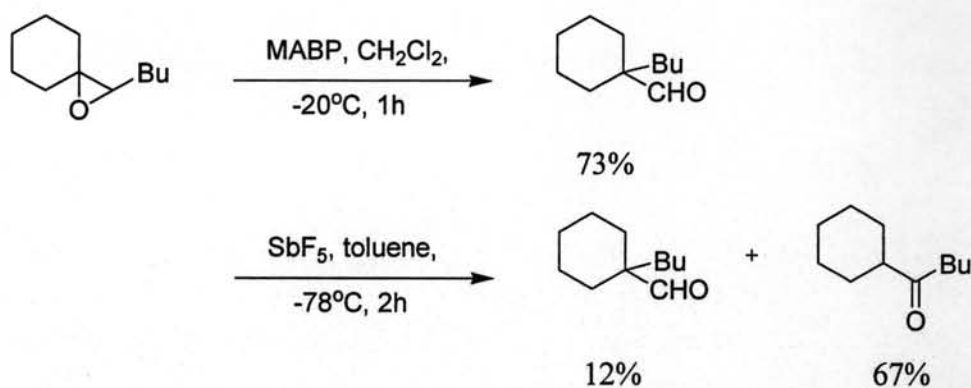
Epoxides are one of the most useful and versatile intermediates that serve as prominent building block in organic synthesis [3]. Not only are these compounds easily prepared from a variety of starting materials, but also the inherent polarity and strain of their three-membered ring makes them susceptible to the reactions with a large number of reagents. While epoxides are frequently employed as electrophiles in ring-opening nucleophilic-addition reactions, another common, useful and atom-economical reaction is isomerization to form other functional groups. In the presence of a strong and bulky base, an epoxide may undergo a deprotonation-elimination sequence to form an allylic alcohol frequently with high stereoselectivity. Furthermore these epoxide-related transformations, the rearrangement of epoxides to carbonyl compounds have received considerable attention. The most well-known method to isomerize epoxides to carbonyl compounds involves the use of Lewis acids, generally *via* hydride, alkyl, or aryl 1,2-migration pathways. The synthetic applications of epoxides have been the subject of number of recent and through reviews.

The synthetically useful reactions of epoxide are indeed important in organic synthesis, pharmaceutical industries, perfumery and other chemical fields. For example: ring opening of epoxides with heteroatomic nucleophiles [4-12], ring opening of epoxides with carbon nucleophiles [13], intramolecular ring opening of epoxides [14], reduction of epoxides to alcohols [15, 16], deoxygenation of epoxides to olefins [17-19], rearrangement of epoxides to allylic alcohols [20-21], rearrangement of epoxides to carbonyl compounds [22-50], *etc.* Among those epoxide-related transformations, the rearrangement of epoxides such as those bearing aryl-, vinyl-, silyl- and trialkyl-substituents to carbonyl compounds is a well-investigated reaction.

### 1.2.1 By homogeneous catalysts

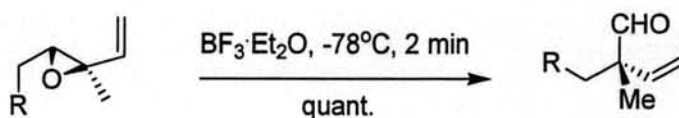
In 1970 Rickborn and Gerkin reported that LiBr could be solubilized in benzene by the addition of equivalent amount of hexamethylphosphoramide (HMPA) or other phosphine oxide. The resultant complex was an efficient catalyst for the rearrangement of epoxides to aldehydes and/or ketones.



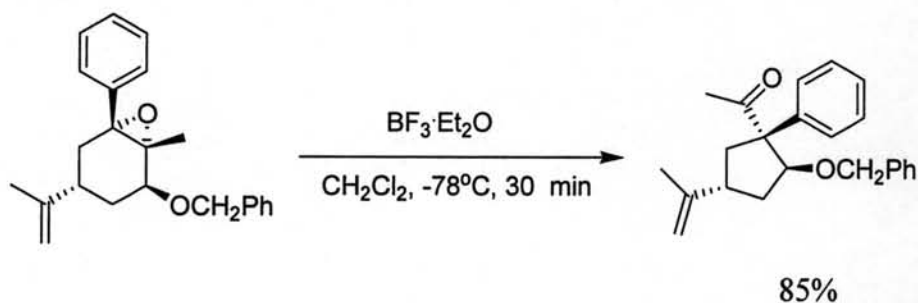


For the aldehyde synthesis, the use of a sterically hindered, oxygenophilic MABP would be the most suitable to affect the initial epoxide-cleavage followed by smooth alkyl transfer, in view of the increasing steric repulsion between a bulky organoaluminum ligand and butyl group of epoxide [24].

