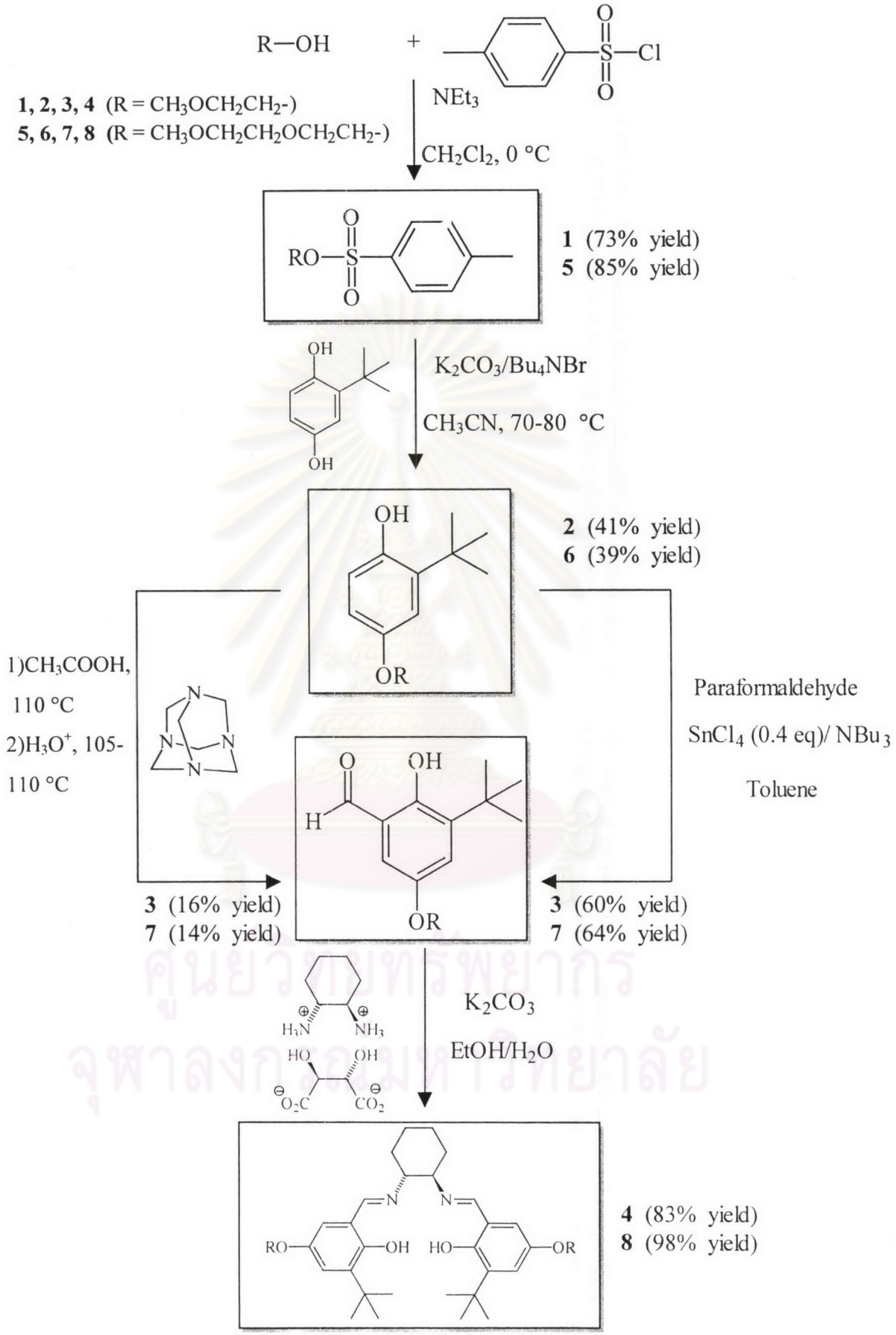
CHAPTER III

RESULTS AND DISCUSSION

3.1 Synthesis and characterization of chiral salen complexes containing ethylene glycol chains 9 and 10

The syntheses of ligands **4** and **8** were conducted according to Scheme 3.1. In the first step, tosylated compounds were prepared by a tosylation of the corresponding monomethyl ether of ethylene glycol chains with 4-toluenesulfonyl chloride (TsCl). Nucleophilic substitutions of the tosylates with *t*-butylhydroquinone gave the monoalkylated products. The following formylations of the monoalkylated phenols afforded the desired salicylaldehyde derivatives. The final step was performed using a condensation reaction between the salicylaldehydes and *(R,R)*-1,2-diaminocyclohexane to give the target chiral salens.

