CHAPTER III

RESULTS AND DISCUSSION

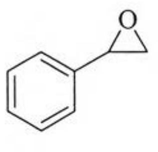
The rearrangement of epoxides to ketones or aldehydes is one of viable methodology to manipulate the corresponding carbonyl compounds. One of the most frequently used atom economical reactions of epoxides is their rearrangement to carbonyl compounds, and a number of reagents including a variety of Lewis acids have been elaborated for this purpose. This research demonstrates a new method for high-yielding, selective rearrangement of epoxides to ketonic compounds using iron salts and complexes. Advantages of this method include the highly catalytic nature of the reagent, low toxicity, low cost, commercially available, rapid reaction rate and insensitivity to air and moisture. Styrene oxide (**1**) was selected as a model substrate for conditions optimization. In general, the system was composed of iron salt or complex as a reagent and THF was mostly employed as a solvent. Other substrates including cyclohexene oxide, 1-dodecene oxide, butyl glycidyl ether, *tert*-butyl glycidyl ether, 4-chlorostyrene oxide, 4-methylstyrene oxide, 4-methoxylstyrene oxide, α-methyl styrene oxide, β-methylstyrene oxide, *trans*-stilbene oxide, benzalacetophenone oxide, methyl *trans*-3-(4-methoxyphenyl)-glycidate, 1,1-diphenylethylene oxide and anethole oxide were selected as chemical probes to observe the regioselectivity of the reaction. To our best knowledge the utilization of iron salts and complexes, particularly $FeCl_3$ and $Fe(acac)_3$ have never been reported in chemical literature for the rearrangement of epoxides.

3.1 The optimum conditions for the rearrangement of styrene oxide by $FeCl_3$

In fact, there are various factors that need to be evaluated to optimize the rearrangement explored such as type and amount of iron salt and complex, atmosphere, time and temperature. Styrene oxide was chosen as a chemical model for this preliminary study.

3.1.1 Effect of the amount of $FeCl_3$ on styrene oxide rearrangement

The rearrangement of epoxides catalyzed by metal complex was emerging as a synthetically useful transformation **[41]**. For utilizing a wide variety of metal complexes for rearrangement, Lewis acids were found to be effective as explicitly seen from many successful reports **[42]**. Although there have been some investigations on the use of metal complexes for the rearrangement of epoxides, there was no report of utilizing $FeCl_3$ as a reagent. In this study the effort was thus focused on screening of $FeCl_3$ for the epoxide rearrangement. Under this particular condition, the rearrangement of styrene oxide (Table 3.1) provided acetophenone **(2)** as a major product, while phenylacetaldehyde **(3)** and 2-chloro-2-phenylethanol **(4)** being minor ones.



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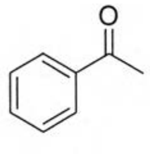

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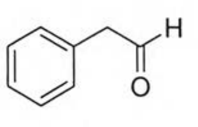

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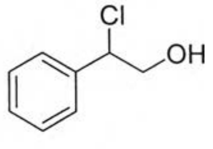

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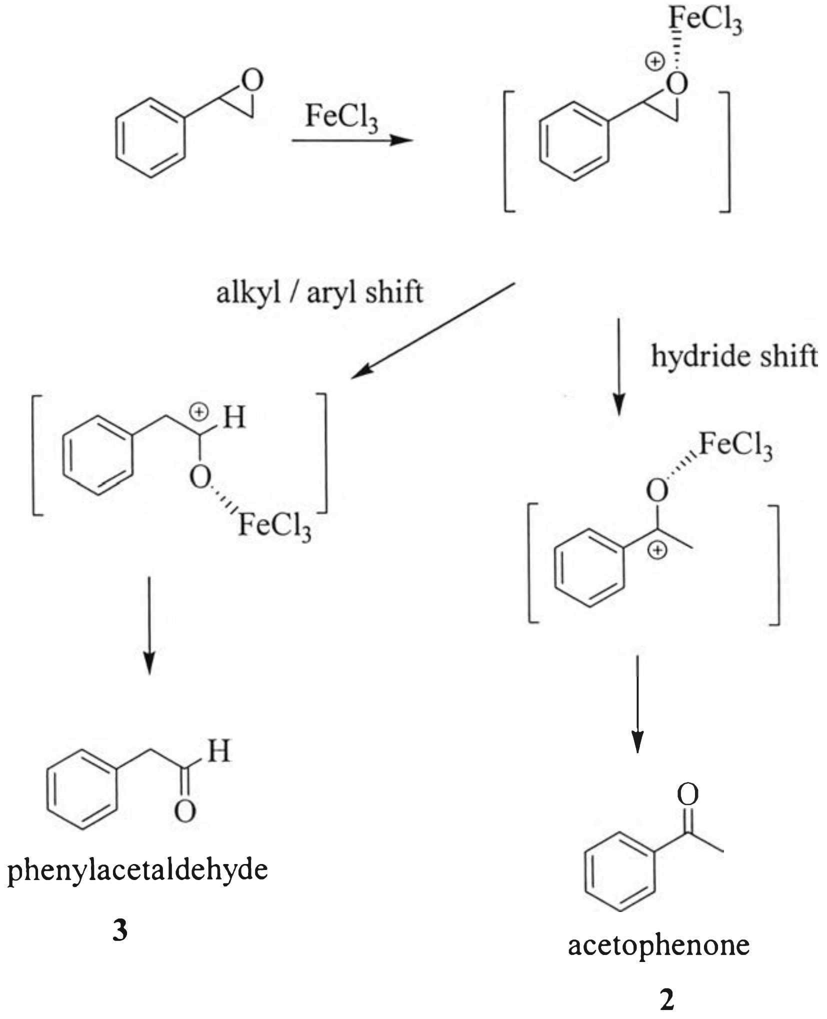
Table 3.1 Effect of the amount of $FeCl_3$ on styrene oxide rearrangement

Entry	**$FeCl_3$ (mmol)**	**%Substrate (recovered)**	**%Yield**			**Σ (%product)**	**MB**
			2	**3**	**4**		
1	0	100	-	-	-	-	100
2	0.05	58	40	5	4	49	107
3	0.5	37	54	8	6	68	105
4	1.0	24	62	11	5	78	102

reaction conditions: styrene oxide (1 mmol), THF (5 mL), room temp (30 °C) under N_2 atmosphere for 15 min

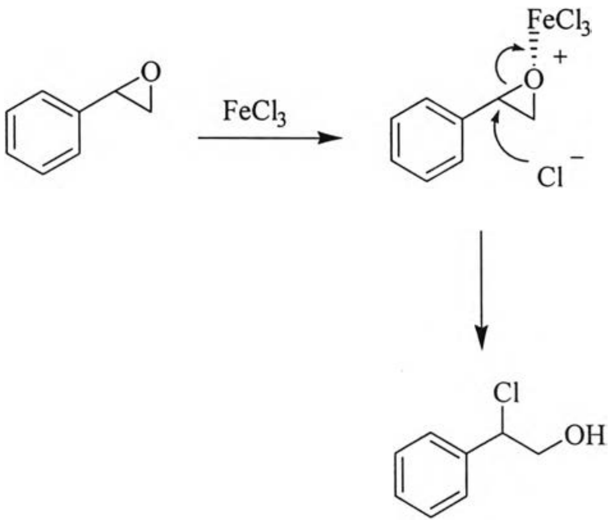
The observations obtained from Table 3.1 provided an interesting result. A blank experiment clearly revealed that in the absence of $FeCl_3$, no reaction occurred. Under standard conditions, $FeCl_3$ was found to be an efficient reagent yielding acetophenone as a major product. Increase amount of $FeCl_3$ did affect on the yield of the desired product.

In principle, two types of rearrangements are possible to take place for substituted epoxides depending on the migration pathways following Lewis acid promoted C-O bond cleavage (Scheme 3.1). The rearrangement of stryrene oxide with hydride or alkyl/aryl migration would lead to ketone **2** or aldehyde **3**, respectively. Cabocation formed in the intermediate step of hyhride migration was more stable than that of alkyl/aryl migration possibly due to aryl substituent stabilization.



Scheme 3.1 Proposed mechanistic pathway of the rearrangement of styrene oxide to acetophenone (**2**) and phenylacetadehyde (**3**)

Another detected product, 2-chloro-2-phenylethanol **(4)** was identified by GC compared with authentic sample. It was believed to take place *via* another mechanism. The chloride ion acting as a nucleophile was attacked at α-position of styrene oxide coordinated with iron complex in the same fashion as in S_N1 mechanism of nucleophilic ring opening of substituted epoxide (Scheme 3.2).



2-chloro-2-phenylethanol

4

Scheme 3.2 Proposed mechanistic pathway for the formation of 2-chloro-2-phenylethanol (**4**)

$FeCl_3$ was thus selected to employ as a reagent for the rearrangement of epoxide due to its low toxic, high efficiency, and easily removal from the attained product.

3.1.2 Effect of reaction atmosphere on styrene oxide rearrangement

According to the reaction procedures cited in many literatures, the epoxide rearrangement reaction was generally performed under N_2. It seemed that the rearrangement may need to proceed under an inert condition. On the account of $FeCl_3$ as a reagent in rearrangement, the amount of the desired product under various atmospheric conditions could be observed as presented in Table 3.2.

Table 3.2 Effect of reaction atmosphere on styrene oxide rearrangement

Entry	Atmosphere	% Substrate (recovered)	%Yield			%Σ (product)	MB
			2	3	4		
1	air	53	34	4	3	41	94
2	N_2	58	40	5	4	49	107
3	O_2	64	36	4	2	42	106

reaction conditions: styrene oxide (1 mmol), $FeCl_3$ (0.05 mmol), THF (5 mL),
room temp (30 °C) for 15 min

2 : acetophenone, **3** : phenylacetaldehyde, **4** : 2-chloro-2-phenylethanol

From Table 3.2, it could be noticed that the rearrangement could proceed under either air N_2, or O_2 atmosphere, without significantly major difference in the yield of product. Therefore, the rearrangement employing $FeCl_3$ did not require the use of an inert atmosphere. According to the results shown above, the reaction conditions carried out under air atmosphere were selected as a standard condition for the rearrangement of styrene oxide for further investigation.

3.1.3 Study on the effect of reaction time and temperature on styrene oxide rearrangement catalyzed by $FeCl_3$

Time and temperature are another important factor for condition optimization on the rearrangement of epoxides. The rearrangement of styrene oxide utilized $InCl_3$, for instance, was successfully performed within 15 min under mild conditions to yield the desired products, phenylacetaldehyde [**19**]. Therefore the effects of reaction time and temperature on the rearrangement of styrene oxide catalyzed by $FeCl_3$ were thoroughly carried out and the outcomes are tabulated in Table 3.3 and Fig 3.1.