In 1995 Jung and Amino reported the rearrangement of tertiary allylic epoxides to give quaternary aldehydes. 2-Methyl-2-vinyl-3-alkyloxiranes readily underwent 1,2-alkyl migration leading to 2-methyl-2-vinylaldehydes. The reaction conditions necessary for rearrangement are generally quite mild by  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  at  $-78^{\circ}\text{C}$  for 2 min, 5M  $\text{LiClO}_4$  in refluxing ether, anhydrous  $\text{Zn}(\text{OTf})_2$  or  $\text{ZnCl}_2$ ,  $\text{EtAlCl}_2$ , silica gel and sonication [25].

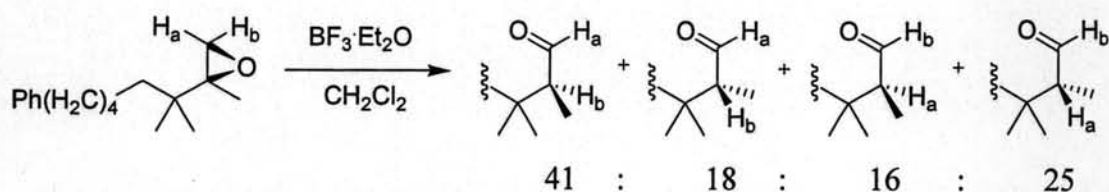


Moreover in 1999, Neef and colleagues reported the use of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  to catalyze the rearrangement of epoxides. The  $\text{BF}_3$ -etherate treatment of benzyl ether-protected epoxy alcohol proceeded with clean and high yield formation of a single ring-contracted ketone [26].

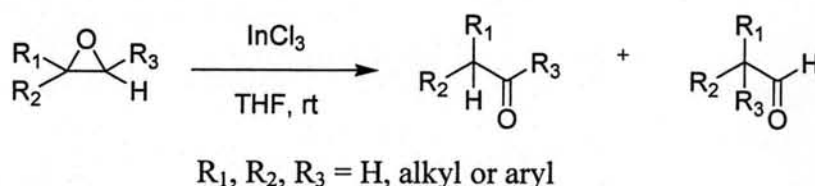


A number of examples have been reported on epoxides embedded in cyclic systems, while few studies have been done on the stereochemistry at the migration terminus in the rearrangement of acyclic epoxides. In 2000 Hara and colleagues reported that mechanistic studies on the  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed rearrangement of

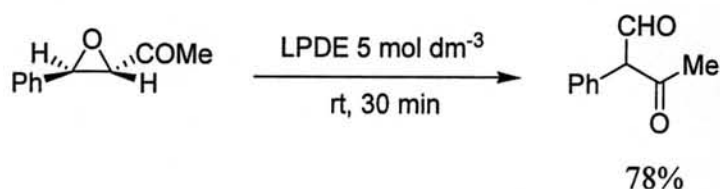
optically active, regioselectively deuterated 1,1-disubstituted epoxides to aldehydic products revealed that the two hydrogens migrate at the migration terminus with opposite stereochemical preferences, *i.e.* H<sub>b</sub>, the hydrogen *anti* to the bulky substituent prefers to migrate with inversion of configuration, whereas H<sub>a</sub>, the hydrogen *syn* to the bulky substituent prefers to migrate with retention of configuration [27].



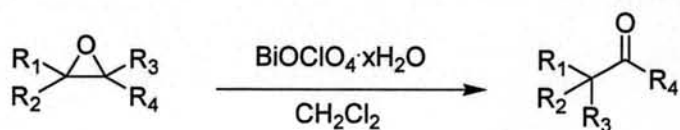
In 1998 Ranu and Jana reported a simple and efficient procedure for the rearrangement of substituted epoxides catalyzed by InCl<sub>3</sub>. Aryl-substituted epoxides isomerized with complete regioselectivity to form a single carbonyl compound *via* cleavage of the benzylic C-O bond. 1-Aryl-, 1,1-diaryl- and 1,1-alkyl, aryl-substituted epoxides underwent rearrangement by exclusive hydride shift to give the respective aryl-substituted acetaldehydes as the only isolable compounds. While the rearrangement of tri- and tetra-substituted aryl epoxides selectively produced the corresponding ketones. The other notable advantages offered by the procedure are fast reaction, mild reaction conditions, simplicity in operation, mild nature of InCl<sub>3</sub> in comparison to BF<sub>3</sub> and other Lewis acid and its compatibility with several acid-sensitive functionalities [28].



In 1998 Sankararaman and Nesakumar reported the highly chemo- and regioselective rearrangement of  $\alpha,\beta$ -epoxy ketones to 1,3-dicarbonyl compounds in lithium perchlorate-diethyl ether (LPDE) medium by a 1,2-migration of the carbonyl group at ambient conditions [29].