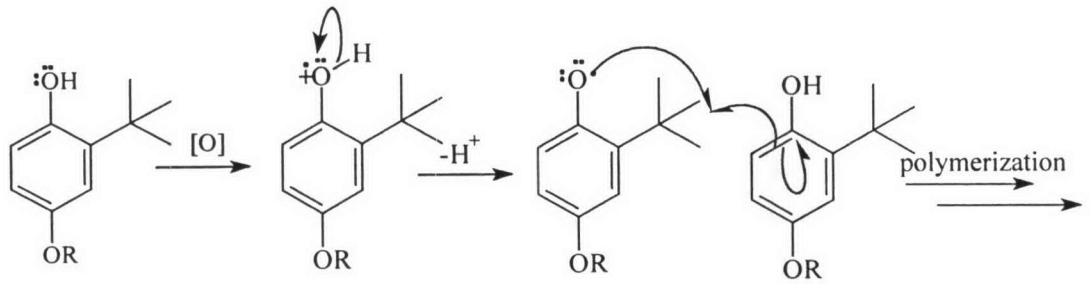
The tosylation of ethylene glycol monomethyl ether with 1 equivalent of TsCl in dichloromethane gave a viscous pale yellow liquid **1** (73% yield), which was sufficiently pure for the next synthesis without further purification after the work-up process. The ^{1}H-NMR spectrum of **1** showed doublets of doublet signals of aromatic protons (Ar<u>H</u>) at 7.31 and 7.77 ppm and a singlet signal of the methyl group (Ar<u>CH</u>$_3$) at 2.43 ppm instead of a broad peak of the hydroxy proton at 4.30 ppm (<u>H</u>OCH$_2$CH$_2$OCH$_3$) found in the spectrum of the starting monomethyl ether. The tosylate ester **5** was synthesized from diethylene glycol monomethyl ether by the same procedure. It was obtained as a viscous pale yellow liquid (85% yield) after the work-up process. The yield of the tosylates was noted to depend on the storage time of TsCl.



Scheme 3.1 Synthetic pathway of chiral salens containing ethylene glycol chains.

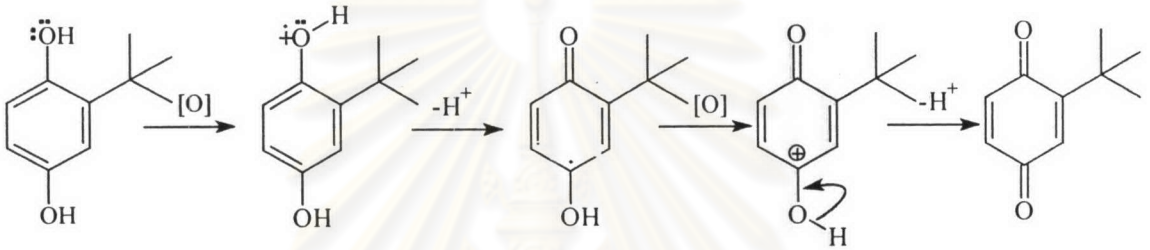
The nucleophilic substitution of tosylate **1** with *t*-butylhydroquinone gave the alkylated product **2** as a viscous dark brown liquid. The first condition of alkylation was performed by mixing *t*-butylhydroquinone with 1 equivalent of tosylated **1** in a presence of 2 equivalents of K_2CO_3 as a base and 10 mol% of tetrabutylammonium bromide as a phase transfer catalyst to give the desired product (34% yield). In the second condition, Cs_2CO_3 was used instead of K_2CO_3 as a base in the reaction in order to reduce the ion pairing effect in the nucleophile. The yield of product was improved only slightly (41% yield). The low yield of this S_N2 reaction was presumably due to competitive polymerization of *t*-butylhydroquinone, dialkylation reaction and oxidation reaction of *t*-butylhydroquinone and its monoalkylated product (Scheme 3.2). The ^{1}H-NMR spectrum of **2** showed a broad peak of hydroxy group at 4.95 ppm and a peak of *t*-bu^{t}yl group at 1.35 ppm indicating the attachment of *t*-butylhydroquinone group. The integrals of signals corresponded very well with the monosubstitution of the ethylene glycol chain on *t*-butylhydroquinone.

