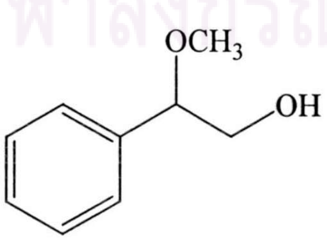
CHAPTER III

RESULTS AND DISCUSSION

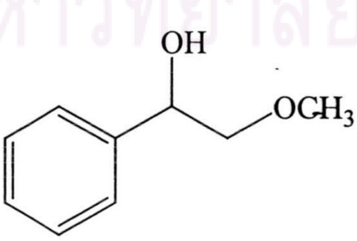
The main features of this research focused on the methodology towards ring opening of epoxides to more valuable products. Styrene oxide was selected as a model substrate for the reaction conditions optimization. In general, the system is composed of styrene oxide, solvent and catalyst. Other substrates such as 1-dodecene oxide, cyclohexene oxide, butyl glycidyl ether, *tert*-butyl glycidyl ether and α-pinene oxide were chosen to examine the capability of the catalytic system and to explore the scope of this developed ring opening system.

3.1 Effects of types of catalysts on the reactivity of styrene oxide ring opening

Generally, epoxides can be opened by the aids of either acid, base or Lewis acid catalysts.[7-8] The salts of transition metals or their complexes as Lewis acid could be employed as a synthetic reagent for such kind of transformatiom. Within the scope of this preliminary investigation, styrene oxide was reacted with methanol in the presence of various transition metal salts and complexes. 2-Methoxy-2-phenylethanol **(1)** was detected as a sole product, none of 2-methoxy-1-phenylethanol **(2)** being observed on GC chromatogram. This desired product was indeed important in pharmaceutical industries.[23] The outcomes are presented in Table 3.1.



(1)



(2)

Table 3.1 Effect of catalyst on styrene oxide ring opening

catalyst	% yield (based on substrate)		
	styrene oxide (recovered)	**1**	Σ
none	102.08	0	102.08
$FeCl_3$(anhydrous)	47.25	46.16	93.41
$FeCl_2$(anhydrous)	45.21	47.80	93.01
$FeCl_3 \cdot 6H_2O$	5.30	88.21	93.51
$FeCl_3/SiO_2$	47.63	52.89	100.52
$FeSO_4 \cdot 7H_2O$	99.15	0.67	99.82
Fe(salen)	94.01	0	94.01
$Fe(acac)_3$	106.25	0	106.25
$Fe(TFA)_3$	0	101.64	101.64
$Fe(TCA)_3 \cdot 1.5H_2O$	0	104.05	104.25
$Fe(palmitate)_3$	91.96	0	91.96
$Fe(stearate)_3$	92.94	0	92.94
$Fe(naphthenate)_3$	94.50	0	94.50
$Fe(behenate)_3$	101.11	0	101.11
Ferrocene	89.31	6.19	95.50
$Fe(benzoate)_3$	98.02	0	98.02
$Fe(4\text{-nitrobenzoate})_3$	94.95	0	94.95
$Fe(2,4\text{-dinitrobenzoate})_3$	98.10	2.52	100.62
Cr(salen)Cl	97.71	1.79	99.50
$Co(OAc)_2 \cdot 4H_2O$	93.42	0	93.42
$CoCl_2 \cdot 6H_2O$	96.42	0	96.42
$Co(palmitate)_2$	95.90	0	95.90
$Co(stearate)_2$	95.46	0	95.46
$Co(naphthenate)_2$	94.69	0	94.69
Co(salen)OMe	94.89	0	94.89
$Co(salen)(pyridine)_4$	107.31	0	107.31
Co(salop)	95.53	0	95.53
Co(salen)	103.40	0	103.40
$Co(salen)^{*}$	94.76	0	94.76
Co(salth)	101.71	0	101.71
Co(sal)-*m*-phen.	96.77	0	96.77

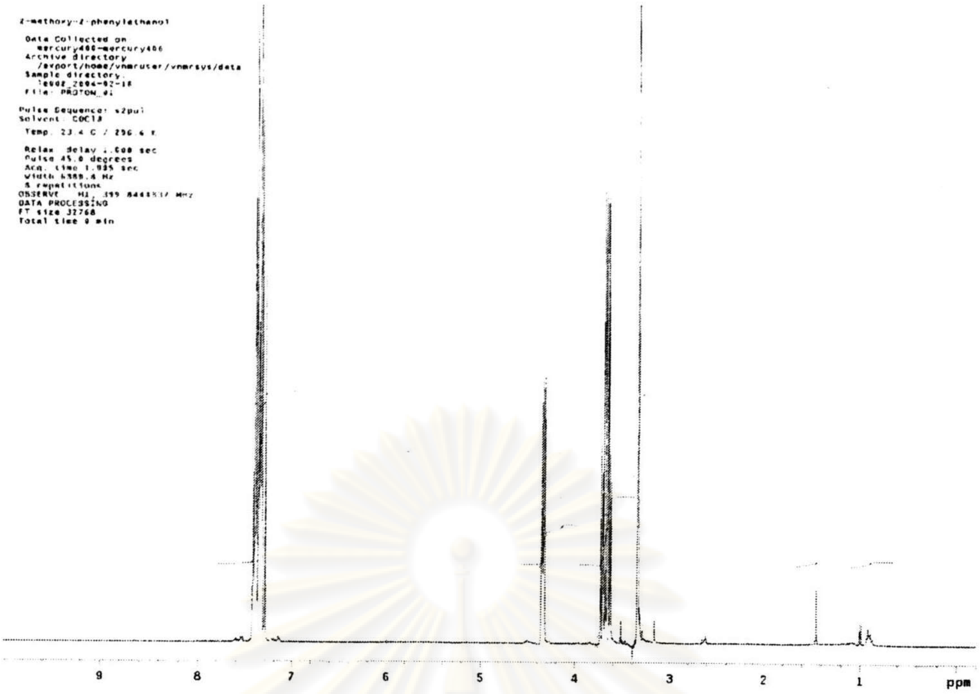
Reaction conditions: styrene oxide (1 mmol), catalyst (0.05 mmol), methanol (3 mL) reaction time (10 min) at room temperature (30°C)

Fe(II), Fe(III), Co(II) and Cr(III) salts and their complexes were mainly employed as a catalyst in styrene oxide ring opening due to their availabity in the laboratory and in the viewpoint of their convenience in preparation and inexpensiveness. Some Fe(II) and Fe(III) complexes had been addressed to be of Lewis acid properties.[1,23,25] On the contrary, some such as $Fe(TCA)_3 \cdot 1.5H_2O$, $Fe(benzoate)_3$, $Fe(4\text{-nitrobenzoate})_3$ and $Fe(2,4\text{-dinitrobenzoate})_3$ were first prepared and these carboxylate complexes to our best knowledge had never been utilized as a catalyst in epoxide ring opening reaction. The use of Co(II) complexes such as Co(salen) and $CoCl_2$ for epoxide ring opening has been cited in literature.[34-37] In the case of Cr(III) complexes, recent literature revealed the use of Cr(salen)Cl for epoxide ring opening reaction to provide good %ee and high yield.[38-41]

The catalysts used in this research could be classified into three groups. The first group included transition metal salts: $FeCl_2$ (anhydrous), $FeCl_3$ (anhydrous), $FeCl_3.6H_2O$, $FeCl_3/SiO_2$ and $CoCl_2 \cdot 6H_2O$. This class of catalyst could assist the opening of styrene oxide under mild conditions and gave the desired product in good yield. The second group was transition metal carboxylate complexes: $Fe(acac)_3$, $Fe(TFA)_3$, $Fe(TCA)_3 \cdot 1.5H_2O$, $Fe(palmitate)_3$, $Fe(stearate)_3$, $Fe(naphthenate)_3$, $Fe(behenate)_3$, $Fe(benzoate)_3$, $Fe(4\text{-nitrobenzoate})_3$, $Fe(2,4\text{-dinitrobenzoate})_3$, $Co(OAc)_2 \cdot 4H_2O$, $Co(palmitate)_2$, $Co(stearate)_2$ and $Co(naphthenate)_2$. Within 10 min at room temperature (30°C) the ring opening reaction could not take place in the presence of these catalysts except for $Fe(TFA)_3$ and $Fe(TCA)_3 1.5H_2O$. The latter two catalysts could facilitate the reaction to yield the target molecule in excellent yields. The last group of catalysts composed of metal salen complexes: Fe(salen), Cr(salen)Cl, Co(salen)OMe, $Co(salen)(pyridine)_4$, Co(salop), Co(salen), $Co(salen)^*$, Co(saltn), and Co(sal)-*m*-phen. Among several metal salen catalysts studied, Cr(salen)Cl was noticed to be able to employ as an active catalyst to open styrene oxide, however with the low extent of the desired product. Under this particular conditions, the most appropriate catalysts for ring opening reaction were $Fe(TFA)_3$ and $Fe(TCA)_3 \cdot 1.5H_2O$.

On the viewpoint of the selectivity of reaction, this reaction gave excellent regioselectivity; only **1** being detected. The electronic effect to stabilize (formally) benzylic cation may preferentially induce the nucleophilic attack at this position of styrene oxide.

It should be mentioned here that both authentic samples of **1** and **2** were accomplishly manipulated. For **1**, the preparation involved the reaction of styrene oxide in methanol using $FeCl_3$(anhydrous) as a catalyst.[31] The ^1H-NMR spectrum (Fig 3.1) revealed the peak of $-C\mathbf{H}_2OH$ as a double doublet with 1H intensity at 3.71 ppm (J = 8.43, 11.62 Hz) and a double doublet at 3.64 ppm (J = 11.65, 3.88 Hz), those of aromatic protons as multiplet (5H) at 7.40-7.21 ppm, that of $-OC\mathbf{H}_3$ as a singlet (3H) at 3.34 ppm and that of $-C\mathbf{H}OCH_3$ as a double doublet (1H) at 4.34 ppm (J = 3.90 Hz).[31] In addition, the synthesis of **2** was conducted by the reaction of styrene oxide with NaOMe in methanol at room temperature as that previously cited in literature.[31] Characterization of the product by ^1H-NMR (Fig 3.2) was fully proved the structure of this product. The observed peak of $-C\mathbf{H}OH$ as a double doublet (1H) was detected at 4.92 ppm (J = 2.34 Hz), aromatic protons were appeared as a multiplet (5H) centered at 7.40-7.21 ppm, the peak of $-OC\mathbf{H}_3$ as a singlet (3H) at 3.34 ppm and that of $-C\mathbf{H}_2OCH_3$ being a double doublet (1H) at 3.64 ppm (J = 11.68, 3.80 Hz) and a double doublet (1H) at 3.58 ppm (J = 9.79, 3.09 Hz).



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2-methoxy-2-phenylethanol

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 Sample directory
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 File: PROTON_01

Pulse Sequence: s2pul
Solvent  CDCl3
 Temp. 23.4 C / 296.6 K

 Relax  delay 1.000 sec
 Pulse 45.0 degrees
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 Width 6389.4 Hz
 8 repetitions
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DATA PROCESSING
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Total time 0 min
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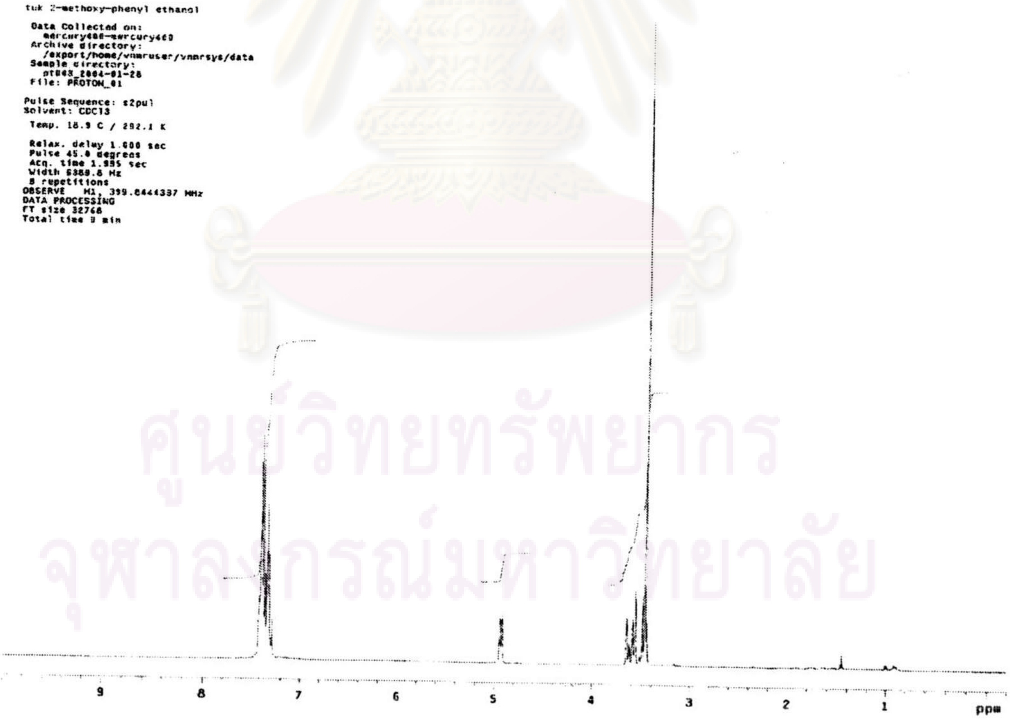
Figure 3.1 ^{1}H-NMR spectrum of 2-methoxy-2-phynylethanol



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tuk 2-methoxy-phenyl ethanol

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 File: PROTON_01

Pulse Sequence: s2pul
Solvent: CDCl3
 Temp. 18.9 C / 292.1 K

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 Pulse 45.0 degrees
 Acq. time 1.995 sec
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 8 repetitions
OBSERVE   H1, 399.8444337 MHz
DATA PROCESSING
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Total time 0 min
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Figure 3.2 ^{1}H-NMR spectrum of 2-methoxy-1-phynylethanol

3.2 Study on the optimum conditions for styrene oxide ring opening by metal Schiff's base complexes

From Table 3.1, the reaction time of styrene oxide ring opening was perhaps too short under ambient conditions studied. This condition seemed not suitable for studying the effect of catalyst except for $Fe(TFA)_3$ and $Fe(TCA)_3 \cdot 1.5H_2O$. For metal salen complexes, there were many reports concerning the epoxide ring opening reactions to furnish the desired products in high yield with good %ee.[30,32-35] Thus, various diverse conditions were needed to be explored to observe the reactivity of metal salen complexes in such kind of reactions.