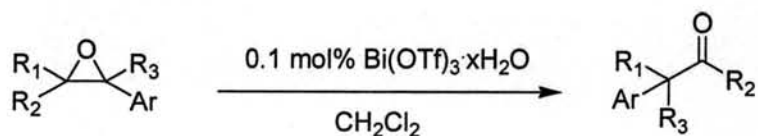


Recently, bismuth compounds have become attractive candidates for use as reagents in organic synthesis due to their low toxicity. In an earlier study, in 1999, Anderson and colleagues reported that aryl-substituted epoxides and aliphatic epoxides with a tertiary epoxide carbon underwent smooth rearrangement in the presence of 10-50 mol%  $\text{Bi}(\text{OClO}_4) \cdot x\text{H}_2\text{O}$ , to give carbonyl compounds. The rearrangement was regioselective with aryl-substituted epoxides and a single carbonyl compound arising from cleavage of benzylic C-O bond was formed [30].



The rearrangement of both *cis*- and *trans*-stilbene oxides gave diphenylacetaldehyde as the only product in high yield. Nevertheless, the rearrangement of styrene oxides did not give a very pure product together with very low yields (15%) of phenylacetaldehyde.

In addition 2001 Bhatia and colleagues reported that aryl-substituted epoxides underwent rearrangement smoothly in the presence of  $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$  (0.1 mol%) to carbonyl compounds [31].

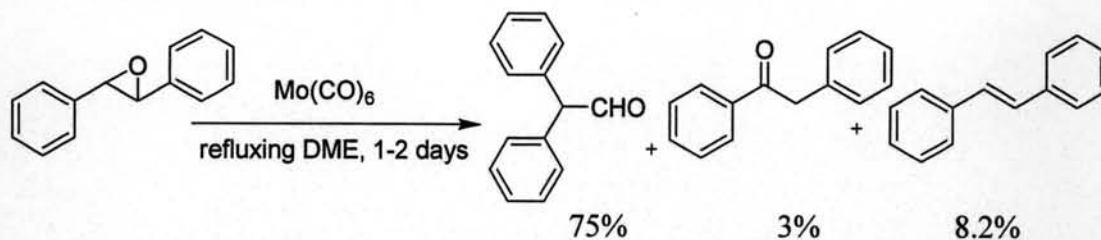


In recent years, the promise of increased chemo-, regio-, and stereoselectivity available *via* transition metal catalysis has led investigators to study the interactions of epoxides with transition metal complexes, and a number of interesting and useful isomerization reactions have been reported. Notably, epoxides activated by adjacent aryl, vinyl, silyl, or carbonyl substituents were isomerized to carbonyl compounds by complexes of Rh, Pd, Mo, Sm, Fe, etc. For instance in 1976 Alper and colleagues reported the use of the cheap metal carbonyl, molybdenum hexacarbonyl  $[\text{Mo}(\text{CO})_6]$  as a homogeneous catalyst for the rearrangement of epoxides to aldehydes in synthetically useful yields.

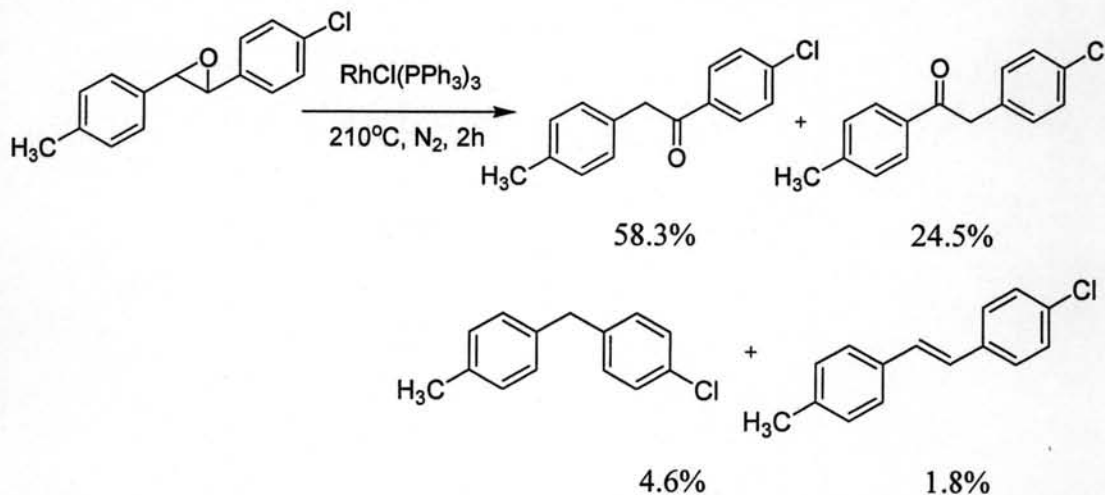
Treatment of the epoxides of *trans*-stilbene, styrene,  $\alpha$ -methylstyrene and 1,1-diphenylethylene with a catalytic amount of  $\text{Mo}(\text{CO})_6$  in refluxing 1,2-DME afforded the rearranged aldehydes in 36-75% yields. A by-product of all reactions was the