Polymerization reaction :

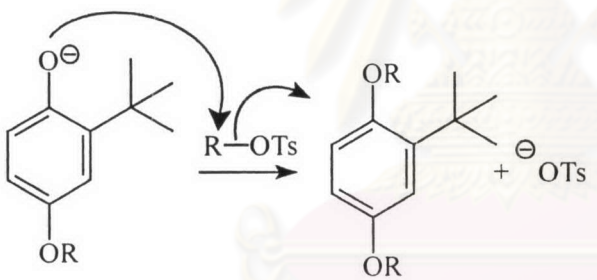


R = H, $CH_3OCH_2CH_2$-

Oxidation reaction :



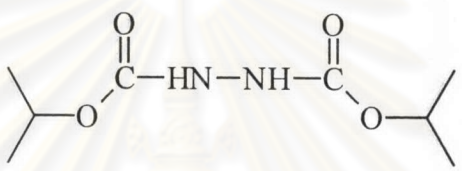
Dialkylation :



Scheme 3.2 Possible competitive reactions during monoalkylation of *t*-butylhydroquinone.

The synthesis of alkylated *t*-butylhydroquinone **6** by an alkylation of *t*-butylhydroquinone by tosylate **5** was carried out under varied reaction conditions. The alkylation of *t*-butylhydroquinone by the tosylate ester of diethylene glycol monomethyl ether **5** in acetonitrile in the presence of 2 equivalents of K_2CO_3 as a base and 10 mol% of tetrabutylammonium bromide gave the product in 39% yield (entry 1, Table 3.1). In another condition, a few drops of H_2O was deliberately added into the reaction aiming to increase the solubility of K_2CO_3 in the reaction media. The alkylation yield however disappointingly decreased to 10% (entry 2). Furthermore, the reaction was also performed under sonication in place of heating in order to reduce oxidation

and other side reactions of *t*-butylhydroquinone. The sonication at 50°C was however not effective enough to allow the alkylation to proceed (entry 3). In another condition, the preparation of **6** by using a strong base, sodium hydride, was performed. This condition however gave dialkylated *t*-butylhydroquinone as a major product (entry 4). The attempt to use Mitsunobu reaction for synthesis of **6** by condensation of *t*-butylhydroquinone with diethylene glycol monomethyl ether in the presence of triphenyl phosphine and diisopropyl azadicarboxylate (DIAD) was carried out.[26] The difficulty in isolating of the desired product **6** from the urethane byproduct **11** prevented the useful application of this reaction for synthesis of **6** (entry 5).



Compound 11

Table 3.1 The percent yield of **6** in various reaction conditions

Entry	Condition	% yield
1	K_2CO_3(1.1 eq), Bu_4NBr(10%),CH_3CN, 70-80 °C	39
2	K_2CO_3(1.1 eq), Bu_4NBr(10%),CH_3CN, 2 drops H_2O, 70-80 °C	10
3	K_2CO_3(1.1 eq), Bu_4NBr(10%),CH_3CN, sonication, 50 °C	trace(TLC)
4	NaH(1 eq), dry THF, 0 °C	dialkylation
5	$CH_3O(CH_2CH_2O)_2H$, DIAD, PPh_3, dry THF, 0-5 °C	cannot purify

