อิพอกซิเดชันเชิงเร่งปฏิกิริยาด้วยสารประกอบเชิงซ้อนโคบอลต์ (II) คาลิกซ์[4]พิโรล และโคบอลต์ (II) ซิฟเบส

นายพงศ์ชาติ บูรณะประเสริฐสุข

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
สาขาวิชาเคมี ภาควิชาเคมี
คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2550

CATALYTIC EPOXIDATION WITH COBALT(II) CALIX[4]PYRROLE AND COBALT(II) SCHIFF BASE COMPLEXES

Mr. Pongchart Buranaprasertsuk

A Dissertation Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy Program in Chemistry
Department of Chemistry
Faculty of Science
Chulalongkorn University
Academic Year 2007

Thesis Title	CATALYTIC EPOXIDATION WITH COBALT(II) CALIX[4]PYRROLE AND COBALT(II) SCHIFF BASE COMPLEXES
By	Mr. Pongchart Buranaprasertsuk
Field of Study	Chemistry
Thesis Advisor	Assistant Professor Warinthorn Chavasiri, Ph.D.

Accepted by the Faculty of Science, Chulalongkorn University in Partial Fulfillment of the Requirements for the Doctoral Degree

.....Dean of the Faculty of Science
(Professor Supot Hannongbua, Ph.D.)

THESIS COMMITTEE

..... Chairman
(Professor Udom Kokpol, Ph.D.)

..... Thesis Advisor
(Assistant Professor Warinthorn Chavasiri, Ph.D.)

..... Member
(Professor Padet Sidisunthorn, Ph.D.)

.....Member
(Associate Professor Nuanphun Chantarasiri, Ph.D.)

..... Member
(Associate Professor Thawatchai Tuntulani, Ph.D.)

..... External Member
(Assistant Professor Tienthong Thongpanchang, Ph.D.)

พงศ์ชาติ บูรณะประเสริฐสุข: อิพอกซิเดชันเชิงเร่งปฏิกิริยาด้วยสารประกอบเชิงซ้อนโคบอลต์ (II) คาลิกซ์[4]พิโรลและโคบอลต์ (II) ชิฟเบส (CATALYTIC EPOXIDATION WITH COBALT(II) CALIX[4]PYRROLE AND COBALT(II) SCHIFF BASE COMPLEXES) อ. ที่ปรึกษา: ผศ. ดร. วรินทร ชวศิริ, 119 หน้า

ได้ศึกษาอิพอกซิเดชันของแอลคีนที่เร่งปฏิกิริยาด้วยสารประกอบเชิงซ้อนโคบอลต์ calix[4]pyrrole ที่มี 2-ethylbutyraldehyde/O_2 อยู่ด้วย ไซโคลเฮกซีนเปลี่ยนเป็นไซโคลเฮกซีนออกไซด์ในปริมาณสูงและมีความเลือกจำเพาะที่ดีมาก ชนิดของลิแกนด์และตัวทำละลายเป็นสองตัวแปรหลักที่มีความสำคัญต่อปฏิกิริยา สารประกอบเชิงซ้อนโคบอลต์ของ calix[4]pyrrole **(68)** และ benzimidazole **(72)** พบว่ามีประสิทธิภาพในการเป็นตัวเร่งปฏิกิริยาได้เลือกสารตั้งต้นหลากหลาย เช่น (*R*)- และ (*S*)-limonenes, geraniol, geranyl acetate, 4-vinylcyclohexene, *trans*-2-hexen-1-ol, 3-octen-1-ol, *cis*- และ *trans*-stilbene และอนุพันธ์ของ cholesterol เพื่อศึกษา regio-, chemo- และ stereoselectivity ของปฏิกิริยา กลไกการเกิดปฏิกิริยานี้เชื่อว่าเกิดผ่านกรดเปอร์ออกซีและกระบวนการฟรีแรดิคัล

ได้ศึกษาปฏิกิริยาการควบแน่นของแอโรมาติกแอลดีไฮด์กับไดแอมีนหลายชนิด ผลที่ได้ชี้ให้เห็นอย่างชัดเจนว่า ชิฟเบสจะเกิดได้เมื่อใช้ 1,2-ethylenediamine หรือ 1,3-propylenediamine ในขณะที่การปิดวงจะเกิดขึ้นเมื่อใช้ 1,2-phenylenediamine ความไม่ยืดหยุ่นของโครงสร้างของไดแอมีนจะเหนี่ยวนำการเกิดโครงสร้างที่เสถียรและมีความเป็นแอโรมาติกสูง อย่างไรก็ตามในกรณีของ 1,2-phenylenediamine อัตราส่วนของสารตั้งต้นสองชนิดและการเลือกตัวทำละลายจะมีผลต่อการเกิดปฏิกิริยาเป็นอย่างมาก

ภาควิชา.....เคมี..... ลายมือชื่อนิสิต.....พงศ์ชาติ บูรณะประเสริฐสุข.....

สาขาวิชา.....เคมี..... ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา.....2550.....

4673818823 : MAJOR CHEMISTRY
KEY WORD: EPOXIDATION / COBALT COMPLEX / CALIX[4]PYRROLE / SCHIFF BASE / BENZIMIDAZOLE

PONGCHART BURANAPRASERTSUK: CATALYTIC EPOXIDATION WITH COBALT(II) CALIX[4]PYRROLE AND COBALT(II) SCHIFF BASE COMPLEXES THESIS ADVISOR: ASSIT. PROF. WARINTHORN CHAVASIRI, Ph.D., 119 pp.

The epoxidation of alkenes catalyzed by cobalt(II) calix[4]pyrrole in the presence of 2-ethylbutyraldehyde/O_2 was examined. Cyclohexene was converted to cyclohexene oxide in high yield and excellent selectivity. Ligands and solvents are two major influent parameters affecting on the reaction. Cobalt(II) calix[4]pyrrole **(68)** and cobalt(II) benzimidazole **(72)** were disclosed to be the most efficient catalyst tested. Various substrates such as (*R*)- and (*S*)-limonenes, geraniol, geranyl acetate, 4-vinylcyclohexene, *trans*-2-hexen-1-ol, 3-octen-1-ol, *cis*- and *trans*-stilbenes and cholesterol derivatives were chosen to explore the regio-, chemo- and stereoselectivity of the reaction. The mechanism of the reaction was believed to take place *via* peroxy acid and free radical process.

The condensation of aromatic aldehydes with several diamines was examined. The results clearly indicated that only Schiff bases were formed when using 1,2-ethylenediamine or 1,3-propylenediamine, while an apparent intramolecular cyclization took place with the use of 1,2-phenylenediamine. In the latter case, rigid structure of the diamine should be able to induce the formation of more stable and highly aromatic products. Intriguingly, in the case of 1,2-phenylenediamine, the ratio of the two starting materials and the choice of solvent played significant role in the reaction outcomes.

Department:.....Chemistry..... Student's signature:Pongchart Buranaprasertsuk
Field of study:...Chemistry..... Advisor's signature:W. Chavasiri
Academic year:....2007.....

ACKNOWLEDGEMENTS

The author wishes to express his deep gratitude to his advisor Assistant Professor Dr. Warinthorn Chavasiri, for his very kind assistance, generous guidance and encouragement throughout the course of this research. Sincere thanks are extended to Natural Products Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University for the support of chemical and laboratory facilities.

The greatest thanks are also extended to Professor Dr. Udom Kokpol, Professor Dr. Padet Sidisunthorn, Associate Professor Dr. Nuanphun Chantarasiri, Associate Professor Dr. Thawatchai Tuntulani and Assistant Professor Dr. Tientong Thongpanchang for their comments, correcting and helps as thesis examiners. Moreover, thanks are extended to the Department of Chemistry, Faculty of Science, Chulalongkorn University for the financial support.

A deep affectionate gratitude is acknowledged to his parents and family members for their love, understanding, encouragement and support throughout the entire course of study. Thanks to his friends for friendship and helps throughout the entire course of study. Without them, the author would never have been able to achieve this goal.

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LIST OF ABBREVIATIONS

br	broad (IR)
TBHP	*t*-Butyl hydroperoxide
δ	chemical shift
J	coupling constant (NMR)
^{o}C	degree celsius
$CDCl_3$	deuterated chloroform
DET	diethyl tartrate
DMSO	dimethylsulfoxide
d	doublet (NMR)
eq	equation or equivalent
GC	gas chromatography
g	gram(s)
Hz	hertz
hr	hour(s)
IR	infrared
MB	mass balance
MS	mass spectrometry
m/z	mass to charge ratio
m	medium (IR)
m.p.	melting point
m-CPBA	*meta*-chloroperbenzoic acid
mL	milliliter(s)
mmol	millimole
mg	milligram(s)
min	minute(s)
m	multiplet (NMR)
NMR	nuclear magnetic resonance

ppm	part per million
PTC	phase transfer catalyst
q	quartet (NMR)
R_f	retardation factor
s	singlet (NMR)
s	strong (IR)
TLC	thin layer chromatography
t	triplet (NMR)
w	weak (IR)

CHAPTER I

EPOXIDES AND THEIR PREPARATIONS

1.1 Introduction

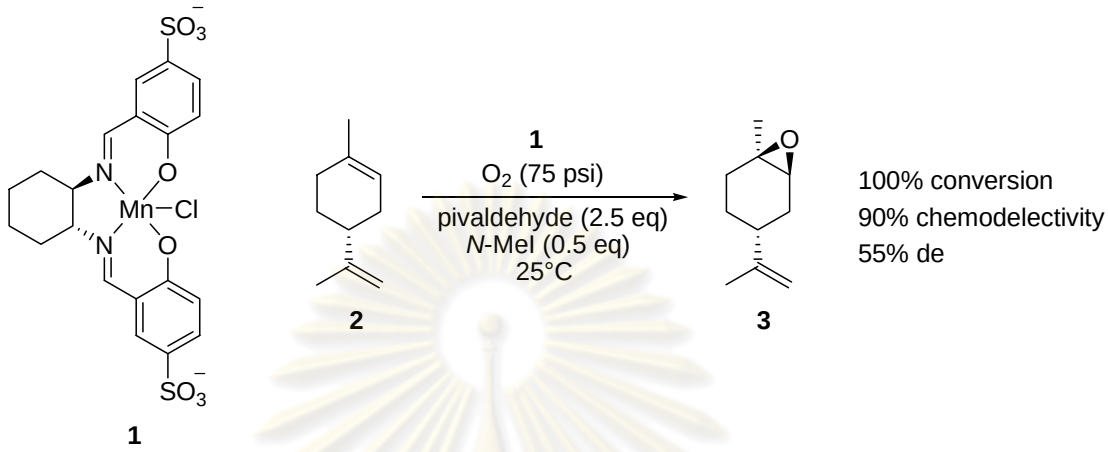
There is a special allure in three-member heterocycles which is the derivative of their apparent simplicity and spartan architecture. However, in terms of preparative routes and subsequent transformations, the heterocycles are multifaceted, and lead to continuous literature their diversity evidence. The special property of these smallest heterocycles is the useful balance between stability and reactivity; therefore, they can be employed as versatile and selective intermediates. Moreover, the heterocycles has a potential to introduce two adjacent chiral centers with high atom economy, leading to the right deserved place of prominence in synthetic organic chemistry.

1.2 Preparation of Epoxides

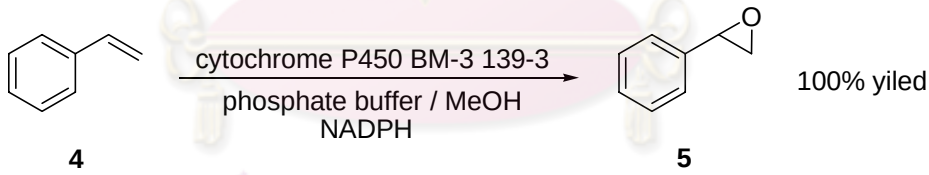
In the recent literature, the development of preparative methodology of Mn(salen) mediated epoxidation of alkenes (the Jacobsen-Katsulki) has been growing rapidly. However, the practical utility, mechanistic foundation, which has been debate, is indisputable. The theory of the salen ligand itself involved in the transition state of the epoxidation was introduced in the recent study. In one outcome on a rather complex reaction surface, a covalent bond is formed between the carbon atom of the substrate and the oxygen atom of the salen framework [1].

A chiral sulfonato-salen complex into a zinc-aluminum layered double hydroxide (LDH) host construct a novel immobilized Mn(salen) catalyst. The active catalyst is the key for existing as an intercalated species spanning the interlayer space. Under Mukaiyama conditions, at RT and the presence of pivaldehyde and *N*-methylimidazole (*N*-MeI), the selective epoxidation of limonene **(2)** with O_2 was promoted in the complex. The catalyst is very stable even after multiple cycles without the presence of leaching of manganese [2]. In the mechanistic literature found

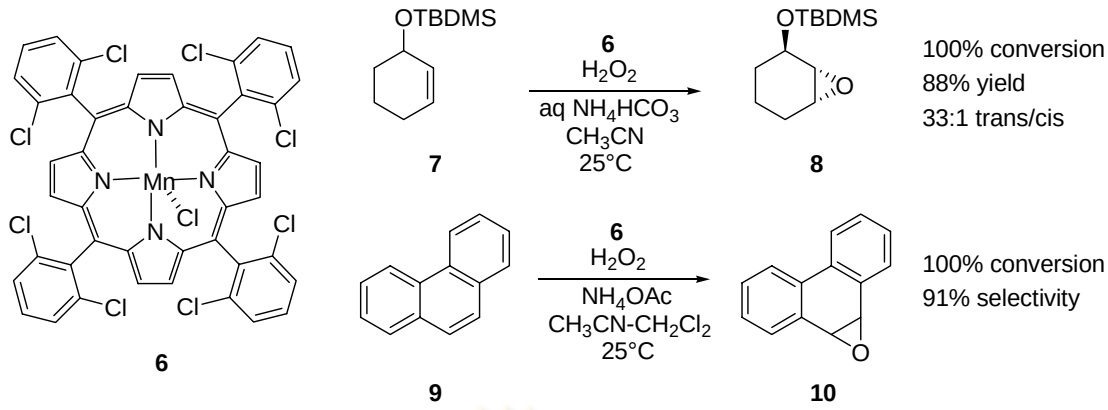
that the epoxidation proceeds *via* the *in situ* formation of a peracid through autoxidation of the aldehyde, which subsequently serves as an oxygen donor during the epoxidation [3].