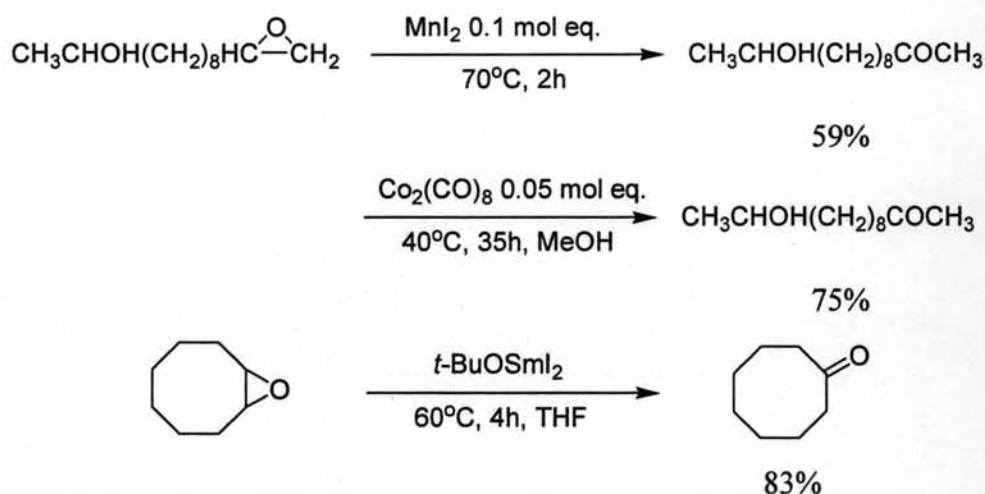
deoxygenated alkene having the same stereochemistry as the reactant epoxide. Small amounts of ketones were formed in several instances [32].



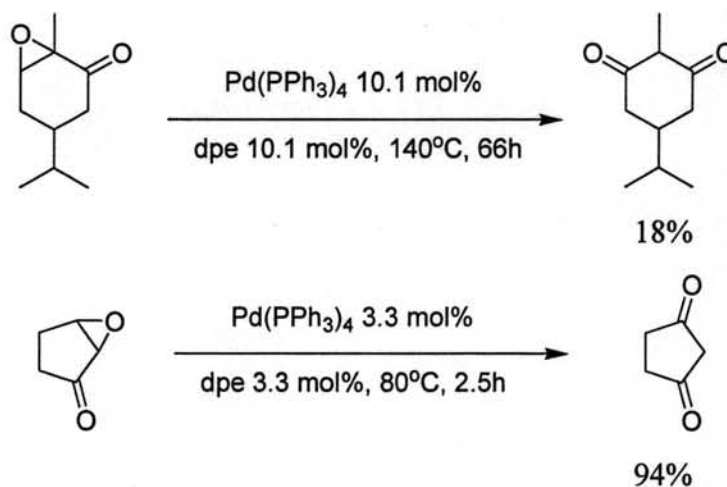
In 1977 Milstein and Buchman reported that  $\text{RhCl}(\text{PPh}_3)_3$  displayed the selective rearrangement of many vicinal-disubstituted epoxides to ketones between 150 and 210°C. While both acid- and base-catalyzed isomerization of *trans*-stilbene oxide gave usually diphenylacetaldehyde as the main product, the  $\text{RhCl}(\text{PPh}_3)_3$ -promoted reaction afforded 88% deoxybenzoin. The only by-products in this reaction are diphenylmethane (7.9%), *trans*-stilbene (2.8%), *cis*-stilbene (0.3%) and benzene (1%). When two substituents of different electronic nature are being attached to the phenyl rings (one to each) the C-O bond that is closer to the more electron-donating group is expected to be the weaker one and to be cleaved preferentially [33].



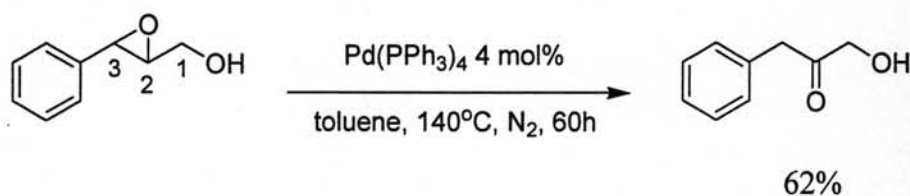
In 1985 Prandi and colleagues reported that terminal epoxide could selectively convert into methyl ketones by some lanthanide derivatives,  $\text{Co}_2(\text{CO})_8$  and  $\text{MnI}_2$  catalysts. The choice of catalyst will depend on the structural features and the nature of the functional groups in the molecular. For example *t*-BuOSmI<sub>2</sub> or SmI<sub>2</sub> were not suitable for some hydroxyl or keto epoxy, while  $\text{Co}_2(\text{CO})_8$  or  $\text{MnI}_2$  gave reasonable yields of rearranged products. In contrast, *t*-BuOSmI<sub>2</sub> catalyzed the conversion of epoxycyclooctane to cyclooctanone, whereas  $\text{Co}_2(\text{CO})_8$  or  $\text{MnI}_2$  were inactive [34].