Table 3.3 Effect of reaction time and temperature on styrene oxide rearrangement

Entry	Time (mins)	%Styrene oxide (recovered)	%Yield 2	3	4	Σ (product)	MB
1	5	76	18	1	1	20	96
2	15	53	34	4	3	41	94
3	30	50	40	4	3	47	97
4	30	38	49	9	6	64	102
5	45	45	48	3	5	56	101
6	60	32	49	6	4	59	91
7	120	35	49	5	3	57	92
8	180	44	48	5	3	56	100

reaction conditions: styrene oxide (1 mmol), $FeCl_3$ (0.05 mmol), THF (5 mL), room temp (30 °C)

* reflux at 70 °C

2 : acetophenone, **3** : phenylacetaldehyde, **4** : 2-chloro-2-phenylethanol

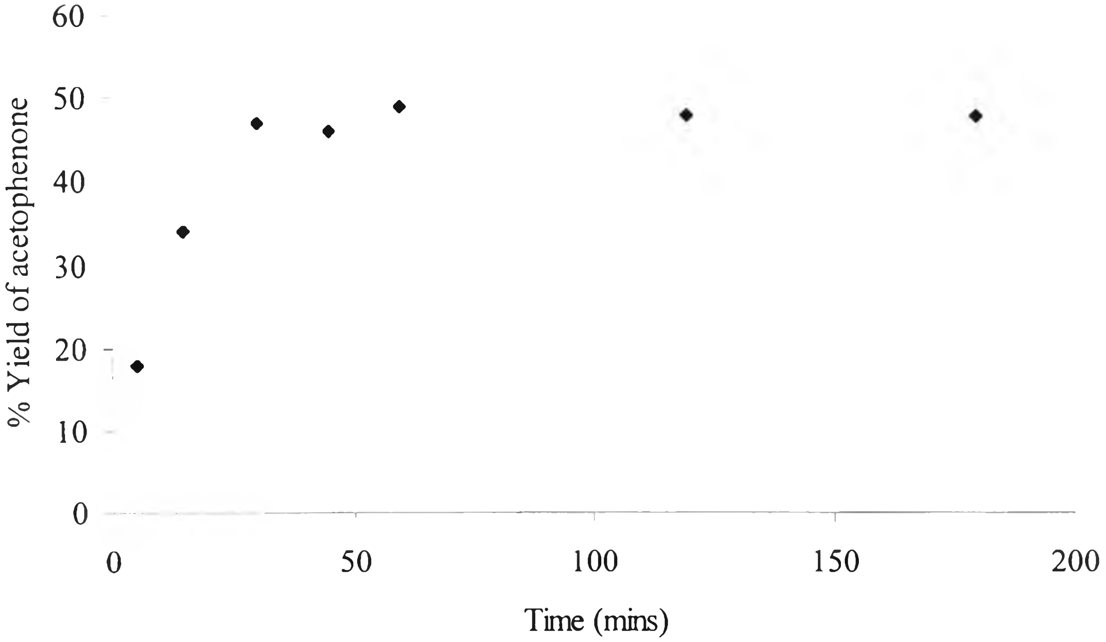


Figure 3.1 Effect of reaction time on styrene oxide rearrangement at room temperature catalyzed by $FeCl_3$

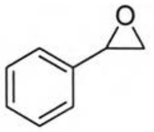
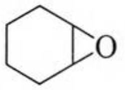
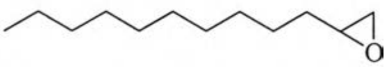
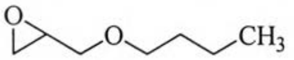
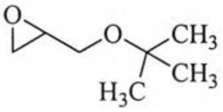
As noticed from Table 3.3 and Fig 3.1, it was clearly seen that the increasing of reaction time affected on the increment yield of the desired product (entries 1-3 and 5-8). Increasing of temperature from room temperature (30 °C) to refluxing THF (70 °C) was also affected on the increment of the yield of the desired product (entry 5). It could thus be summarized that the advantage of this developed system that the reaction could proceed in a short period of time and the temperature also accelerate the rate of the reaction.

According to the results shown above, the reaction time of 30 min at 70 °C (refluxing THF) was selected as an appropriate condition for the rearrangement of styrene oxide for additional investigation.

3.2 Effect of $FeCl_3$ on selected epoxides

Under the optimized conditions as discussed in section 3.1, styrene oxide could be transformed to acetophenone in high yield. This developed system was therefore attempted to test for a variety of epoxides. Cyclohexene oxide, 1-dodecene oxide, butyl glycidyl ether and *tert*-butyl glycidyl ether were used as a substrate. The outcome of the rearrangement of selected epoxides is summarized in Table 3.4.

Table 3.4 Rearrangement of selected epoxides by $FeCl_3$

Entry	**Substrate**	**%Substrate**	**%Yield**			**MB**
		(recovered)	**2**	**3**	**4**	
1		38	49	9	6	102
2		100	-	-	-	100
3		102	-	-	-	102
4		99	-	-	-	99
5		102	-	-	-	102

reaction conditions: substrate (1 mmol), $FeCl_3$ (0.05 mmol), THF (5 mL), 70 °C for 30 min

2 : acetophenone, **3** : phenylacetaldehyde, **4** : 2-chloro-2-phenylethanol

Table 3.4 presents the outcomes of the rearrangement of selected epoxides under developed reaction conditions. These data clearly showed that $FeCl_3$ could be carried out for the rearrangement of epoxide by H-migration, only styrene oxide being transformed to produce acetophenone in moderate yield (entry 1). Nevertheless, the rearrangement of cyclohexene oxide, 1-dodecene oxide, butyl glycidyl ether and *tert*-butyl glycidyl ether reaction was not occur (entries 2-5).

It can thus be summarized that $FeCl_3$ was a selective reagent for the rearrangement of aryl-substituted epoxide. This was probably unique regioselectivity of this iron-mediated reaction and made this reaction far superior to the use of nonselective BF_3-etherate [**17**] or $InCl_3$ reagents as cited in the literature [**19**].

3.3 Effect of types of iron complexes on styrene oxide rearrangement

Although $FeCl_3$ was an efficient reagent for this reaction, it possessed low selectivity of the desired ketone product with the product ratio of 6:1:1 (ketone:aldehyde:alkyl chloride). Various types of iron salts and complexes were screened to observe the product distribution derived from the rearrangement of styrene oxide. The effects of iron salts and complexes on styrene oxide rearrangement are consequently examined and the results are presented in Table 3.5.

Table 3.5 Effect of iron salts and complexes on styrene oxide rearrangement

Entry	Iron salt or complex	%Styrene oxide (recovered)	Product (%)			MB
			2	**3**	**4**	
1	$FeCl_3$	38	49	9	6	102
2	$FeCl_3.6H_2O$	38	48	5	5	96
3	$Fe(TCA)_3$	72	24	-	-	96
4	$Fe(TFA)_3$	78	26	-	-	104
5	Fe(palmitate)	86	11	-	-	97
6	$Fe(naphthenate)_3$	90	11	-	-	101
7	$Fe(stearate)_3$	82	18	-	-	100
8	$Fe(picolinate)_3$	84	19	-	-	103
9	$Fe(4\text{-nitrobenzoate})_3$	86	18	-	-	104
10	Fe(porphyrin)	64	35	-	-	99
11	$Fe(salen)_2O$	92	10	-	-	102
12	Fe(salen)Cl	85	15	-	-	100
13	$Fe(BZA)_3$	81	22	-	-	103
14	$Fe(acac)_3$	43	59	-	-	102
15	Ferrocene	87	9	-	-	96

reaction condition: styrene oxide (1 mmol), iron salt or complex (0.05 mmol),
THF (5 mL), temp (70 °C) for 30 min

2 : acetophenone, **3** : phenylacetaldehyde, **4** : 2-chloro-2-phenylethanol

From Table 3.5, iron salts and complexes used in this research could be classified into five groups. The first group included iron salts: $FeCl_3$ (anhydrous) and $FeCl_3.6H_2O$. This class of iron could assist the rearrangement of styrene oxide under mild conditions yielding the desired product in moderate yield (entries 1 and 2). It could also be seen that the hydrated forms of iron(III) chloride could be utilized comparably with anhydrous iron salt for this reaction. However, the drawback of these two reagents as aforementioned was low selectivity of the product distribution obtained. The second group was iron carboxylate complexes: $Fe(TCA)_3$, $Fe(TFA)_3$, $Fe(palmitate)_3$, $Fe(naphthenate)_3$, $Fe(stearate)_3$, $Fe(picolinate)_3$ and $Fe(4\text{-nitrobenzoate})_3$. This class of iron complexes exhibited high selectivity towards the formation of the desired product, acetophenone (**2**) (entries 3-9). Nevertheless, the yield of product was poor. One of the main reasons may be because these iron complexes could not be homogeneously dissolved in THF. The third group included other types of iron complexes: Fe(porphyrin), $Fe(salen)_2O$ and Fe(salen)Cl. This class of iron complex gave only small amount of acetophenone (**2**). It could also be observed that highly steric-hindrance ligand influenced the yield of the desired product (entries 10-12). The fourth group was 1,3-dicarbonyl iron complexes: $Fe(BZA)_3$ and $Fe(acac)_3$. The potential iron complex was lucidly observed in the case of using $Fe(acac)_3$ which gave the desired product in good yield (entry 14). The last group of reagent was organometallic reagent: ferrocene. This reagent displayed low efficiency to the rearrangement due to steric hindrance (entry 15) [**44**].

According to the results shown above, $Fe(acac)_3$ was selected to use as a reagent for further examination.

3.4 Study on the optimum conditions for the rearrangement of styrene oxide by $Fe(acac)_3$

The first target catalyst $FeCl_3$ was selected as a convenient reagent for the rearrangement of epoxides; however, the drawback of using this reagent invariably low selectivity upon product formation. Stemmed from the preliminary results mentioned in section 3.3, the most suitable reagent disclosed was $Fe(acac)_3$. Therefore, this iron complex would be utilized as a reagent to optimize the conditions for the rearrangement of styrene oxide. Variable parameters studied included time and temperature, amount of $Fe(acac)_3$ and solvent.

3.4.1 Effect of reaction time and temperature on the rearrangement of styrene oxide by Fe(acac)$_3$

With the aim to maximize the yield of the desired product, both reaction time and temperature were carefully examined. The results are shown in Table 3.6.

Table 3.6 Effect of reaction time and temperature on the rearrangement of styrene oxide by Fe(acac)$_3$

Entry	**Time (mins)**	**% Styrene oxide (recovered)**	**% Yield**	**MB**
			2	
1	7	74	24	98
2	15	59	41	100
3	30	56	47	103
4	30*	46	59	105
5	45	55	47	102
6	60	58	47	105
7	120	56	46	102

reaction condition: styrene oxide (1 mmol), Fe(acac)$_3$ (0.05 mmol), THF (5 mL)

* reflux at 70 °C

2 : acetophenone

As noticed from Table 3.6, the rearrangement of styrene oxide assisted by Fe(acac)$_3$ was completed within a short period of time approximately 30 min (entry 3). The highest yield of acetophenone was accomplished in refluxing THF (70 °C) (entry 4). It could be summarized that the advantage of this reagent was the short reaction time needed to complete the reaction and temperature had a profound effect on the reaction.

According to the results shown above, reaction time of 30 min and temperature 70 °C (refluxing THF) were selected and kept constant as a standard condition for the rearrangement of styrene oxide for further investigation.

3.4.2 Effect of the amount of Fe(acac)$_3$ on rearrangement of styrene oxide

A simple and efficient procedure for the rearrangement of styrene epoxide facilitated by Fe(acac)$_3$ as presented in Table 3.6 has been developed. One of the advantages of this reaction was that it proceeded selectively to yield exclusively the desired product (acetophenone). The effect of the amount of Fe(acac)$_3$ on the rearrangement of styrene oxide was thoroughly examined and the results are tabulated as shown in Table 3.7.

Table 3.7 Effect of the amount of Fe(acac)$_3$ on styrene oxide rearrangement

Entry	Amount of Fe(acac)$_3$ (mmol)	%Styrene oxide (recovered)	%Yield	MB
			2	
1	0.05	56	47	103
2	0.1	41	55	96
3	0.3	32	68	100
4	0.5	23	75	98
5	1.0	24	76	100
6	2.0	20	76	96

reaction condition: styrene oxide (1 mmol), THF (5 mL), room temp (30 °C) for 30 min

2 : acetophenone

Table 3.7 clearly reveals that the amount of Fe(acac)$_3$ was directly influenced the outcome of rearrangement of styrene oxide. Judging from the yield of the desired product, it was observed that increasing the amount of Fe(acac)$_3$ affected on the increment of the target product. Fe(acac)$_3$ 1 mmol was optimized for this particular reaction.

3.4.3 Kinetics study on the rearrangement of styrene oxide by Fe(acac)$_3$

The kinetics study on the rearrangement of styrene oxide using various amounts of Fe(acac)$_3$: 0.05, 0.3, 1.0 mmol was investigated. The kinetic analysis result of this reaction is presented in Fig 3.2.