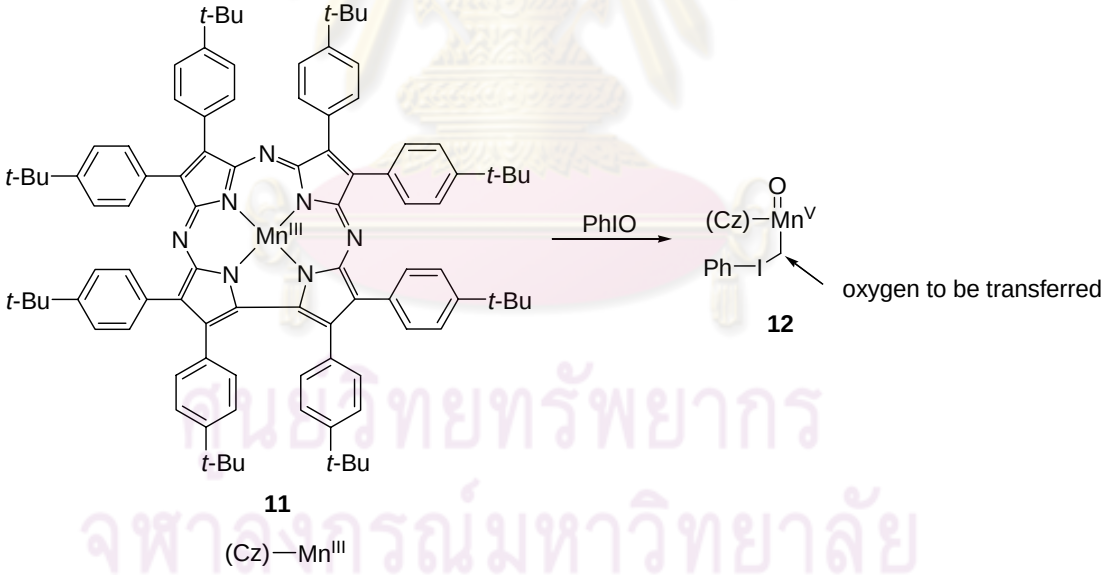
The outstanding diverse of metal mediated with many types of ligand systems has been representing. For example, a cytochrome P450 BM-3 mutant has been developed by direct evolution, exhibiting high activity towards epoxidation of several non-natural substrates resulted in the quantitative conversion to styrene oxide **(5)** by the exposure of styrene **(4)** to BM-3 variant (139-3) in phosphate buffer containing methanol and NADPH [4].



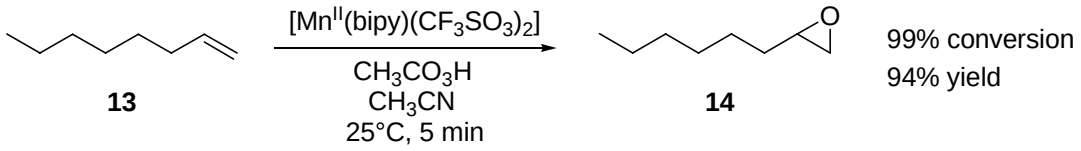
By using H_2O_2 as the terminal oxidant, the mild and highly diastereoselective epoxidation of protected cyclohexenol derivative **(7)** was catalyzed by the sterically stabilized metalloporphyrin [Mn(TDCPPCl)] **(6)**. *Trans*-epoxides prefer a rationalized on the basis of non-bonded interactions between the allylic substituent on the substrate and the bulky porphyrin ligand. Since diasteroselectivies increase with steric demand of the substituent [5]. These metalloporphyrins catalyze the epoxidation of aromatic substrates, which found in the synthetic methodology and with respected to the toxicology of environmental polycyclic aromatic hydrocarbons. Therefore, the conversion of phenanthrene **(9)** to epoxide **(10)** gives excellent yield in three hours with 0.3 mol% of catalyst [6].



Conventional wisdom holds that these epoxidation reactions occur *via* oxygen atom transfer directly from the catalyst *via* the metal-oxo species, Goldberg and co-workers studied the structure similarity of Mn-corroles **(11)** and proposed the existing of a secondary pathway in which the metal-oxo species activates the terminal oxidant through simple Lewis acid catalysis **(12)**. Later works by ^{18}O labeling describe the long-recognized, however, not enough reason of the terminal oxidant on the course of these epoxidations [7].

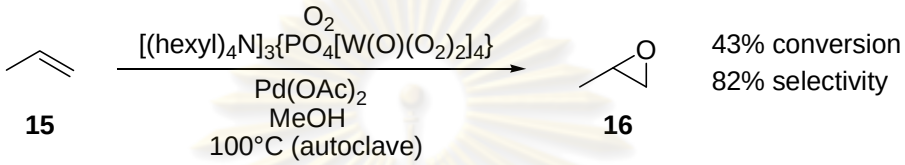


Metal catalyzed epoxidations have a significant ligand system which is simple and work well. For example, the presence of Mn(II) bipyridyl complex at 0.1% catalyst can convert 1-octene (**13**) into its epoxide, less than 5 min with good yield [8].



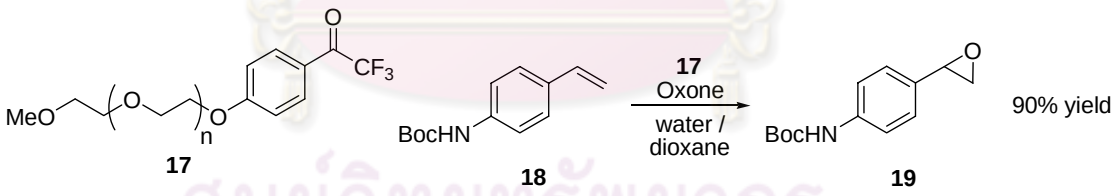
13 **14**

Even in industry, metal catalyzed epoxidations become more useful with the use of O_2 as the terminal oxidant. One spectacular example is propylene oxide (**16**) which is introduced by $Pd(OAc)_2$ catalytic systems and a peroxo-heterophy in MeOH [9].



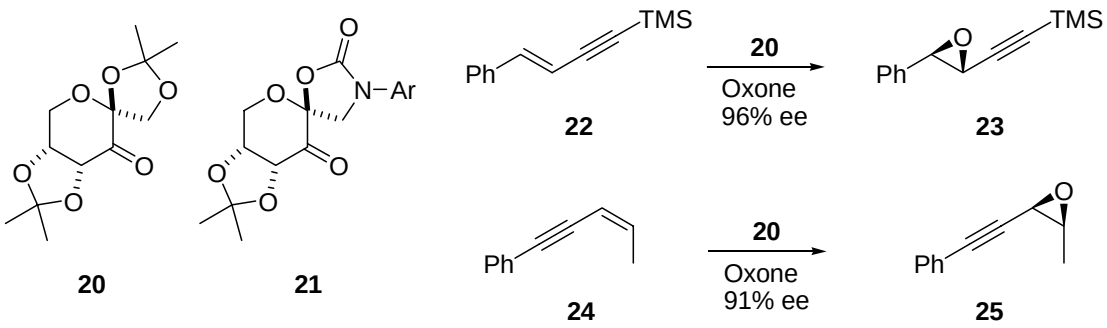
15 **16**

The PEG-immobilized trifluoroacetophenone (**17**) is the dioxirane precursor which is very soluble in both water and organic solvents, and very easy for recovery and reuse. In the presence of oxone, in the molecule mediates the epoxidation of substrates, BOC-protected aminostyrene (**18**) [10]. The reason behind this reaction can be explained that the epoxidations without using transition metals, dioxirane mediated processes are versatile, while using stoichiometric of the simplest dioxiranes can be experimentally cumbersome.

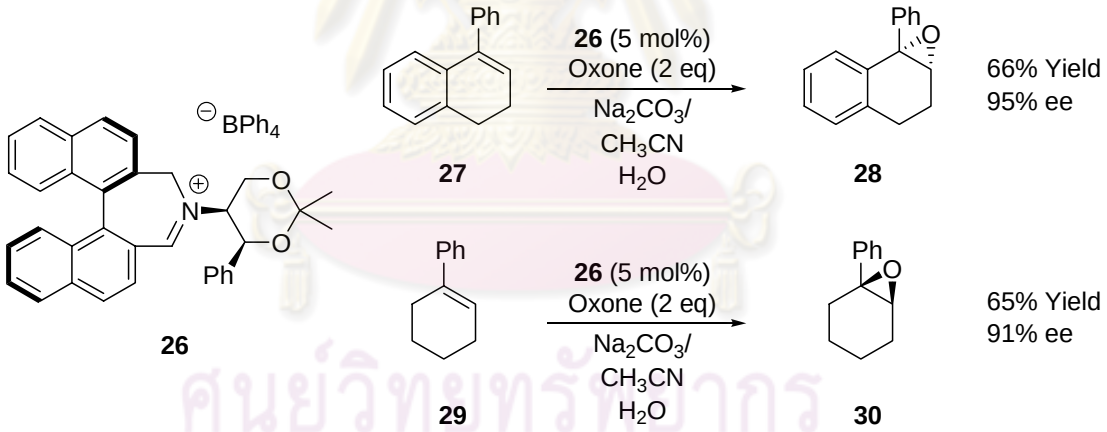


17 **18** **19**

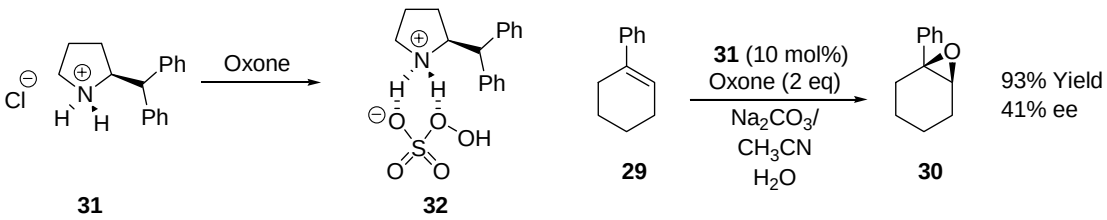
Another point of ketone precursors is that it can be chiral auxiliaries as the dioxirane from fructose derived ketone (**20**) can convert trisubstituted and *trans*-disubstitued alkenes (**22**) to the epoxides. However, there is a problem with those reactions. Their terminal and *cis*-disubstituted substrates are not effective. However, the oxazolidino (**21**) shows the unexpected scope of the high yield with enantioselectivities for olefins (**24**). Some researches have been using a buffered oxone solution [11, 12] for the *in situ* generation of dioxiranes with mild homologous conditions.



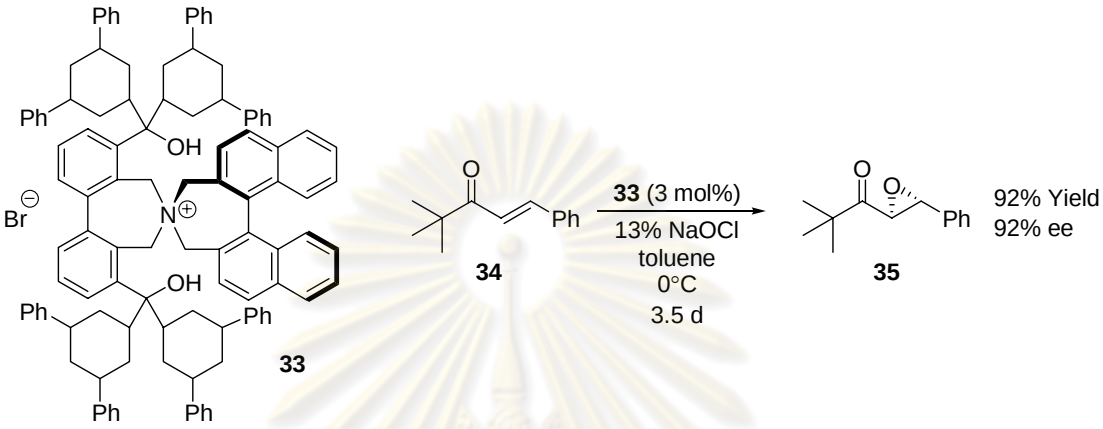
Asymmetric epoxidation of unfunctionalized olefins using chiral iminium salts had been studied by Page *et al.* [13]. Structure **(26)** shows an example of chiral iminum salt. Oxaziridium, the oxygen transferring agent, was produced from the reaction of iminium salt with oxone neutralized and sodium bicarbonate. The epoxidation of 1-phenyl-3,4-dihydronaphthalene **(27)** is a good example for highly yields and high enantioselectivity. Moreover, some chiral iminiums are also conversion beneficial in low consumed of catalyst such as 1-phenylcyclohexane **(29)** which used only 0.5 mol% of catalyst [14].



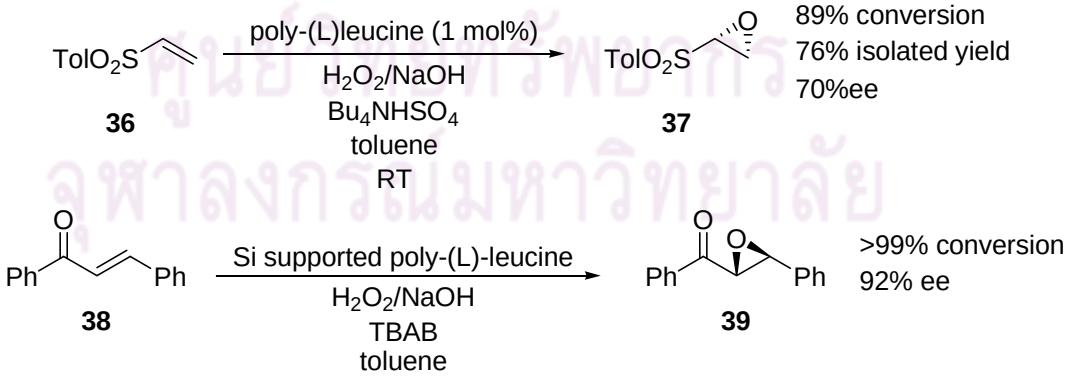
Chiral ammonium salts **(31)** produced enantiomeric excess in the oxone-mediated epoxidation of trisubstituted alkenes. The proposed mechanism is through the formation of chiral salts with oxone itself [15].