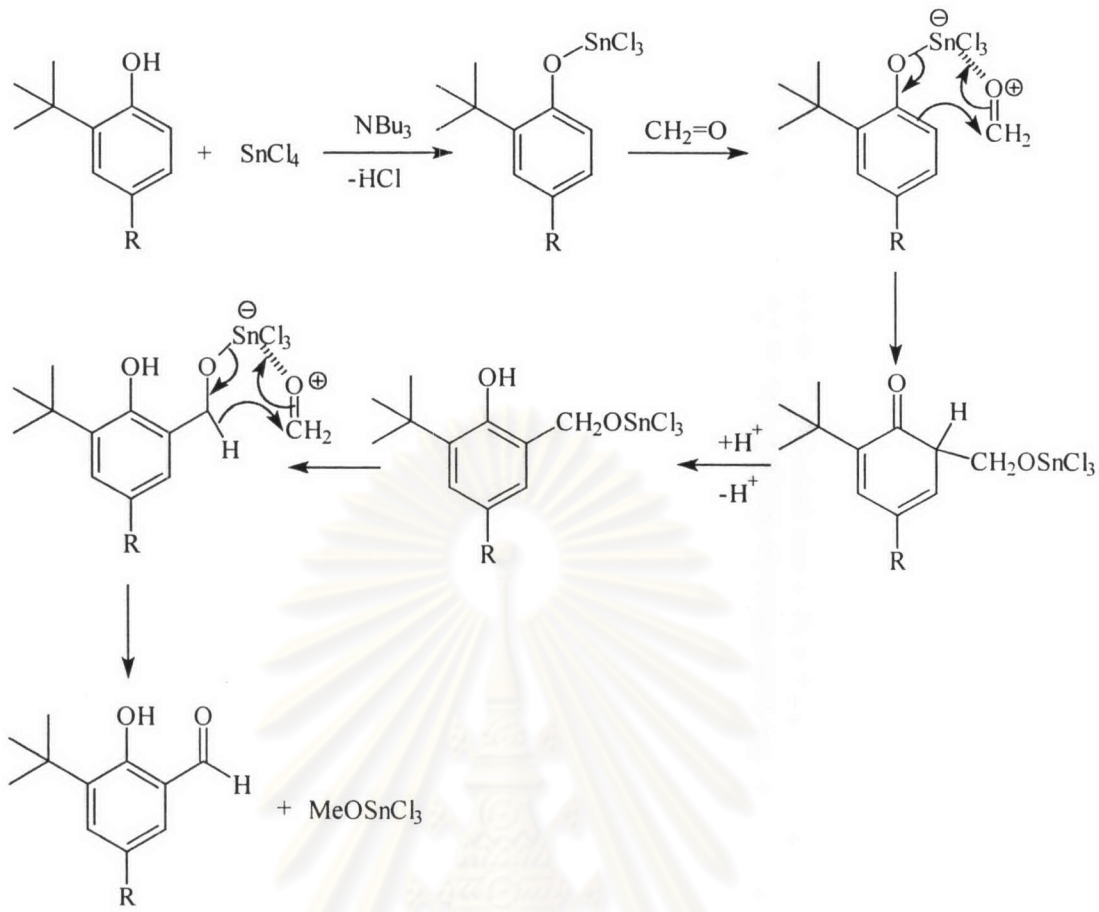
The formylation of products **2** and **6** with hexamethylenetetramine (HMT) in glacial acetic acid (Duff reaction)[27] gave salicylaldehydes **3** and **7** as viscous yellow liquids in 16% and 14% isolated yields, respectively (entry 1 and 6, Table 3.2). The Duff reaction offered significant advantages over other formylation methods that it involves less toxic reagents and the reagents do not require special handling. In the synthesis of **3** and **7**, the reaction however gave low yields of the desired aldehydes. Another method for ortho-

formylation of phenol was thus investigated. This reaction was performed by mixing *t*-butylhydroquinone derivatives with paraformaldehyde in the presence of 0.4 equivalent of $SnCl_4$ and tributylamine as a base in dry toluene.[28] The yields of **3** and **7** from this reaction increased to 60% and 64% respectively. Unlike Duff reaction, the reaction is irreversible. The mechanism of this reaction was shown in Scheme 3.3. The suitable amount of $SnCl_4$ for this reaction is 0.4 equivalent to 1 equivalent of the starting phenols. Another formylation used paraformaldehyde as a formylating agent and $MgCl_2$ as an ortho-directing reagent in the presence of triethylamine.[29] But the desired product **3** was not observed after work-up process. This may be due to the competitive of complexation of Mg^{2+} by ethylene glycol chain of the phenol **2** that reduces the ability of chelation by phenolic oxygen (Figure 3.1).

Table 3.2 The percent yield of **3** and **7** in various reaction conditions

Entry	Product	Condition	% yield
1	**3**	HMT, CH_3COOH, 110 °C	16
2	**3**	paraformaldehyde, $SnCl_4$(0.4 eq), NBu_3, Toluene, 100 °C	60
3	**3**	paraformaldehyde, $SnCl_4$(1.0 eq), NBu_3, Toluene, 100 °C	52
4	**3**	paraformaldehyde, $MgCl_2$(1.1 eq), NEt_3, CH_3CN, reflux	NR
5	**3**	paraformaldehyde, $MgCl_2$(3.0 eq), NEt_3, CH_3CN, reflux	NR
6	**7**	HMT, CH_3COOH, 110 °C	14
7	**7**	paraformaldehyde, $SnCl_4$(0.4 eq), NBu_3, Toluene, 100 °C	64

NR = no reaction



Scheme 3.3 Mechanism of $SnCl_4$-mediate formylation reaction.