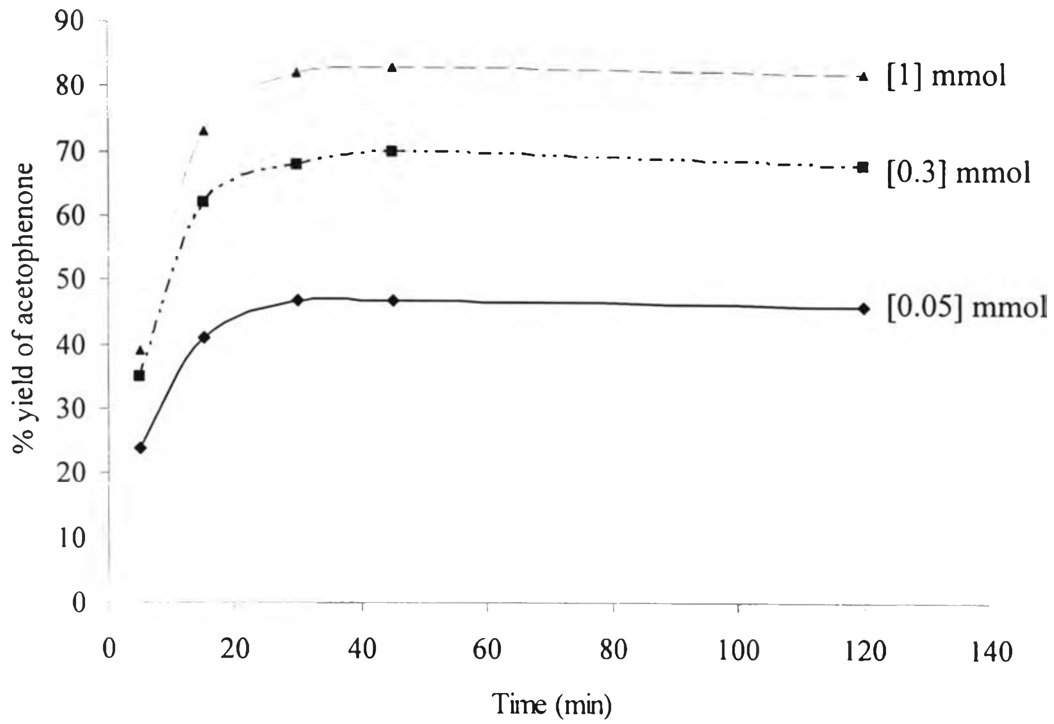


Figure 3.2 Kinetics study of the rearrangement on styrene oxide

Fig 3.2 displays the productivity of the desired product derived from the variation of the amount of Fe(acac)$_3$: 0.05, 0.3 and 1 mmol. Styrene oxide was converted to acetophenone in moderate to high yield. As proceeding, 30 min was taken as the most favorable reaction time at which the maximum yield of the rearrangement was occurred. The maximum yield was about 47%, 68% and 76% using Fe(acac)$_3$ 0.05, 0.3 and 1 mmol, respectively. The half-life of the rearrangement of styrene oxide by Fe(acac)$_3$ in each case was approximately 7 min. So this reaction was completely in short period of time.

It could be summarized that the amount of Fe(acac)$_3$ employed was markedly influenced on the yield of acetophenone.

3.4.4 Effect of solvent on styrene oxide rearrangement by Fe(acac)$_3$

From the experimental conditions described above, THF was used as a homogeneous medium. Several solvents were chosen to evaluate their compatibility with Fe(acac)$_3$ in the rearrangement of styrene oxide and to observe whether they could replace THF. The results of the variation of solvents such as toluene, acetonitrile, dichloromethane, 1,4-dioxane, hexane, EtOAc and 1,2-dichloroethane in the rearrangement of styrene oxide using Fe(acac)$_3$ as a reagent are presented in Table 3.8.

Table 3.8 Effect of solvent on styrene oxide rearrangement

Entry	Solvent	%Styrene oxide (recovered)	%Yield 2	MB
1	THF	53	47	100
2	THF(dry)	52	46	98
3	Toluene	50	51	101
4	dichloromethane	47	48	95
5	acetronitrile	55	53	108
6	1,4-dioxane	54	47	101
7	Hexane	49	57	106
8	EtOAc	45	56	101
9	1,2-dichloroethane	62	42	104

reaction condition: styrene oxide (1 mmol), Fe(acac)$_3$ (0.05 mmol), solvent (5 mL), room temp (30 °C) for 30 mins

2 : acetophenone

Among several diverse solvents studied, THF was the first solvent chosen as a reaction medium because it could dissolve both iron complex and a substrate. Comparison with THF, %yield of product from the reaction performed in dry THF was close to that obtained from commercial THF (entries 1 and 2). It was thus clearly seen that moisture in solvent did not affect on the rearrangement of epoxides. According to the literature reviews, toluene and dichloromethane were reported to be employed as a reaction solvent on the rearrangement of aryl-substituted epoxide by bismuth(III)oxide perchlorate yielding the corresponding (ketone and aldehyde) in high yield (70-90%) *(19)*. For example, the rearrangement of styrene oxide by bismuth(III)oxide perchlorate gave a major product, phenylacetaldehyde (**3**) 91% and a minor product, acetophenone (**2**) 5%. In addition, in this present study, it was found that %yield of the desired product in toluene and dichloromethane was comparable (entries 3 and 4). The rearrangement of epoxides under this developed conditions could also accomplishedly be performed in acetonitrile, 1,4-dioxane and 1,2-dichloroethane (entries 5, 6 and 9) giving the yield of the desired product comparable with that carried out in toluene and dichloromethane. Interestingly, non polar solvent such as hexane and slightly polar solvent EtOAc also served as a suitable solvent (entries 7 and 8). From the above results, it seemed that the polarity and the dielectric constant of the solvent do not have any close correlation with the rearrangement of epoxide.

From Table 3.8, hexane and EtOAc were uncovered with surprise to be the best solvents for the rearrangement of styrene oxide utilizing a catalytic amount of Fe(acac)$_3$. Gaining the information from previous experiments, increasing the amount of Fe(acac)$_3$ may assist the formation of the desired product, a series of experiments involving the increment of the amount of Fe(acac)$_3$ upon the efficiency of the reaction in three new finding media was carried out and the results are presented in Table 3.9.

Table 3.9 Effect of solvent and the amount of Fe(acac)$_3$ on styrene oxide rearrangement

Entry	**Solvent**	**%Styrene oxide (recovered)**	**%Yield**	**MB**
			2	
1	THF	24	76	100
2	hexane	17	86	103
3	EtOAc	17	85	102

reaction condition: styrene oxide (1 mmol), Fe(acac)$_3$ (1 mmol), solvent (5 mL), room temp (30 °C) for 30 mins

2 : acetophenone

Table 3.9 clearly reveals that EtOAc and hexane are efficient solvents for the rearrangement of styrene oxide, presumably having a bit advantage over THF due to their inexpensive, commercial and availability. It would then be curious whether a mixture of EtOAc and hexane would affect on this reaction. Various ratios of hexane and EtOAc as 1:9, 3:7, 1:1 and 7:3 were therefore examined. The results are accumulated as shown in Table 3.10.

Table 3.10 Effect of a mixture of hexane and EtOAc on styrene oxide rearrangement by $Fe(acac)_3$

Entry	**Solvent (EtOAc:Hex)**	**%Styrene oxide (recovered)**	**%Yield**	**MB**
			2	
1	1:0	17	85	102
2	0:1	17	86	103
3	1:9	22	76	98
4	3:7	20	82	102
5	1:1	13	90	103
6	7:3	22	70	92

reaction condition: styrene oxide (1 mmol), $Fe(acac)_3$ (1 mmol), solvent (5 mL), room temp (30 °C) for 30 mins

2 : acetophenone

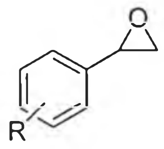
A mixture of EtOAc and hexane 1:1 seemed to be a right choice of combination. Reaction carried out in this matrix gave acetophenone in surprisingly quite good yield (entry 5).

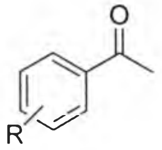
3.5 Rearrangement of selected aryl-substituted epoxides by $Fe(acac)_3$

After the reaction conditions were optimized using styrene oxide as a model substrate, the extended study involved the rearrangement of other aryl-substituted epoxides. Styrene oxide derivatives: α-methylstyrene oxide, 4-chlorostyrene oxide, 4-methylstyrene oxide, 4-methoxystyrene oxide and β-methylstyrene oxide were synthesized employing epoxidation with oxone [44]. Other epoxides included benzalacetone oxide, benzalacetophenone oxide and 1,1-diphenylethylene oxide were prepared by epoxidation upon treatment with H_2O_2 [45]

3.5.1 Rearrangement of styrene oxide derivatives

Styrene oxide with various substituents on an aromatic ring was the next chemical models to be explored. The main aim was to test the versatility of this developed method and to observe the relative reactivity of the substrate due to subtle changes in the electronic effects from the substituents.





1 R = H

4 R = 4-CH_3

5 R = 4-Cl

6 R = 4-CH_3O

2 R = H

7 R = 4-CH_3

8 R = 4-Cl

9 R = 4-CH_3O

Styrene oxide derivatives used in this study were not commercially available. These substrates were therefore needed to be synthesized employing oxone epoxidation *(44)* and purified by silica gel column chromatography. All styrene oxide derivatives were verified their identities by ^{1}H-NMR spectra. The ^{1}H-NMR spectrum of 4-methylstyrene oxide (**4**) (Fig 3.3) visualized a singlet signal of methyl protons adjacent to aromatic moiety at δ 3.80 (3H, s). Two terminal protons could be observed at δ 2.95 (1H, d, J = 4.02) and 2.70 (1H, m). The proton adjacent to aromatic moiety could be detected at δ 3.80 (1H, t, J = 3.56 Hz) and aromatic protons could be assigned at δ 7.11-7.39 (5H, m).

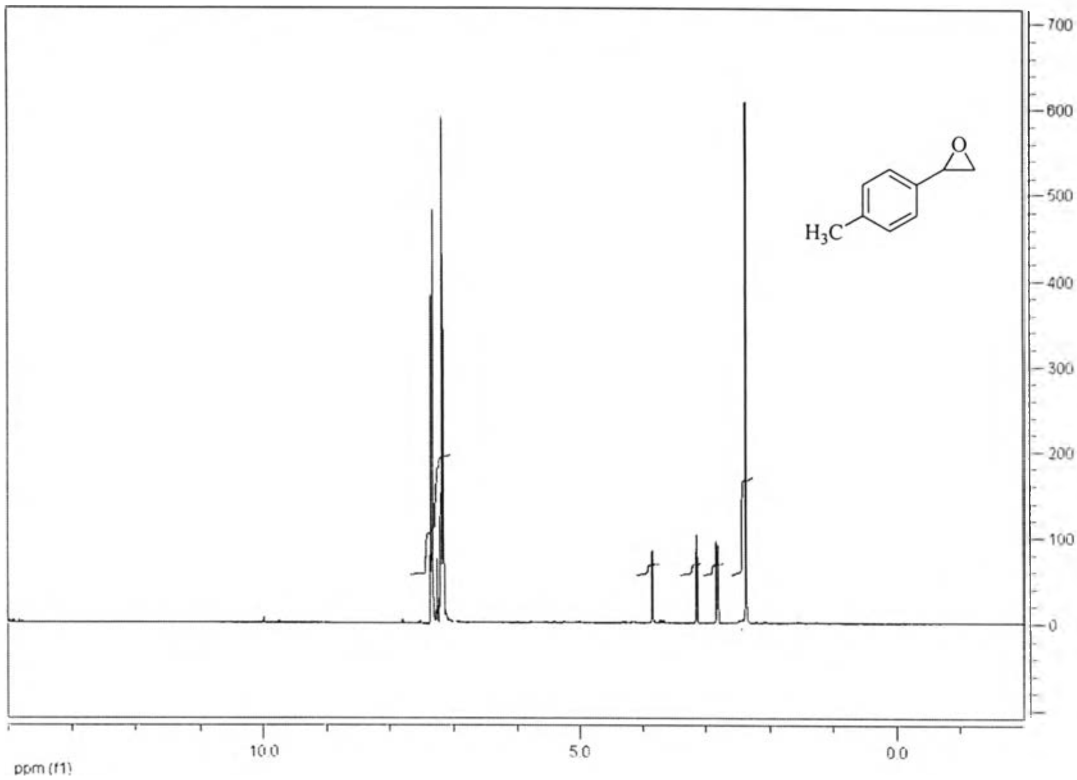


Figure 3.3 ^{1}H-NMR spectrum of 4-methylstyrene oxide (**4**)

The ^{1}H-NMR spectrum of 4-chlorostyrene oxide (**5**) visualized two terminal protons at δ 2.84 (1H, d, J = 4.11 Hz) and δ 3.18 (1H, d, J = 4.12 Hz). The proton adjacent to aromatic ring was detected at δ 3.87 (1H, t, J = 3.42 Hz) and aromatic protons could be observed around δ 7.24-7.35 (5H, m). The ^{1}H-NMR spectrum of 4-chlorostyrene oxide is presented in Fig 3.4.