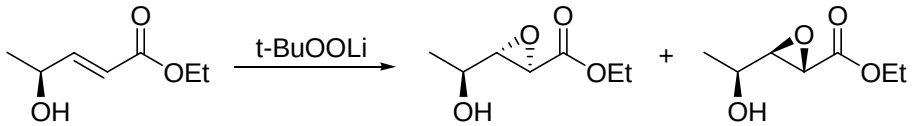
Binaphthyl derivative spiro ammonium salts **(33)** were used as a phase transfer catalyst in the catalytic asymmetric epoxidation of enones such as in the conversion of enone **(34)** to the epoxy ketone **(35)** [16]. A catalyst like sodium hypochlorite was used to attain high yields and high *ee* of epoxidation varieties of electron-deficient trisubstituted and *trans*-disubstituted olefins.



The Juliá-Colonna procedure is another approach for the enantioselective epoxidation. In this process, H_2O_2 is used as an oxygen source, and polyleucine is used as a chiral auxiliary. The preparation of epoxysulfone **(37)** [17] is a good example of this procedure in that poly-(L)-leucine in a mixture of water/toluene reacts with tetrabutylammonium bisulfate. The reaction approach for poly-(L)-leucine is that polyamino acid consumes H_2O_2 and provides O_2 in the organic phase. Silica supported type of poly-(L)-leucine has been used and a good yield and enantiomeric excess in the epoxidation of *trans*-chalcone **(38)** can be obtained [18].



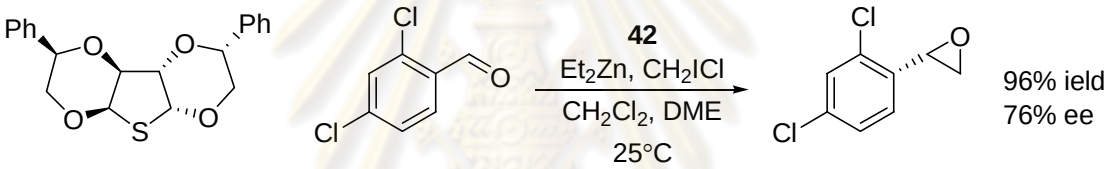
The dependability of solvent affected on diastereoselective epoxidation of γ-hydroxy-α,β-unsaturated esters. Using THF as a solvent produces *anti*-epoxidation whereas, non-polar solvents produce *syn* epoxidation. Temperature effect has not been found and the stereochemical [19].



40 *anti*-**41** *syn*-**41**

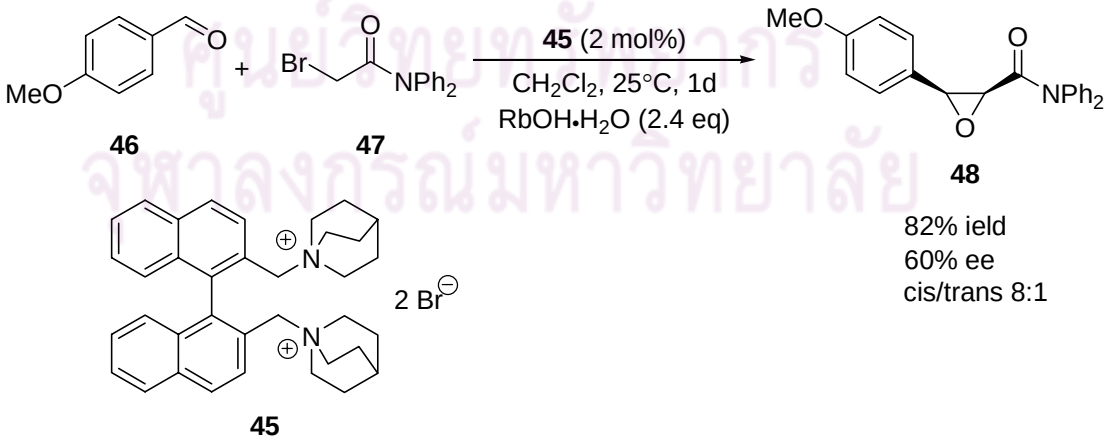
Solvent	anti	syn	yield
THF	75	25	40%
toluene	32	68	53%

The mechanism has been discussed on a source of electrophilic oxygen as a route to epoxide. Recently, the conversion of aldehydes and ketones to epoxides using sulfonium has been focused for asymmetric induction [20]. For instance, D-mannitol obtained by using chiral sulfide **(42)** in the sulfonium methylide epoxidation of aldehydes [21].



42 **43** **44**

Another conversion of aldehydes to epoxides is accomplished by Darzens reaction, such as the reaction between haloamide **(47)** with benzaldehyde in novel phase transfer catalyst **(45)**. 1,2-Disubstituted epoxides were derived from BINOL. This procedure can be used in both aromatic and aliphatic aldehydes [22].



46 **47** **48**

45

Finally, carbenoid species can be used as the carbon donor in aldehyde epoxidations. For example spiro-indolooxiranes **(50**) with *Z* stereochemistry were obtained in the stereoselective reaction of rhodium carbenoid which derived from the

cyclic diazoamide **(49)** and rhodium(II) acetate with aryl aldehyde. The reaction is believed to proceed *via* the formation of a carbonyl ylide (51), which undergoes stereospecific thermal conrotatory electrocyclization to form the observed epoxide [23].

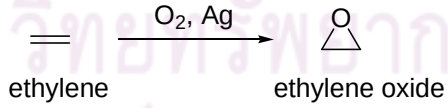
CHAPTER II

CATALYTIC EPOXIDATION WITH COBALT(II) CALIX[4]PYRROLE AND COBALT(II) SCHIFF BASE COMPLEXES

The epoxidation of alkenes is the most fundamental oxygen functionalization of carbon-carbon double bonds [24]. The importance of this transformation is a direct consequence of the utility of the product epoxides as synthetic intermediates. A great deal of effort has been expanded in attempts to develop a new process based upon catalytic epoxidation which will produce such products selectively.

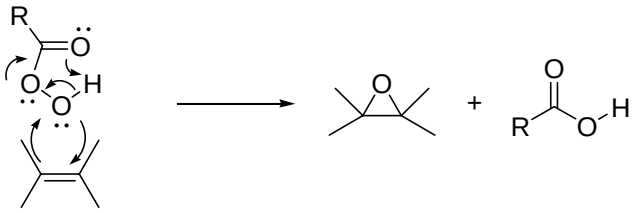
2.1 Epoxidaton of Alkenes

An epoxide is three-membered cyclic ether, sometimes called an oxirane. Epoxides are valuable synthetic intermediates for organic chemistry, used to convert alkenes to a variety of other functional groups. The most important epoxide is the simplest one, ethylene oxide. It is prepared industrially by direct air oxidation of ethylene by silver catalyst [25].

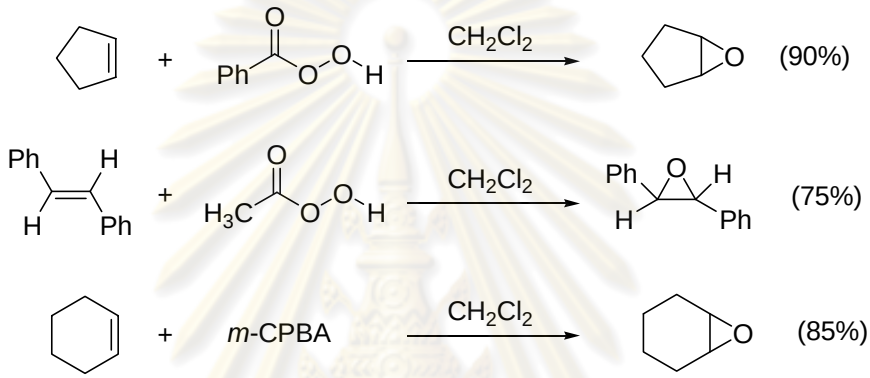


2.2 Epoxidaton of Alkenes with Peroxy Acids

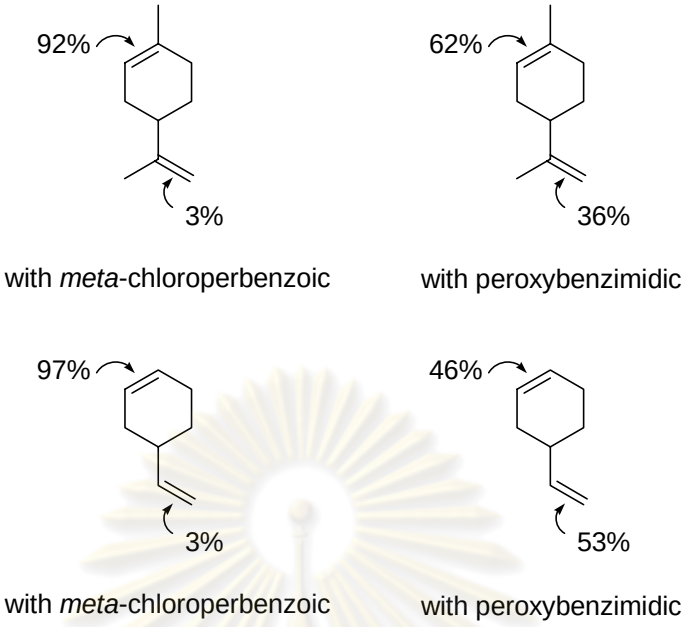
The reaction of alkenes with peroxy acids to produce epoxides has been known for almost 90 years. The mechanism [26] of peracid epoxidation is believed to include a cyclic, concerted transition state, in which oxygen is transferred to alkene at the same time that the carbon-carbon bond is broken and the proton is transferred to the carbonyl oxygen.



The examination of this mechanism suggests that the nature of R group not make much difference in the reaction. In fact, a number of different percarboxylic acids can be used to epoxidize alkenes, as is illustrated in the following examples [27].

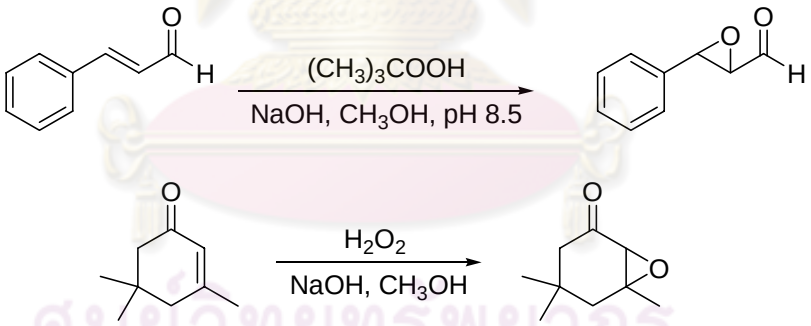


In addition, 4-vinylcyclohexene and *d*-limonene [28] were epoxidized with *m*-CPBA and peroxybenzimidic acid. It is clear from these results that peroxybenzimidic acid is a far less selective reagent for the epoxidation of double bonds than are peracids. Although the reaction of peracids with alkenes is very markedly accelerated by the presence of electron-donating alkyl groups and a trisubstituted double bond is epoxidized approximately 275-300 times as fast as a monosubstituted double bond, the relative rates are greatly attenuated with peroxybenzimidic acid [29] and trisubstituted double bond is only five times as reactive as a monosubstituted olefin. As in peracid oxidations [30], however, the *cis* isomer of a *cis-trans* pair is oxidized more rapidly. In contrast to a number of other addition reactions [31], cyclopentene is oxidized less readily than both cyclohexene and cycloheptene.



2.3 Epoxidation of alkenes with peroxides

Selective epoxidation of α,β-unsaturated ketones and aldehydes may be talented by the oxidation with sodium salts of H_2O_2 or sodium salts of TBHP rather than peroxy acids [32]

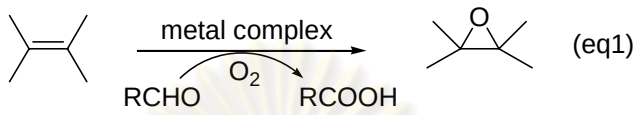


In contrast to the epoxidaiton with peroxy acids, these reactions are stereoselective rather than stereospecific. For example, only one isomer is obtained by the epoxidation of either isomer of the unsaturated ketone [33].