3.2.1 Effect of metal salen complexes

To search for appropriate metal salen complexes that could selectively catalyze the ring opening reaction of styrene oxide to 2-methoxy-2-phenylethanol **(1)** in high yield, various metal salen complexes were screened. Table 3.2 presents the results of the utilization of various metal salen complexes on the ring opening of styrene oxide.

Table 3.2 Ring opening reaction of styrene oxide catalyzed by various metal salen catalysts

entry	metal salen	% yield (based on substrate)		
		styrene oxide (recovered)	**1**	Σ
1	Fe^{II}(salen)	99.36	0.91	100.27
2	Fe^{III}(salen)Cl	98.81	2.96	101.77
3	Co^{II}(salen)	106.65	0	106.65
4	Cu^{II}(salen)	84.22	10.96	95.15
5	Cr^{III}(salen)Cl	83.73	16.10	99.83
6	Ni^{II}(salen)	103.68	0	103.68
7	$V^{IV}O$(salen)	104.71	0	104.70
8	Mn^{II}(salen)	99.38	0.71	100.09

Reaction conditions: styrene oxide (1 mmol), metal salen (0.05 mmol), methanol (3 mL), room temperature (30°C) for 30 min

It was clearly seen from Table 3.2 that among eight transition metal salen complexes, Cr(salen)Cl (entry 5) was the most effective catalyst for styrene oxide ring opening. Cu(salen) was also found to be an interesting catalyst in this class. Thus, Cr(Salen)Cl was selected for further study to observe the effect of reaction time and temperature.

3.2.2 Effect of reaction time and temperature for Cr(salen)Cl catalyzed ring opening of styrene oxide

The effect of reaction time on the reactivity of styrene oxide ring opening was studied. From Tables 3.1 and 3.2, in the presence of Cr(Salen)Cl, it could be seen that the amount of product was increased when the reaction time increased. The effect of the reaction time on the reactivity of styrene oxide ring opening was studied. The results are presented in Table 3.3 and Figure 3.3.

Table 3.3 Effect of reaction time and temperature on the ring opening of styrene oxide catalyzed by Cr(salen)Cl

entry	time	% yield (based on substrate) at room temperature (30°C)			% yield (based on substrate) at 70 °C		
		styrene oxide (recovered)	**1**	Σ	styrene oxide (recovered)	**1**	Σ
1	10 min	99.71	1.79	99.50	90.04	9.54	99.58
2	30 min	83.73	16.10	99.83	68.28	29.11	97.99
3	1 h	-	-	-	35.67	68.14	103.81
4	2 h	-	-	-	19.85	83.84	103.69
5	4 h	-	-	-	4.40	96.43	100.83
6	6 h	48.34	47.74	96.08	-	-	-
7	8 h	-	-	-	0	106.15	106.15
8	24 h	6.29	90.55	96.84	-	-	-

Reaction conditions: styrene oxide (1 mmol), Cr(salen)Cl (0.05 mmol), methanol (3 mL)

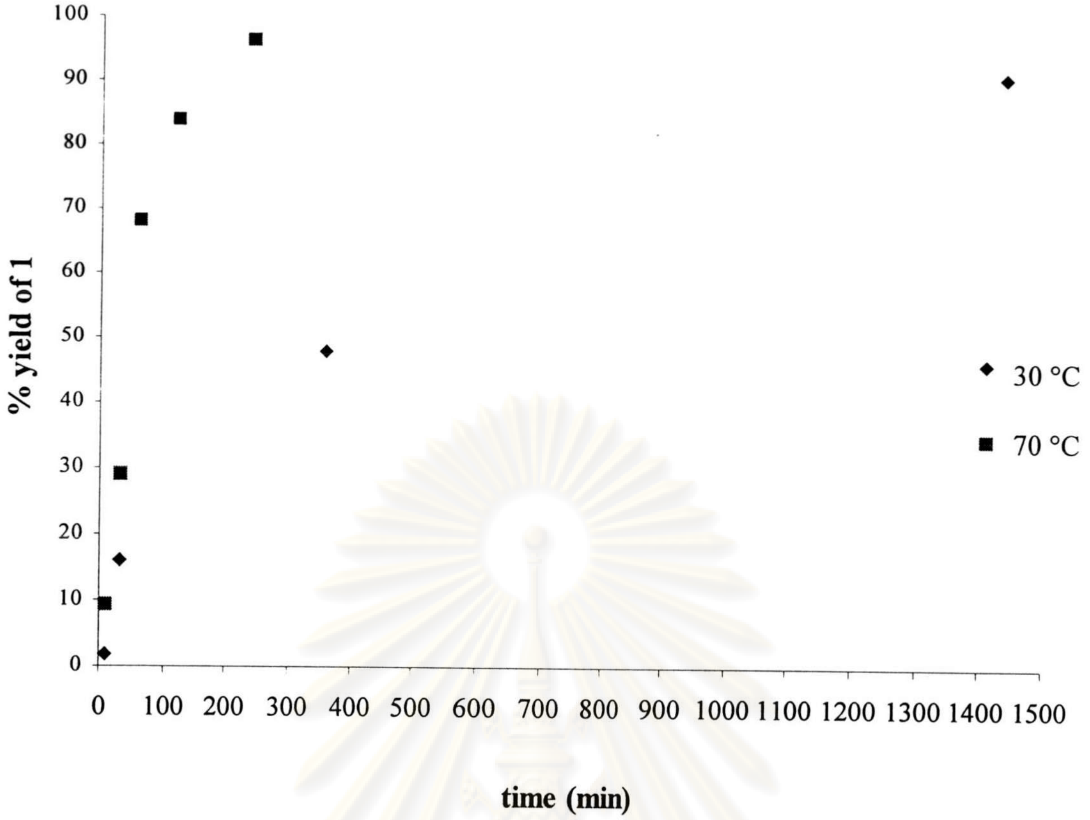


Figure 3.3 Effect of reaction time and temperature on the ring opening of styrene oxide catalyzed by Cr(salen)Cl

As noticed from Table 3.3 and Fig 3.3, the ring opening reaction of styrene oxide at room temperature selectively gave **1** in high yield within 24 h and the half-life of the reaction was about 7 h. Increasing the reaction temperature to 70°C, the half-life of the reaction was shortened to about 45 min and the reaction was completed within 8 h. It could thus be summarized that the reaction time and temperature had a profound effect on this reaction.

The outcome of this reaction was in good agreement with those obtained from Jacobsen and coworkers work on an asymmetric epoxide ring opening catalyzed by Cr(salen)Cl.[38-41]

3.3 Study on the optimum conditions for styrene oxide ring opening by metal carboxylate complexes

3.3.1 Effect of metal carboxylate complexes

Some metal carboxylate catalysts have been documented to exploit in an epoxide ring opening reaction. A few reports concerning with the use of

Cr(III)enolate or Fe(III) complexes as a catalyst were among those examples.[22-23] In this research work, nine synthesized Cr(III) and Fe(III) carboxylate complexes were explored for their capability on styrene oxide ring opening and the results are presented in Table 3.4.

Table 3.4 Effect of metal carboxylate complexes on styrene oxide ring opening

entry	catalyst	% yield (based on substrate)		
		styrene oxide (recovered)	**1**	Σ
1	Fe(picolinate)$_3$	83.21	16.88	100.09
2	Fe(benzoate)$_3$	99.41	0.86	101.27
3	Fe(4-nitrobenzoate)$_3$	88.73	12.31	101.04
4	Fe(2,4-dinitrobenzoate)$_3$	40.47	53.54	94.01
5	Cr(stearate)$_3$	101.23	0	101.23
6	Cr(behenate)$_3$	100.21	0	100.21
7	Cr(alanine)$_3$	95.00	0	95.00
8	Cr(benzoate)$_3$	101.01	0	101.01
9	Cr(4-nitrobenzoate)$_3$	95.68	4.52	101.20

Reaction conditions: styrene oxide (1 mmol), catalyst (0.05 mmol), methanol (3 mL), at room temperature (30°C) for 6 h

The synthesis of metal carboxylate complexes was generally very facile with high yield of product. In this research, with the use of metal carboxylate complexes, the operational procedure could be conducted at room temperature and the reaction required short period of time. From the results obtained (Table 3.4), it was observed that metal carboxylate complexes containing powerful electron withdrawing group such as a nitro group enhanced the reactivity of epoxide ring opening reaction (entries 3, 4 and 9). This may be because those complexes exhibited more prevailed Lewis acid properties than others bearing not powerful electron withdrawing substituents. Comparing Fe(III) and Cr(III) complexes with the same liganating agents, the former revealed better efficiency than the latter (entries 3 and 9). Among nine metal carboxylate complexes studied, Fe(2,4-dinitrobenzoate)$_3$ was disclosed to be the best catalyst in this group.

3.3.2 Effect of reaction time for styrene oxide ring opening

From Table 3.4, it could be concluded that Fe(2,4-dinitrobenzoate)$_3$ was the best catalyst in metal carboxylate group for styrene oxide ring opening. Nevertheless, the amount of the obtained product catalyzed by this catalyst was relatively moderate while Fe(4-nitrobenzoate)$_3$ gave lower yield of product. Increasing the reaction time may enhance the yield of the desired product, **1**. The outcome from the study on the effect of reaction time on styrene oxide ring opening catalyzed by Fe(4-nitrobenzoate)$_3$ is tabulated as shown in Table 3.5.

Table 3.5 Effect of the reaction time on styrene oxide ring opening catalyzed by Fe(4-nitrobenzoate)$_3$

entry	time	% yield (based on substrate)		
		styrene oxide (recovered)	**1**	Σ
1	10 min	103.25	0	103.25
2	0.5 h	100.47	0	100.47
3	6 h	88.73	12.31	101.04
4	24 h	46.81	57.06	103.87
5	48 h	16.61	79.49	96.10
6	72 h	7.34	86.46	93.80

Reaction condition: styrene oxide (1 mmol), Fe(4-nitrobenzoate)$_3$ (0.05 mmol), methanol (3 mL), at room temperature (30°C)

As seen from Table 3.5, it could be observed that 2-methoxy-2-phenylethanol **(1)** was produced in high yield at 72 h. The reaction nonetheless required quite long time to gain satisfactory yield compared with other previous systems cited in literature.[23] Increasing temperature was another factor that normally performed to enhance the yield and shorten the reaction time acquired. The results obtained from the comparative study on the effect of the reaction time for styrene oxide ring opening catalyzed by Fe(4-nitrobenzoate)$_3$ and Fe(2,4-dinitrobenzoate)$_3$ are demonstrated in Table 3.6 and Figure 3.4.

Table 3.6 Effect of reaction time on styrene oxide ring opening catalyzed by Fe(4-nitrobenzoate)$_3$ and Fe(2,4-dinitrobenzoate)$_3$

time	% yield (based on substrate) using Fe(4-nitrobenzoate)$_3$			% yield (based on substrate) using Fe(2,4-dinitrobenzoate)$_3$		
	styrene oxide (recovered)	**1**	Σ	styrene oxide (recovered)	**1**	Σ
0.5 h	104.12	0	104.12	71.59	31.96	103.55
1 h	107.05	0	107.05	43.46	50.03	93.09
2 h	76.70	23.64	100.34	13.85	92.45	106.30
4 h	62.83	32.96	95.89	5.64	96.54	102.78
8 h	14.37	84.48	98.85	0	103.45	103.45

Reaction condition: styrene oxide (1 mmol), catalyst (0.05 mmol), methanol (10 mL), at 70°C

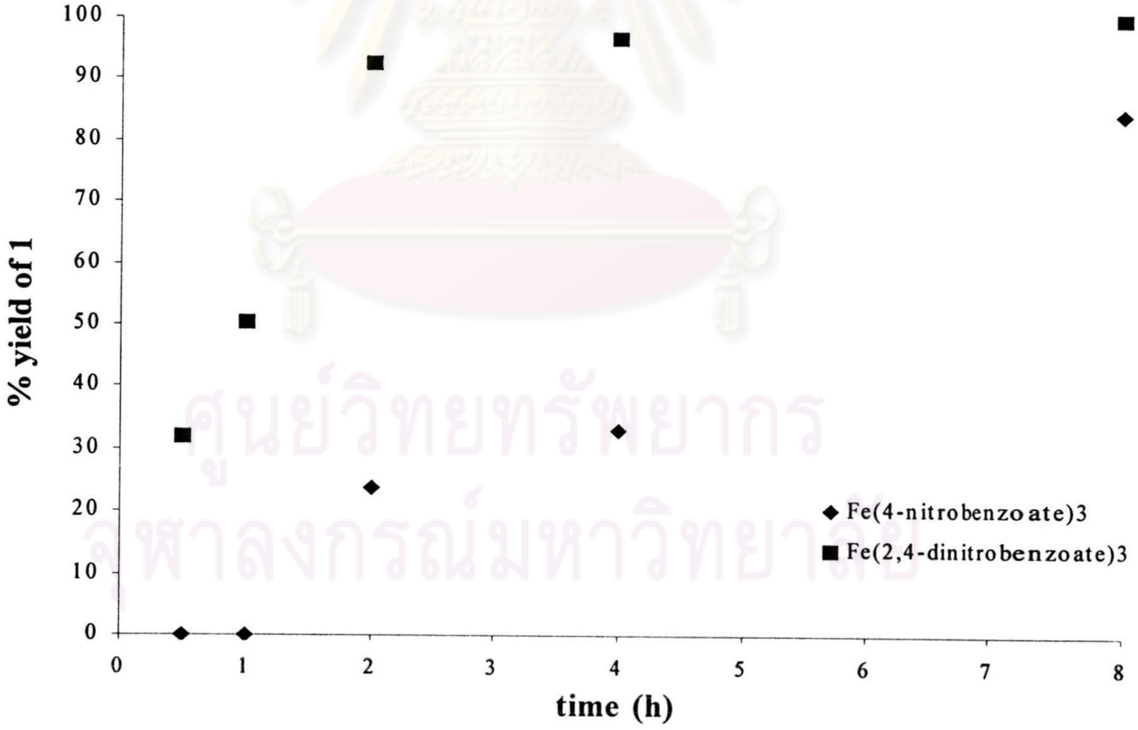


Figure 3.4 Effect of reaction time on styrene oxide ring opening reaction catalyzed by Fe(4-nitrobenzoate)$_3$ and Fe(2,4-dinitrobenzoate)$_3$

According to the experimental results, the rate of ring opening of styrene oxide catalyzed by Fe(2,4-dinitrobenzoate)$_3$ was found to be faster than that catalyzed by Fe(4-nitrobenzoate)$_3$. The half-life of the reaction catalyzed by Fe(2,4-dinitrobenzoate)$_3$ was about 1 h whereas that of Fe(4-nitrobenzoate)$_3$ was approximately 5 h. This result confirmed the capability of Lewis acid properties of Fe(2,4-dinitrobenzoate)$_3$.