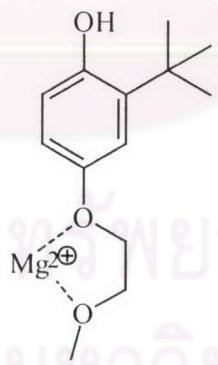


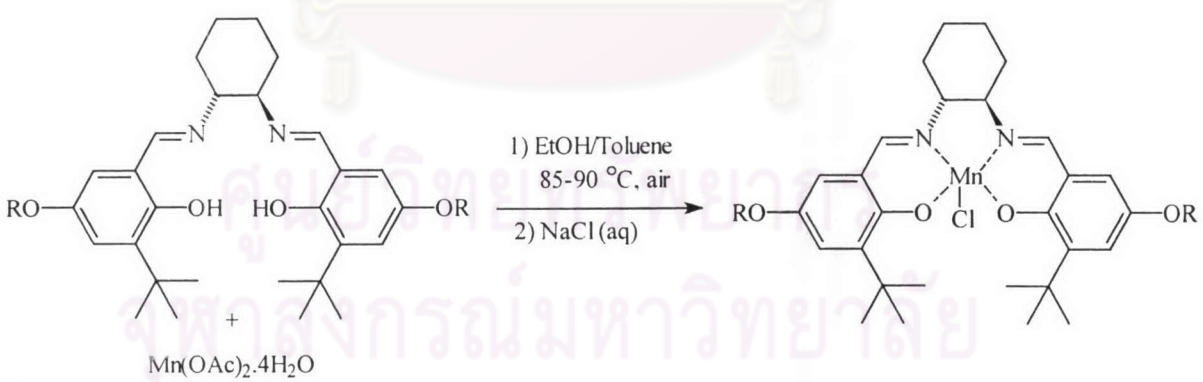
Figure 3.1 Chelation of Mg^{2+} by phenolic oxygen of the phenol **2**.

The ^{1}H-NMR of salicylaldehyde **3** shows a singlet peak of the aldehyde proton at 9.77 ppm and a singlet peak of the hydroxy proton at 11.48 ppm indicating strong intramolecular hydrogen bonding between the *o*-

hydroxy group and the formyl group that confirmed the ortho regioselectivity of this formylation.

The condensation reaction between the salicylaldehyde **3** and *(R,R)*-1,2-cyclohexanediammonium mono(+)-tartrate salt in ethanol/H_2O in the presence of 2 equivalents K_2CO_3 gave chiral salen **4** as a yellow liquid in good yield (83%). The ^{1}H-NMR of salen **4** shows singlet peak of imine proton at 8.01 ppm in place of the vanished aldehyde peak at 9.77 ppm. The complex signals of cyclohexane ring proton appears in the range of 1.67-3.42 ppm. The signal of hydroxy proton shifts from 11.48 ppm to 13.50 ppm. Chiral salen **8** was also prepared in excellent yield (98%) under the similar reaction condition. Due to their solubility in H_2O, several back-extraction of the aqueous layer by dichloromethane during work-up was necessary in order to recover **4** and **8** from the aqueous layer.

The Mn salen complexes **9** and **10** were prepared by refluxing the chiral salen **4** and **8** with $Mn(OAc)_2 \cdot 4H_2O$ in toluene and bubbling air through a reaction mixture (Scheme 3.4). Isolation of **9** and **10** as dark brown air- and water-stable solids was achieved by partial evaporation of 1:1 CH_2Cl_2/heptane solution, following by filtration. Elemental analysis and ESI mass spectra of complexes **9** and **10** confirmed the complexation of salens **4** and **8** with Mn(III) ion.



9, R = $CH_3OCH_2CH_2$- (50% yield)
10, R = $CH_3OCH_2CH_2OCH_2CH_2$- (38% yield)

Scheme 3.4 The synthesis of Mn(salen) complexes **9** and **10**.

3.2 Analytical method for determination of enantiomeric excess of epoxides

Enantiomeric excess of chiral epoxides are usually determined by using chiral lanthanide shift reagents. Chiral lanthanide shift reagents form diastereomeric complexes with enantiomeric substrate in a solution. The induced shift of some particular resonances will be different in each diastereomeric complex. The magnitude of the separation of the non-equivalent chemical shifts depends on the strength of the complexation. The difference of chemical shift of racemic epoxides could be resolved in the presence of chiral europium shift reagent. One disadvantage of this technique is the line broadening which occurs from paramagnetic properties of lanthanide shift reagent.