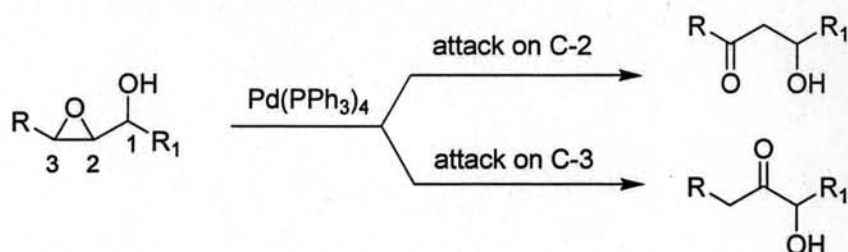
From the published data, it has been known that palladium(0) catalyzed the isomerization of epoxides to carbonyl compounds. In 1980 Suzuki and colleagues reported that  $\text{Pd}(\text{PPh}_3)_4$  catalyzed reaction of  $\alpha,\beta$ -epoxy ketones leading to  $\beta$ -diketones. Addition of the bidentate auxiliary ligand (dpe) was necessary to obtain reasonable reaction rate and to avoid metal precipitation so that the  $\text{Pd}(0)$  catalyst gave a high turnover. Strained epoxides appeared to undergo the isomerization facily [35].



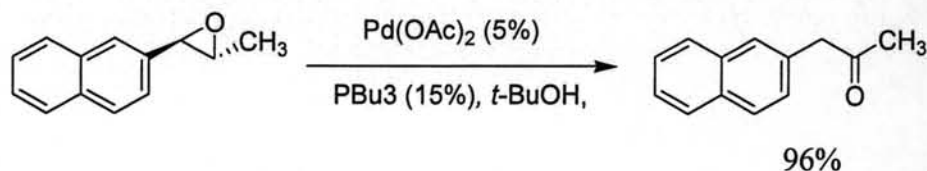
In continuation to further explore the use of  $\text{Pd}(\text{PPh}_3)_4$  catalyst became interested in finding out its behaviour. In 1986 Vankar and colleagues reported that the use of  $\text{Pd}(\text{PPh}_3)_4$  in bringing about the isomerization of 2,3-epoxy alcohols into  $\beta$ -hydroxy ketones.



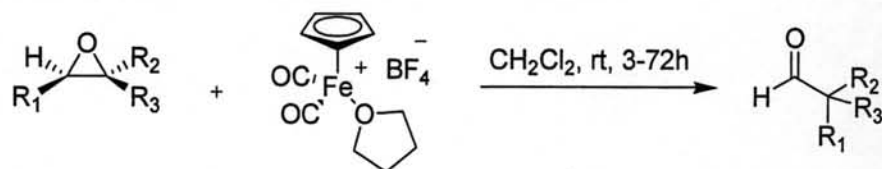
Epoxy alcohols derived from aliphatic systems did not undergo any isomerization at all indicating clearly that a hydroxyl group was not sufficiently powerful to make C-2 electrophilic enough for Pd(0) attack. On the other hand, epoxy alcohols, possessing an aryl group (R= aryl group), underwent isomerization leading to the formation of  $\alpha$ -hydroxy ketones. But when both R and R<sub>1</sub> were aryl groups the formation of  $\alpha$  as well  $\beta$ -hydroxy ketones took place, the ratio of which depended upon the nature of the substituents on R [36].



In 1997 Kulasegaram and Kulawiec reported isomerization of aryl-substituted epoxides bearing multiple methyl substituents on the epoxide ring in presence of Pd(OAc)<sub>2</sub>/PR<sub>3</sub> (R= *n*-Bu, Ph) to form the corresponding benzylic aldehyde or ketone, with complete regioselectivity for the carbonyl compound formed *via* cleavage of the benzylic C-O bond. In both reactions, the products were formed in high yield under mild conditions and depended on the substitution pattern of epoxides [37, 38].