2.4 Epoxidation of Alkenes Catalyzed by Metal Complexes

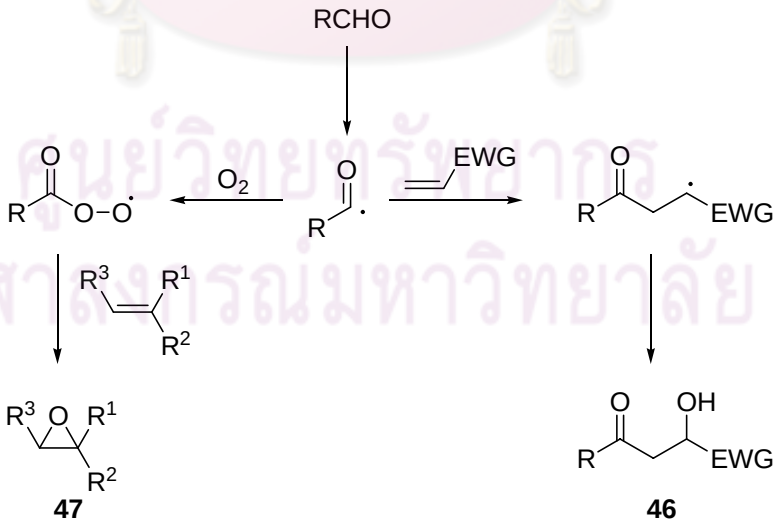
Biomimetic oxygenations of organic substrates using soluble metal coordination complexes as catalysts ideally should use O_2 [34], as a source of oxygen atoms, since O_2 is used directly by oxygenase enzymes [35]. In most cases, however, the successful catalysts that have been developed for such reactions, *i.e.* metalloporphyrins and metal complexes of non-porphyrin ligands, require alternative

oxidants [36], *e.g.* H_2O_2, organic peroxides, or iodosylbenzene, since reactions using O_2 itself either give no reaction or predominantly the undersirable side products of free-radical autoxidation. An apparent exception to this rule occurs when an aldehyde is added to the reaction mixture. In this case, it has been observed that olefins are epoxidized by O_2, in the presence of aldehydes and transition metal-containing catalysts, to give epoxides in high yield (eq 1) [37]



(eq1)

[Bis(salicylidene-*N*-phenethyl)]cobalt(II) complex or Co(II) SANP catalyzed the reaction of enolizable aliphatic aldehyde with an electron-deficient alkene leads to the formation of **46**, whereas the reaction with unactivated alkene affords the corresponding epoxide **47** in good yields. This process seems to be proceeding *via* a common pathway involving an acyl radical [38] which reacts preferentially with electron-deficient alkenes to give an adduct radical, and the latter terminates by incorporation of O_2 followed by the reduction to afford **46**. On the other hand unactivated alkenes do not undergo addition of acyl radical as the latter perferentially reacts with O_2 to give a peroxy carbonyl species which readily affords the epoxide **47** on interaction with carbon-carbon double bond. (Scheme 2.1)



Scheme 2.1 The proposed mechanistic pathway for Co SANP catalyzed the reaction of alkenes [38]

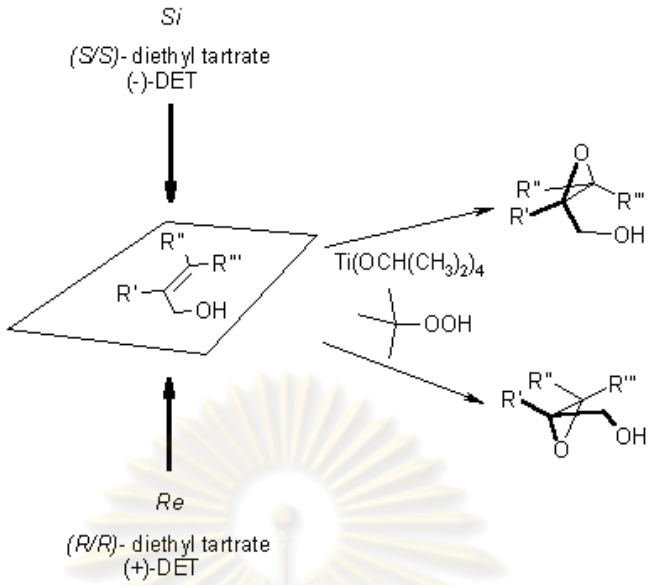
Interestingly, the reaction with unactivated alkenes favors the formation of the epoxide **5** exclusively. Thus, styrene and 1-dodecene afforded the corresponding epoxides in excellent yields (88% and 62%, respectively). Similarly, the disubstituted olefins like (*E*)-stilbene and (*Z*)-2-octene gave the corresponding *trans*- and *cis*-epoxide 90% and 45%, respectively.

2.5 Asymmetric Epoxidation of Alkenes Catalyzed by Metal Complexes

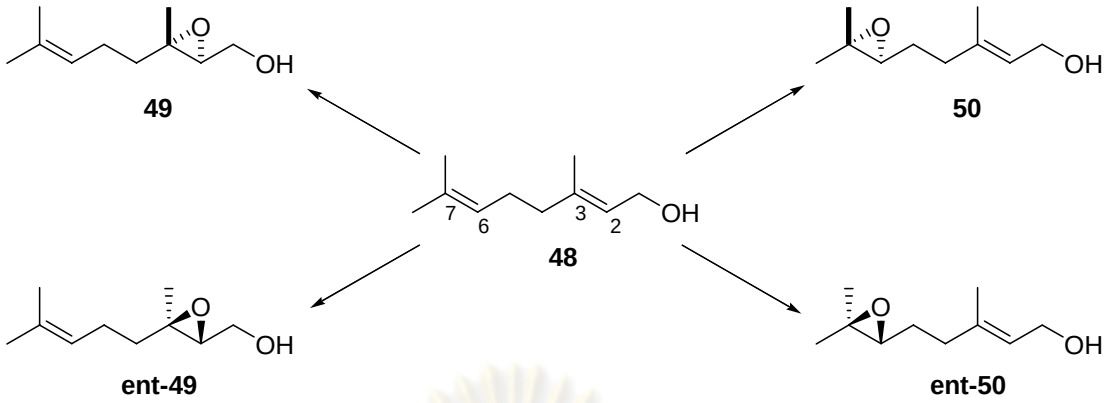
Chiral epoxides are very important building blocks for the synthesis of enantiomerically pure complex molecules, in particular, of biologically active compounds [39, 40]. Catalytic asymmetric epoxidation is an especially useful technique for the synthesis of chiral compounds in both academic and industry because a chiral catalyst molecule can act as an enzyme to induce million-level chiral product molecules [41]. The development of chiral catalysts capable of inducing asymmetric centers with high efficiency has always been an important task for asymmetric synthesis.

2.5.1 Sharpless Systems

Allylic alcohols can be converted in a single reaction into the corresponding epoxide with high stereoselectivity. This efficient procedure for the epoxidation of allylic alcohols was developed by Sharpless *et al*. [42]. The catalyst is a complex prepared from titanium-*iso*-propoxide and an enantiomerically pure tartaric acid ester. Since both enantiomers of the tartaric acid derivatives are readily available, both enantiomers of the desired epoxide can be obtained with high enantiomeric excess. The catalyst employs the hydroxyl function of the allylic alcohol as a handle to accomplish high enantioselectivity. Most functionality, except the strongly coordinating protic ones are compatible with this reaction. TBHP is used as the oxidant. A variety of allylic alcohols can be epoxidized using this catalyst and enantiomeric excess (*ee*) usually exceed 90 % and yields are generally above 80%.



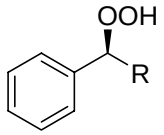
In Scheme 2.2, geraniol **48** has four possible epoxides, racemic (**49**) and (**50**) that can be made through improving either regio or chemiselectivity. However, it required the enantioselectivity in the formation of individual enantiomers [43]. The previous literature in 1957 Henbest *et al.* reported that the electronic deactivation at oxygen substitute coordinated at C1 reasons from the selective coordination of peroxoacids to the 6,7-double bond position which made racemic **(50)** [44]. In 1973, Michaelson *et al*. solved the cause of represented regioselectivity for the epoxidation of geraniol. Alkyl hydroperoxides catalyzed geraniol **38** with transition metals gave of very high selective for the 2,3 double bond compounds (racemic **49**) [45]. Recent publication by Katsuki *et al*. found that titanium could catalyze asymmetric epoxidation of olefins bearing allylic hydroxy groups into either (**49**) or (ent-**49**). This assumption explains the enantioselectivity [46]. In addition, not late after Katsuki, Sharpless *et al*. showed chiral ligands substitute into transition metals Mo, Ti, and V, for the first time. These developed an asymmetric epoxidation system. Very good yield with more than 90%*ee* had found in the conversion of allylic alcohols into asymmetric epoxides using transition metal catalyst $Ti(OPr^{i})_4$ and TBHP, and a chiral additive DET. Later, new efficient systems have been invented for the epoxidation of allylic alcohols such as the catalytic systems of vanadium catalysts and hydroxamic acids derivatives [47].



Scheme 2.2 Regio- and enantioselective monoepoxidations of geraniol

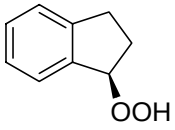
Chiral Titanium Catalysts

Over the past two decades, it has been widely studied for titanium alkoxide complexes using as a catalyst for the asymmetric epoxidation of allylic alcohols [46]. Sharpless *et al*. has a spectacular epoxidation process, which the impact of a chiral ligand on enantioselectivity is critical [48]. With metal catalysts, the structure of hydroperoxides [49] is important for the enantioselectivity of the system. In Sharpless epoxidation, the oxygen donor was achiral TBHP. The contribution of optically active tartrate with catalytic amounts as chiral auxiliary [46, 48] resulted in the asymmetric. Hydroperoxides can be the oxygen donors and the sources of chirality if optically active hydroperoxides are used. The oxygen donors like the optical active hydroperoxide provided the chiral environment. Ti had been studied by many researchers. In 1997, Adam *et al*. published a yield of 50%*ee* [49] when using Ti-mediated asymmetric epoxidation of a variety of prochiral allylic alcohols with optically active hydroperoxides (**51**, **52**, and **53b**) and multidentate ligands as achiral additives. In the same year, Lattanzi *et al.* reported the application of several furylhydroperoxides **53** in Sharpless asymmetric epoxidation of allylic alcohols [50]. The results showed that the enantioselectivity depended on the substitution near the reactive sites. The reproducible had been made by Corey [51] and Sharpless *et al.* [48]. Tertiary or alkyl hydroperoxide has been proven to ensure high *ee*'s [52]. However, there is a limit which is the imposed of the essential coordinated functional groups on the substrate.



a: R=Me
b: R=Et

51



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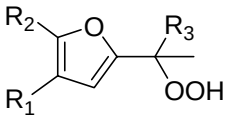
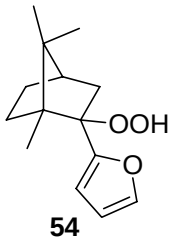


a: R_1=H, R_2=H, R_3=Me
b: R_1=COOEt, R_2=Me, R_3=H
c: R_1=COOEt, R_2=Me, R_3=Me

53



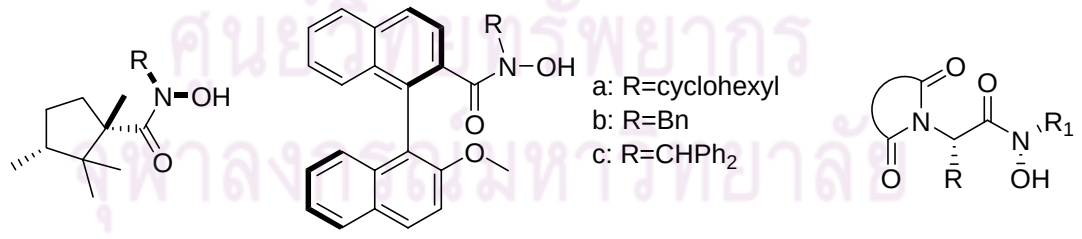
54

In 2003, Lattanzi *et al.* first synthesized an enantiopure tertiary hydroperoxide **52** from camphor *via* a stereospecific nucleophilic substitution of hydroxyl group bound to the chiral carbon center of the alcohol molecule by H_2O_2 (unlike TADOOH), The reaction introduced by peroxo (-OOH) group bound to the sterogenic carbon center. 46% and 59% are received with the chiral tertiary hydroperoxide and the asymmetric epoxidation of allylic alcohols, respectively. At the end of epoxidation, the chiral tertiary alcohol is isolated and recycled for the synthesis of the hydroperoxide. These provide a chiral protocol. The benefit of using optically active hydroperoxides as oxygen donors in the presence of multidentate diols (as chiral ligand) is lower enantioselectivities, unlike using TBHP as an achiral oxygen donor and C_2-symmetric tartrate as chiral auxiliary.

Chiral Vanadium Catalysts

A number of asymmetric epoxidations based on chiral vanadium(V) complexes with TBHP have been reported, [53] in which the epoxidation of allylic alcohols is the most well-known [54]. Vanadium(V) alkylperoxo complexes were widely accepted as intermediates in the catalytic systems of $VO(acac)_2$/TBHP [45, 55] and $VO(acac)_2$/ligand/TBHP [56]. Prior to the appearance of titanium-based catalysts, the Sharpless group had first developed asymmetric epoxidation (50%*ee*) catalyzed by the chiral vanadium hydroxamate complex **55**. A few years later, they found again that when using proline-derived hydroxamic acid as the chiral ligand, up to 80%*ee* could be achieved [57]. Additionally, in 1999 Yamamoto *et al.* successfully applied a new chiral hydroxamic acid **56**, derived from 2,2′-binaphthol, serving as monovalent ligand coordinated with a vanadium complex in the asymmetric epoxidation of allylic alcohols to obtain an *ee* up to 94% [58]. To explore the potentials of these new

catalysts, they extensively tested the epoxidation of various substituted allylic alcohols. The results showed that the epoxidation of 3,3′-disubstituted allylic alcohols catalyzed by $VO(OPr^i)_3$ and **56c** proceeded smoothly to yield the corresponding epoxides in moderate to good yields (70~87%) with mediocre *ee*'s (41~78%*ee*). However, in the case of 2,3-disubstituted allylic alcohols, high *ee* around 90%*ee* was obtained, irrespective of bearing aromatic groups. It should be noted that unlike titanium tartrate system, molecular sieves to sequester water, which has a deleterious effect on both the rate and selectivity, were not required in this case [59]. It seems that several characteristics of chiral vanadium complex played an important role in increasing the rate and enantioselectivity, *i.e.*, the starting oxidation state of vanadium, the coordination ability of hydroxamic acids, and π-interaction or steric repulsion between the metal-binding site and oxidant. To improve the efficiency of vanadium-based catalysts, Yamamoto *et al.* in 2000 developed a family of chiral hydroxamic acid ligands with a structure similar to the complex **57**, [60] and found that the product selectivity increased gradually with an increase of the steric hindrance in the side chain of amino acid, in which the best result was achieved when using *tert*-leucine-derived hydroxamic acid as the ligand. When L-α-amino acid was partly changed into imido group, the best result (87%*ee*) was achieved for the epoxidation of 2,3-diphenyl-prop-2-en-1-ol with 1,8-naphthalene-dicarbonyl-protected hydroxamic acid. Whereas for the same reaction, if aryl group near the metal-coordinated site was changed, the highest *ee* value could reach 96% when using *N*-bis(1-naphthyl) methylsubstituted hydroxamic acid as the ligand.