At the beginning, racemic styrene oxide was used to find an optimum condition for determination the enantiomeric purity. After 9 mol% of $Eu(hfc)_3$ was added. The peak of β_1-proton of styrene oxide at 3.14 ppm was resolved into two signals of equal intensity (Figure 2.1). The peaks of α-proton and β_2-proton of styrene oxide were resolved worse than β_1-proton. The integrals of resolved peaks of β_1-proton were thus used to calculate the percentage of the enantiomeric excess (see section 2.4.3).

A racemic indene oxide was also performed by using $Eu(hfc)_3$. After 10 mol% $Eu(hfc)_3$ solution was added, the peak of α-H (1*R*,2*S* isomer), α-H (1*S*,2*R* isomer) and β-H (1*R*,2*S* isomer) were shifted and overlapped. But peak of β-H (1*S*,2*R* isomer) did not overlap (Figure 2.2). The percentage of enantiomeric excess could not be calculated directly by integrals of the single enantiomer. The integrals of resolved peaks of β-H (1*S*,2*R* isomer) were used to calculate the percentage of the enantiomeric excess (see section 2.4.3).

3.3 The catalytic property studies of synthesized chiral salen manganese (III) complexes

3.3.1 Enantioselective epoxidation by *m*-CPBA/NMO system

The parameters that varied in the study of enantioselective epoxidation by *m*-CPBA/ NMO system included solvents, amounts of NMO, amounts of catalysts, alkene substrates, reaction time and temperature.

1) Effect of solvents

Five different kinds of solvents were investigated in the enantioselective epoxidation reaction (Table 3.3). High % conversion and % yield were observed in the epoxidation using solvents such as acetone, acetonitrile and dichloromethane as salen complex **9** has good solublity in these solvents. The low solubility of the complex in ether resulted in low % conversion of the alkene in this solvent. Although the catalyst was soluble in methanolic solvent, this solvent was apparently not suitable for the epoxidation of styrene as both % conversion and % yield were rather low. When comparing % ee of the styrene oxide product, dichloromethane was the most suitable solvent among the five solvents for this epoxidation. Dichloromethane is a common solvent of the choices in the Jacobsen's epoxidation by *m*-CPBA/NMO system.[8]

Table 3.3 Enantioselective epoxidation of styrene catalyzed by **9** in various solvents[a]

Solvent	% conversion[b]	% yield[b,c]	% ee[d]
CH_2Cl_2	67	85	51
CH_3CN	80	76	32
Methanol	33	58	-
Acetone	58	74	-
Diethyl ether	12	33	-

[a]Reaction conditions: *m*-CPBA (2 equiv), NMO (5 equiv), catalyst (0.04 equiv), -10-0 °C, 20 minutes [b]Determined by GC analysis with cyclohexanone as an internal standard [c]% yield of the epoxide based on 100% conversion assumption of styrene [d]Determined by ^{1}H-NMR spectroscopy of the crude product in the presence of chiral shift reagent $Eu(hfc)_3$

2) Effect of amounts of NMO

There were literatures[8,30] report that an addition of NMO in the *m*-CPBA epoxidation could enhance the enantioselectivity of the epoxide product. In this research, the amounts of NMO were varied from 0 to 7.5 eq to substrate (Table 3.4). The % ee increased dramatically from 3 to 51 when the amount of NMO was changed from 0 to 5 eq. The % conversion and % yield were however rarely affected from this variation. When the amount of NMO was extended to 7.5 eq, the % ee was only slightly increased.

The use of excess NMO as an additive in the epoxidation shuts down the pathway of uncatalyzed reaction between *m*-CPBA and alkenes that leading to the racemic epoxide by generating 1:1 salt of NMO and *m*-CPBA. This salt was unreactive toward olefins yet which appeared to oxidize the Mn (III) salen complex with high efficiency even at low temperature.[8]

Table 3.4 Enantioselective epoxidation of styrene catalyzed by **9** using various amounts of NMO[a]

Amount of NMO(eq)	% conversion[b]	% yield[b,c]	%ee[d]
0	68	88	3
1	67	84	21
2.5	66	91	40
5	67	85	51
7.5	54	89	53

[a]Reaction conditions : *m*-CPBA (2 equiv), NMO, catalyst (0.04 equiv), -10-0 °C, 20 minutes [b]Determined by GC analysis with cyclohexanone as internal standard [c]% yield of the epoxide based on 100% conversion assumption of styrene [d]Determined by ^{1}H-NMR spectroscopy of the crude product in the presence of chiral shift reagent Eu(hfc)$_3$

3) Effect of reaction time

When the reaction time was increased from 20 minutes to 60 minutes, almost no improvement on % conversion was observed. This result indicated that the reaction was nearly terminated after 20 minutes. The slight improvement of % yield and % ee may be due to other factors rather than the reaction time itself.