3.4 Effect of metal salen and metal carboxylate on styrene oxide ring opening: A Comparative study

From the aforementioned result of the effect of metal salen and metal carboxylate complexes towords epoxide ring opening, it was noticed that Cr(salen)Cl was the best catalyst in metal salen complexes studied while Fe(2,4-nitrobenzoate)$_3$ was the best catalyst in metal carboxylate group. The comparative study results on the effect of these two catalysts on the rate of styrene oxide ring opening are shown in Table 3.7 and Figure 3.5.

Table 3.7 Comparative study on the effect of Fe(2,4-dinitrobenzoate)$_3$ and Cr(salen)Cl on styrene oxide ring opening

time	% yield (based on substrate) using Cr(salen)Cl			% yield (based on substrate) using Fe(2,4-dinitrobenzoate)$_3$		
	styrene oxide (recovered)	**1**	Σ	styrene oxide (recovered)	**1**	Σ
0.5 h	83.73	16.10	99.83	71.59	31.96	103.55
1 h	35.67	49.74	103.81	43.46	50.03	93.09
2 h	19.85	83.84	103.69	13.85	92.45	106.30
4 h	4.40	96.43	100.83	5.64	96.54	102.78
8 h	0	106.15	106.15	0	103.45	103.45

Reaction condition: styrene oxide (1 mmol), catalyst (0.05 mmol), methanol (10 mL), at 70°C

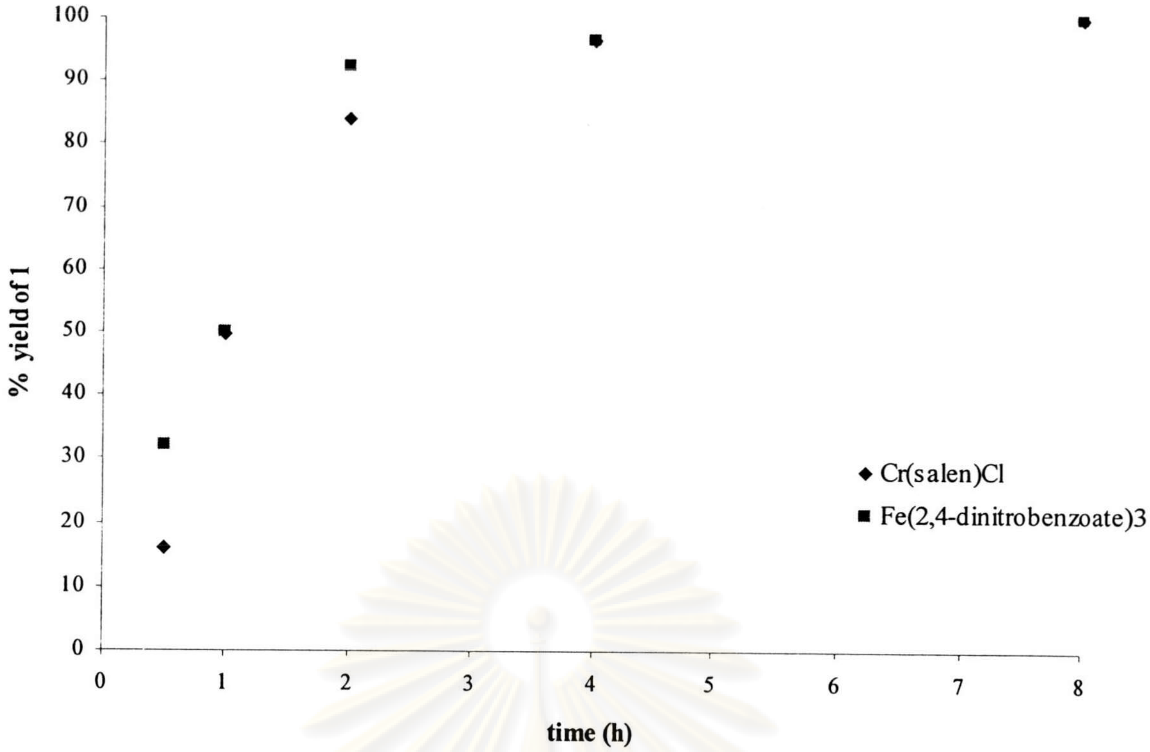


Figure 3.5 Comparative study on the effect of Fe(2,4-dinitrobenzoate)$_3$ and Cr(salen)Cl on styrene oxide ring opening

From Table 3.7 and Figure 3.5, it could be observed that Fe(2,4-dinitrobenzoate)$_3$ was more efficient catalyst than Cr(salen)Cl at initial reaction time (30 mins) The reaction utilized Fe(2,4-dinitrobenzoate)$_3$ gave moderate yield of the desired product in the first 0.5 h and the reaction was completed within 4 h. The half-life of this reaction was around 1h. On the other hand, the reaction utilized Cr(salen)Cl as a catalyst produced lower yield of product in 0.5 h. However the reaction was completed almost the same time as the above catalyst with the half-life approximately 1 h. Since there was no report concerning Fe(2,4-dinitrobenzoate)$_3$ as a catalyst in epoxide ring opening, this catalyst was selected for further exploration.

3.5 Effect of the amount of nucleophile on the epoxide ring opening reaction

3.5.1 Effect of the amount of nucleophile on the ring opening reaction catalyzed by Fe(TCA)$_3$·1.5H$_2$O and Fe(2,4-dinitrobenzoate)$_3$

The purpose to explore the effect of the amount of nucleophile on styrene oxide ring opening was stemmed from the high cost and relative toxicity of some nucleophiles which were employed as a solvent. In order to minimize the amount of nucleophile while maintaining the efficiency of the reaction, CH_3CN was picked up as a reaction media in this study. The variation of the amount of methanol in styrene oxide ring opening catalyzed by two effective catalysts, namely $Fe(TCA)_3{\cdot}1.5H_2O$ and $Fe(2,4\text{-dinitrobenzoate})_3$ was performed. The results of observation are exhibited in Table 3.8, Figures 3.6 and 3.7.

Table 3.8 Effect of the amount of methanol on the styrene oxide ring opening catalyzed by $Fe(TCA)_3{\cdot}1.5H_2O$ and $Fe(2,4\text{-dinitrobenzoate})_3$

entry	methanol (mmol)	% yield of **1** using $Fe(TCA)_3{\cdot}1.5H_2O$				% yield of **1** using $Fe(2,4\text{-dinitrobenzoate})_3$			
		time (min)				time (min)			
		10	30	60	120	10	30	60	120
1	5	3.38	5.27	5.83	6.61	0	0	0	1.04
2	20	12.08	22.49	26.97	30.73	0	1.33	3.19	9.89
3	50	43.76	65.34	74.86	83.65	2.68	5.09	10.46	14.18
4	100	61.84	84.56	94.91	102.02	3.42	8.64	12.80	22.69

Reaction condition: styrene oxide (1 mmol), catalyst (0.05 mmol), CH_3CN (3 mL), methanol, at room temperature (30°C)

It should be noted at this point that the use of $Fe(TCA)_3{\cdot}1.5H_2O$ and $Fe(2,4\text{-dinitrobenzoate})_3$ could selectively produce **1** almost quantitative yield within one hour using methanol 100 mmol. A comparative study on the effect of $Fe(TCA)_3{\cdot}1.5H_2O$ and $Fe(2,4\text{-dinitrobenzoate})_3$ was conducted and it was found that $Fe(TCA)_3{\cdot}1.5H_2O$ exhibited its capability more effective than $Fe(2,4\text{-dinitrobenzoate})_3$. As mentioned earlier, there was no report concerning the use of this complex in epoxide ring opening, therefore the following study will concentrate on the development of $Fe(TCA)_3.1.5H_2O$ as a catalyst in epoxide ring opening reaction.

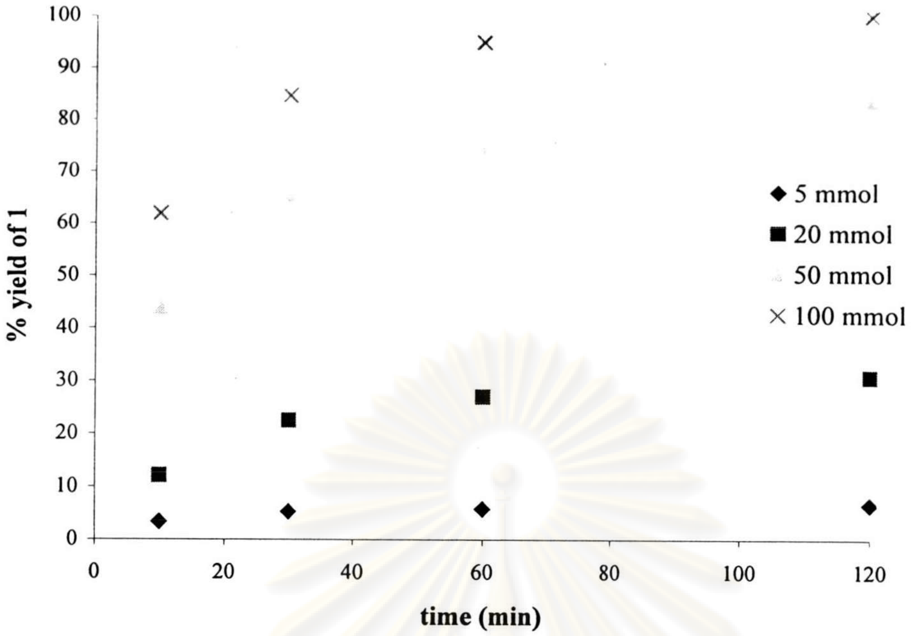


Figure 3.6 Effect of the amount of methanol on the styrene oxide ring opening catalyzed by $Fe(TCA)_3 \cdot 1.5H_2O$

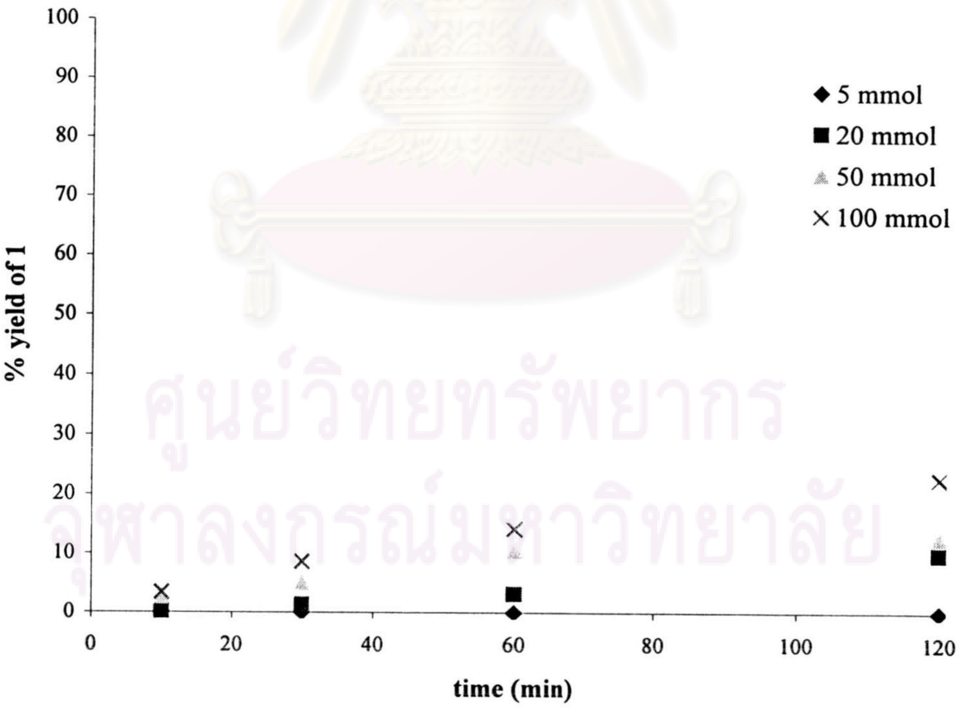


Figure 3.7 Effect of the amount of methanol on the styrene oxide ring opening catalyzed by Fe(2,4-dinitrobenzoate)$_3$

3.6 Effect of solvent on styrene oxide ring opening reaction

Solvents always play an important role to control the selectivity of the reaction. To observe the effect of various solvents on styrene oxide ring opening, a series of experiments was carried out and the results are displayed as shown in Table 3.9.