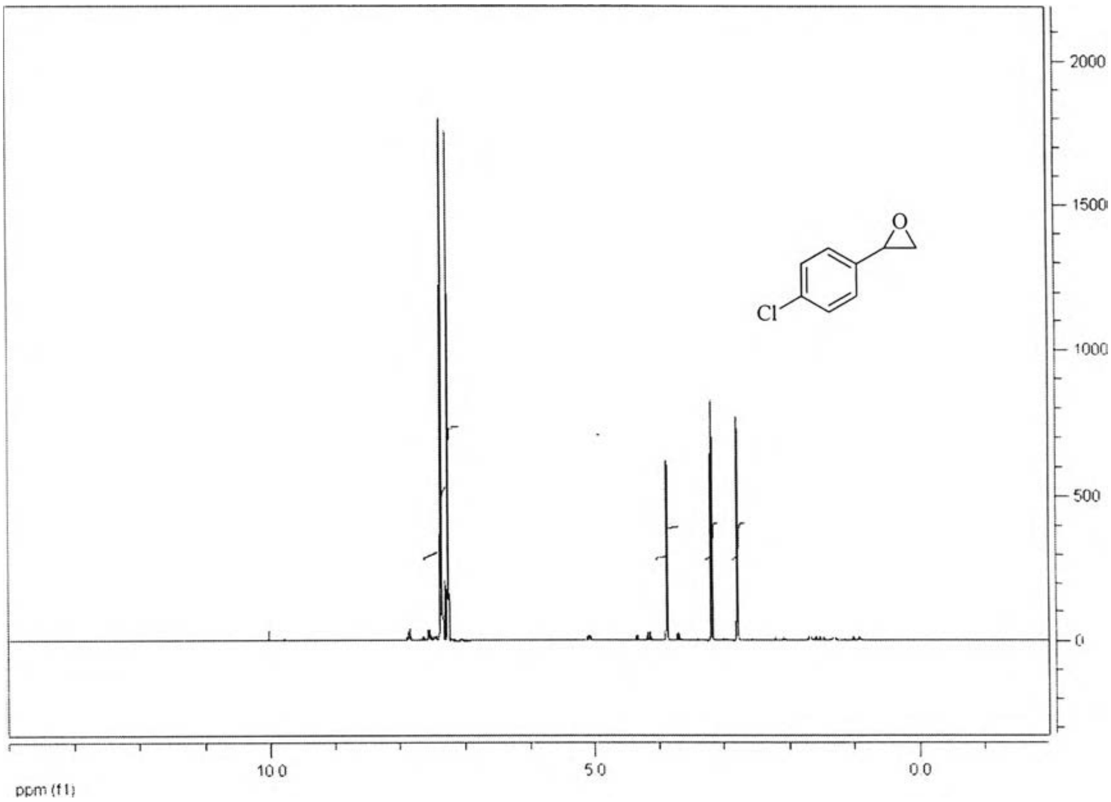


Figure 3.4 ^{1}H-NMR spectrum of 4-chlorostyrene oxide (**5**)

The ^{1}H-NMR spectrum of 4-methoxystyrene oxide (**6**) revealed the same pattern as those aforementioned two synthesized epoxides. Two protons at β-position could be visualized at δ 2.80 (1H, t, J = 4.80 Hz) and 2.70 (1H, m). A singlet signal of methoxy proton could be observed at δ 3.82 (3H, s). The proton next to aromatic ring could be detected around δ 3.90 (1H, t, J = 3.46 Hz) and aromatic protons could be assigned around δ 6.82-7.04 (5H, m). The ^{1}H-NMR spectrum of 4-methoxy oxide (**6**) is presented in Fig 3.5.

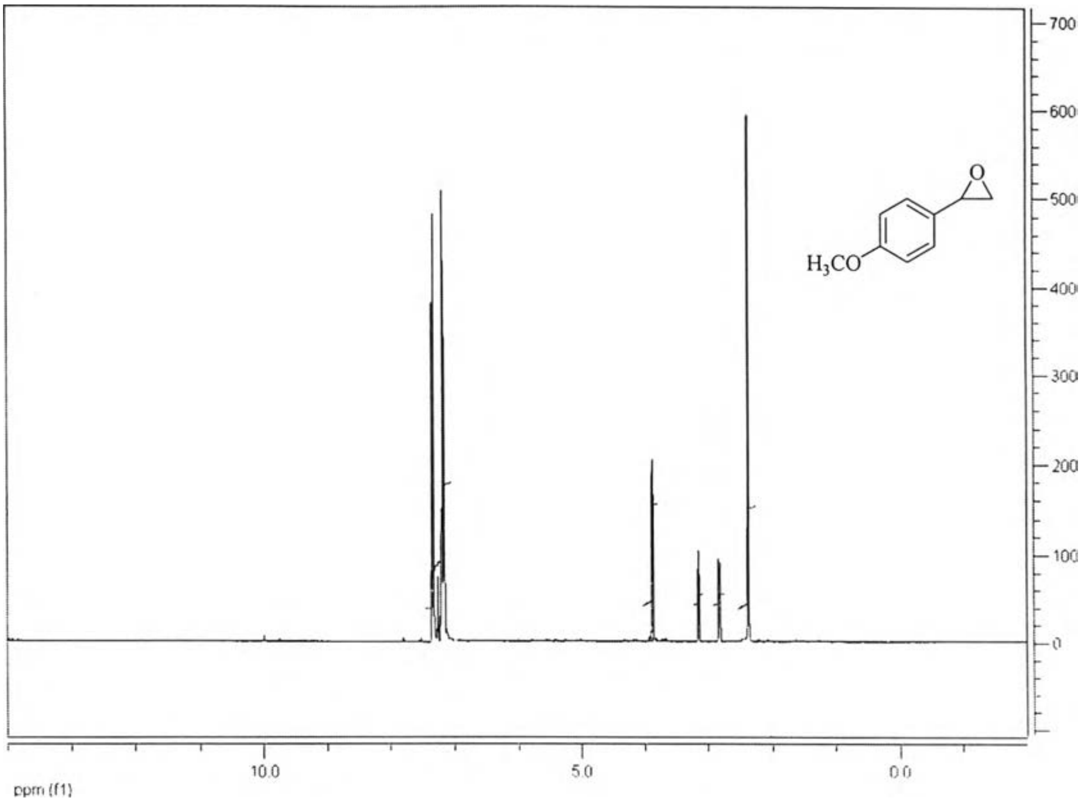


Figure 3.5 ^{1}H-NMR spectrum of 4-methoxystyrene oxide (**6**)

All styrene oxide derivatives synthesized were thus subjected to the rearrangement under the same reaction conditions generally used. The results are summarized in Table 3.11.

Table 3.11 Rearrangement of styrene oxide and its derivatives by Fe(acac)$_3$

Entry	Substrate	Time	%Substrate (recovered)	% Yield	MB
1	**1**	15 min	13	**2** (90)	103
2	**4**	15 min	43	**7** (48)	91
3	**4**	5 h	45	**7** (55)	100
4	**5**	15 min	45	**8** (51)	96
5	**5**	4 h	44	**8** (59)	103
6	**5***	15 min	20	**8** (77)	97
7	**5****	15 min	22	**8** (82)	104
8	**6**	15 min	42	**9** (63)	105
9	**6**	4 h	38	**9** (65)	103

reaction condition: substrate (1 mmol), Fe(acac)$_3$ (1 mmol), EtOAc :hexane 1:1 (5 mL) at 70 °C

* substrate 0.5 mmol was used

** substrate 0.1 mmol was used

Apparently, it was found that the rearrangement of styrene oxide and its derivatives gave a fair yield of desired ketone product. Styrene oxide derivatives underwent smooth rearrangement with exclusive migration of hydrogen group. The rearrangement of 4-methylstyrene oxide (**4**), 4-chlorostyrene oxide (**5**), 4-methoxystyrene oxide (**6**) utilized Fe(acac)$_3$ gave 4-methylacetophenone (**7**), 4-chloroacetophenone (**8**), 4-methoxyacetophenone (**9**) as a solely isolable product in 55% , 59% and 65% yield, respectively (entries 2-5, 8 and 9). Surprisingly %yield of these ketone products were lower than that observed for acetophenone. Nevertheless, %yield of desired product could be improved from 51% to 77% and 82% when using a smaller amount of substrate **5.** This finding was also essential for lifting up the yield of the unreactive substrates by employing excessive of iron complex reagent (entries 4, 6 and 7).

3.6 Competitive study on the rearrangement of styrene oxide and its derivatives

The effect of substituents of an aromatic ring on the rearrangement reaction was competitively studied using styrene oxide (**1**), 4-methylstyrene oxide (**4**), 4-chlorostyrene oxide (**5**) and 4-methoxystyrene oxide (**6**) as a substrate. The results are presented in Table 3.12.

Table 3.12 Competitive study on the rearrangement of styrene oxide and derivatives

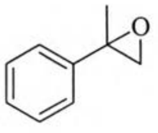
Entry	Substrate	% Yield		Relative reactivity
		(A)	(B)	(B)/ (A)
1	**1** vs **4**	**2** (42)	**8** (28)	0.66
2	**1** vs **5**	**2** (40)	**9** (32)	0.80
3	**1** vs **6**	**2** (42)	**10** (39)	0.92

reaction condition: substrate (1 mmol each), Fe(acac)$_3$ (1 mmol), EtOAc:hexane 1:1 (5 mL), temp (70°C) for 15 min

From Table 3.12, the reactivity of each styrene oxide derivative was compared with that of styrene oxide. It was observed that the rearrangement of styrene oxide could take place very rapidly with high yield. The relative reactivity of three styrene oxide derivatives comparing with styrene oxide was 0.66, 0.80 and 0.92 for 4-methylstyrene oxide (**4**), 4-chlorostyrene oxide (**5**) and 4-methoxystyrene oxide (**6**), respectively. One of the main reasons was plausibly derived from the inductive effect of these substituents. Generally, the aromatic ring could itself stabilize the generated carbocation by resonance effect, the extra substituent as methoxy, chloro and methyl groups may reduce the electron density of the phenyl ring by inductive effect. However, the increment of acetophenone derivative product among three styrene oxide derivatives selected could be arranged in order of CH_3O > Cl > CH_3, respectively, possibly depending on the electron donation ability by resonance effect.

3.7 Rearrangement of substituted styrene oxides

Styrene oxide was first selected as a chemical probe to investigate the rearrangement of epoxide. The hypothesis to explain a mechanistic pathway to the ketone product involved the migration of hydrogen atom at α-position of styrene oxide. The rearrangement of styrene oxide (**1**), α-methylstyrene oxide (**10**) and β-methylstyrene oxide (**11**) was explored to examine the influence of substituents toward the rearrangement of epoxides. The results are summarized in Table 3.12.