55 **56** **57**

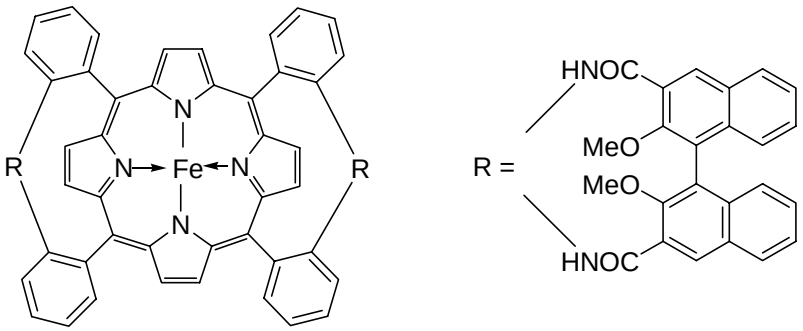
The asymmetric epoxidation of homoallylic alcohols was difficult to conduct with the other metal-based catalysts reported previously [61]. However, vanadium complexes could effectively catalyze the occurrence of this reaction to yield the corresponding epoxy alcohols with good to high stereoselectivities [62].

2.5.2 Porphyrin Systems

Porphyrin is important in a bewildering array of proteins which has functioned as of O_2 storage, O_2 transport, oxidation of inactivated carbon-hydrogen bonds, and oxygen reduction. There homoproteins have diversity that is dictated by many factors, like the number and nature of axial ligands, the spin and oxidation state of the metal center, the nature of the polypeptide chain, and the geometry of the prophyrin ring. The asymmetric epoxidation of alkenes occurs basically *via* high reactive oxometal (Mdo) intermediate. The important catalyst class for asymmetric epoxidation is chiral metalloporphyrins [63]. Porphyrins have a rigid macrocyclic core and alterable periphery which are useful for building asymmetric catalysts. A metalloporphyrin catalyst has been introduced to the porphyrin complexes of Fe [64], Mg [65], Ru [66], and Mo [67]. In order to append potically active groups onto the macrocyclic ring of metalloporphyrins [68], the consideration is the nature of oxidants and metals (Fe, Ru and Mo etc) [69]. Iron and ruthenium comples with the same chiral prophyrin ligand better than magnesium, due to the co-interaction of oxidant, axial ligand, and oxygen transfer [70], using 2,6-dichloropyridine-*N*-oxide as the oxidant with the same chiral porphyrin ligand gave different *ee* values for stoichiometric and catalytic reaction. When using oxygen or iodosylbenzene as the oxidant, the same reactions with *ee* was received, which are from Berkessek [71] and Che *et al.* [72]. Halterman [73] also reported the high efficiency of the catalyst systems using 2,6-dichloropyridine-*N*-oxide as terminal oxidant. 77% *ee* and 90% yield [71] of the epoxide of 1,2-dihydronaphthalene was received.

Iron Porphyrins

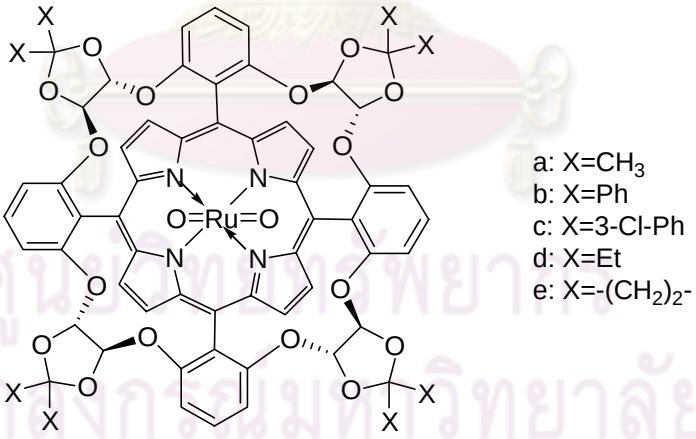
The synthetic iron (II) porphyrins without imposed of protection upon both faces tend to be oxidized only to form μ-oxo Fe (III) dimers [74]. The development of model structures with protected face is avoiding those unfavorable oxidations [75]. Based on a chiral iron porphyrin **58** [76], Collman *et al*. found a high efficient catalyst in 1999. With this method 83%*ee* for styrene, 88%*ee* for pentafluorostyrene and 82%*ee* for *m*-chlorostyrene were achieved. In 3,3-dimethylbutene and vinyltrimethylsilane, *ee* values exceeded the highest values obtained from previous catalytic systems [77].



58 isomer: ααββ

Ruthenium Porphyrins

Ruthenium has been introduced in coordinated with D_4 chiral porphyrins or homochiral porphyrins [78], however, low yields of the oxidation of styrene derivatives which is catalyzed by chiral metalloporphyrins [79]. It can be seen that identical chiral porphyrin ligands ruthenium complexes worked well with inducing asymmetry not iron, manganese, or rhodium derivatives [80]. The epoxidation catalyzed by a homochiral ruthenium porphyrin **59a** [66] reported by Gross *et al*. in 1996, and this epoxidation shows solvent effect on the enantioselectivity of chiral epoxy styrene.



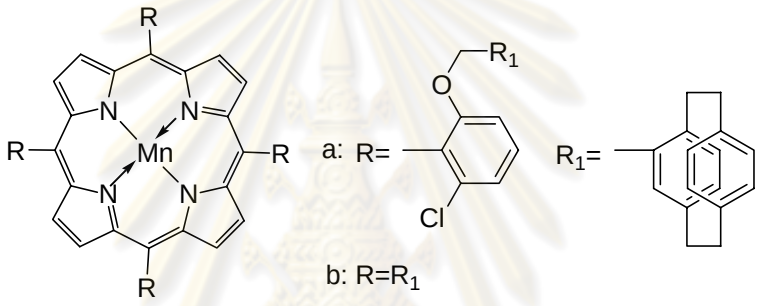
59

The properties of highly enantioselective epoxidation of unfunctionalized trans-disubstituted alkenes are reactive, isolable, and chiral metal oxo complexes. The catalyze alkenes give enatioselectivities better than *cis*-counterparts in epoxides [66]. The study of stoichiometric epoxidations of alkenes had been done and produced the relationship of structure-enantioselectivity, which can be used in development of better metal catalysts. In 1999, Zhang *et al.* applied D_2-symmetric chiral *trans*-

dioxoruthenium(VI) porphyrins **59a**, **d,** and **e**, which encumbered to catalyze the enantioselective epoxidation of *trans*-β-methylstyrene (70% *ee*) and cinnamyl chloride (76% *ee*) [72].

Manganese Porphyrins

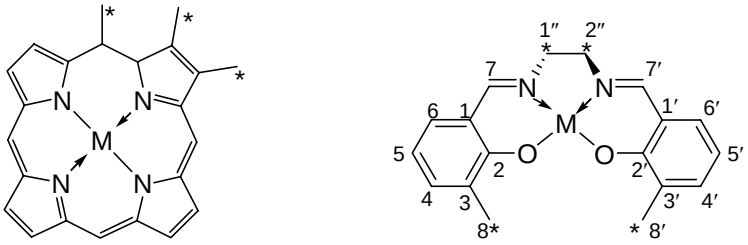
In 1998, Rispens *et al.* reported homochiral, atropisomerically pure manganese complexes **60** containing a [2,2]-*para*-cyclophane-4-carbaldehyde building block group which were used as the catalysts in the epoxidation of unfunctionalized olefins using aqueous NaClO, 30%-H_2O_2 and PhIO as oxygen donors [81]. They found that NaClO and PhIO gave good overall munbers, but 30% H_2O_2 gave low enantioselectivity.



60

2.5.3 Salen Systems

Because of the enantiomerical pure epoxides which are good intermediates, the unfunctional alkene asymmetric epoxidation is interested. The key to solve the difficulty from an effective porphyrin catalyst is its π-conjugated planar structure, and its prohibited the stereogenic carbons in the porphyrin ring. To be able to form complex, salen complex has sterogenic carbons at C1′′, C2′′, C8, and C8′ carbons (Scheme 2.3) [82]. Since the chiral porphyrin synthesis to be a very long period of time, salen Mn catalysts are introduced as in the industrial purposes. One benefit of manganese is a quite nontoxic and its complexs are superior to iron complexes as in the olefins.

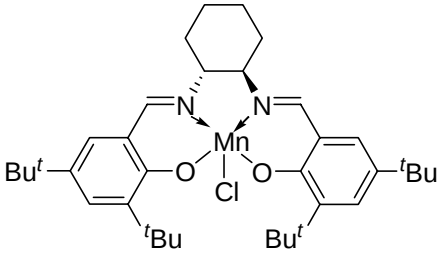


Scheme 2.3. Asymmetric Carbons in Porphyrin and Salen

Manganese and Chromium Salens

A variety of chiral salen-Mn (III) catalysts was first introduced by Katsuki *et al.* These have been interesting for efficient epoxidation of non-functionalized alkenes with different oxidants at high enantioselectivity [83]. The enentioselective epoxidation of variety alkenes with simple oxidants like PhIO, NaOCl, H_2O_2 and oxone have been reported. The perfect catalyst and reaction conditions [84] are needed to achieve an optimal enantioselectivity. The condensations of diamines with salicylaldehyde derivatives make understand of a unique tune the steric and electronic properties of the catalyst [85]. In essentially, chiral salen systems give the known chiral porphyrins since the symmetric centers in salen complexes are in good proximity to reactive sites.

As the model to mimic the function of cytochrome P450, a transition metal Schiff-base has several advantages: (a) easy availability, (b) low cost, and (c) high epoxidation activity toward a wide range of unfunctionalized olefins. This should make it to be a very attractive candidate for laboratory and industrial uses [86]. The discovery of chiral salen-Mn(III) complexes has, for the first time, allowed a convenient and inexpensive route for the efficient asymmetric epoxidation of unfunctionalized olefins [87]. The *tert*-butyl substituted catalyst **61** consisting of both commercially available enantiomers is not the most enantioselective but is much easier to prepare [88]. Note that the Jacobsen catalyst is air-stable and can be stored for a long period without appreciable decomposition [89]. Katsuki catalyst **62** is also effective [88].



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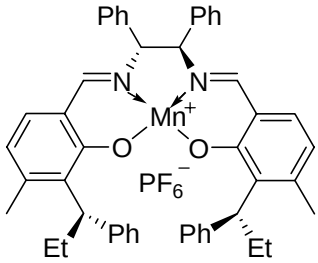
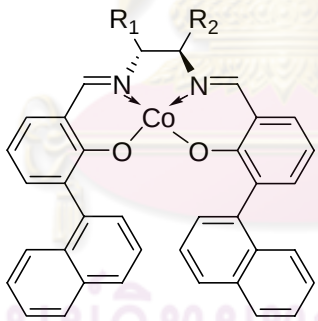


62

Cobalt Salens

Much attention has been paid to the development of direct and selective epoxidation of olefins by the use of molecular oxygen and a suitable reductant, such as a primary alcohol, [90] aldehyde, [91] and cyclic ketone [92] that can accept one oxygen atom from molecular oxygen to enable the reaction. In 1997, Kureshy *et al.* first reported the asymmetric epoxidation of nonfunctionalized prochiral olefins by combined use of an atmospheric pressure of molecular oxygen and a reductant of isobutylaldehyde catalyzed by chiral salen-Co (II) complexes **63** with or without PyNO co-oxidant [93]. An up to 55%*ee* and a yield of 90% were achieved for the catalytic epoxidation of *trans*-3-nonene.



a: $R_1=R_2=-(CH_2)_4-$
b: $R_1=H$, $R_2=Me$
c: $R_1=R_2=Ph$

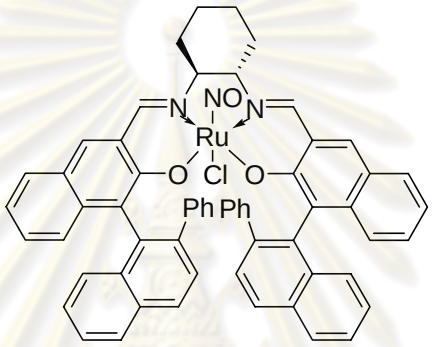
63

Ruthenium Salens

In 1999, Takeda *et al.* published the synthesis and catalytic application of (ON+)(salen) ruthenium (II) complex [(ON)Ru-salen complex] **64** in the asymmetric epoxidation of 6-acetamido-2,2-dimethyl-7-nitrochromene in the presence of various oxidants, for which 2,6-dichloropyridine *N*-oxide as terminal oxidant was preferred [94]. In spite of conjugated olefins substitution pattern, high enantioselectivities are more than 80%*ee*. On the other hand, the enantioselectivity decreased with long reaction time. The (ON)Ru-salen complex **64** can be decomposed during the reaction

to generate fragmental Ru-species. Morever, it can be accelerated with sunlight and its asymmetric induction is similar to that of the Mn-salen complex.

The properties of metallosalens are first effectively catalysts for asymmetric epoxidation of conjugated *cis*-, di-, tri-, and some tetra-substituted olefins [95], second, easily synthesized from salicylaldehyde derivatives, diamines, and metal ions. In addition, there are reasons of making metallosalens convenient and the application of such catalysts such as the availability in the industry with choice of chiral and/or achiral salicyladehydes, chiral diamines, and metal ions, and the short preparation of metallosalen complex catalysts.



64

The production of new receptors for anions and neutral species which are easy to synthesize and yet effective and selective in their guest binding properties is an area of supramolecular chemistry. Calix[4]pyrrole(*meso*-octaalkylporphyrinogens) are stable tetrapyrrolic macrocycles first synthesized in the 19th century by Baeyer *via* acid-catalyzed condensation of pyrrole with acetone to produce *meso*-octamethylcalix[4]pyrrole. These species as receptors for anions and neutral molecules [106] has been disclosed in the production of fluorescent, colorimetric, and electrochemical sensors for anions, in addition to new solid supports capable of separating mixtures of anions including oligonucleotides.