Table 3.9 Effect of solvent on styrene oxide ring opening reaction.

entry	solvent	% yield of **1** (based on substrate)			
		time (min)			
		10	30	60	120
1	CH_3CN	43.69	65.34	74.86	83.64
2	CH_2Cl_2	33.09	64.67	82.26	95.57
3	THF	6.50	16.30	26.64	45.59
4	DMF	0	0	0	0
5	EtOAc	30.27	64.00	82.45	89.48
6	CH_3CN : CH_2Cl_2 (70: 30)	37.69	72.21	78.84	79.52
7	CH_3CN : CH_2Cl_2 (50: 50)	40.17	59.15	83.61	84.42
8	CH_3CN : CH_2Cl_2 (30: 70)	45.21	75.75	91.53	97.39

Reaction condition: styrene oxide (1 mmol), $Fe(TCA)_3 \cdot 1.5H_2O$ (0.05 mmol), solvent (3 mL), methanol (50 mmol), at room temperature (30°C)

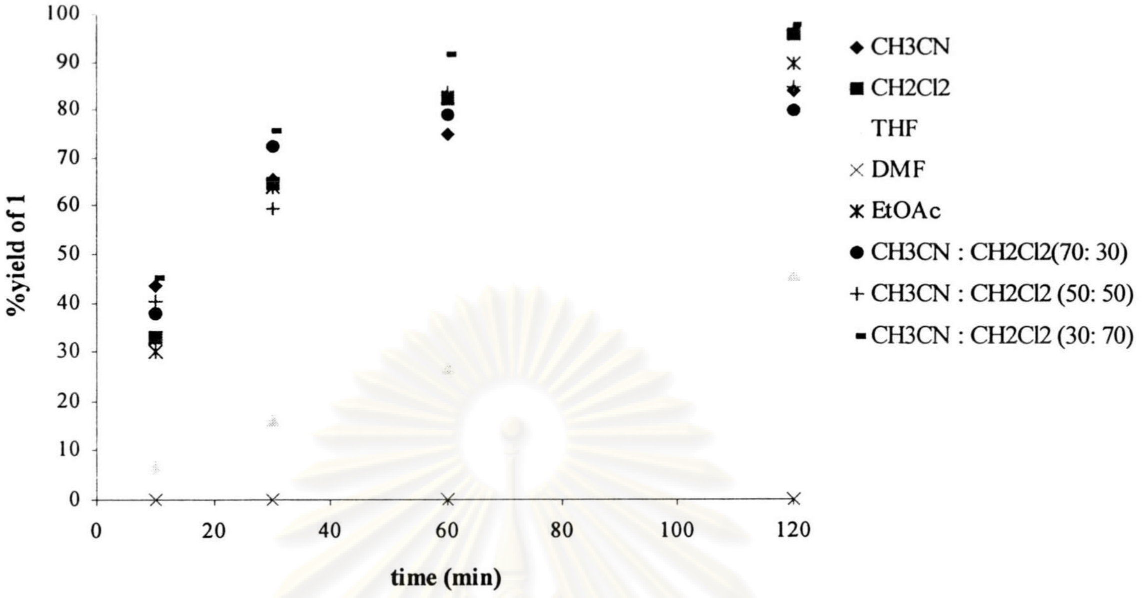


Figure 3.8 Effect of solvent on styrene oxide ring opening reaction

From the above results concerning with the variation of solvent, CH_3CN provided the highest yield of product in 10 min, however, for the long run within 120 min CH_2Cl_2 was superior in terms of producing the highest yield of **1**. On the contrast, DMF could not be used as a solvent for styrene oxide ring opening reaction. It was therefore noticed that under this particular conditions, aprotic polar solvent was suitable for this reaction. The mixed solvent of CH_3CN and CH_2Cl_2 was employed in the following experiments. This was stemmed from the observation that CH_3CN was an effective solvent for the first 10 min and CH_2Cl_2 was found to be good when the reaction was performed for some period of time. It was found that the ratio of CH_3CN:CH_2Cl_2 as 30:70 was suitable for this reaction. Nonetheless, in this research work, for convenience, CH_2Cl_2 was chosen as a solvent for studying the optimum conditions of epoxide ring opening.

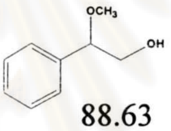
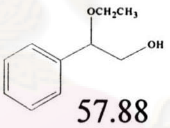
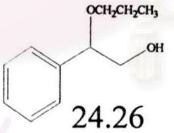
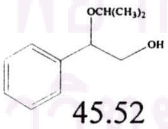
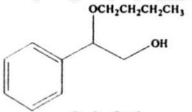
3.7 Variation of nucleophile for epoxide ring opening reaction

The nucleophilic addition of epoxide ring would transform epoxide into other important products in organic chemistry. Methanol was selected as a nucleophile to react with styrene oxide to yield 2-methoxy-2-phenylethanol **(1)** which had been reported to use as a calcium inhibitor.[42] Study on the variation of nucleophile for styrene oxide ring opening was therefore another important parameter that should be examined in this study.

3.7.1 Oxygen nucleophile

Methanol was primarily used as a nucleophile for studying ring opening of styrene oxide. The product obtained from using $Fe(TCA)_3 \cdot 1.5H_2O$ as a catalyst was found to be **1** selectively. Other alcohols including ethanol, *n*-propanol, *iso*-propanol and *n*-butanol were used as a nucleophile in this reaction and the outcome is presented in Table 3.10.

Table 3.10 Variation of oxygen nucleophile in styrene oxide ring opening

entry	nucleophile	% yield (based on substrate)		
		styrene oxide (recovered)	product	Σ
1	methanol	10.23	 88.63	98.86
2	ethanol	44.47	 57.88	102.35
3	*n*-propanol	70.47	 24.26	94.73
4	*iso*-propanol	56.59	 45.52	101.11
5	*n*-butanol	78.65	 24.96	102.91

Reaction condition: styrene oxide (1 mmol), alcohol (50 mmol), CH_2Cl_2 (5 mL), $Fe(TCA)_3 \cdot 1.5H_2O$ (0.05 mmol) at 40°C for 2 h

It could be seen that all alcohols selected could be utilized in as a nucleophile styrene oxide ring opening; however, with the different extent. Under this particular condition, the bulkier alcohol rendered the yield of the product from the epoxide ring opening. For instance, ethanol, *n*-propanol, isopropanol and *n*-butanol produced the corresponding products in lower yield than methanol. This was no doubt stemmed from the steric hindrance of bulky nucleophile to attack the electrophilic site of the molecule.[23] The selectivity of this reaction was however still superb. All reactions preferentially produced the sole product.

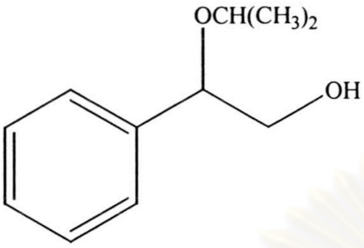
The structures of all products obtained were fully characterized by ^{1}H-NMR spectroscopy. To illustrate this, the peak $\mathrm{-C\mathbf{H}OEt}$ of 2-ethoxy-2-phenylethanol was detected a double doublet (1H) at 4.42 ppm (J = 8.78, 3.51 Hz), those of the $\mathrm{C\mathbf{H}_2OH}$ as a multiplet (2H) at 3.69-3.57 ppm, that of $\mathrm{OC\mathbf{H}_2CH_3}$ as a quartet (2H) at 3.42 ppm (J =7.00 Hz), the peak of $\mathrm{–CH_2C\mathbf{H}_3}$ as a triplet (3H) at 1.22 ppm (J = 7.03 Hz) and aromatic proton as a multiplet (5H) at 7.36-7.26 ppm.

The ^{1}H-NMR spectrum of 2-proproxy-2-phenylethanol clearly revealed the presence of aromatic protons as a mutiplet (5H) at 7.41-7.29 ppm. The peak of $\mathrm{–C\mathbf{H}CH_2OH}$ as a double doublet (1H) at 4.43 ppm (J = 7.80, 3.90 Hz), those of the $\mathrm{–CHC\mathbf{H}_2OH}$ as a double doublet (2H) at 3.69 ppm (J = 11.62, 3.88 Hz), $\mathrm{-OC\mathbf{H}_2CH_2}$ as a triplet (2H) at 3.40 ppm (J = 6.88 Hz), - $\mathrm{CH_2C\mathbf{H}_2CH_3}$ as a sextet (2H) at 1.65 ppm (J = 7.17 Hz) and $\mathrm{-CH_2C\mathbf{H}_3}$ as a triplet (3H) at 0.96 ppm (J = 7.41 Hz) were lucidly detected. The ^{1}H-NMR spectrum of 2-isopropoxy-2-phenylethanol exhibited the peaks of aromatic as a multiplet (5H) at 7.42-7.30 ppm, that of $\mathrm{–C\mathbf{H}(O}i\mathrm{-Pr)}$ as a double doublet (1H) at 4.57 ppm (J = 7.99, 4.47 Hz), those of $\mathrm{-C\mathbf{H}_2OH}$ and $\mathrm{–OC\mathbf{H}(CH_3)_2}$ as a mutiplet (3H) at 3.67-3.59 ppm, and those of the $\mathrm{–OCH(C\mathbf{H}_3)_2}$ as a doublet at 1.23 ppm (3H, J = 6.03 Hz) and 1.16 ppm (3H, J = 6.22 Hz), respectively.

The characterization of 2-butoxy-2-phenylethanol by ^{1}H-NMR spectrum was found the peak of aromatic as a multiplet (5H) at 7.39-7.33 ppm, the peak of $\mathrm{–C\mathbf{H}CH_2OH}$ as a double doublet (1H) at 4.47 ppm (J = 8.50, 3.83 Hz), $\mathrm{-CHC\mathbf{H}_2OH}$ as a multiplet (2H) at 3.79-3.68 ppm, those of $\mathrm{–OC\mathbf{H}_2CH_2}$ as a triplet (2H) at 3.42 ppm (J = 6.88 Hz), the peak of $\mathrm{–OCH_2C\mathbf{H}_2CH_2}$ as a multiplet (2H) at 1.63-1.60 ppm, those of $\mathrm{–CH_2C\mathbf{H}_2CH_3}$ as a sextet (2H) at 1.40 ppm (J = 7.25 Hz) and those of $\mathrm{–OCH_2CH_2CH_2C\mathbf{H}_3}$ as a triplet (3H) at 0.93 ppm (J = 7.41 Hz).

Further examination of isopropanol as an oxygen nucleophile

From Table 3.10, it could be noticed that under standard conditions, using isopropanol as a nucleophile yielded moderate yield of a ring opening product, namely 2-isopropoxy-2-phenylethanol **(3)**. Very trace amount of 2-isopropoxy-1-phenylethanol **(4)** was detected.



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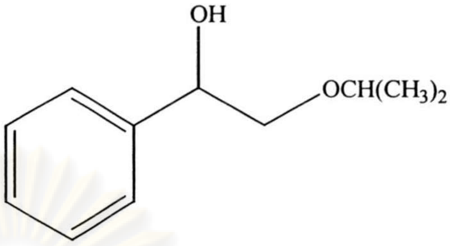


(4)

Various factors were therefore chosen to carry on the experiments to see whether under different conditions employed, the yield of target compound could be improved. Three main parameters including type of catalyst, temperature and reaction time, and the amount of catalyst were explored in details.

Effect of type of catalysts on styrene oxide ring opening by *iso*-propanol

Four catalysts were selected to observe their capability for styrene oxide ring opening using *iso*-propanol as a nucleophile. The results are presented in Table 3.11.

Table 3.11 Effect of type of catalysts on styrene oxide ring opening by *iso*-propanol

entry	catalyst	% yield (based on substrate)		
		styrene oxide (recovered)	**3**	Σ
1	Fe(TCA)$_3$·1.5H$_2$O	53.21	45.52	98.73
2	Fe(2,4-dinitrobenzoate)$_3$	72.14	28.13	100.27
3	Co(salen)	98.31	0	98.31
4	Cr(salen)Cl	96.74	0.88	97.62

Reaction condition: styrene oxide (1 mmol), *iso*-propanol (50 mmol), catalyst (0.05 mmol), CH_2Cl_2 (3 mL) at 40°C for 2 h

As it was previously noticed, Fe(TCA)$_3$·1.5H$_2$O was still the best catalyst for styrene oxide ring opening with *iso*-propanol Fe(2,4-dinitrobenzoate)$_3$ was also quite efficient catalyst for this reaction whereas both Co(salen) and Cr(salen)Cl were inactive. Thus, Fe(TCA)$_3$·1.5H$_2$O was chosen as a catalyst for this transformation with altering other reaction conditions parameters.

Effect of temperature and reaction time

With the aim to maximize the yield of the desired product, both temperature and reaction time were varied. The results are collected in Table 3.12.