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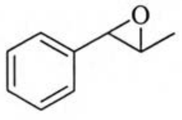

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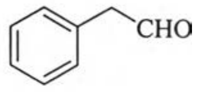

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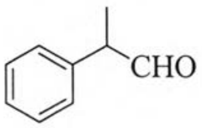

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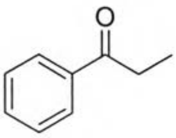

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α-Methylstyrene oxide (**10**) and β-methylstyrene oxide (**11**) employed in this study were prepared from the reaction with oxone following standard procedure [**37**]. The ^{1}H-NMR spectrum of α-methylstyrene oxide revealed the significant singlet signal of methyl protons adjacent to an aromatic ring visualized at δ 1.73 (3H, s). Two terminal protons could be assigned at δ 2.98 (1H, d, *J* = 5.40 Hz) and 2.82 (1H, d, *J* = 5.40 Hz) and aromatic protons could be detected around δ 7.23-7.42 (Fig 3.6).

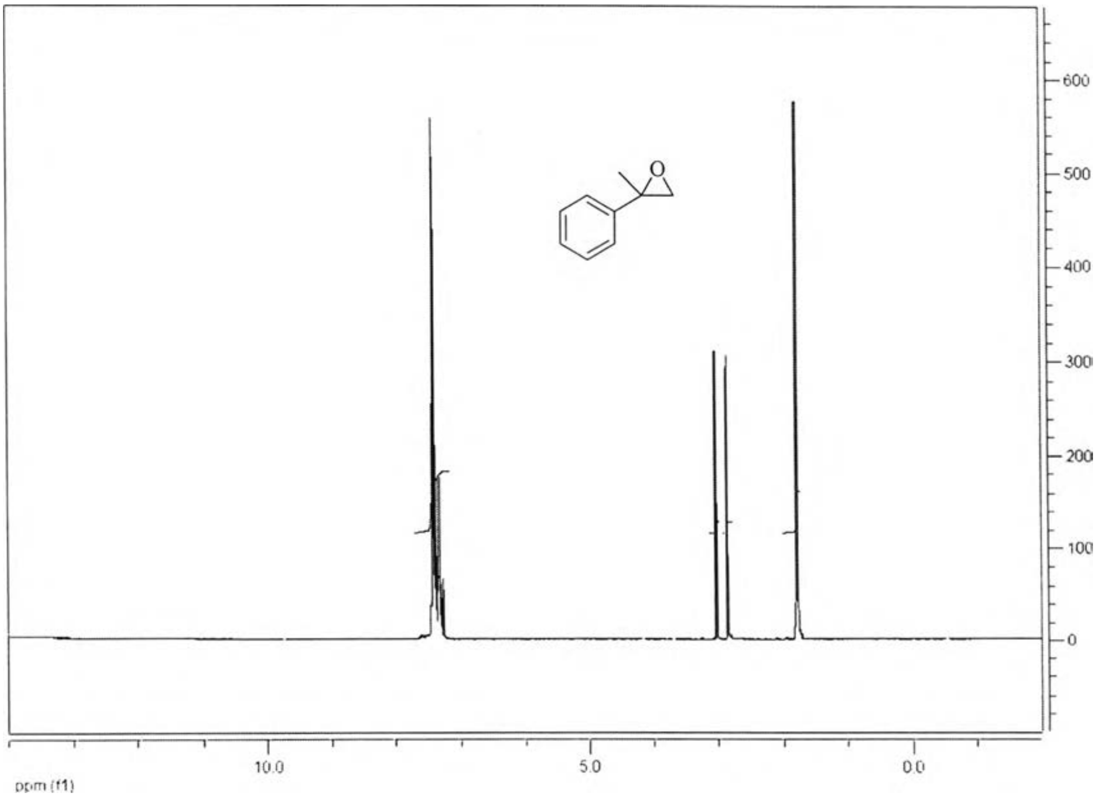


Figure 3.6 ^{1}H-NMR spectrum of α-methylstyrene oxide (**10**)

The ^{1}H-NMR spectrum of β-methylstyrene oxide (**11**) exhibited the significant doublet signal of terminal methyl protons at δ 1.89 (3H, d, *J* = 6.47 Hz). The β-proton could be visualized at δ 3.05 (1H, m). The proton adjacent to an aromatic ring was visualized at δ 3.58 (1H, d, J = 3.54 Hz) and aromatic protons as usual could be detected around δ 7.26-7.34 (5H, m) (Fig 3.7).

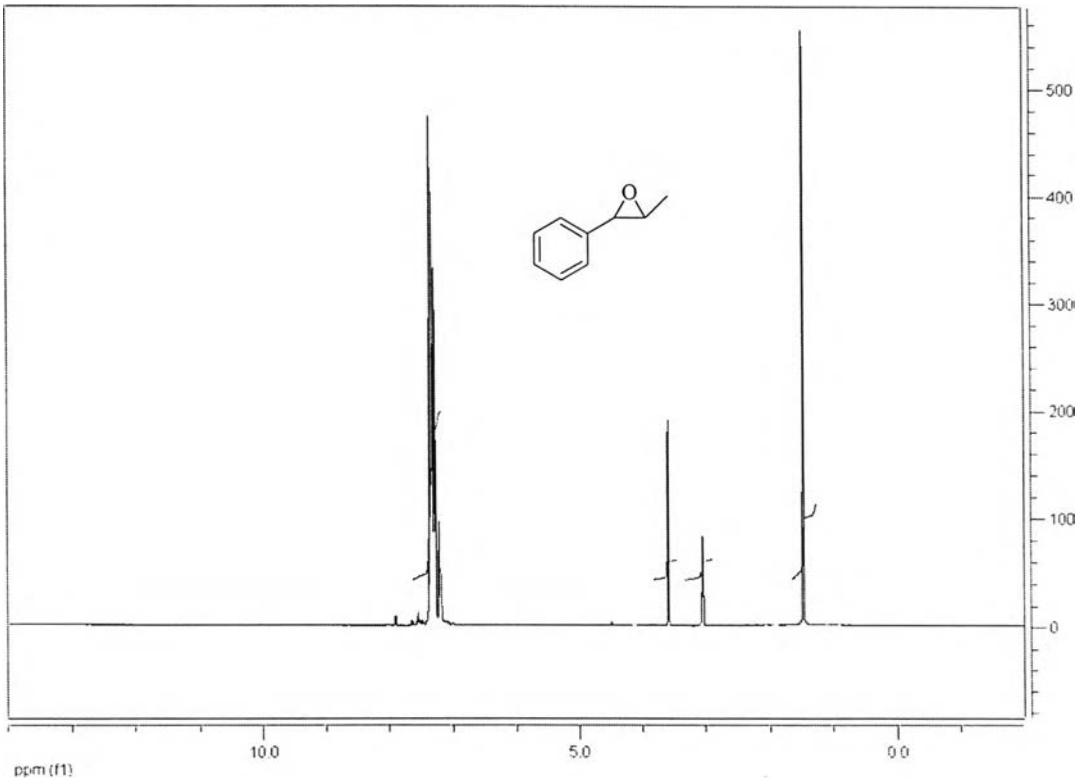


Figure 3.7 ^{1}H-NMR spectrum of β-methylstyrene oxide (**11**)

α-Methylstyrene oxide (**10**) and β-methylstyrene oxide (**11**) synthesized were thus subjected to the rearrangement under the same reaction conditions generally used to examine a mechanistic pathway. The results are summarized in Table 3.13.

Table 3.13 Effect of substituent on the rearrangement of substituted styrene oxides

Entry	Substrate	Time	%Substrate (recovered)	% Yield	MB
1	**1**	15 min	23	**2** (80)	103
2	**1***	15 min	12	**12** (85)	97
3	**10**	15 min	100	-	100
4	**10**	12 h	100	-	100
5	**10***	15 min	23	**13** (81)	104
6	**11**	15 min	103	-	103
7	**11**	12 h	24	**14** (74)	98

reactions condition: substrate (1 mmol), Fe(acac)$_3$ (1 mmol), EtOAc :hexane 1:1 (5 mL) at 70 °C

* InCl$_3$ (1 mmol) was used

From Table 3.13, it was found that the rearrangement of styrene oxide (**1**) by Fe(acac)$_3$ gave acetophenone (**2**) in 80% yield while there was no reaction taken place when α-methylstyrene oxide (**10**) was used as a substrate. All starting material was recovered. The main reason to explain this observation was that the hydrogen at α-position of styrene oxide which was replaced by methyl group, made this substrate no hydrogen migrate and proceed to the ketone product. The use of InCl$_3$ as a catalyst in rearrangement of styrene oxide gave solely phenylacetadehyde (**13**) in high yield with good accordance with previous report [**15**]. By purifying with silica gel column chromatography, the structure of the obtained product **13** was verified by ^{1}H-NMR spectrum (Fig 3.8). The aldehydic proton could be observed at δ 9.74 (1H, s). The aromatic protons could be detected at δ 7.41-7.29 (6H, m) while those at benzylic prosition could be visualized at δ 3.93 (1H, s).

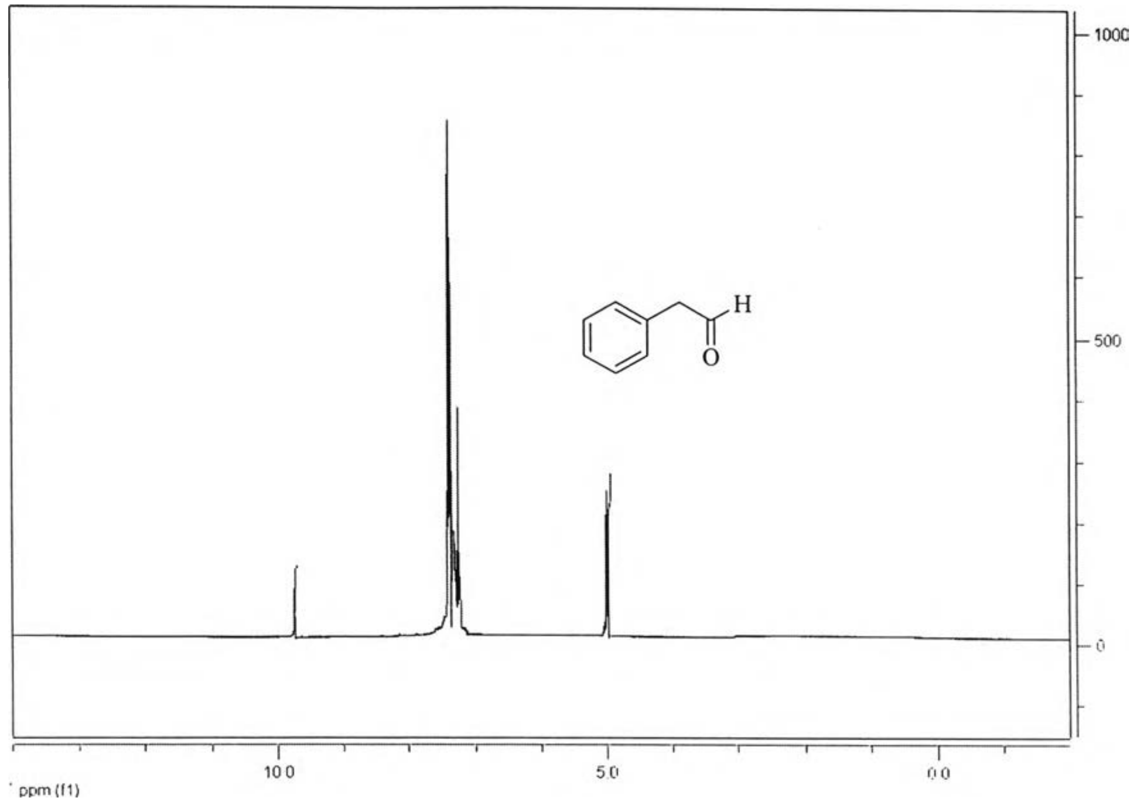


Figure 3.8 ^{1}H-NMR spectrum of phenylacetaldehyde (**12**)

The rearrangement of β-methylstyrene oxide (**11**) by Fe(acac)$_3$ for 15 min did not occur. The starting material was all recovered. However, when the reaction was prolonged for 12 h, 74% yield of the ketone product, propiophenone (**14**) was observed. Comparing with styrene oxide where then was no substituent on β-position, the reaction occurred very fast, the steric effect of methyl group at β-position of β-methylstyrene oxide (**11**) should thus be the main reason why this reaction took place slower. Therefore the reaction time needed to be longer. By purifying with silica gel column chromatography, the structure of the obtained product **14** was verified by ^{1}H-NMR spectrum (Fig 3.9). The ^{1}H-NMR spectrum exhibited a significant signal of terminal methyl protons at δ 1.39 (3H, t, *J* = 5.14 Hz). The protons adjacent to a carbonyl group were visualized at δ 3.03 (2H, q, J = 3.45 Hz), whereas the aromatic protons could be detected at δ 7.25-7.34 (5H, m).