Encouraged by the facile synthesis of both calix[4]pyrrole and benzimidazole ligands in high yield, together with there was no report cited in chemical literature to utilize these cobalt(II) calix[4]pyrrole and cobalt(II) benzimidazole complexes in the epoxidation reaction, the selectively catalytic epoxidation of alkenes under mild condition will be thoroughly investigated in this research.

2.6 Scope of This Work

The aim of this research can be summarized as follows:

1. To synthesize calix[4]pyrrole, Schiff base and benzimidazole ligands and their cobalt (II) complexes
2. To study the optimum conditions for alkene epoxidation using cobalt(II) calix[4]pyrrole and cobalt(II) benzimidazole as catalyst
3. To study the stereoselectivity, regioselectivity and chemoselectivity of the developed system using those mentioned catalysts
4. To apply the optimum conditions for the epoxidation of various selected alkenes
5. To apply this catalyst for the epoxidation of natural product compound
6. To apply this catalyst for the epoxidation of terminal alkenes
7. To develop this catalyst for one-pot synthesis to halohydrins
8. To apply this catalyst for the epoxidation of imine

2.7 Experimental

2.7.1 Instruments and Equipment

Melting points were measured on Fisher-Johns melting point apparatus. Fourier Transform-Infrared Spectra (FT-IR) were recorded on Nicolet Impact 410 FT-IR spectrometer. The ^{1}H and ^{13}C-NMR spectra were performed in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as an internal reference on a Varian Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ^{1}H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons. Specific rotations were measured on a Jasco P-1010 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg $\cdot$ cm^2 $\cdot$ g^{-1}.

Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck's, Kieselgel 60 G) and aluminium oxide 90 (70-230 mesh ASTM). Gas chromatography analysis was carried out on a Shimadzu gas chromatograph GC-14A and Varian gas chromatograph CP-3800 instrument equipped with flame ionization detector (FID) with nitrogen as a carrier gas. The column used for chromatography was a capillary column type of DB-wax (30 m x 0.25 mm) for

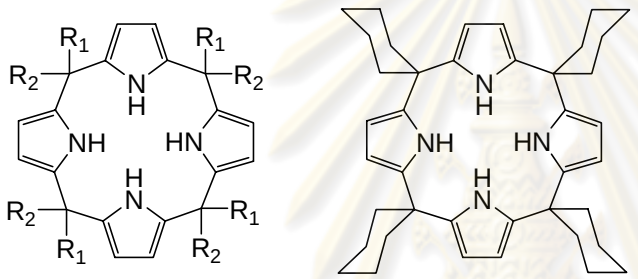
GC-14A and a capillary column type of CP-Sil 5 (30 m x 0.25 mm), CP-Sil 8 (30 m x 0.25 mm) and CP-Wax (30 m x 0.25 mm) for GC CP-3800.

2.7.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades. The reagents utilized for synthesizing the ligands, metal complexes and all alkenes were purchased from Fluka chemical company or otherwise stated and were used without further purification.

2.7.3 General Procedure

2.7.3.1 Preparation of Calix[4]pyrrole ligands [96, 97]



67

65 $R_1 = R_2 = Me$
66 $R_1 = R_2 = Et$
68 $R_1 = Me$, R_2 = 4-methoxyphenyl
69 $R_1 = Me$, R_2 = phenyl
70 R_1 = phenyl, R_2 = phenyl
71 $R_1 = Me$, R_2 = 4-*tert*-butylphenyl

Calix[4]pyrrole ligands were prepared by slowly adding methanesulfonic acid (7% mol) to a solution of ketone (0.1 mol), pyrrole (0.1 mol) and EtOH 50 mL. The mixture was allowed to reflux for 4 hours and then cooled. The brown solid was filtered off, washed with several portions of EtOH and dried at room temperature, the Calix[4]pyrrole ligands were obtained.

***meso*-Octamethylcalix[4]pyrrole (65)**: White crystal (82%); m.p. 220-222°C; IR (KBr, cm^{-1}): 3437 (s), 2978 (s), 1640 (m), 1451 (m), and 1272 (m); ^{1}H-NMR ($CDCl_3$) δ 7.04 (4H, bs, pyrrole NH), 5.89 (8H, d, J = 2.6 Hz, pyrrole CH), 1.50 (24H, s, CH_3); ^{13}C-NMR ($CDCl_3$): δ 138.4, 102.8, 35.2 and 29.1.

***meso*-Octaethylcalix[4]pyrrole (66)**: White crystal (80%); m.p. 119-220°C; IR (KBr, cm^{-1}): 3454 (s), 2979 (s), 1644 (m), 1498 (m) and 1235 (m); ^{1}H-NMR ($CDCl_3$) δ 7.00 (4H, s, bpyrrole NH), 5.94 (8H, d, J = 2.7 Hz, pyrrole CH), 1.83 (16H, m, ethyl CH_2), 0.62 (24H, t, J = 7.5 Hz, ethyl CH_3); ^{13}C-NMR ($CDCl_3$): δ 136.8, 105.5, 43.5, 28.8 and 8.4.

Tetraspirocyclohexylcalix[4]pyrrole (67): White solid (85%); m.p. 268-269°C; IR (KBr, cm^{-1}): 3446 (s), 2931 (s), 2856 (m), 1630 (s) and 1451 (m); ^{1}H-NMR ($CDCl_3$) δ 7.04 (4H, bs, pyrrole NH), 5.87 (8H, d, *J* = 3.0 Hz, pyrrole CH), 1.88 (16H, m, cyclohexyl CH_2), 1.42 (24H, m, cyclohexyl CH_2); ^{13}C-NMR ($CDCl_3$): δ 136.4, 103.4, 39.6, 37.1, 26.0 and 22.7.

***meso*-Tetrakis(4-methoxyphenyl)-tetramethyl-calix[4]pyrrole (68)**: Brown solid (99%); m.p. 121-122 °C; IR (KBr, cm^{-1}): 3431 (s), 2970 (s), 2832 (m), 1608 (s), 1456 (s), and 1250 (s); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (2H, bs, NH), 7.53 (2H, bs, NH), 7.15-6.92 (8H, m, phenyl), 6.85-6.50 (8H, m, phenyl), 5.92-5.66 (8H, m, pyrrole CH), 3.78 (12H, s, -OCH_3) and 1.85 (12H, s); ^{13}C-NMR ($CDCl_3$) δ (ppm): 157.5, 139.4, 136.8, 128.3, 113.0, 105.5, 55.0, 43.6 and 17.8.

***meso*-Tetrakis(phenyl)-tetramethyl-calix[4]pyrrole (69)**: Brown solid (65%); m.p. 296-297°C; IR (KBr, cm^{-1}): 3428 (s), 2968 (s), 1635 (m), 1489 (m) and 1121 (m); ^{1}H-NMR ($CDCl_3$) δ 7.46 (4H, bs, pyrrole NH), 7.27-7.07 (20H, m), 5.62-5.94 (8H, m, pyrrole CH) and 1.93 (12H, m); ^{13}C-NMR ($CDCl_3$): δ 147.7, 136.8, 136.5, 127.9, 126.5, 105.9, 44.7 and 29.0.

***meso*-Octaphenyllcalix[4]pyrrole (70)**: white solid (45%); m.p. 193-195°C; IR (KBr, cm^{-1}): 3418 (s), 1545 (m), 1484 (m) and 1225 (m); ^{1}H-NMR ($CDCl_3$) δ 7.91 (4H, bs, pyrrole NH), 7.27-6.72 (40H, m, phenyl), 6.14 (4H, m, pyrrole CH) and 5.96 (4H, m, pyrrole CH); ^{13}C-NMR ($CDCl_3$): δ 146.0, 135.3, 129.2, 127.8, 126.7, 109.6, 108.0 and 44.4.

***meso*-Tetrakis(4-*tert*-butylphenyl)-tetramethyl-calix[4]pyrrole (71)**: Brown solid (80%); m.p. 115-116°C; IR (KBr, cm^{-1}): 3431 (s), 2970 (s), 1573 (m), 1265 (m) and 1199 (m); ^{1}H-NMR ($CDCl_3$) δ 7.84 (2H, bs, NH), 7.58 (2H, bs, NH), 7.27-7.00 (16H, m, phenyl), 5.90 (4H, d, *J* = 2.5 Hz, pyrrole CH), 5.71 (4H, d, *J* = 2.5 Hz, pyrrole CH) 1.89 (12H, s, CH_3) and 1.30 (36H, s, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 149.2, 144.3, 136.8, 136.5, 127.0, 124.6, 106.2, 105.3, 44.3, 34.3, 31.3, and 29.1.

2.3.3.2 General Preparation of Polyanion Calix[4]pyrrole [34]

To a solution of calix[4]pyrrole 7 mmol in tetrahydrofuran (THF) 40 mL was added butyl lithium (BuLi) 28 mmol. The reaction mixture was refluxed under stirring for 2 h. The solvent was evaporated in vacuo and the residue was washed with dry hexane to afford the brown solid to give polyanions.

Lithium of meso-octamethylcalix[4]pyrrole: Yellow solid (73%); IR (KBr, cm^{-1}); 3104 (m), 2965 (s), 2868 (w), 1787 (m), 1680 (s), 1419 (s) and 1244 (s); ^{1}H- NMR ($CDCl_3$) δ 6.00 (s, 8H), 4.29 (bs, 16H, THF), 1.48 (s, 24H) and 1.21 (m, 16H, THF).

Lithium of meso-octaethylcalix[4]pyrrole: Yellow solid (71%); IR (KBr, cm^{-1}); 3124 (w), 2937 (w), 2844 (w), 1575 (s), 1431 (m) and 1203 (w); ^{1}H-NMR ($CDCl_3$) δ 6.00 (s, 8H), 4.73 (bs, 16H, THF), 1.83 (m, 16H), 1.20 (m, 16H, THF) and 0.74 (t, J = 14.8 Hz, 24H).

Lithium of tetraspirocyclohexylcalix[4]pyrrole: Light brown solid (81%); IR (KBr, cm^{-1}); 3108 (m), 2919 (s), 2842 (s), 1567 (m), 1444 (m) and 1291 (m); ^{1}H-NMR ($CDCl_3$) δ 5.93 (s, 8H), 4.70 (bs, 16H, THF), 1.91-1.42 (m, 40H) and 1.21 (m, 16H, THF).

Lithium of meso-tetrakis(4-methoxyphenyl)-tetramethyl-calix[4]pyrrole: Dark brown solid (79%); IR (KBr, cm^{-1}); 3090 (w), 2631 (w), 1607 (w), 1456 (m) and 1250 (m); ^{1}H NMR ($CDCl_3$) δ 7.15-6.93 (m, 8H), 6.78-6.64 (m, 8H), 5.90-5.78 (m, 8H), 3.77 (m, 12H), 4.68 (bs, 16H, THF), 1.86 (m, 12H) and 1.75 (bs, 16H, THF).

Lithium of meso-tetrakis(phenyl)-tetramethyl-calix[4]pyrrole: Dark brown solid (65%); IR (KBr, cm^{-1}); 3043 (s), 2968 (m), 1574 (s), 1489 (s) and 1028 (m); ^{1}H-NMR ($CDCl_3$) δ 7.28–7.02 (m, 20H), 5.92-5.65 (m, 8H), 3.75 (m, 16H, THF), 1.89 (bs, 12H) and 1.42 (m, 16H, THF).

Lithium of meso-octaphenyllcalix[4]pyrrole: Bright purple solid (61%); IR (KBr, cm^{-1}); 3090 (w), 1588 (w), 1489 (w) and 1235 (m); ^{1}H-NMR ($CDCl_3$) δ 7.28-6.71 (m, 40H), 6.17 (m, 4H), 5.97 (m, 4H), 3.76 (m, 16H, THF) and 1.84 (m, 16H, THF).

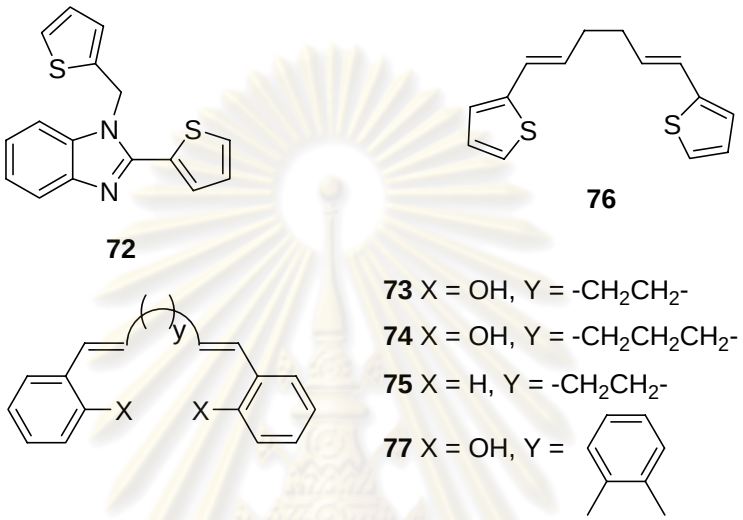
Lithium of meso-tetrakis(4-tert-butylphenyl)-tetramethyl-calix[4]-pyrrole: brown solid (77%); IR (KBr, cm^{-1}); 3025 (w), 2618 (w), 1532 (w), 1445 (m) and 1228 (m); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.25 (d, J =8.4, 8H), 7.08 (d, J =8.4, 8H), 5.95 (s, 4H), 5.65 (s, 4H), 3.78 (m, 16H, THF), 1.85-2.00 (s, 20H), 1.42 (m, 16H, THF) and 1.25 (s, 36H).

2.7.3.3 General Preparation of Co(II) Calix[4]pyrrole

Cobalt (II) chloride (3.3 mmol) and a polyanion of **(68)** (4 mmol) were dissolved in toluene 40 mL. The reaction mixture was stirred at room temperature for

48 h. After the reaction completed, the brown solid was filtered off and washed with several portions of toluene. The filtrate was collected and kept in refrigerator for 24 h. The solvent was evaporated in vacuo to give brown solid 87% yield; m.p. 116–117°C, IR (KBr, cm^{-1}): 2959 (w), 1724 (s), 1672 (m), 1597 (s) and 1254 (s).