Table 3.12 Effect of temperature and reaction time on styrene oxide ring opening by *iso*-propanol

temp (°C)	% yield of **3** (based on substrate)		
	time (h)		
	6	10	24
30	38.72	42.46	47.94
40	55.37	99.05	-

Reaction condition: styrene oxide (1 mmol), *iso*-propanol (50 mmol), CH$_2$Cl$_2$ (3 mL), Fe(TCA)$_3$·1.5H$_2$O (0.05 mmol)

It could be obviously seen that when the reaction conditions were a bit modified, the yield of the desired product, **3** was more satisfied. For instance, to rise up the reaction temperature from room temperature (30°C) to refluxing dichloromethane temperature, the yield of 2-isoproproxy-2-phenylethanol **(3)** was significantly increased. Within 10 h, styrene oxide was quantitatively converted to the ring opening product.

Effect of the amount of catalyst

Another plausible parameter that may affect the outcome of the reaction was the amount of catalyst. The effect of the amount of Fe(TCA)$_3$·1.5H$_2$O on styrene oxide ring opening was examined and the results are tabulated as shown in Table 3.13.

Table 3.13 Effect of the amount of catalyst on styrene oxide ring opening reaction

entry	catalyst (mmol)	% yield (based on substrate)		
		styrene oxide (recovereed)	**3**	Σ
1	0	96.36	0	96.36
2	0.01	96.08	7.06	103.14
3	0.05	51.71	45.52	98.17
4	0.10	17.45	84.74	102.19
5	0.30	0	103.39	103.39
6	0.50	0	96.66	96.66

Reaction condition: styrene oxide (1 mmol), *iso*-propanol (50 mmol),
CH_2Cl_2 (5 mL), $Fe(TCA)_3 \cdot 1.5H_2O$ at 40°C for 2 h

It was lucidly seen that the amount of catalyst was directly influenced the epoxide ring opening reaction. Increasing the amount of catalyst from 0.05 mmol to 0.30 mmol, styrene oxide could quantitatively transform to 2-isopropoxy-2-phenylethanol **(3)** within 2 hours.

From the series of experiments performed, the product derived from styrene oxide and *iso*-propanol could be achieved in excellent yield by various routes. To increase the temperature, reaction time or the amount of catalyst were three instances to be acquired to enchance the yield of products.

3.7.2 Nitrogen nucleophile

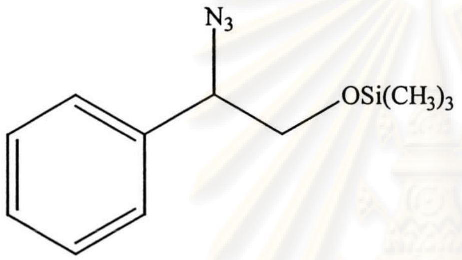
Many literatures reported the importance of amino alcohols.[13] These compounds could be synthesized by an epoxide ring opening reaction with amine or azide as a nucleophile. The nitrogen nucleophiles both amine and azide were thus selected to apply to the styrene oxide ring opening reaction under the particular conditions conducted in this work and the results are demonstrated in Table 3.14.

Table 3.14 Variation of nitrogen nucleophile in styrene oxide ring opening

entry	nucleophile	nucleophile (mmol)	% yield (based on substrate)				selectivity
			styrene oxide (recovered)	pdt-1	pdt-2	Σ	
1	diethylamine	50	106.76	0	0	106.76	-
2	$TMSN_3$	20	14.14	**(5)** 40.91	**(6)** 45.19	97.24	0.90

Reaction condition: styrene oxide (1mmol), nucleophile , CH_2Cl_2 (5 mL),

$Fe(TCA)_3 \cdot 1.5H_2O$ (0.05 mmol) at 40°C for 2 h



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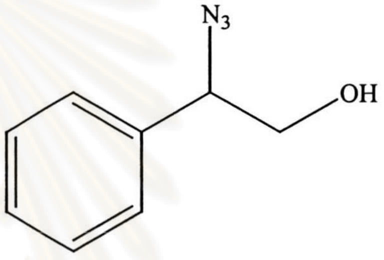


(6)

Under this particular condition, amines were found not to be appropriate nucleophile for epoxide ring opening in the presence of $Fe(TCA)_3 \cdot 1.5H_2O$. This may be because the Lewis acid property of the catalyst was rendered by amines added. Nonetheless, this studied conditions worked well for a nuclephile as trimethylsilyl azide ($TMSN_3$). Two products were obtained almost 1:1 with good mass balance of the reaction. Without the catalyst, almost of styrene oxide was recovered. 2-Azido-2-phenylethanol **(6)** was fully characterized by ^1H-NMR spectroscopy. To illustrate this, the peaks belonging to aromatic protons as a multiplet (5H) at 7.67-7.15 ppm, that of -C**H**N_3 as a triplet (1H) at 4.69 ppm (J = 6.24 Hz) and that of -C**H**$_2$OH as a doublet (2H) at 3.75 ppm (J = 7.80 Hz) were observed. The ^1H-NMR spectrum of **5** displayed the peak corresponded to aromatic protons as a multiplet at 7.21-7.08 ppm (5H) and that of –C**H**$_2$OSi(CH_3)$_3$ as a doublet (2H) at 4.10 ppm (J = 4.50 Hz), that of -C**H**N_3 as a triplet (1H) at 2.90 ppm (J = 2.20 Hz) and that of –CH_2OSi(C**H**$_3$)$_3$ as a singlet (9H) at 0.08 ppm.[12]

Chini and co-workers in 1990[46] reported the azidolysis of styrene oxide catalyzed by $Mg(ClO_4)_2$ to give the corresponding product in 78% yield. The reaction was performed at 80°C for 2 h. In this present work, the reaction was carried out at only 40°C for 2 h and gave the desired product in 86% yield. It was accordingly clearly seen that this reaction gave the higher yield of products at lower reaction temperature.

The products of azidolysis (**5** and **6**) could be applied for the production of an amino alcohol, an important product in medicinal industry, followed the cited methodology.[39] For instance, the removal of trimethylsilyl group in **5** could be accomplished in methanol using a catalytic amount of trifluoroacetic acid (0.1 mol%) at room temperature. The reduction of azide by the addition of 2 mol% PtO_2 to the resulting methanolic solution and hydrogenolysis under balloon pressure at room temperature yielded the amino alcohol in essentially quantitative yields.[39]

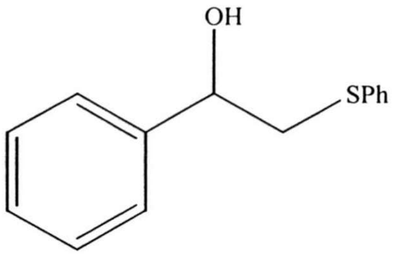
3.7.3 Sulfur nucleophile

Thiophenol was selected as a representative of sulfur nucleophile. Various catalysts including $Fe(TCA)_3{\cdot}1.5H_2O$, Fe(2,4-dinitrobenzoate)$_3$, Cr(salen)Cl and Co(salen) were exploited and the results are summarized in Table 3.15.

Table 3.15 Effect of type of catalysts on styrene oxide ring opening by thiophenol

entry	catalyst	% yield (based on substrate)				selectivity
		styrene oxide (recovered)	**7**	**8**	Σ	
1	$Fe(TCA)_3{\cdot}1.5H_2O$	39.50	17.88	43.64	101.02	0.41
2	$Fe(DNB)_3$	51.28	14.52	32.66	98.64	0.44
3	Co(salen)	91.89	2.45	5.57	99.91	0.44
4	Cr(salen)Cl	9.98	27.55	62.56	100.09	0.44

Reaction condition: styrene oxide (1mmol), thiophenol (50 mmol),
catalyst (0.05 mmol), CH_2Cl_2 (5 mL) at 40°C for 2 h



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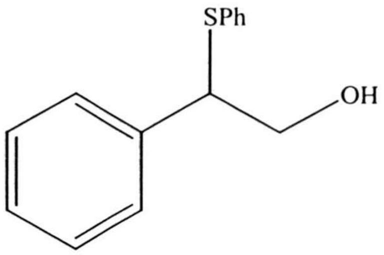


(8)

From the above results, Cr(salen)Cl was the best catalyst for styrene oxide ring opening reaction with thiophenol as a nucleophile. The selectivity for the product formation was not significantly different in any case. This may be because all of selected catalysts were of Lewis acid properties to induce benzylic carbon become positive site, at the same time steric hindrance of a nucleophile may influence on the selectivity of the ring opening reaction. Hence, the ratio of the isomeric products was different from those observed in the case of styrene oxide reacting with methanol. For the latter, the sole product was obtained since the nucleophile was not at all bulky. To characterize the two products received from the reaction, the separation of the crude product derived from the reaction employing Cr(selen)Cl as a catalyst was carried out using silica gel column chromatography with hexane:ethyl acetate (6:1) as an eluent. Two isolated products were achieved. The ^{1}H NMR spectrum of the major product, designated as **8** revealed the peak of aromatic protons as a mutiplet (10H) at 7.38-7.11 ppm, -**CH**SPh as a multiplet (1H) at 4.37-4.17 ppm and -**CH**$_2$OH as a multiplet (2H) at 3.99-3.74 ppm. This product was clearly characterized as 2-phenyl-2-phenylsulfanyl ethanol **(8)**. The ^{1}H NMR spectrum of the minor product displayed the peak of aromatic protons as a multiplet (10H) at 7.42-7.20 ppm, the peak of -C**H**OH as a doublet (1H) at 4.71 ppm (J = 9.30 Hz), and those of -C**H**$_2$SPh as a double doublet at 3.30 ppm (1H, J = 13.80, 3.60 Hz) and 3.08 ppm (1H, J = 13.80, 9.40 Hz).[12] The minor product was 1-phenyl-2-phenylsulfanyl ethanol **(7)**.

Another related work had previously been reported concerning the styrene oxide ring opening reaction with thiophenol as a nucleophile in the presence of tributylphosphine as a catalyst.[12] The reaction was stirred at room temperature under argon atmosphere for 12 h and yielded **7** and **8** in 88% yield. According to the conditions performed in this research, Cr(salen)Cl could catalyze styrene oxide ring opening reaction to give the desired product in 90% yield within 2 hours at 40°C.

$Fe(TCA)_3 \cdot 1.5H_2O$ could also catalyze this reaction to furnish 62% yield of **7** and **8**. The reaction conditions conducted in this research were found to be milder with short reaction time compared with those cited in the literature.

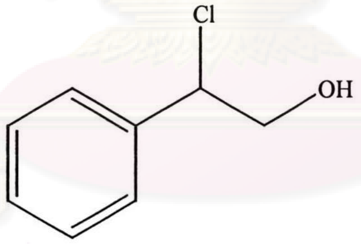
3.7.4 Halogen nucleophile

Lithium chloride was utilized as a halogen nucleophile. Since lithium chloride was a solid nucleophile, there was no choice to examine the effect of solvent. The results are accumulated in Table 3.16.

Table 3.16 Effect of solvent on styrene oxide ring opening by lithium chloride

entry	solvent	% yield (based on substrate)		
		styrene oxide (recovered)	2-chloro-2-phenylethanol	Σ
1	CH_2Cl_2	91.14	8.32	99.46
2	$CH_3CN:CH_2Cl_2$ (7:3)	98.86	0	98.86
3	CH_2Cl_2:DMF (5:12)	90.22	12.14	102.36

Reaction condition: styrene oxide (1mmol), LiCl (20 mmol), $Fe(TCA)_3 \cdot 1.5H_2O$ (0.05 mmol), solvent (10 mL) at 40°C for 2 h



From Table 3.16, it was observed that styrene oxide could be opened by a chloride nucleophile; however, the yield of the desired product was relatively low. Various solvents were chosen to dissolve lithium chloride prior to add to the reaction. The best mixed solvents studied was a mixture of CH_2Cl_2 and DMF (5:12). The product occurred from the reaction was characterized by ^{1}H-NMR spectroscopy. This product revealed a multiplet signal (5H) attributed to aromatic protons at 7.41-7.29 ppm, the peak of -**CH**Cl as a triplet (1H) at 3.90 ppm (J = 3.18 Hz), -**CH$_2$**OH as a double doublet (1H) at 3.19 ppm (J = 5.46, 3.90 Hz) and -**CH$_2$**OH as a double doublet (1H) at 2.85 ppm (J = 5.46, 2.71 Hz). From ^{1}H NMR spectrum, it was lucid that the product gained was 2-chloro-2-phenylethanol.

3.8 Rearrangement of styrene oxide

The rearrangement of epoxide has been extensively examined. The use of metal salt as a reagent for styrene oxide rearrangement are among those examples.[43] Recently, indium (III) chloride was claimed as a good reagent for this type of reaction and could transform styrene oxide into phenylacetaldehyde in good yield.[43] Under this particular conditions explored, $FeCl_3$ (anhydrous) and $Fe(TCA)_3\cdot 1.5H_2O$ were selected to observe whether the rearrangement of styrene oxide could be taken place. The results are presented as shown in Table 3.17.

Table 3.17 Effect of catalysts on rearrangement of styrene oxide

entry	catalyst	% yield (based on substrate)					selectivity
		styrene oxide (recovered)	acetophenone	phenyl acetaldehyde	2-chloro-2-phenylethanol	Σ	
1	$FeCl_3$	45.93	43.34	4.85	3.75	97.87	12:1.3:1
2	$Fe(TCA)_3\cdot 1.5H_2O$	88.92	8.32	0	0	97.24	-

Reaction condition: styrene oxide (1 mmol), catalyst (0.05 mmol), THF (5mL), at room temperature (30°C)

From Table 3.17, it was observed that using $FeCl_3$ (anhydrous) as a catalyst styrene oxide could be transformed to acetophenone as a major product and phenylacetaldehyde being a minor one if the reaction was performed in the absence of good nucleophile. Vary trace amount of 2-chloro-2-phenylethanol was also detected. The mechanism of rearrangement of styrene oxide was believed to depend on the migration pathway following Lewis acid promoted C-O bond cleavage. The rearrangement of styrene oxide with hydride migration would lead to acetophenone or phenylacetaldehyde, respectively.[43]

Comparing the effect of anhydrous $FeCl_3$ and $Fe(TCA)_3\cdot 1.5H_2O$, it could be observed that in the case of the rearrangement anhydrous $FeCl_3$ was more efficient catalyst than $Fe(TCA)_3\cdot 1.5H_2O$ to furnish the high yield of product. However $Fe(TCA)_3\cdot 1.5H_2O$ displayed better regioselectivity than $FeCl_3$ (anhydrous); only acetophenone was detected as a sole product. The development of this catalytic system for rearrangement of epoxide is still called for and will be another extensive task to be explored as the proposed future work.