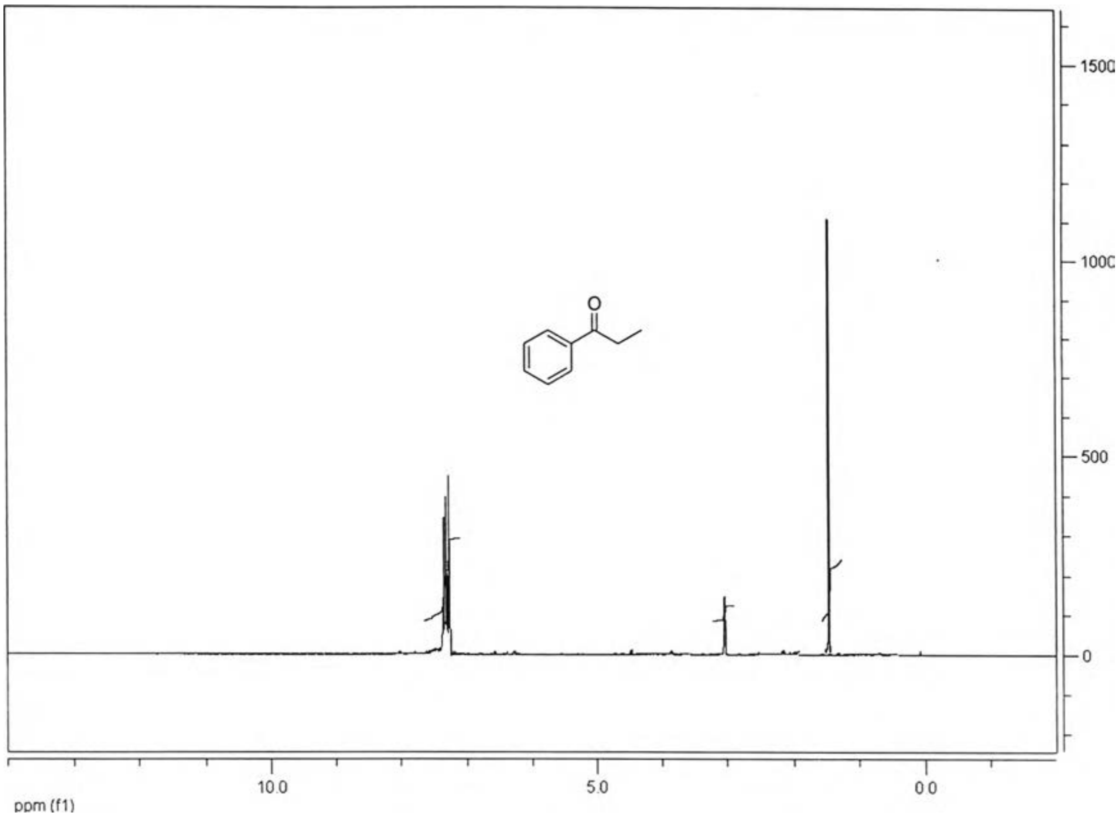
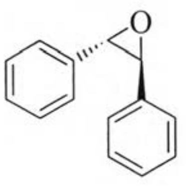


Figure 3.9 ^{1}H-NMR spectrum of propiophenone (**14**)

3.8 Rearrangement of other selected aryl-substituted epoxides

Under the optimized conditions as discussed in section 3.7, styrene oxide was transformed to acetophenone in high yield with superb selectivity. This developed system was therefore attempted to extend for other aryl-substituted epoxides. Stilbene oxide (**15**), benzalacetophenone oxide (**16**), methyl *trans*-3-(4-methoxyphenyl)-glycidate (**17**), 1,1-diphenylethylene oxide (**18**) and anethole oxide (**19**) were used as examples. The results of the rearrangement of selected epoxides are summarized in Table 3.13.



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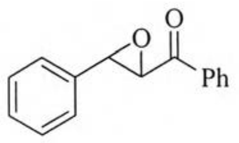

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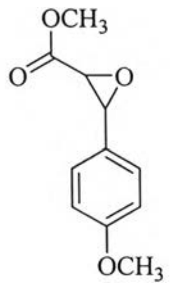

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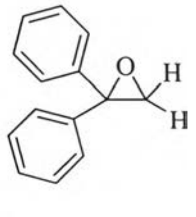

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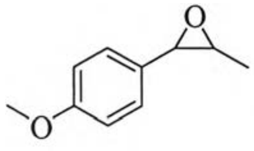

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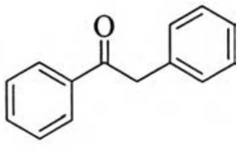

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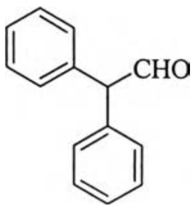

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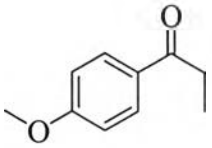

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Benzalacetophenone oxide (**16**) and 1,1-diphenylethylene oxide (**18**) in this study were derived by accomplishedly epoxidize by treatment with H_2O_2 [**44**]. The ^{1}H-NMR spectrum of benzalacetophenone oxide (**16**) (Fig 3.10) displayed the signal of the proton adjacent to a carbonyl group visualized at around δ 4.12 (1H, d, *J* = 1.70 Hz). The proton adjacent to aromatic ring could be observed at δ 4.34 (1H, d, *J* = 1.83 Hz) and aromatic protons could be detected around δ 7 (10H, m).

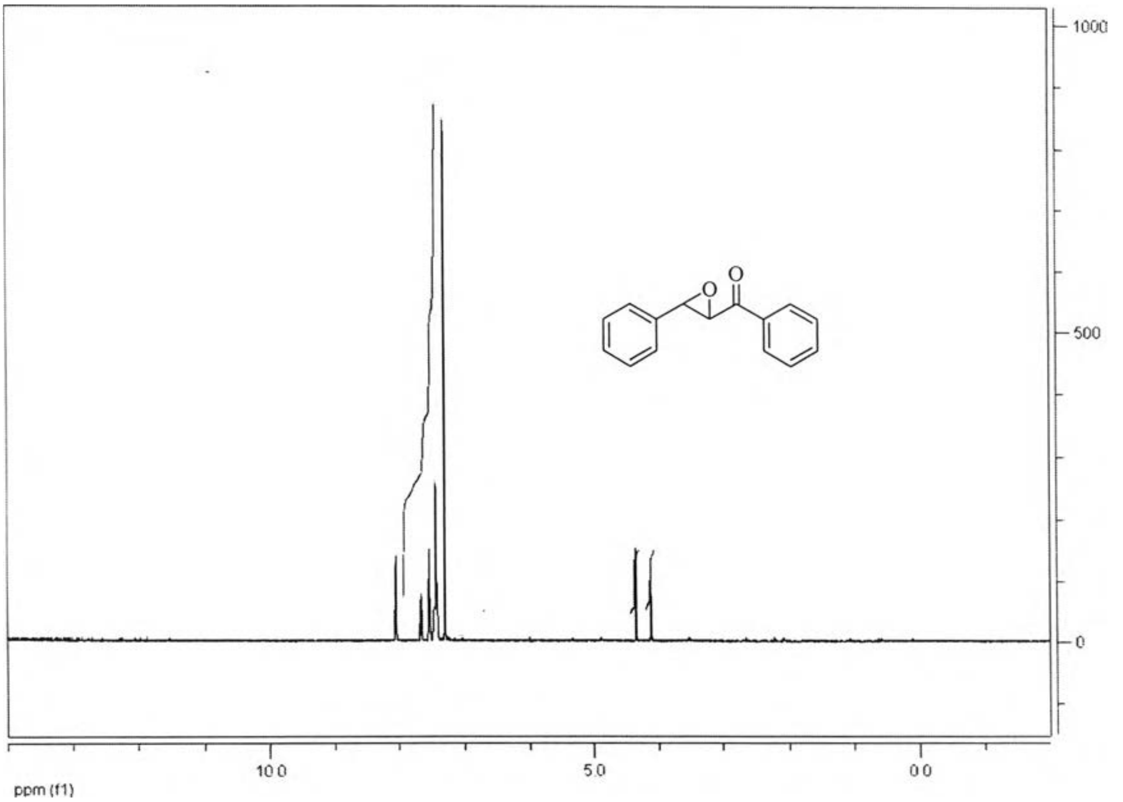


Figure 3.10 ^{1}H-NMR spectrum of benzalacetophenone oxide (**16**)

The ^{1}H-NMR spectrum of 1,1-diphenylethylene oxide (**18**) as presented in Fig 3.11 displayed two terminal protons at δ 3.21 (2H, s) and aromatic protons around δ 7.30 (10, m) (Fig 3.11).

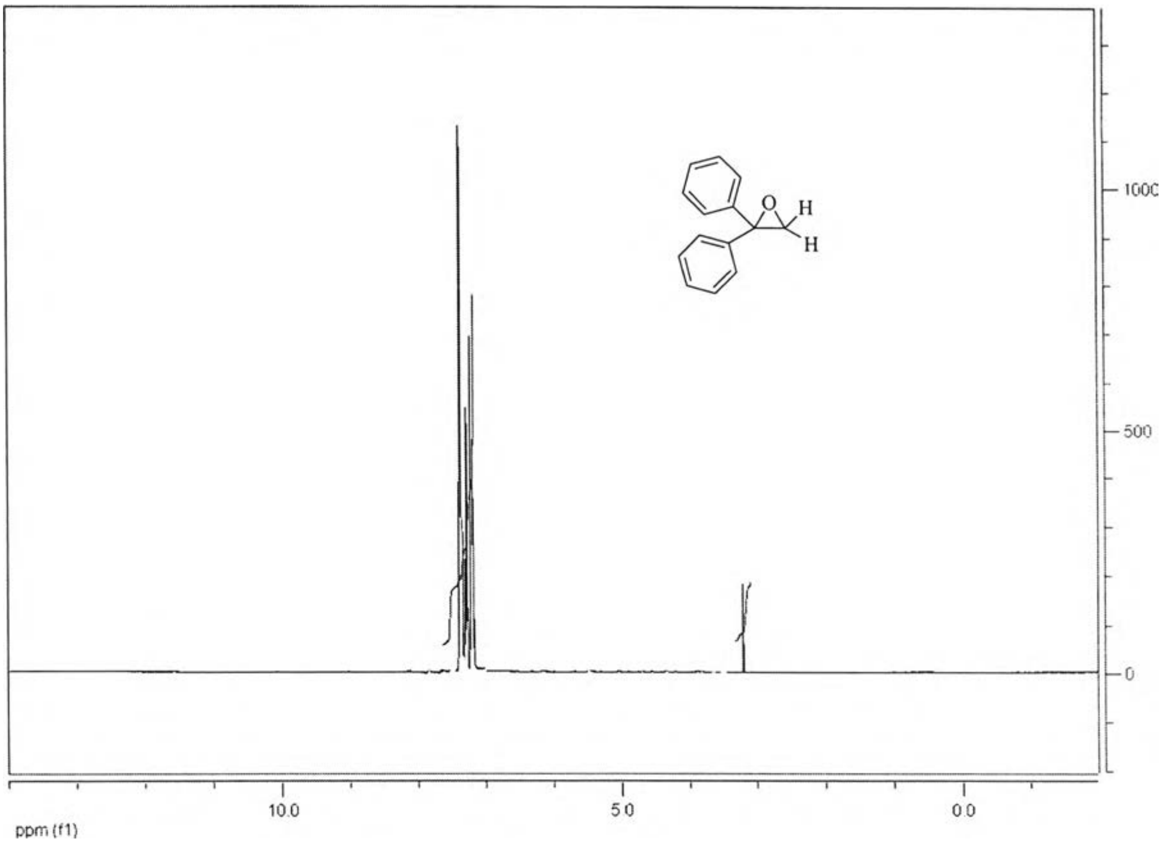


Figure 3.11 ^{1}H-NMR spectrum of 1,1-diphenylethylene oxide (**18**)

The ^{1}H-NMR spectrum of anethole oxide (**19**) revealed the significant doublet signal of terminal methyl protons at δ 1.48 (3H, d, *J* = 5.18 Hz). The multiplet signal at δ 3.07 (1H, m) could be assigned for β-proton. The proton next to aromatic ring could be visualized at δ 3.72 (1H, d, *J* = 1.59 Hz). A singlet signal of methoxy protons could be observed at δ 3.83 (3H, s) and aromatic protons could be clearly detected δ 6.77 (2H, d, *J* = 8.67 Hz) and 7.18 (2H, d, *J* = 8.68 Hz) (Fig 3.12).