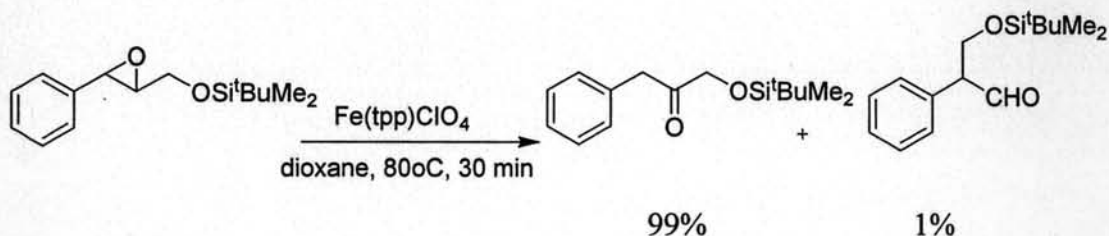


Many literatures addressed the isomerization reactions of epoxides to the corresponding aldehyde and/or methyl ketones by iron complexes. In 1998 Picione and colleagues reported that the iron Lewis acid  $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2(\text{THF})^+\text{BF}_4^-]$  catalyzed the ring opening isomerization of aryl substituted epoxides to aldehydes in high yield. The iron Lewis acid was relatively inexpensive, easy to synthesize, and stable for an indefinite period of time in a refrigerated area, making a new efficient synthesis of diaryl-substituted aldehydes available [39].

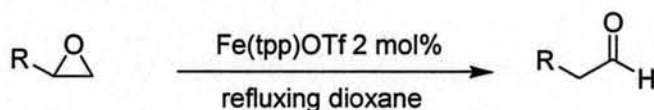


The development of novel and synthetically useful chemical properties of metalloporphyrins worked as a mild and characteristic Lewis acid catalyst prompted

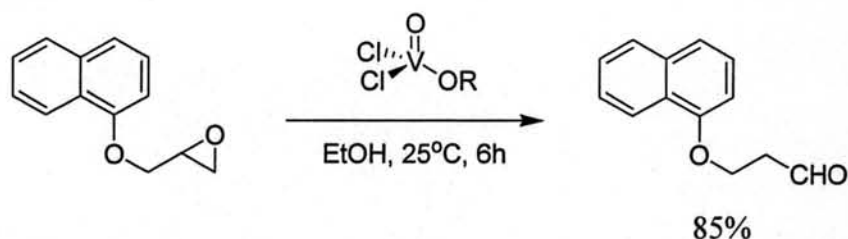
several research groups to explore the potential of electron-deficient metalloporphyrins as a catalyst for the rearrangement of epoxides. For instance in 1996 Takanami and colleagues reported iron(III) tetraphenylporphyrin,  $\text{Fe}(\text{tpp})\text{ClO}_4$  is an efficient and highly regioselective catalyst for the isomerization of various epoxides to carbonyl compounds [40].



Moreover, in 1999 Suda and colleagues reported the regioselective rearrangement of monoalkyl-substituted epoxides into aldehydes by  $\text{Fe}(\text{tpp})\text{OTf}$ . The total yield and regioselectivity of the products in the rearrangement were independent of the chain length of the epoxides used [41].

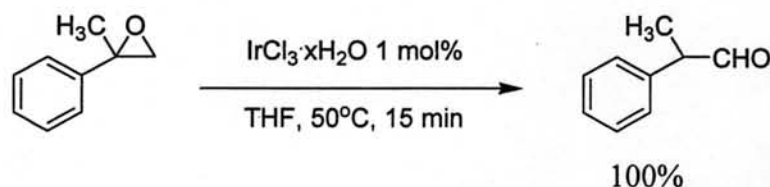


In 2000 Martínez and colleagues reported that high valence vanadium complexes induced the selective rearrangement of epoxides. The monosubstituted epoxides were isomerized with complete regioselectivity each forming a single carbonyl compound exclusively.



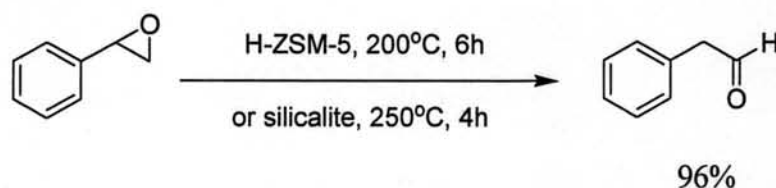
Under their conditions, the rearrangement of epoxides by vanadium complex, addition to the C-O bond of mono-substituted and 1,1-disubstituted epoxides promoted their rupture, and hydrogen migration occurred selectively producing the corresponding aldehydes [42].

In 2003 Karamé and colleagues reported that the first use of an iridium species as regioselective catalyst for the rearrangement of epoxides. The hydrated iridium complex ( $\text{IrCl}_3 \cdot x\text{H}_2\text{O}$ ) used was very stable and the reaction could be run under mild reaction conditions (no inert atmosphere or high temperature are required) [43].