Table 3.5 Enantioselective epoxidation of styrene by catalyst **9** in different reaction time[a]

Reaction time (minutes)	% conversion[b]	% yield[b,c]	% ee[d]
20	67	85	51
60	69	93	60

[a]Reaction conditions : *m*-CPBA (2 equiv), NMO (5 equiv), catalyst (0.04 equiv), -10-0 °C [b]Determined by GC analysis with cyclohexanone as an internal standard [c]% yield of the epoxide based on 100% conversion assumption of styrene [d]Determined by ^{1}H-NMR spectroscopy of the crude product in the presence of chiral shift reagent $Eu(hfc)_3$

4) Effect of the amounts of catalyst

The epoxidation of styrene by *m*-CPBA/NMO oxidizing system with 2, 3, 4 and 10 mol% **9** was carried out at -10-0 °C. The results showed that the increasing amounts of catalyst **9** improved % conversion of alkene to epoxide significantly (Table 3.6). The enantioselectivity of this epoxidation was also improved significantly with increasing amount of **9**. The enantioselectivity of styrene oxide obtained with catalyst **9** was comparable to that with commercially available Jacobsen's catalyst (49% ee at 4 mol % catalyst) under the same condition.[8] In both cases, (*R*)-styrene oxide was the preferred isomer indicating their similarity in mechanism for stereo control.

Table 3.6 Enantioselective epoxidation of styrene catalyzed by the various amounts of catalyst **9**[a]

Amount of catalyst	% conversion[b]	% yield[b,c]	% ee[d]
2 mol%	45	87	47
3 mol%	48	94	50
4 mol%	67	85	51
10 mol%	88	85	66

[a]Reaction conditions: *m*-CPBA (2 equiv), NMO (5 equiv), catalyst, -10-0 °C, 20 minutes [b]Determined by GC analysis with cyclohexanone as an internal standard [c]% yield of the epoxide based on 100% conversion assumption of styrene [d]Determined by ^{1}H-NMR spectroscopy of the crude product in the presence of chiral shift reagent Eu(hfc)$_3$

5) Effect of types of catalysts and substrates

Mn (III) complexes **9** and **10** showed similar catalytic properties in enantioselective epoxidation of both styrene and indene in terms of reactivity and selectivity as their reaction yields and % ee were comparable (Table 3.7). Encouragingly, epoxidation of indene with both **9** and **10** gave very high yields and enantioselectivity, especially when 10 mol% catalysts were used. These results came with no surprise since there were reports demonstrate that epoxidation of *cis*-disubstitued olefins with salen type catalysts usually gave higher yields and enantioselectivity than those of monosubstituted alkenes.[4,5] Indene oxide obtained from the epoxidation with catalysts **9** and **10** preferred (1*R*, 2*S*) isomer as predicted by Jacobsen's mechanism.

Table 3.7 Enantioselective epoxidation of styrene and indene catalyzed by catalysts **9** and **10**[a]

Substrate	catalyst	amount of catalyst	% conversion[b]	% yield[b,c]	% ee[d]
Styrene	**9**	4 mol%	67	85	51
Styrene	**9**	10 mol%	88	85	66
Styrene	**10**	4 mol%	71	82	49
Styrene	**10**	10 mol%	92	80	55
Indene	**9**	4 mol%	91	97	81
Indene	**9**	10 mol%	99	90	93
Indene	**10**	4 mol%	93	78	88
Indene	**10**	10 mol%	>99	92	92

[a]Reaction conditions: *m*-CPBA (2 equiv), NMO (5 equiv), catalyst, -10-0 °C, 20 minutes [b]Determined by GC analysis with cyclohexanone as internal standard [c]% yield of the epoxide based on 100% conversion assumption of alkene [d]Determined by ^{1}H-NMR spectroscopy of the crude product in the presence of chiral shift reagent Eu(hfc)$_3$