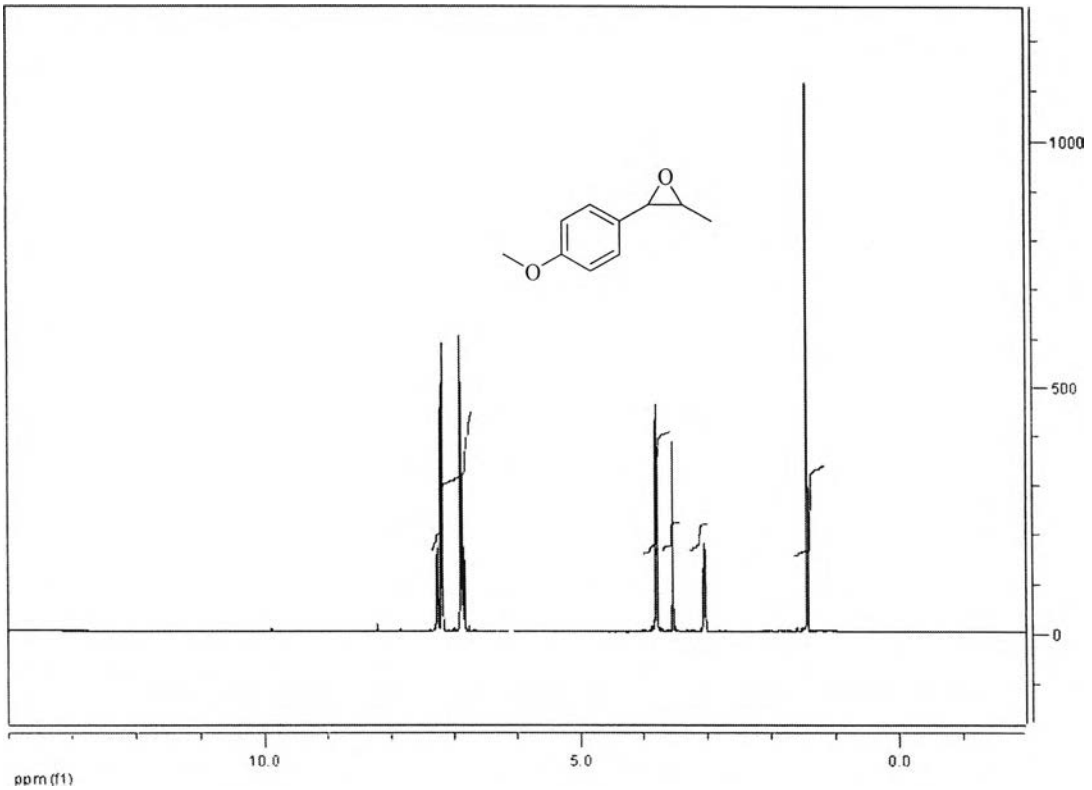


Figure 3.12 ^{1}H-NMR spectrum of anethole oxide (**19**)

All selected epoxides synthesized were thus subjected to the rearrangement under the same reaction conditions generally used. The results are summarized in Table 3.14.

Table 3.14 Rearrangement of selected epoxides

Entry	Substrate	Time	%Substrate (recovered)	%Isolated yield	MB
1	**15**	15 min	13	**20** (80)	93
2	**15**	1 h	10	**20** (86)	96
3	**15***	15 min	24	**21** (74)	98
4	**16**	15 min	100	-	100
5	**16**	12 h	100	-	100
6	**16***	15 min	44	**21** (63)	107
7	**17**	15 min	100	-	100
8	**17**	12 h	100	-	100
9	**18**	15 min	100	-	100
10	**18**	12 h	100	-	100
11	**18***	15 min	84	**21** (77)	105
12	**19**	15 min	56	**22** (41)	97
13	**19**	4 h	26	**22** (78)	104

reactions condition: substrate (1 mmol), Fe(acac)$_3$ (1 mmol), EtOAc:hexane 1:1 (5 mL) at 70 °C

* InCl$_3$ (1 mmol) was used

The wide range of structurally varied epoxides were subjected to the rearrangement with Fe(acac)$_3$ under optimized conditions providing the corresponding carbonyl compounds as summarized in Table 3.14. *Trans*-stilbene oxide (**15**) underwent rearrangement by exclusive migration of the hydrogen to give the respective benzyl phenyl ketone (**20**) in 80% and 86% isolated yield (entries 1 and 2). By purifying with silica gel column chromatography, the structure of the obtained product **20** was verified by ^{1}H-NMR spectrum (Fig 3.13). The aromatic protons could clearly be observed at δ 7.74 (2H, m), 7.40 (3H, m) and 7.31 (5H, m). The proton adjacent to carbonyl group could be detected at δ 3.87 (2H, s). Comparing with the result using InCl$_3$, the rearrangement of **15** by InCl$_3$ exclusively yielded 1,1-diphenylacetaldehyde (**21**), taking place *via* phenyl migration in high isolated yield (74%) (entry 3). The structure of the obtained product **21** was also clearly identified by ^{1}H-NMR spectrum (Fig 3.14). The significant singlet signal of the aldehyde proton could be observed at δ 9.96 (1H, s). The aromatic protons could be detected at δ 7.22-7.40 (10H, m) whereas the benzylic proton could be observed as a singlet signal at δ 4.91 (1H, s).

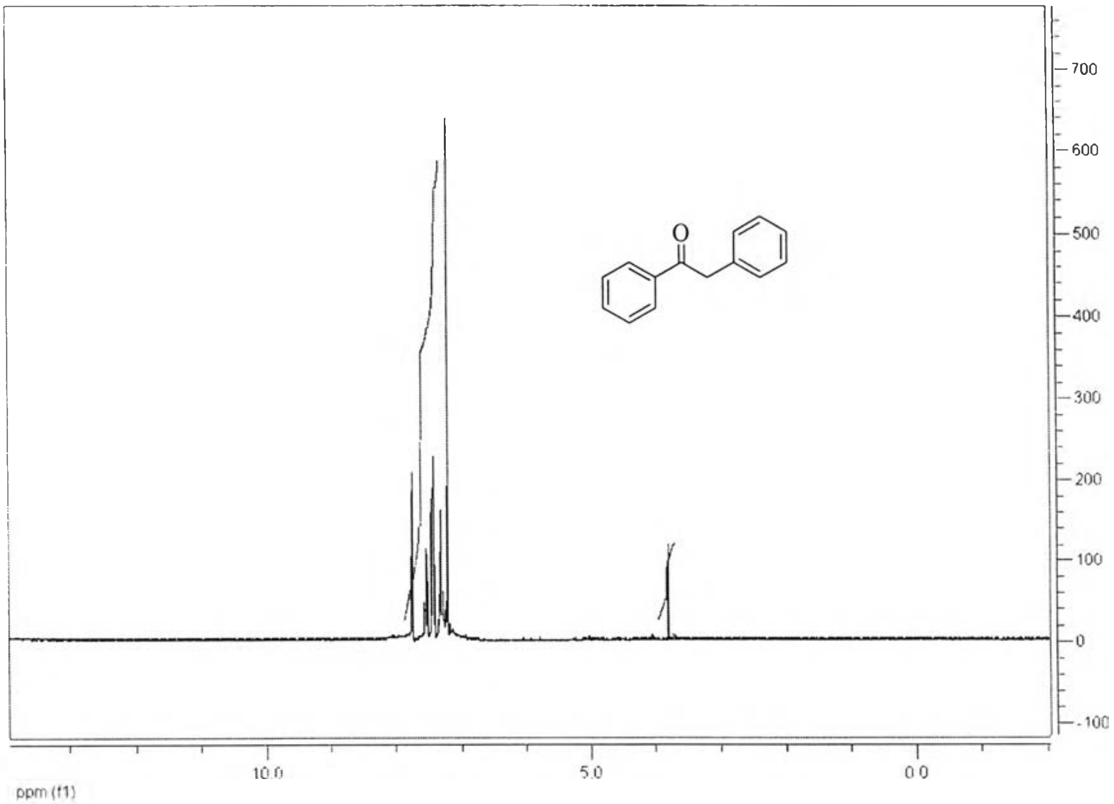


Figure 3.13 ^{1}H-NMR spectrum of benzyl phenyl ketone (**20**)

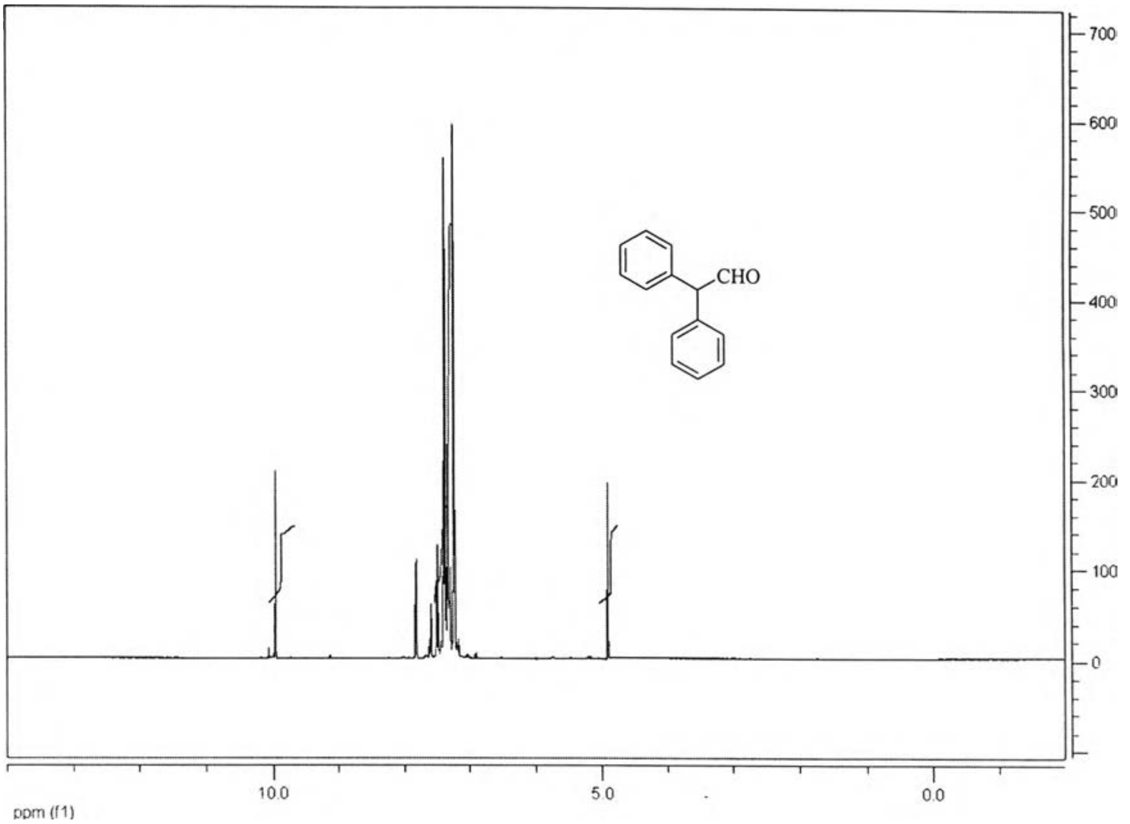


Figure 3.14 ^{1}H-NMR spectrum of 1,1-diphenylacetaldehyde (**21**)

The rearrangement of acyl-substituted epoxides benzalacetophenone oxide (**16**) and methyl *trans*-3-(4-methoxyphenyl)-glycidate (**17**) utilized Fe(acac)$_3$ was not fruitful. This may be because of carbonyl moiety effect as electron withdrawing group at β-position (entries 4-7). The rearrangement of **16**, on the other hand by InCl$_3$ cleanly gave benzyl phenyl ketone **20** 63% isolated yield (entry 6). This reaction was in good agreement with that addressed in the literature and the product was proposed to derive from the initial benzoyl shift, which then underwent retroaldol cleavage with loss of the formyl group to yield the final ketone **20** [**19**].