3.9 Preliminary study on asymmetric ring opening of styrene oxide

Another important feature that needed to investigate was the enantioselectivity of the reaction. (*R*)-Styrene oxide was selected as a model substrate in this research to explore the enantioselective ring opening reaction using methanol as a nucleophile in the presence of $Fe(TCA)_3 \cdot 1.5H_2O$ as a catalyst.

Under the same strandard reaction conditions, styrene oxide and (*R*)-styrene oxide were reacted with methanol. Both substrates were quantitatively transformed to the corresponding ring opening product within 10 min. The products of (*R*)-styrene oxide and racemic styrene were separately analyzed by chiral column GC to observe the enantioselectivity of the reaction. The results are presented in Table 3.18 and Figures 3.9 and 3.10.

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Table 3.18 Preliminary study on asymmetric ring opening of styrene oxide

entry	substrate	% yield (based on substrate)			% enantiomeric of **1**			optical rotation (°)
		styrene oxide (recovered)	**1**	Σ	(*R*)-**1**	(*S*)-**1**	*ee*	
1	(*R*,*S*)-styrene oxide	0	99.02	99.02	49.69	50.31	0.62	-0.05
2	(*R*)-styrene oxide	0	100.00	100.00	11.74	88.25	76.51	+3.30

Reaction conditions: substrate (1 mmol), catalyst (0.05 mmol), methanol (3 mL) reaction time (10 min) at room temperature (30°C)

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system for rearrangement of epoxide is still called for and will be another extensive task to be explored as the proposed future work.

3.9 Preliminary study on asymmetric ring opening of styrene oxide

Another important feature that needed to investigate was the enantioselectivity of the reaction. (*R*)-Styrene oxide was selected as a model substrate in this research to explore the enantioselective ring opening reaction using methanol as a nucleophile in the presence of $Fe(TCA)_3{\cdot}1.5H_2O$ as a catalyst.

Under the same standard reaction conditions, styrene oxide and (*R*)-styrene oxide were reacted with methanol. Both substrates were quantitatively transformed to the corresponding ring opening product within 10 min. The products of (*R*)-styrene oxide and racemic styrene were separately analyzed by chiral column GC to observe the enantioselectivity of the reaction. The results are presented in Table 3.18 and Figures 3.9 and 3.10.

Table 3.18 Preliminary study on asymmetric ring opening of styrene oxide

entry	substrate	% yield (based on substrate)			% enantiomeric of **1**			optical rotation of **1**
		styrene oxide (recovered)	**1**	Σ	(*R*)-**1**	(*S*)-**1**	*ee*	
1	(*R,S*)-styrene oxide	0	99.02	99.02	49.69	50.31	0.62	-0.05
2	(*R*)-styrene oxide	0	100.00	100.00	11.74	88.25	76.51	+3.30

Reaction conditions: substrate (1 mmol), catalyst (0.05 mmol), methanol (3 mL)
reaction time (10 min) at room temperature (30°C)

Polarimeter condition: Bellingham+Stanley Ltd. ADP 220 quartz cell, $CHCl_3$ as a solvent at 25°C (5 mL)

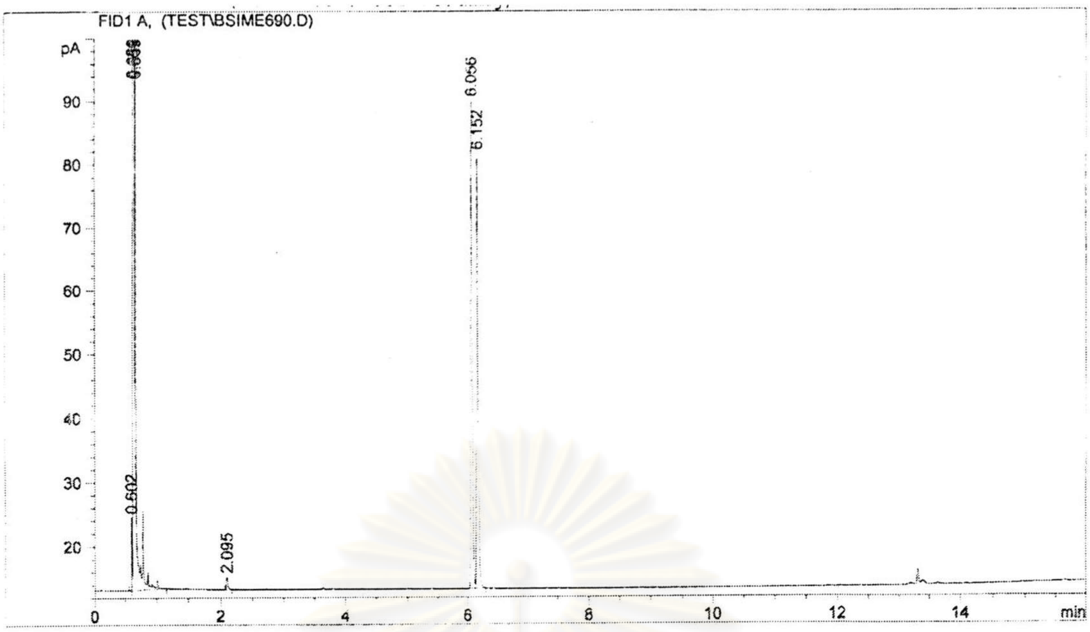


Figure 3.9 Chiral GC chromatogram of styrene oxide ring opening utilized $Fe(TCA)_3 \cdot 1.5H_2O$

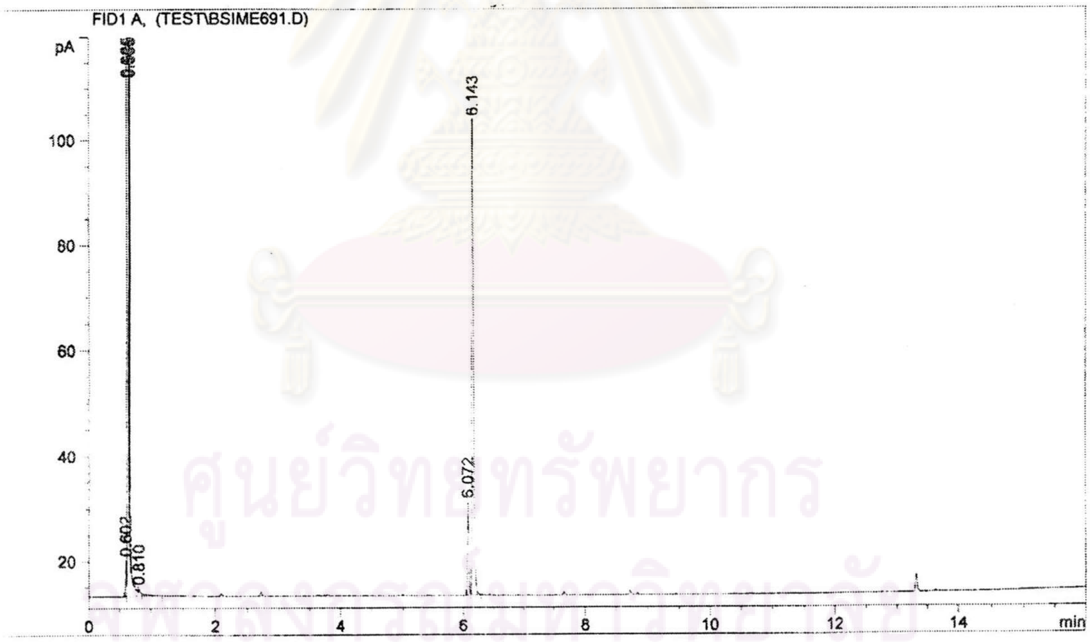
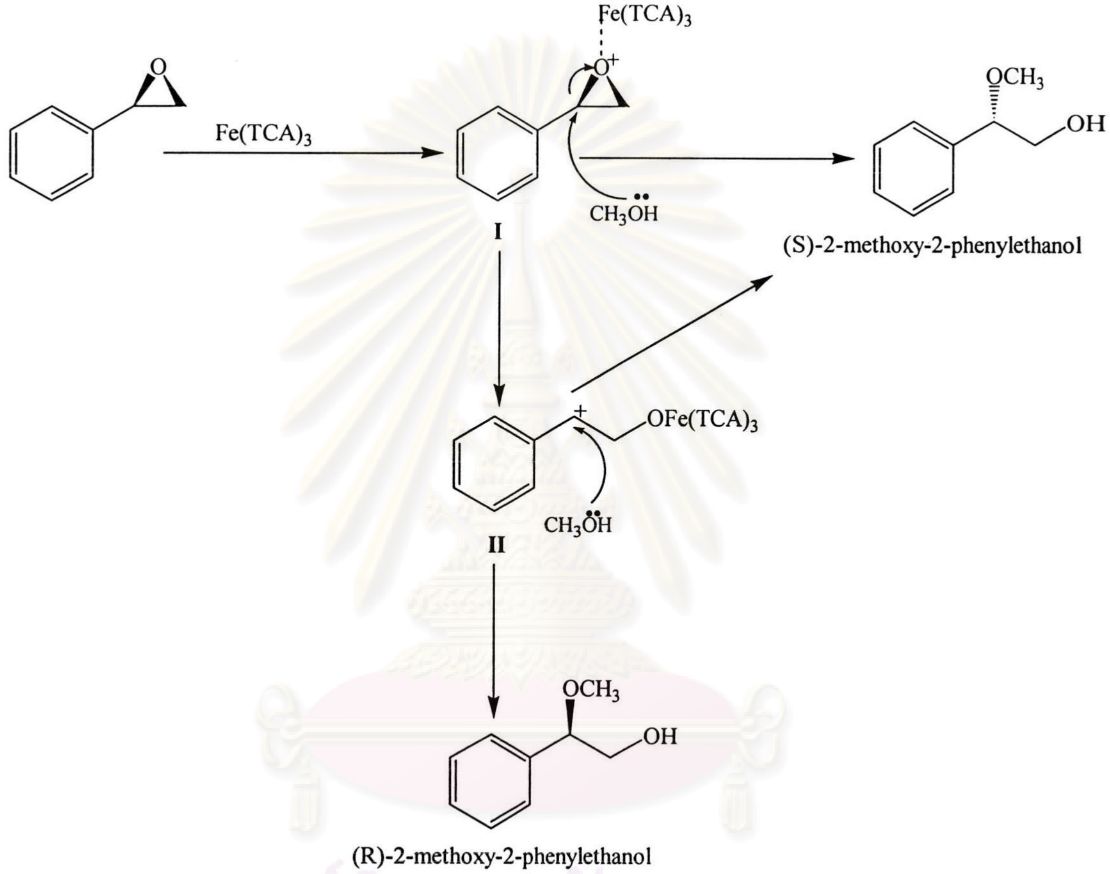


Figure 3.10 Chiral GC chromatogram of (*R*)-Styrene oxide ring opening utilized $Fe(TCA)_3 \cdot 1.5H_2O$

From the outcome of the reaction, it was observed that racemic styrene oxide gave two enantiomeric products of 2-methoxy-2-phenylethanol in ratio of about 1:1. Using (*R*)-styrene oxide as a starting material, (*S*)-2-methoxy-2-phenylethanol was obtained as a major product with 76.51 %*ee*. The outcome from this reaction gave a hint on the mechanism of (*R*)-styrene oxide ring opening reaction which was summarized in Scheme 3.1.



Scheme 3.1 Proposed mechanism of (*R*)-styrene oxide ring opening with methanol

The reaction was believed to take place in the similar fashion of S_N-1 reaction. (*R*)-Styrene oxide was first coordinated with $Fe(TCA)_3 \cdot 1.5H_2O$. The more stable benzylic position was a predominant site to be attacked by a methanol nucleophile yielding (*S*)-2-methoxy-2-phenylethanol. Nevertheless, since the formation of (*R*)- 2-methoxy-2-phenylethanol occurred in a ratio of (*S*):(*R*) 3:1, the free carbocation as II was ascertained to be formed. The latter, a minor pathway would lead to the production of (*R*)- 2-methoxy-2-phenylethanol.

3.10 Study on the ring opening of other epoxides catalyzed by $Fe(TCA)_3 \cdot 1.5H_2O$

To extened the scope of utilizing $Fe(TCA)_3 \cdot 1.5H_2O$ as a catalyst in epoxide ring opening, various epoxides, namely 1-dodecene oxide, cyclohexene oxide, butyl glycidyl ether, *tert*-butyl glycidyl ether and α-pinene oxide were chosen as a chemical probe.

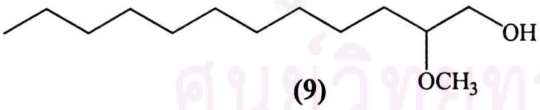
3.10.1 Ring opening of 1-dodecene oxide

1-Dodecene oxide was chosen as a representative of terminal aliphatic epoxide. This type of epoxide was relatively stable and not generally facile to be opened compared with other epoxides. Various factors including temperature, reaction time, amount of catalyst and solvent were investigated to optimize the reaction conditions of 1-dodecene oxide ring opening reaction. The results are tabulated in Table 3.19.