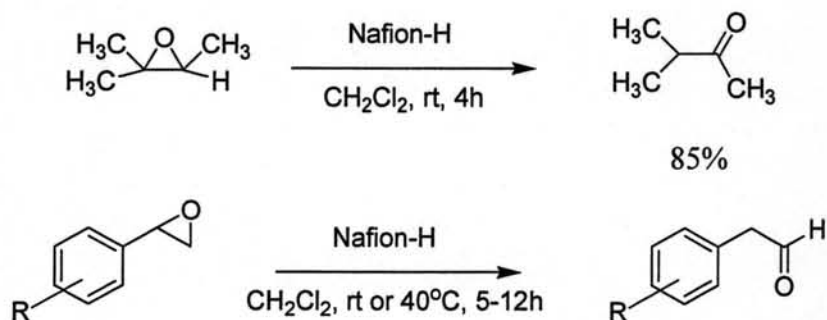


### 1.2.2 By heterogeneous catalysts

An important role in organic synthesis of heterogeneous catalysts was increasingly playing the same as homogeneous catalysts. For instance in 1988 Paparatto and Gregorio reported the use of H-ZSM-5 zeolite and silicalite as catalysts to convert styrene oxide to phenylacetaldehyde in almost quantitative yield. The reactions are carried out in a fixed bed catalytic reactor fed by a gaseous mixture of reagent and steam [44].

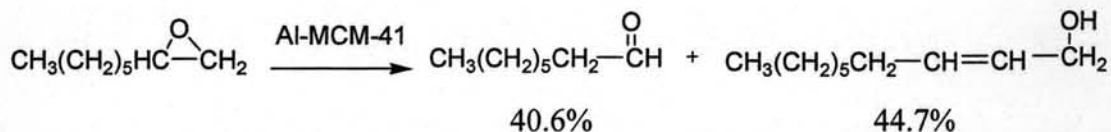


In 1999 Prakash and colleagues reported that Nafion-H, a perfluorinated resin sulphonic acid was found to be an efficient and simple catalyst for the isomerization of epoxides to ketones or aldehydes depending on the nature of the substituents on the epoxide carbons. The reaction was very straightforward which gave the products in high yield. Isoamylene oxide gave isopropyl methyl ketone and styrene oxide and its derivatives gave phenylacetaldehyde [45].



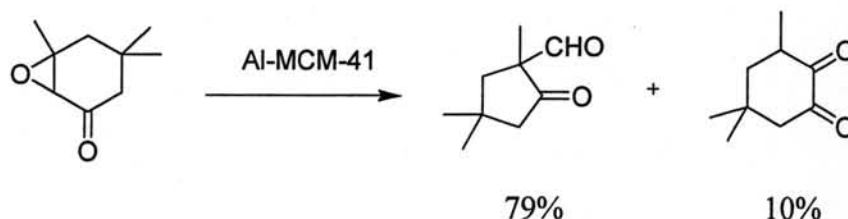
A number of zeolites, including H-ZSM-5, H-Beta, mordenite, *etc.* have been tested in the rearrangement of aromatic or cyclic alkane epoxides as well as epoxides with tertiary carbons linked to the oxirane ring. Some reports have been published on the use of zeolites as catalysts in the isomerization of small size aliphatic epoxides, such as ethylene and propylene oxides. In 2004 Serrano and colleagues reported that liquid phase rearrangement of long straight-chain epoxides over a variety of materials

with different structural features and acid properties, including amorphous, mesostructured and zeolitic catalysts. The structure and acid strength of the catalysts influenced strongly on the activity and product selectivity. Acid sites in the amorphous materials underwent a poor catalytic activity. Al-MCM-41 synthesized by a sol-gel method at room temperature expressed much higher activities than amorphous and zeolitic catalysts yielded selectivities to octaldehyde and octen-1-ols of 40.6% and 44.7%, respectively, with a high catalyst activity [46].



In the same year, Serrano and colleagues continuously reported that effect of the solvent in the liquid phase rearrangement of 1,2-epoxyoctane over Al-MCM-41 and Al-TS-1 catalysts. The solvent polarity influenced strongly on the activity and product selectivity. The catalytic activity decreased with the increasing of solvent polarity especially for Al-MCM-41 materials. The use of CH<sub>3</sub>CN as solvent yielded a low conversion of epoxide as a consequence of its basic character. Toluene displayed the best catalytic performance in regards to activity and selectivity towards valuable products, with both Al-TS-1 and Al-MCM-41 catalysts, in comparison to those obtained with more polar solvents [47].

In 2005 Serrano and colleagues ceaselessly reported that the first time the catalytic performance of Al-MCM-41 materials with different Si/Al molar ratios on the liquid-phase isophorone oxide rearrangement. The main rearrangement products were the keto aldehyde and the  $\alpha$ -diketone. The best catalytic performance in terms of epoxide conversion was obtained for a catalyst with a molar Si/Al ratio around 40 due to the proper contribution of acid site concentration and pore size. However, irrespective of the aluminium content of the catalysts and the reaction temperature, the selectivity to the desired keto aldehyde was around 80% [48].