The rearrangement of 1,1-diphenylethylene oxide (**18**) by Fe(acac)$_3$, was also not taken place (entries 11 and 12). This supported previous proposed mechanistic pathway for iron mediated reaction that hydrogen should be a migrating group. Since in **18**, the phenyl group was placed in stead of hydrogen, thus no migration of hydrogen to proceed the rearrangement reaction could be possible. The rearrangement of **18** by InCl$_3$, on the contrary, gave 1,1-diphenylacetaldehyde (**21**) as a sole product in 77% isolated yield.

The rearrangement of anethole oxide (**19**) utilized Fe(acac)$_3$ yielded 4-methoxypropiophenone (**22**) as a main product 78% isolated yield. The structure of the obtained product **22** was characterized based upon the ^{1}H-NMR data (Fig 3.15). The significant signal of terminal methyl protons could be observed at δ 1.32 (3H, t, *J* = 5.39 Hz). Two protons adjacent to carbonyl group could be detected at δ 2.98 (2H, q, *J* = 7.09 Hz). The significant singlet signal of methoxy protons could be conceivably assigned at δ 3.61 (3H, s) and the signal around δ 7.12 (2H, d, *J* = 8.63 Hz) and 7.24 (2H, d, *J* = 8.75 Hz) could be ascribed for aromatic protons.

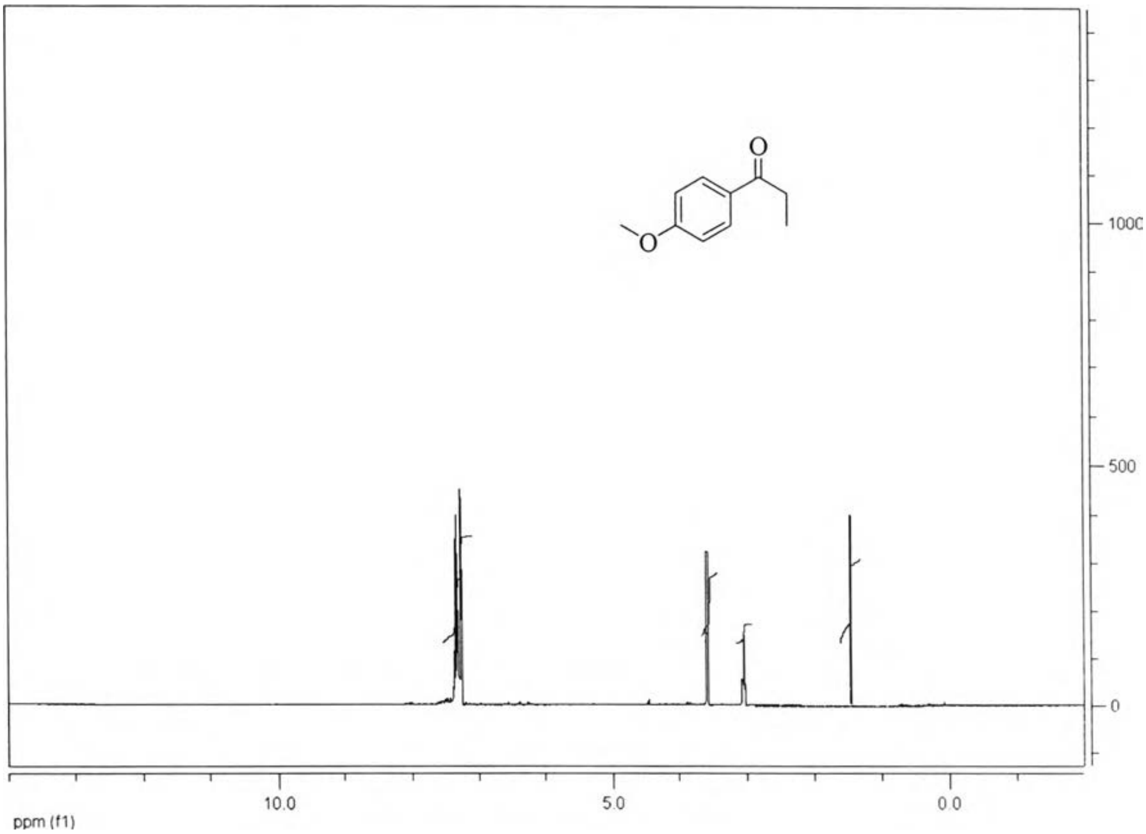
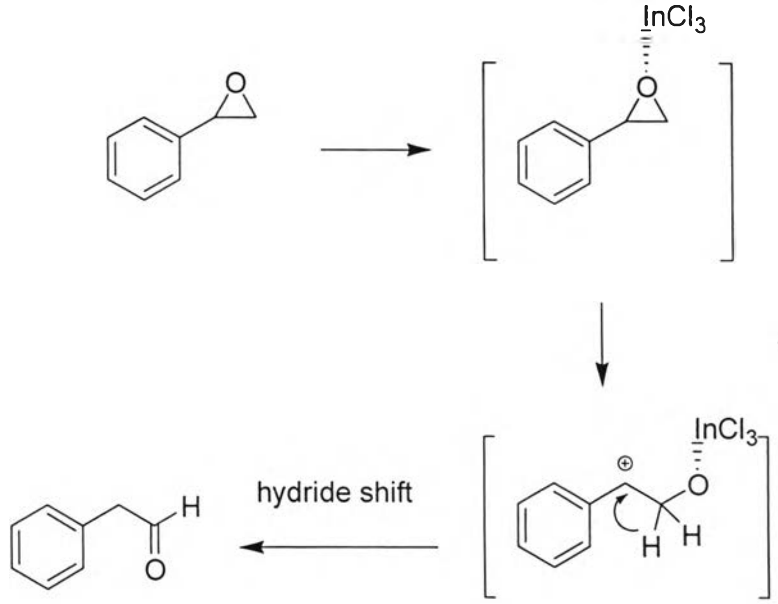


Figure 3.15 ^{1}H-NMR spectrum of 4-methoxypropiophenone (**22**)

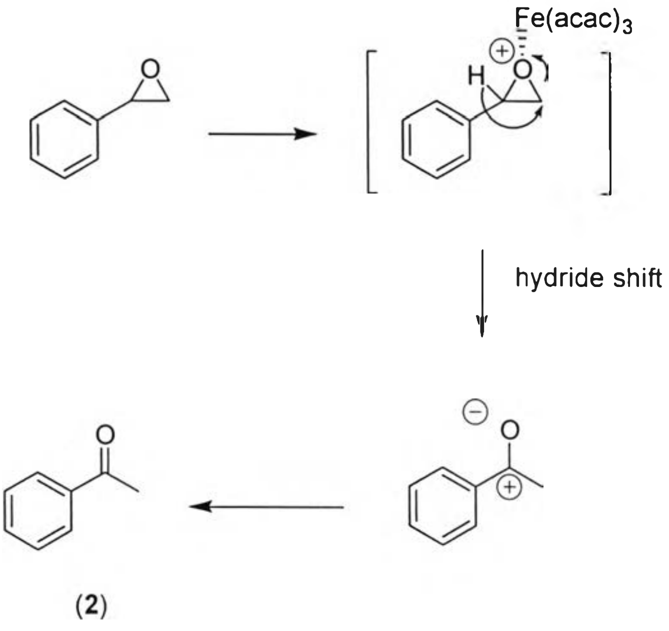
Reaction conditions and regioselectivity of the reaction utilizing Fe(acac)$_3$ compared with those of InCl$_3$ upon the rearrangement of certain epoxides were investigated. Fe(acac)$_3$ as a reagent exclusively promoted the hydrogen migration of styrene oxide to give only acetophenone (**2**) as a sole product. On the other hand, the use of InCl$_3$ as a reagent preferentially brought about the cleavage of C-O bond of epoxide ring to the carbocation intermediate followed by the hydrogen migration to furnish phenylacetaldehyde (**3**) as a sole product [**18**] (Scheme 3.3). The possible reason could be InCl$_3$ was stronger Lewis acid than Fe(acac)$_3$ [**51**].



(3)

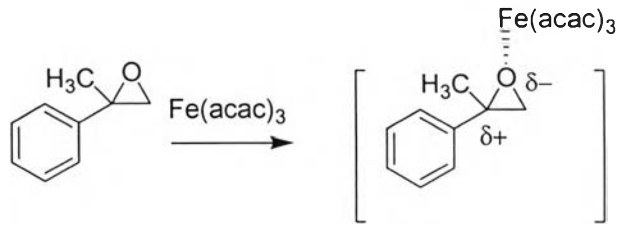
Scheme 3.3 Mechanistic pathway of rearrangement of epoxides by InCl$_3$ to phenylacetadehyde (**3**)

Nevertheless, the cleavage of C-O bond of the epoxide ring could not occur due to Fe(acac)$_3$ as a weak Lewis acid. The stable carbocation was later generated by hydrogen migration as a driving force for C-O bond cleavage (Scheme 3.4).



Scheme 3.4 Mechanistic pathway of rearrangement of epoxides by Fe(acac)$_3$ to acetophenone (**2**)

Moreover, no reaction was observed when α-methylstyrene oxide (**10**) or diphenylethylene oxide (**18**) was used as a substrate and Fe(acac)$_3$ as a reagent. The hydrogen at α-position of styrene oxide which was replaced by methyl or phenyl group, made this substrate be of no hydrogen to migrate and proceed to the ketone product. The possible explanation for this hypothesis was: (a) the selective migrating of hydrogen, methyl or phenyl group depends on the electron availability at β-position. Carbon atom at β-position of styrene oxide was soft acid site so hydrogen (soft base) was migrated while methyl and phenyl groups (hard base) could not migrate followed by hard-soft acid-base theory [**52**] and (b) Methyl and phenyl groups can stabilize partial positive charge and the stability of intermediate was decreased when either methyl or phenyl group was migrated to β-position.



All the attained observations were in good agreement with the rearrangement of epoxides by Fe(acac)$_3$: (a) reaction could be selectively employed only for aryl-substituted epoxides, (b) no reaction was taken place in α-methylstyrene oxides, (c) no reaction occurred in α,β-unsaturated epoxides. This Fe(acac)$_3$-promoted procedure provides an efficient methodology for a highly regioselective isomerization of aryl-substituted epoxides and demonstrates useful protocol for the high yield synthesis of ketone with complete predictability. The other notable advantages offered by this procedure are (a) fast reaction (generally 15 min), (b) mild reaction conditions (room temperature), (c) simplicity in operation (no special apparatus or technique required) and (d) mild nature of Fe(acac)$_3$ in comparison to BF$_3$ and other Lewis acids.