3.3.2 Enantioselective epoxidation by NaOCl/4-PPNO system

In addition to the homogeneous *m*-CPBA/NMO catalytic system, a heterogeneous sodium hypochlorite (NaOCl) catalytic system was also investigated. NaOCl has been one of the favorite choices of terminal oxidant for salen(Mn)-catalyzed asymmetric epoxidation due to low cost.[5] In the absence of 4-PPNO additive, less than 20% of styrene converted to styrene oxide (Table 3.8). In the presence of 0.15 eq. 4-PPNO, over 90% of styrene converted to styrene oxide with over 60% yield for both catalysts **9** and **10**. For styrene substrate, only moderate enantioselectivity was achieved as styrene oxide was obtained with 65% and 55% ee for catalysts **9** and **10**, respectively. Indene was also epoxidized under the same condition. Both catalysts **9** and **10** gave excellent conversion, yield and enantiomeric excess of indene oxide. Interestingly, in this heterogeneous NaOCl/4-PPNO oxidizing system, the increasing amount of catalyst did not significantly affect yields and enantioselectivity of the reaction. Furthermore, this heterogeneous NaOCl/4-PPNO oxidizing system in which only 4 mol% catalysts employed gave

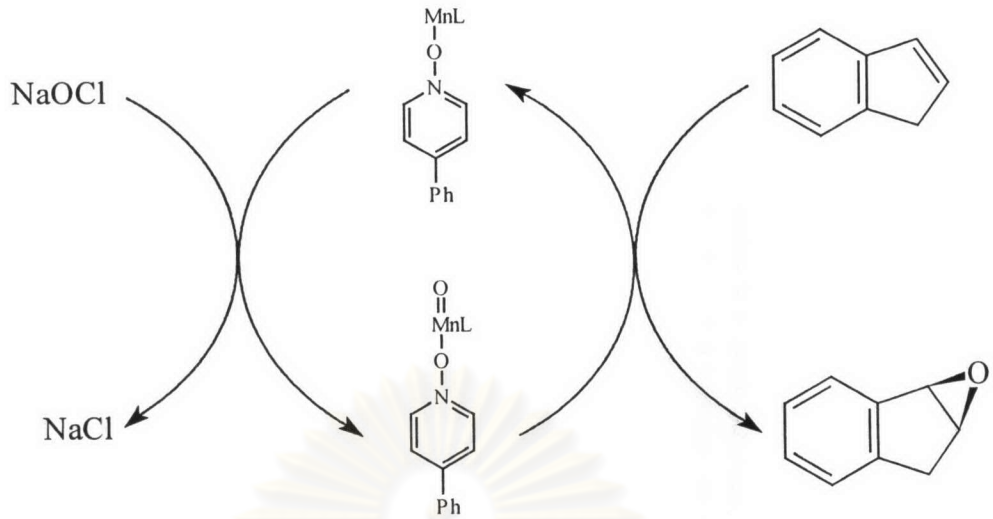
comparable yields and enantioselectivity to that of the homogeneous *m*-CPBA/NMO oxidizing system with 10 mol% catalyst employed.

Table 3.8 Enantioselective NaOCl/4-PPNO epoxidation of styrene and indene catalyzed by catalysts **9** and **10** using heterogeneous NaOCl catalytic system[a]

Substrate	catalyst	additive	amount of catalyst	% conversion[b]	% yield[b,c]	%ee[d]
Styrene	**9**	-	4 mol%	17	100	-
Styrene	**10**	-	4 mol%	19	95	-
Styrene	**9**	4-PPNO	4 mol%	95	60	65
Styrene	**10**	4-PPNO	4 mol%	92	63	55
Styrene	**9**	4-PPNO	10 mol%	94	66	60
Styrene	**10**	4-PPNO	10 mol%	91	56	62
Indene	**9**	4-PPNO	4 mol%	99	86	90
Indene	**10**	4-PPNO	4 mol%	>99	87	91

[a]Reaction conditions: NaOCl Buffered to pH ~ 11 (2 equiv), 4-PPNO (0 or 0.15 equiv), catalyst (0.04 or 0.10 eq), 0-10 °C, 6 hours [b]Determined by GC analysis with cyclohexanone as internal standard [c]% yield of the epoxide based on 100% conversion of alkene [d]Determined by ^{1}H-NMR spectroscopy of the crude product in the presence of chiral shift reagent Eu(hfc)$_3$

Since the oxidation to the O=Mn(salen) is generally rate limiting step, the observed increasing conversion and enantioselectivity induced by the *N*-oxide could be attributed to the stabilizing effect on the key active [Mn=O (salen)] species.[7] This hypothesis was confirmed by the electrochemical study that exhibited significantly lower oxidation potentials for (salen)Mn complex to [Mn=O(salen)] in the presence of *N*-oxide.[30] The stabilizing effect was due to the association of the 4-PPNO additive with the metal center during the generation of the reactive oxo intermediate (Scheme 3.5).



Scheme 3.5 The role of 4-PPNO in the epoxidation by NaOCl.