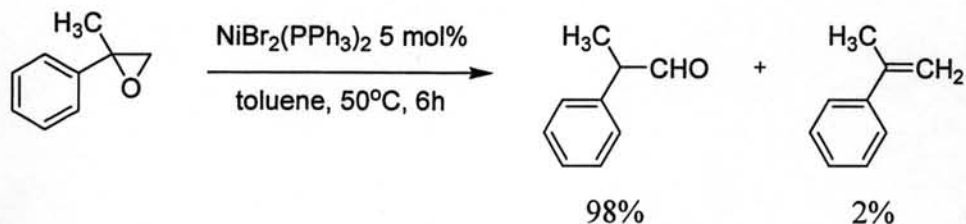
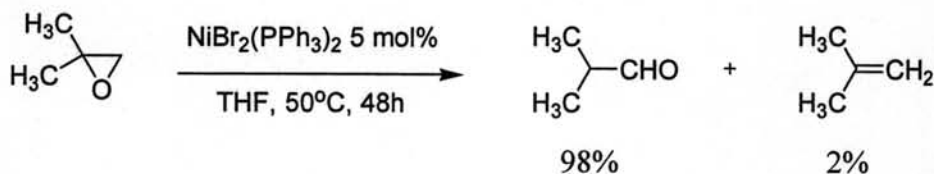
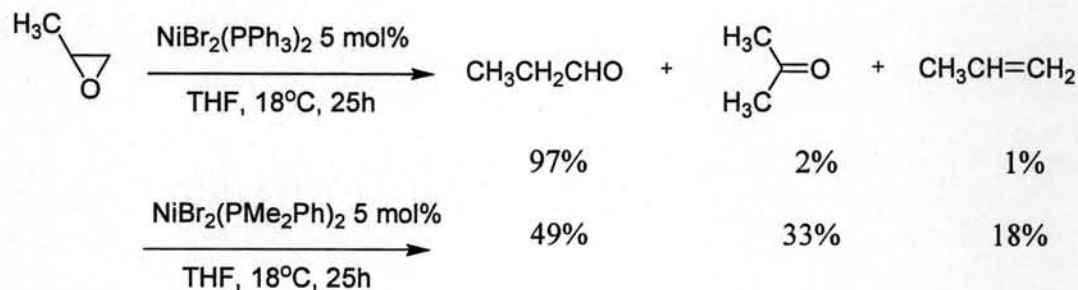


Recently, the use of zeolites as catalysts for the isomerization of epoxide was of increasing interest. Mordenite is one of the zeolites catalogued as a strong acid

zeolite. In 2005 Salla and colleagues reported that isomerization of styrene oxide to phenylacetaldehyde by fluorinated mordenites using microwaves [49].

### 1.3 Nickel-catalyzed rearrangement in organic synthesis

From previous literatures, although several articles of homogeneous catalytic rearrangement reactions have been reported, only a few studies concerned with cheap, simple, selective and efficient rearrangement of epoxides by nickel catalysts have been discovered. For instance in 1986 Miyashita and colleagues reported that  $\text{NiBr}_2(\text{PPh}_3)_2$  could catalyze ring opening isomerization of 1,2-epoxypropane to propionaldehyde under mild conditions, while  $\text{NiBr}_2(\text{PMe}_2\text{Ph})_2$  gave a mixture of acetone, propylene and aldehyde.  $\text{PPh}_3$  was inactive for deoxygenation of epoxide under the same conditions. Regioselectivity for a C-O bond cleavage of epoxides was determined by the nature of the ligand coordinated to the metal center and the substitution pattern of epoxides [50].



The development of more efficient homogeneous catalyst for the rearrangement of epoxides has been an important goal for organic synthesis and industrial point of view. Nickel catalysts have been reported as an efficient catalyst in the epoxide rearrangement. Although there have been few investigations on the  $\text{NiBr}_2\text{L}_2$  ( $\text{L} = \text{PPh}_3, \text{PMe}_2\text{Ph}, \text{PEt}_3$  and  $\text{PCy}_3$ ), there was no report on the utilization of other nickel reagents for catalytic rearrangement of epoxides. Catalytic efficiency of these complexes was screened using the rearrangement of styrene oxide as a model substrate reaction. After the reaction was optimized, it would be apply to a variety of different epoxides.

#### **1.4 The goal of this research**

The aims of this research can be summarized as follows:

1. To study the optimum conditions for styrene oxide rearrangement by using nickel reagents.
2. To apply the optimum conditions for the rearrangement of some selected epoxides.