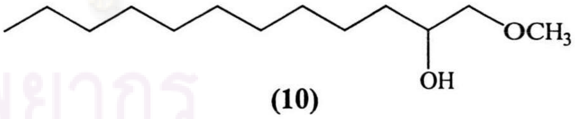
Table 3.19 Study on the optimum conditions of 1-dodecene oxide ring opening

entry	solvent	temp (°C)	time (h)	$Fe(TCA)_3\cdot 1.5H_2O$	% yield (based on substrate)				selectivity
					1-d.o. (recovered)	**9**	**10**	Σ	
1	none	40	2	0	95.89	0	0	95.89	-
2	none	30	2	0.05	36.50	35.52	24.90	96.92	1.4
3	none	40	2	0.05	0	56.52	43.42	99.94	1.3
4	none	40	1	0.05	47.34	27.59	19.94	94.87	1.4
5	none	40	1	0.1	3.22	52.91	42.90	99.03	1.2
6	none	40	1	0.2	0.95	56.80	44.36	102.11	1.3
7	CH_3CN	40	2	0.05	77.30	11.96	7.64	96.90	1.6
8	CH_3CN	40	4	0.05	70.30	18.44	11.69	100.43	1.6
9	CH_3CN	40	8	0.05	56.77	29.45	18.31	104.53	1.6
10	CH_3CN	80	2	0.05	66.61	17.65	11.45	95.71	1.5
11	CH_2Cl_2	40	2	0.05	94.22	6.10	4.33	104.65	1.4
12	THF	40	2	0.05	93.08	5.74	0.1	98.92	57.4
13	DMF	40	2	0.05	103.45	0	0	103.45	0

Reaction condition: 1-dodecene oxide (1 mmol), methanol (50 mmol), solvent (3 mL), $Fe(TCA)_3\cdot 1.5H_2O$ as catalyst



(9)



(10)

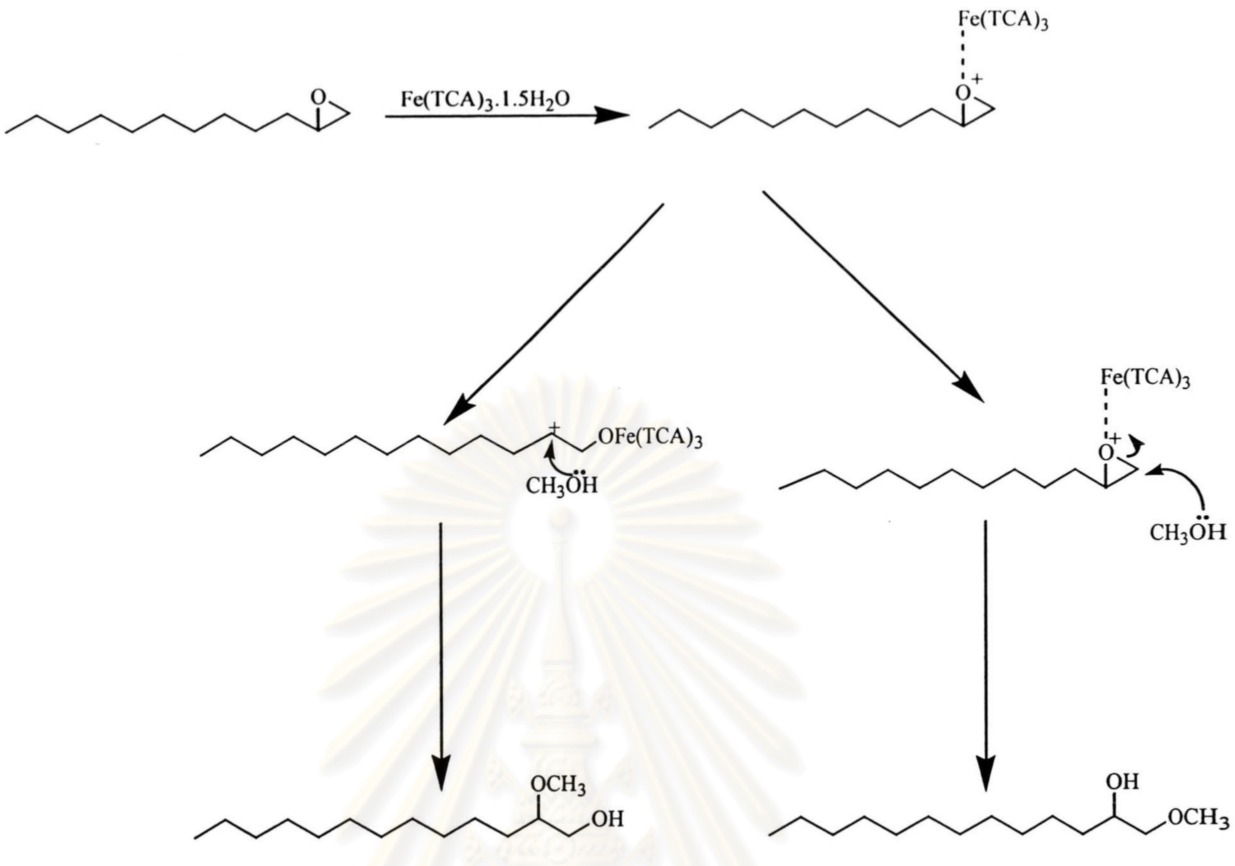
Table 3.19 displays various intriguing points. Without $Fe(TCA)_3\cdot 1.5H_2O$ (entry 1), the reaction did not take place; almost starting material, 1-dodecene oxide was recovered. The reaction using this catalyst at room temperature (30°C) (entry 2) yielded two isomeric products: 2-methoxy-1-dodecanol **(9)** and 1-methoxy-2-dodecanol **(10)** approximately 1.4:1 ratio with good mass balance. The structures of these two products were verified by ^{1}H-NMR spectroscopy. To illustrate this, **9** exhibited the methylene protons belonging to –CH_2OH as a double of doublet at 3.70 ppm (1H, J = 11.14, 2.93 Hz) and 3.52 ppm (1H, J =11.72, 6.44 Hz), the signal of

-OC$\mathbf{H}_3$ as a singlet (3H) at 3.44 ppm, of –C$\mathbf{H}$OCH_3 as a multiplet (1H) at 3.38-3.23 ppm, -C$\mathbf{H}_2$CH(OCH_3) as a multiplet (2H) at 1.68-1.44 ppm, of -(C$\mathbf{H}_2$)$_8$ as a multiplet (16H) at 1.40-1.22 ppm and of -C$\mathbf{H}_3$ as a triplet (3H) at 0.92 ppm (J = 6.73 Hz). The ^{1}H-NMR spectrum of **10** displayed the signal of –C$\mathbf{H}$(OCH_3) as a multiplet (1H) at 3.88-3.75 ppm, -C$\mathbf{H}_2$OH as two peak of doublet (1H) at 3.45 ppm (J = 2.93 Hz) and triplet (1H) at 3.52 ppm (J = 8.20 Hz), -OC$\mathbf{H}_3$ as a singlet (3H) at 3.44 ppm, -C$\mathbf{H}_2$CH (OCH_3) as a multiplet (2H) at 1.48-1.44 ppm, -(C$\mathbf{H}_2$)$_8$ as a multiplet (16H) at 1.38-1.23 ppm and -C$\mathbf{H}_3$ as a triplet (3H) at 0.90 ppm (J = 6.76 Hz).

It is worth noting that the use of this catalyst at an elevated temperature (40°C) provided predominant results. % Conversion of styrene oxide was quantitative and yielded **9** and **10** in higher yield than those using previous conditions (entries 1-2). When the reaction time was reduced to 1 h, the total yield became less. However, the yield of the desired product was getting better when the amount of the catalyst employed was increased (entries 4-6). The use of CH_3CN as a reaction medium did not enhance the yield of the reaction even the reaction time and temperature were altered. Other solvents either THF or DMF did not produce appreciated yield of the epoxide ring opening product.

Thus, it could be summarized the most appropriate conditions for 1-dodecene oxide ring opening as follows: 1-dodecene oxide 1 mmol, methanol 3 mL as a nucleophile, $Fe(TCA)_3 \cdot 1.5H_2O$ 0.05 mmol as a catalyst, reaction temperature at 40°C and reaction time for 2 h.

The mechanism of 1-dodecene oxide ring opening reaction could be taken place *via* that postulated for styrene oxide. Since the starting material epoxide was an ambident substrate, two sites could be attacked by a nucleophile. In case of styrene oxide, the influence of aromatic moiety induced the formation of benzylic cation prevailing over the other site carbocation possibly due to mainly resonance stabilization effect. Pondering in the case of 1-dodecene oxide, both carbocations generated had almost the same level of stability. Thereby, a nucleophile could possibly attack the epoxide ring either sites, preferably *via* S_N-1-like reaction. The proposed mechanism of 1-dodecene oxide ring opening reaction is shown in Scheme 3.2.



Scheme 3.2 Proposed mechanism of 1-dodecene oxide ring opening reaction

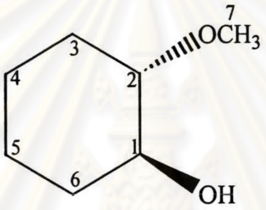
3.10.2 Ring opening of cyclohexene oxide

Cyclohexene oxide as a cyclic epoxide was selected as a chemical probe. Many previous works have reported the opening of cyclohexene oxide catalyzed by metal Schiff's base complexes.[16-19] In this present work, the use of $Fe(TCA)_3 \cdot 1.5H_2O$ as a catalyst for cyclohexene oxide ring opening was carried out. Three parameters: solvent, temperature and reaction time were examined and the results are tabulated as shown in Table 3.20.

Table 3.20 Study on the optimum conditions of cyclohexene oxide ring opening catalyzed by Fe(TCA)$_3$·1.5H$_2$O

entry	time (h)	% yield of **11** (based on substrate)		
		no extra solvent	CH_2Cl_2	
		30°C	30°C	40°C
1	2	98.60	16.78	19.76
2	4	98.47	21.98	24.01
3	8	100.58	22.10	24.92

Reaction condition: cyclohexene oxide (1 mmol), methanol (50 mmol), Fe(TCA)$_3$·1.5H$_2$O (0.05 mmol)



(11)

Cyclohexene oxide could regioselectively be opened to *trans*-2-methoxy-cyclohexanol with quantitative yield in the absence of any extra solvent (neat). It was clearly consistent with the mechanism that cyclohexene oxide ring opening proceeded with almost complete inversion of configuration. The isolated product was identified its identity by ^{1}H-NMR spectroscopy. The ^{1}H-NMR spectral assigment are present in Table 3.21.

Table 3.21 ^{1}H-NMR spectral assignments of **11**

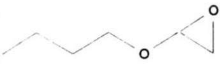
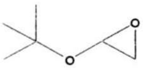
position	chemical shift (ppm)
1	3.16-3.14 (m)
2	2.98-2.88 (m)
3	1.80-1.58 (m)
4-5	1.37-1.00 (m)
6	2.19-1.96 (m)
7	3.33 (s)

The optimum conditions for cyclohexene oxide ring opening reaction were: cyclohexene oxide 1 mmol in methanol 3 mL catalyzed by $Fe(TCA)_3{\cdot}1.5H_2O$ 0.05 mmol at 40°C for 2 h. 98% Yield of desired product **11** was obtained. Comparison with other systems reported in literature,[16-19] it was found that in previous reports, the longer reaction time was required. For example, Jacobsen and coworkers reported the ring opening of cyclohexene oxide catalyzed by Co(salen) under nitrogen atmosphere for 12 h. Yielding 97% yield of product. This present work clearly provided another simply conditions for producing this kind of product with a short time.

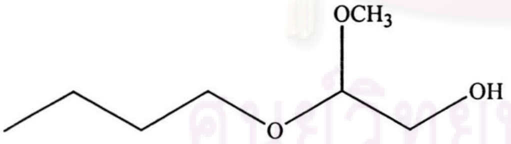
3.10.3 Ring opening of butyl glycidyl ether and *tert*-butyl glycidyl ether

Butyl glycidyl ether and *tert*-butyl glycidyl ether are epoxides containing an other ether functional group. The effects of reaction time and temperature on ring opening reaction of these two substrates are presented in Table 3.22.

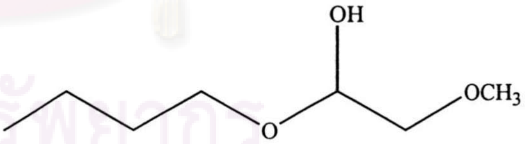
Table 3.22 Study on the optimum conditions of butyl glycidyl ether and *tert*-butyl glycidyl ether ring opening catalyzed by $Fe(TCA)_3{\cdot}1.5H_2O$

substrate	time (h)	temp (°C)	% yield (based on substrate)				selectivity
			starting material (recovered)	**12**	**13**	Σ	
butyl glycidyl ether	2	30	73.32	21.50	3.91	98.73	5.49
	24	30	10.83	68.99	14.86	95.83	4.64
	2	65	28.66	50.18	15.47	97.38	3.24
	4	65	0	66.72	17.00	92.35	3.92
	6	65	1.83	73.32	19.03	83.70	3.85
tert-butyl glycidyl ether				**14**	**15**		
	2	30	74.97	21.42	4.09	101.29	5.23
	24	30	0	81.16	16.92	98.08	4.79
	2	65	11.16	68.52	17.23	103.60	3.98
	4	65	0	72.77	18.56	91.33	3.92
	6	65	0	76.15	22.46	98.66	3.39

Reaction condition: epoxide (1 mmol), methanol (3 mL), $Fe(TCA)_3{\cdot}1.5H_2O$ (0.05 mmol)



(12)



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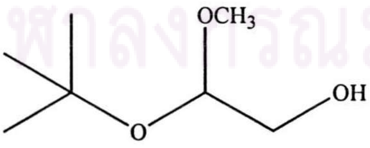
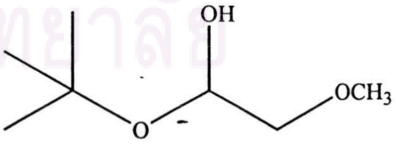


(14)



(15)

It was found that the epoxide ring of butyl glycidyl ether and *tert*-butyl glycidyl ether could be opened within 2 h at room temperature without any cleavage of the additional ether linkage containing in the molecule. The reaction was completed within 24 h at room temperature. When temperature was increased to 65°C, the reaction could be completed within 6 h. Two isomeric products were separated by silica gel column chromatography and characterized by ^{1}H-NMR spectroscopy.