2.7.3.4 Preparation of Schiff Bases Ligands



2-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1H-benzo[*d*]imidazole (72) [98]

Soultion of 1,2-phenylenediamine (0.025 mol) in ethanol (30 mL) was added to thiophene-2-carboxaldehyde (0.05 mol) to give dark green solution which was then heated on the steam-bath for 30 min until the colour turned to red. The reaction mixture was cooled and the clear red solution was decanted from a small amount of brown oil and filtered. The filtrate on standed overnight to deposite yellow needle crystals (86%); m.p. 148-149°C; ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.83 (dd, *J* = 6.87 and 1.83 Hz, 1H), 7.51 (dd, *J* = 5.03 and 1.22 Hz, 1H), 7.47 (dd, *J* = 3.82 and 1.22 Hz, 1H), 7.37 (dd, *J* = 7.32 and 1.22 Hz, 1H), 7.29 (m, 2H), 7.23 (dd, *J* = 4.89 and 1.23 Hz, 1H), 7.13 (t, *J* = 4.27 Hz, 1H), 6.94 (t, *J* = 4.43 Hz, 1H), 6.86 (dd, *J* = 3.36 and 1.22 Hz. 1H) and 5.70 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 147.6, 143.0, 138.8, 135.7, 131.8, 129.0, 128.2, 127.2, 125.2, 123.3, 123.0, 119.9, 109.9 and 44.0.

Bis(salicylaldehyde) *N,N'*-ethylenediimine (salen) (73) [99]

Ligand was prepared by slow adding ethylenediamine (0.06 mol) to salicylaldehyde (0.15 mol) then stirred at room temperature. The yellow solid precipitated immediately and recrystallized was filtered by 95% ethanol. Bright yellow crystals (97%); m.p. 124-125°C; ^{1}H-NMR ($CDCl_3$) δ(ppm): 13.2 (s, 2H), 8.29

(s, 2H), 7.26 (dt, *J* = 7.78 and 1.53 Hz, 2H), 7.18 (dd, *J* = 7.78 and 1.53 Hz, 2H), 6.93 (d, *J* = 8.24 Hz, 2H), 6.83 (dt, *J* = 7.48 and 1.22 Hz, 2H) and 3.84 (s, 4H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 166.3, 160.9, 132.2, 131.4, 118.5, 116.8, and 59.5.

Bis(salicylaldehyde) *N,N′*-trimethylenediimine (saltn) (74) [100]

Solution of 1,3-propylenediamine (0.025 mol) in methanol (30 mL) was added to salicylaldehyde (0.05 mol). The mixture was stirred at room temperature until precipitate occurred. Yellow needle crystals (24%): m.p. 51-52°C; ^{1}H-NMR ($CDCl_3$) δ(ppm): 13.42 (s, 2H), 8.33 (s, 2H), 6.85-7.31 (m, 8H), 3.66-3.69 (dt, 4H *J* = 6.72, 0.92) and 2.02-2.10 (q, 2H *J* = 6.71); ^{13}C-NMR ($CDCl_3$) δ(ppm): 165.3, 161.0, 132.2, 131.2, 118.7, 118.5, 116.9, 56.7 and 31.6.

Bis(benzaldehyde) *N,N′*-ethylenediimine (benz) (75) [101]

Ethylenediamine (0.05 mol) was slowly added to benzaldehyde (0.10 mol). The reaction mixture was heated and stirred until pale yellow solid occurred. Precipitate was filtered and recrystallized by 50% methanol. Yellow crystals (84%); m.p. 48-50°C; ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.28 (s, 2H), 7.71-7.67 (m, 4H), 7.40-3.35 (m, 6H) and 3.97 (s, 4H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 162.6, 136.1, 130.6, 128.5, 128.0 and 61.6.

Bis(2-thiophenealdehyde) *N,N′*-ethylenediimine (thiophen) (76) [98]

Ligand was synthesized by reacting 2-thiophenealdehyde (0.05 mol) and ethylenediamine (0.025 mol). A Small amount of 95% ethyl alcohol was used as solvent. The white solid was filtered and washed with several portions of distilled water-ethanol solution and dried at room temperature. White crystals (80%); m.p. 90-91°C; ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.34 (s, 2H), 7.36 (d, *J* = 5.19 Hz, 2H), 7.24 (d, *J* = 3.66 Hz, 2H), 7.03 (t, *J* = 4.42 Hz, 2H) and 3.90 (s, 4H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 156.2, 142.3, 130.5, 128.7, 127.3 and 60.9.

Bis(salicylaldehyde) *N,N′*-1,2 phenylenediimine (salophen) (77) [102]

Salophen was prepared by slowly adding salicylaldehyde (0.07 mol) to a solution of *o*-phenelenediamine (0.03 mol) in methanol which was being stirred at room temperature. The orange precipitate was recrystallized from acetone. Orange needle crystals (82%); m.p. 164-165°C; ^{1}H-NMR ($CDCl_3$) δ(ppm): 13.0 (s, 2H), 8.60 (s, 2H), 7.31 (m, 2H), 7.20 (m, 4H), 7.02 (d, *J* = 13.24 Hz, 2H) and 6.85 (t, *J* = 7.32 Hz) ^{13}C-NMR ($CDCl_3$) δ(ppm): 163.6, 161.3, 142.4, 133.3, 132.3, 127.7, 119.6, 119.1, 118.9 and 117.5.

2.7.3.5 Preparation of Starting Materials

4-methoxy cinnamic acid [103]

Malonic acid 3.12 g (31 mmol) was dissolved in 6 mL of anhydrous pyridine, 4-methoxybenzaldehyde 3.54 g (26 mmol) and 0.26 mL of piperidine were added. The solution was refluxed approximately 1.5 hr, cooled to room temperature, then poured into a mixture of 16 g of ice, 8 mL of conc HCl and 26 mL of H_2O, precipitating the acid as a colorless solid. The product was filtered, washes with ice water and recrystallized with ethanol. The white mirror-like needle crystal (78% yield); m.p. 173-174°C, R_f 0.62 (ethanol); IR (KBr, cm^{-1}): 3650-3300, 1690, 1630, 1598, 1516, 1446, 1432, 1250, 1210 and 1175; ^{1}H-NMR (DMSO) δ (ppm): 7.64 (d, *J* = 15.87 Hz, 1H), 6.97-7.64 (m, 4H), 6.40 (d, *J* = 16.17 Hz, 1H) and 3.82 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 168.2 (-COOH), 162.5, 130.6 (2x1C), 128.0, 115.2 (2x1C) (aromatic carbon), 145.3, 116.5 (olefinic carbons) and 67.2 (-OCH_3).

2.7.3.6 Synthesis Ethylcinnamate Derivatives

General Procedure [104]

Ethanol (0.01 mol) was dissolved in 10 mL of benzene and then substituted *trans*-cinnamic acid (0.01 mol) was added thereto. After that 0.3 mL of conc H_2SO_4 was added and the mixture was refluxed for 5 hours. The reaction mixture was concentrated to remove benzene and the residue was poured into 8 mL of ice water. The mixture was extracted three time with 10 mL of ether. The combined extracts were washed twice with 10 mL of H_2O, dried over Na_2SO_4, evaporated in vacuum and the residue was fractionally distilled to give the desired compound.

Trans-ethylcinnamate: Yellow oil (57% yield), R_f 0.78 (EtOAc); IR (KBr, cm^1): 1712, 1633, 1446, 1310 and 1267; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.68 (d, *J* = 15.83, 1H), 7.38-7.53 (m, 5H), 6.43 (d, *J* = 15.83 Hz, 1H), 4.26 (q, *J* = 7.04 Hz, 2H) and 1.33 (t, *J* = 7.04 Hz, 3H).

Trans-ethyl 4-methoxycinnamate: Colorless oil (69% yield), R_f 0.56 (EtOH); IR (KBr, cm^{-1}): 1703, 1625, 1602, 1513, 1287, 1248 and 1170; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.67 (d, *J* = 15.83 Hz, 1H), 7.51 (d, *J* = 8.21 Hz, 2H), 6.93 (d, *J* = 8.21 Hz, 2H), 6.34 (d, *J* = 15.83 Hz, 1H), 4.28 (q, *J* = 7.04 Hz, 2H), 3.87 (s, OCH_3) and 1.36 (t, *J* = 7.04 Hz, 3H).

Ethyl sorbate: Colorless liquid (78%), IR (neat, cm^{-1}): 3050, 1720, 1640 and 1620; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.27-7.21 (m, 1H), 6.18-6.13 (m, 2H), 5.17 (d, *J* = 15.3 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.84 (d, *J* = 5.4 Hz, 3H) and 1.28 (t, *J* = 7.2 Hz, 3H).

2.7.3.7 Preparation of Epoxides

To a solution of alkene (5 mmol) in 15 mL of dry methylene chloride at 0°C was added 70% *m*-CPBA acid (7.5 mmol). After the solution was stirred for 3-6 hours, the excess peracid was decomposed with saturated sodium bicarbonate solution, the organic layer was separated, and the aqueous layer was washed twice with dry methylene chloride. The organic layers were combined, washed with brine, dried and evaporated to yield the desired epoxide.

1-methylcyclohexene oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.95 (t, *J* = 3.51 Hz, 1H), 1.45-1.89 (m, 8H) and 1.29 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 59.6, 57.8, 29.9, 25.0, 22.7, 20.1 and 19.7.

α-methyl styrene oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.23-7.42 (m, 5H), 2.98 (d, *J* = 5.4 Hz, 1H), 2.82 (d, *J* = 5.4 Hz, 1H) and 1.73 (s, 3H); ^{13}C- NMR ($CDCl_3$) δ (ppm): 141.3, 128.5, 127.6, 125.4, 57.2 and 56.9.

vinyl cyclohexene 1,2 oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.00-4.75 (m, 3H), 3.01 (m, 2H) and 2.42-1.23 (m 7H).

vinyl cyclohexene 7,8 oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.65 (br s, 2H), 2.53-2.34 (dd, *J* = 5.2, 2.7 Hz, 1H), 2.85-2.50 (m, 2H) and 2.3-1.2 (m, 7H).

***trans*-2-hexen-1-ol oxide**: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.92 (dd, *J* = 12.6, 2.4 Hz, 1H), 3.62 (dd, *J* = 12.6, 4.5 Hz, 1H), 2.95 (m, 2H), 2.31 (br s, OH) 1.50 (m, 4H) and 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 61.5, 58.3, 55.5, 33.0, 18.7 and 13.3.

***cis*-4-hexen-1-ol oxide**: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.01-3.72 (m, 1H), 3.15-2.74 (m, 3H), 1.97 (br s, OH), 1.72-0.85 (m, 11H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 60.4, 59.7, 55.8 28.4, 25.8 and 19.1.

1-octene-3-ol oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, OH), 3.43 (q, *J* = 6.4 Hz, 1H), 2.99 (dd, *J* = 12.2, 2.9 Hz, 1H), 2.82 (t, *J* = 4.2 Hz, 1H), 2.72 (m, 1H), 1.60-1.31 (m, 8H) and 0.88 (t, *J* = 5.8 Hz, 3H).

cinnamyl alcohol oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.37-7.27 (m, 5H), 4.06 (dd, *J* = 12.8, 2.0 Hz, 1H), 3.93 (d, *J* = 1.6 Hz 1H), 3.81(dd, *J* = 12.8, 3.8 2H), 3.23 (m. 1H) and 1.84 (br s, OH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 128.8, 128.5, , 126.1, 116.7, 62.8, 61.7, 55.8.

anethole oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.17 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 3.50 (s *J* = 2.0 Hz, 1H), 3.01 (dd, *J* = 5.2, 2.0 Hz, 1H) and 1.41 (d, *J* = 5.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 160.0, 130.3, 127.2, 114.1, 59.5, 58.9, 18.0.

α-pinene oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.07 (dd, *J* = 4.0, 1.2 Hz, 1H), 2.05-1.85 (m, 4H), 1.76-1.68 (m, 1H), 1.62 (d, *J* = 9.1 Hz, 1H), 1.31 (s, 3H), 1.29 9s, 3H) and 0.94 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 60.2, 56.8, 45.1, 40.5, 39.7, 27.6, 25.8, 22.4 and 20.1.

β-citronellol oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.67 (m, 2H), 2.69 (t, *J* = 5.9 Hz, 1H), 1.64-1.36 (m, 7H), 1.29 (s, 3H), 1.25 (s, 3H) and 0.91 (d, *J* = 6.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 64.6, 60.9, 39.8, 39.5, 33.7, 33.6, 29.3, 29.1, 24.8, 19.6 and 18.6.

geraniol 2,3 oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.07 (t, *J* = 6.9 Hz, 1H), 3.80 (dd, *J* = 12.1, 4.1 Hz, 1H), 3.67 (dd, *J* = 12.1, 6.7 Hz, 1H), 2.97 (dd, *J* = 6.6, 4.2 Hz), 2.10-1.75 (m, 4H), 1.67 (s, 3H), 1.59 (s, 3H) and 1.28 (s, 3H); ^{13}C- NMR ($CDCl_3$) δ (ppm): 132.1, 123.3, 63.0, 61.4, 61.2, 38.4, 25.6, 23.6, 17.6 and 16.7.

geraniol 6,7 oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.44 (t, *J* = 5.63 Hz, 1H), 4.15 (d, *J* = 6.9 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.20-1.68 (m, 4H), 1.66 (s, 3H), 1.29 (s, 3H) and 1.25 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 138.4, 124.0, 64.0, 59.2, 58.4, 36.2, 27.1, 24.8, 18.7 and 16.2.

geranyl acetate 6,7 oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.37 (t, *J* = 7.0 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 2H), 2.69 (t, *J* = 6.0 Hz, 1H), 2.20 (m, 1H), 2.13 (m, 1H), 2.04 (s, 3H), 1.71 (s, 3H), 1.65 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 171.1, 141.2, 118.9, 63.9, 61.2, 58.4, 36.2, 27.1, 24.8, 21.0, 18.7 and 16.4.

cis-stilbene oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.11-7.37 (m, 10H) and 4.37 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 134.3, 127.7, 127.4, 126.8 and 56.7.

trans-stilbene oxide: White solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.24-7.40 (m, 10H) and 3.92 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 137.1, 128.6, 128.6, 125.5 and 62.8.

nopol oxide: Colorless liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.72 (t, *J* = 6 Hz, 2H), 3.34 (d, *J* = 4 Hz, 2H), 2.70 (br, OH), 2.23-1.75 (m, 6H), 1.61 (d, *J* = 8.4 Hz, 1H), 1.32 (s, 3H) and 0.95 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 63.1, 58.6, 54.9, 44.5, 40.6, 40.0, 36.5, 27.5, 26.7, 25.6 and 20.2.

ethyl sorbate oxide: Pale yellow liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.65 (dd, *J* = 8.5, 7.1 Hz, 1H), 6.10 (d, *J* = 15.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.16 (dd, *J* = 5.9, 1.1 Hz, 1H), 2.95 (dd, *J* = 3.3, 1.8 Hz, 1H), 1.36 (d, *J* = 5.1 Hz, 3H) and 1.30 (t, *J* = 7.1 Hz, 3H).

norbornene oxide: White solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.04 (s, 2H), 2.42 (s, 2H), 1.49-1.42 (m, 2H), 1.31-1.26 (m, 1H), 1.21-1.15 (m, 2H), 0.69-0.65 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 51.4, 36.6, 26.2 and 25.1.