The ^{1}H-NMR spectrum of **12** exhibited the signal of $\mathrm{-C\mathbf{H}OCH_3}$ as a multiplet (1H) at 3.91-3.87 ppm, $\mathrm{-OC\mathbf{H}_2CH_2}$ and $\mathrm{-C\mathbf{H}_2OH}$ as a multiplet (4H) at 3.57-3.54 ppm, $\mathrm{-OC\mathbf{H}_3}$ as a singlet (3H) at 3.41 ppm, $\mathrm{-OCH_2C\mathbf{H}_2}$ as a quintet (2H) at 1.59 ppm (J = 7.03 Hz), $\mathrm{-CH_2C\mathbf{H}_2CH_3}$ as a sextet (2H) at 1.32 ppm (J = 7.62 Hz) and $\mathrm{-C\mathbf{H}_3}$ as a triplet at 0.86 ppm (J = 7.32 Hz) while the ^{1}H-NMR spectrum of **13** exhibited the signal of $\mathrm{-C\mathbf{H}OH}$ as a triplet (1H) at 4.90 ppm (J = 3.56 HZ), $\mathrm{–C\mathbf{H}_2OCH_3}$ as a doublet (2H) at 3.69 ppm (J = 2.90 Hz), $\mathrm{-OC\mathbf{H}_2CH_2}$ as a triplet (1H) at 3.49 ppm (J = 3.61Hz), $\mathrm{-OC\mathbf{H}_3}$ as a singlet (3H) at 3.24 ppm, $\mathrm{-OCH_2C\mathbf{H}_2}$ as a quintet (2H) at 1.46 ppm (J = 7.03 Hz), $\mathrm{-CH_2C\mathbf{H}_2CH_3}$ as a sextet (2H) at 1.33 ppm (J = 7.02 Hz) and $\mathrm{-C\mathbf{H}_3}$ as a triplet at 0.96 ppm (J = 7.32 Hz).[23]

The ^{1}H-NMR spectrum of **14** revealed the $\mathrm{-C\mathbf{H}OCH_3}$ signal as a singlet (1H) at 3.80 ppm, $\mathrm{-C\mathbf{H}_2OH}$ as a multiplet (2H) at 3.50-3.31 ppm, $\mathrm{-OC\mathbf{H}_3}$ as a singlet (3H) at 3.39 ppm and $\mathrm{C(C\mathbf{H}_3)_3}$ as a singlet (9H) at 1.20 ppm whereas the ^{1}H-NMR spectrum of **15** revealed the $\mathrm{-C\mathbf{H}OH}$ signal as a triplet (1H) at 4.90 ppm (J = 3.56 Hz), $\mathrm{-C\mathbf{H}_2OCH_3}$ as a doublet (2H) at 3.69 ppm (J = 2.90 Hz), $\mathrm{-OC\mathbf{H}_3}$ as a singlet (3H) at 3.24 ppm and $\mathrm{C(C\mathbf{H}_3)_3}$ as a singlet (9H) at 1.21 ppm.[44]

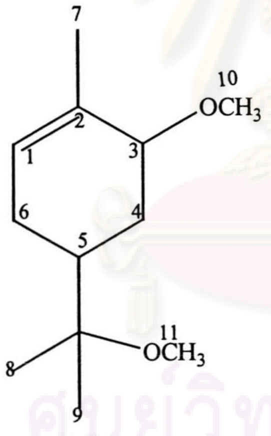
3.10.4 Ring opening of α-pinene oxide

α-Pinene oxide, a bicyclic epoxide was selected as another chemical probe. Under the optimum conditions generally employed, five products from this reaction were detected by GC whereas α-pinene oxide could not be recovered. The products from the reaction were separated by column chromatography yielding two major products. The structures of two products were characterized by ^{1}H-NMR spectroscopy.

Table 3.23 Ring opening of α-pinene oxide

% yield of product (based on substrate)						
α-pinene oxide	t_R = 13.11 min	t_R = 13.72 min	**16**	t_R = 15.06 min	**17**	Σ
0	8.65	9.10	30.31	9.79	37.38	95.23

Reaction condition: α-pinene oxide (1 mmol), methanol (5 mL), $Fe(TCA)_3 \cdot 1.5H_2O$ (0.05 mmol) at 70°C for 2 h



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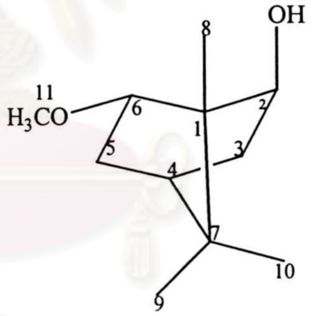


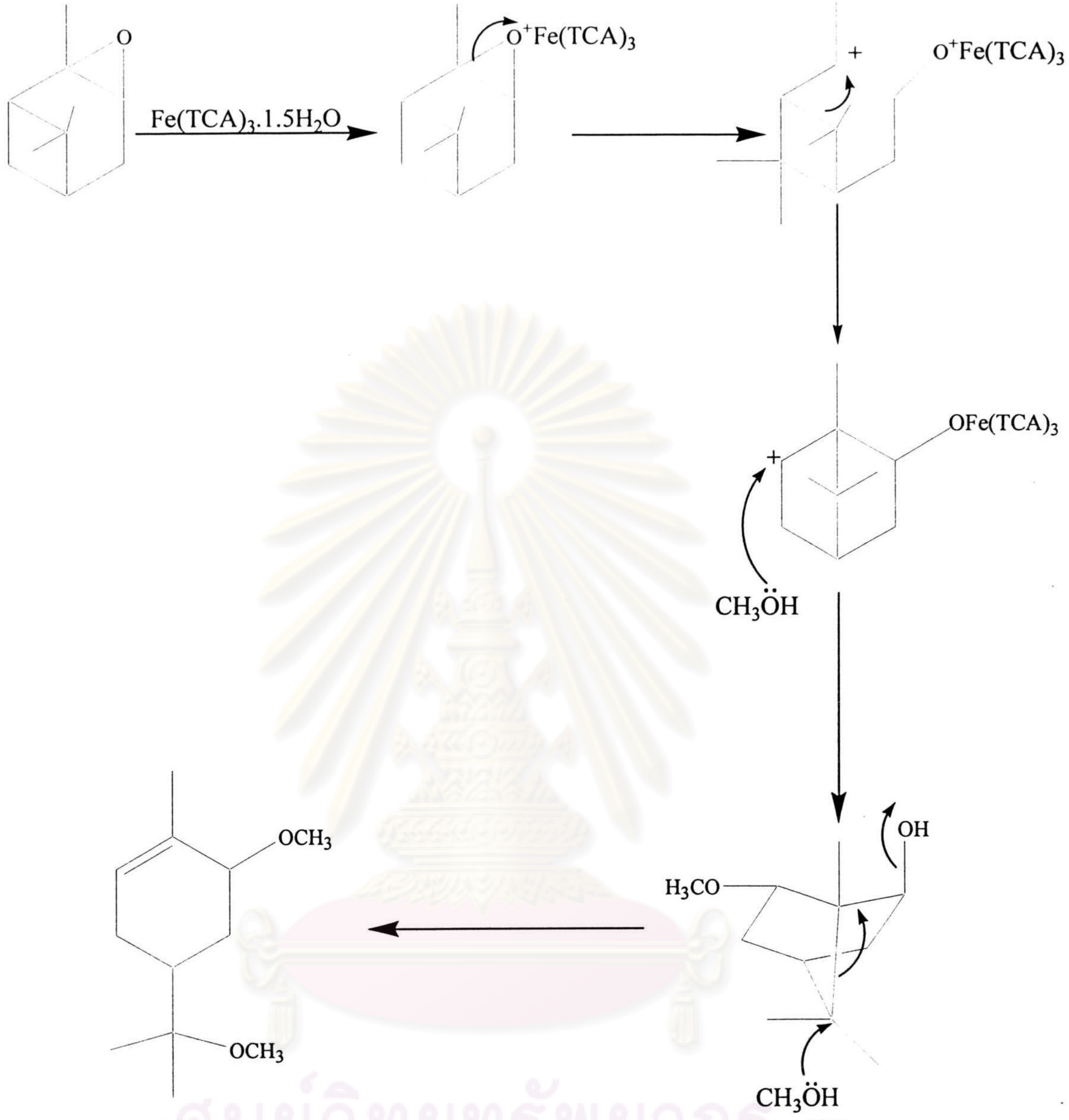
(17)

Comparing with that reported in literature[32], two major products obtained were charaterized as sobrerol dimethyl ether **(16)** and 1,7,7-trimethyl-6-*exo*-methoxy bicyclo [2.2.1]-heptan-*endo*-ol **(17)**. The ^{1}H-NMR spectral assignments are tabulated in Table 3.23.

Table 3.24 ^{1}H-NMR spectral assignments of compounds **16** and **17**

compound	position	chemical shift (ppm)
16	1	5.62 (br s)
	3	3.53 (br s)
	4	1.74-1.70 (m)
	6	2.17 (dd, *J* = 13.26, 1.56 Hz)
		2.03-1.95 (m)
	7	1.79 (br s)
	8	1.15 (s)
	9	1.13 (s)
	10	3.42 (s)
	11	3.21 (s)
17	2	4.12-4.08 (br m)
	3	2.49-2.43 (m)
		1.26 (dd, *J* = 13.26, 3.90 Hz)
	4	1.80-1.77 (m)
	5	2.35-2.27 (m)
		1.38 (dd, *J* = 13.26, 3.12 Hz)
	6	3.86 (d, *J* = 9.35 Hz)
	8	1.09 (s)
	9	0.87 (s)
	10	0.86 (s)
	11	3.37 (s)

The mechanism of α-pinene oxide ring opening reaction was believed to take place *via* the same route as previously proposed.[32] Two postulated pathways of α-pinene oxide ring opening reaction are shown in Scheme 3.3.



(16) **(17)**

Scheme 3.3 Mechanism of α-pinene oxide ring opening reaction

The possible ring opening reaction of α-pinene oxide was believed to initially take place by the iron catalyst to form a coordinate bond with an oxygen of epoxide atom and induced the formation of a partial positive charge at a carbon atom of epoxide ring. Then C-O bond was broken in the way to form a stable carbocation. 1,2-Shift migration was then occurred and methanol as a nucleophile would attack to the carbocation generated to give **17** as a product. Since a bicyclic still had a ring strain in a molecule, methanol could further attack to the bridge head carbon and dehydration was subsequently underwent to yield **16** as another furnish detected product.

3.11 Competitive studies on the ring opening reaction of epoxides

The competitive study on the ring opening reaction among epoxides selected: styrene oxide, 1-dodecene oxide, cyclohexene oxide, butyl glycidyl ether and *tert*-butyl glycidyl ether were performed to observe their reactivity. The results are shown in Table 3.25.

Table 3.25 Competitive study on the ring opening reaction of selected epoxides

entry	substrate		% yield (based on substrate)						reactivity epoxide1/ epoxide2
	epoxide 1	epoxide 2	**1**	pdt. of 1-d.o.		**11**	**12**	**14**	
				9	**10**				
1	s.o.	c.o.	71.47	-	-	34.71	-	-	2.1
2	s.o.	1-d.o.	72.36	9.53	6.49	-	-	-	4.5
3	s.o	BGE	83.54	-	-	-	1.70	-	49.14
4	s.o.	TBGE	86.72	-	-	-	-	2.63	32.97
5	1-d.o	c.o.	-	8.83	7.59	41.15	-	-	0.39
6	1-d.o.	BGE	-	7.08	4.66	-	1.43	-	8.21
7	1-d.o.	TBGE	-	2.80	1.89	-	-	0.64	7.3
8	c.o.	BGE	-	-	-	28.52	1.15	-	24.78
9	c.o.	TBGE	-	-	-	31.51	-	2.15	14.65
10	BGE	TBGE	-	-	-	-	2.03	2.45	0.83

Reaction condition: epoxide (1 mmol each), methanol (3 mL), $Fe(TCA)_3 \cdot 1.5H_2O$ (0.05 mmol) stir at room temperature for 10 min

Table 3.25 reveals the competitive study among selected epoxides: aromatic epoxide (styrene oxide); cyclic epoxide (cyclohexene oxide); terminal aliphatic epoxide (1-dodecene oxide) and epoxide containing etheral linkage (butyl glycidyl ether and *tert*-butyl glycidyl ether). Styrene oxide could be transformed to the ring opening product very efficiently because of the influence from the resonance stabilization effect towards the benzylic site. Since cyclohexene oxide was a cyclic compound containing an epoxide ring, it may have an appropriate compact structure to be facilely attacked by a nucleophile.

The less reactivity epoxides could be observed from 1-dodecene oxide, butyl glycidyl ether and *tert*-butyl glycidyl ether. The possible explanation should be come from the less stable intermediates were consequently generated, the reaction may need some more time to be completed or modified reaction conditions such as increasing temperature or amount of catalyst were required.