1,2-dihydronaphthalene oxide: Pale orange liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.24-7.58 (m, 4H), 4.23 (d, *J* = 3.52 Hz, 1H), 3.00 (m, 1H), 2.21-2.32 (m, 2H) and 2.03-2.08 (m, 2H).

2.7.4 The General Procedure for the Epoxidation of Alkenes

A Ccbalt complex (0.05 mmol) was dissolved in a solvent (15 mL), followed by the addition of alkene (5 mmol) and 2-ethylbutyraldehyde to a round bottom flask fitted with a balloon filled with oxygen. The mixture was stirred for 24 h at RT. After the reaction was completed, 1 mL of the reaction mixture was taken and extracted with Et_2O. The combined extracts were washed with saturated solution of $NaHCO_3$ and brine, respectively. The organic layer was dried over anhydrous Na_2SO_4 and analyzed by GC with the addition of an exact amount of an appropriate internal standard.

2.7.5 Optimum Conditions for the Epoxidation Reaction

2.3.5.1 Effect of Ligand

The epoxidation reaction was carried out in the same manner as previously described employing seven Co(II) calix[4] pyrrole **(65-71)**, Co(II) benzimidazole **(72)** and Co(II) schiff base **(73-77)** complexes as catalyst.

2.7.5.2 Effect of Solvent

The epoxidation reaction was carried as dercribed earlier except for that methanol, ethanol, ether, chloroform, acetonitrile, hexane, toluene, *N*,*N*-dimethylformamide and tetrahydrofuran were used as solvent.

2.7.5.3 Effect of the Amount of 2-Ethylbutyraldehyde

The epoxidation reaction was carried out as previously described but the amount of catalyst was varied (5, 10, 15, 20, 25 and 30 mmol).

2.7.6 Kinetic Study of Alkene Epoxidation Catalyzed by Cobalt(II) Complexes

The general epoxidation procedure utilizing Co(II) calix[4]prrole **(68)** and Co(II) benzimidazole **(72)** as catalyst was carried out. At different reaction times proceeded, an aliquot (0.5, 1.5, 3.0, 5.0 and 7.0 h) (1.0 mL) of the reaction mixture was taken worked up and analyzed by GC.

2.7.7 Stereoselectivity Study

The general epoxidation procedures of *cis*-, *trans*-stilbenes, norbornene, 1,2-dihydronaphthalene, cholesterol acetate and cholesterol benzoate using Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** as catalyst were carried out. An aliquot (1 mL) of the reaction mixture was taken, worked up and analyzed by GC and ^{1}H-NMR spectroscopy.

2.7.8 Regioselectivity Study

Selected alkenes such as 4-vinylcyclohexene, (*R*)-limonene, (*S*)-limonene, geraniol, geranyl acetate and ethyl sorbate were selected as a model for studying this purpose. Regioselective studies were carried out utilizing Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** as catalysts. An aliquot (1 mL) of the reaction mixture was taken, worked up and analyzed by GC and ^{1}H-NMR spectroscopy.

2.7.9 Chemoselectivity Study

Following the general epoxidation procedure, seleceted substrates containing two functional groups in the molecules, namely *trans*-2-hexen-1-ol, 1-octen-3-ol and cinnamyl alcohol were chosen as a chemical model. Chemoselectivity studies were carried out utilizing Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** as

catalysts. An aliquot (1 mL) of the reaction mixture was taken, worked up and analyzed by GC.

2.7.10 Epoxidation of Various Selected Alkenes

Selected alkenes including *cis*-4-hexen-1-ol, anethole, cinnamaldehyde, cinnamic acid, ethylcinnamate and 4-methoxy ethyl cinnamate were subjected to this developed epoxidation reaction catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**. Other procedures were carried out as previously described.

2.7.11 Application of Developed Epixidation Reaction for Terminal Alkenes

Selected terminal alkenes including 1-octene, 1-dodecene, 1-octadecene, α-methylstyrene, allylbenzene, 4-methoxyallylbenzene and allyl phenyl ether were subjected to this develop epoxidation reaction catalyzed by cobalt(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**.

2.7.12 Application of Developed Epoxidation Reaction to Natural Products

Naturally ocurring products containing double bonds namely α-pinene, β-pinene, eugenol methyl ether, nopol, citronellol and citronellal were selected as a substrate under the developed epoxidation reaction utilizing Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** as catalyst.

2.7.13 General Isolation Procedure

After the reaction was completed (followed by TLC), the epoxidation product was separated as follows: the whole reaction mixture was extracted according to that described in the general procedure and all the solvent were removed. The crude product was purified by silica gel column using $CHCl_3$ or a mixture of hexane-EtOAc as an eluent. The equivalent fractions monitored by TLC were combined and the solvents were completely evaporated.

2.8 Results & Discussion

2.8.1 Synthesis and Characterization of Calix[4]pyrroles and Schiff Bases

meso-Tetrakis(4-methoxyphenyl)-tetramethyl-calix[4]pyrrole and 2-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1H-benzo[*d*]imidazole ligands were synthesized and

confirmed their identities by comparing both physical properties and spectroscopic data including IR and ^{1}H-NMR with those reported in literature. [105]

The ^{1}H-NMR spectrum of calix[4]pyrrole displayed the proton signal of NH group at δ_H 7.53. These proton signals were disappeared upon deprotonating to polyanions. The polyanion was further treated with $CoCl_2$.THF to yield the cobalt complex. In addition, the ^{1}H-NMR spectrum of Schiff bases revealed the proton signal of NH group at δ_H ~ 8.28-8.60 and that of benzimidazole exhibited the methylene protons at δ_H 5.70 [106].

All cobalt complexes **(65-77)** used in this study was depicted as shown in sections 2.3.3.1 and 2.3.3.4.

2.8.2 Optimum Conditions for the Epoxidation of Cyclohexene

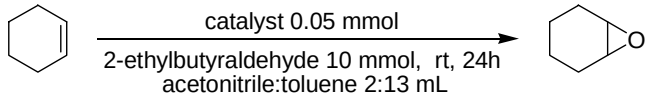
Various parameters are needed to be explored to optimize the epoxidation reaction such as the concentration of catalyst, temperature, type of catalyst and type of oxidant. Based upon the accumulated information derived from previous investigation [106], this present work concentrates on two important parameters including the effect of ligands and the amount of 2-ethylbutyraldehyde. Cyclohexene was chosen as a chemical model.

2.8.2.1 The Effect of Ligand on the Epoxidation of Cyclohexene Catalyzed by Cobalt(II) Schiff Bases

Even though a varity of Co(II) complexes such as Co(II) calix[4]pyrroles and Co(II) Schiff bases have been investigated as a catalyst in the epoxidation of alkenes [107], all Co(II) complexes chosen in this study have never been reported concerning their catalytic activity in the epoxidation reaction.

In order to search for appropriate cobalt complexes that could catalytically convert cyclohexene to cyclohexene oxide selectively, various ligands were examined. The results of the utilization of various cobalt catalysts are presented in Table 2.1.

Table 2.1 Epoxidation of cyclohexene catalyzed by cobalt(II) complexes



Entry	Co catalyst	% Recovery Reactant	% Yield Epoxide	MB
1	**65**	50	44	94
2	**66**	40	57	97
3	**67**	28	74	102
4	**68**	11	85	96
5	**69**	37	60	97
6	**70**	85	16	101
7	**71**	82	25	102
8	**72**	5	94	99
9	**73**	60	37	97
10	**74**	80	22	102
11	**75**	75	22	97
12	**76**	70	31	101
13	**77**	52	50	102

reaction condition : cyclohexene 5 mmol, catalyst 0.05 mmol 2-ethylbutyraldehyde 10 mmol, CH_3CN:toluene 2:13 mL RT, 24h

From Table 2.1, three groups of cobalt complexes could be classified, *i.e.* Co(II) calix[4]pyrroles **(65-71)**, Co(II) benzimidazole **(72)** and Co(II) Schiff bases **(73-77)**. Co(II) calix[4]pyrroles in general could convert cyclohexene to cyclohexene oxide ranging from low to high yield. The complexes bearing electron donating substituents such as methyl **65** or ethyl **66** (entries 1, 2) provided lower yield than those containing more powerful electron-releasing substituents **67** and **68** (entries 3, 4). In addition, steric hindrance and electronic effects of phenyl ring **69**, **70** and **71** (entries 5-7) influenced the yield of the desired products. The most steric effect of biphenyl ring gave only small amount of cyclohexene oxide (entry 6) [108].

In order to investigate the effect of Schiff base structures on the catalytic ability**,** the related Schiff bases **73-77** were screened under the optimal conditions.

The results are summarized in Table 2.1. It is evident that the rigidity and soft donor atom on Schiff bases play important roles on the yield of cyclohexene oxide. Ligands **73**, **75** and **76** (entries 9, 11, 12) derived from salicylaldehyde, benzaldehyde and thiophen-2-carboxaldehyde respectively gave variable amount of yields; however, being not more than 50%. The absence of chelating groups in aldehyde moiety could imply that the effective ligand may be tetradentate ligand. In addition, the elongation of ethylene unit in ligand **73** to propylene unit ligand **74** increasing the flexibility of ligand appeared to show an important effect to drop the yield (entries 9, 10). It can be noticed that the suitable distance of the bridge on ligands may lock the suitable conformation of the lowest energy transition state of reaction.

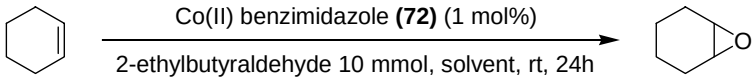
Moreover, the rigidity and planarity of ligand were also investigated. Comparing ligands **74** and **77** (entries 10, 13), the good correlations among rigidity, planarity and yields were observed. When ethylenediamine was changed to phenylenediamine, the structure of the latter was more rigid and planar. Thus, with more rigidity, it could strongly coordinate with cobalt and resulted in higher yield (50%). Interestingly, when salicyl moiety on ligand **77** was changed to thienyl group ligand **72** which contained sulfur as a soft donor atom, the yield of epoxide was sharply increased up to 94%. This could be described by soft-soft interaction between donor atom and metal. Sulfur acted as soft donor atom and cobalt acted as soft metal therefore both cobalt and sulfur had stronger soft-soft interaction than cobalt and oxygen atom [109]. It was evident and confirmed again that a type of donor atom, planarity and rigidity played significant role in catalytic system.

According to the results shown above, Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** were selected to use as a catalyst for further epoxidation reaction study.

2.8.2.2 The Effect of Solvent on the Epoxidation of Cyclohexene Catalyzed by Co(II) Benzimidazole (72)

From the experimental conditions described above, CH_3CN and toluene were used as a homogeneous medium. Several solvents were chosen to evaluate the catalytic abilities of Co(II) benzimidazole **(72)** in these media and to observe whether they could replace CH_3CN:toluene. The results are presented in Table 2.2.

Table 2.2 The effect of solvent on the epoxidation of cyclohexene



Entry	Solvent	% Recovery Reactant	% Yield Epoxide	MB
1	MeOH	88	10	98
2	EtOH	82	16	98
3	ether	80	24	104
4	$CHCl_3$	40	55	95
5	CH_3CN	15	81	96
6	hexane	10	84	94
7	toluene	12	83	95
8	DMF	78	27	105
9	THF	50	47	97

reaction condition: cyclohexene 5 mmol, Co(II) benzimidazole 0.05 mmol, 2-ethylbutyraldehyde 10 mmol, solvent 15 mL, rt, 24h

From Table 2.2, the conditions for the epoxidation in the presence of ligand **72** were optimized. The optimal amount of catalyst used was 1 mol%. The reaction between cyclohexene and 2-ethylbutyraldehyde and O_2 as oxidant using Co(II) benzimidazole **(72)** as catalyst was used as a model. The use of Co(II) calix[4]pyrrole **(68)** as a catalyst was previously experimented and observed [107]. Among various types of solvents examined (Table 2.2), the polarity of solvent appeared to have dramatic effect on the yield of the reaction. The use of polar protic solvents such as MeOH and EtOH (entries 1, 2) gave epoxides in poor yields. Using Et_2O, DMF, $CHCl_3$ and THF as solvents, the reactions provided the products in low to moderate yields (entries 3, 4, 8 and 9) except for CH_3CN giving much higher yield (entry 5). Nonpolar solvents such as haxane and toluene were also tested and it was found to afford as high yield of the desired product as that obtained using CH_3CN (entries 6, 7).

In terms of yield, CH_3CN, hexane and toluene appeared to be the best solvents among the solvents tested, affording the product in 81, 84 and 83% yield, respectively. From the preliminarily investigated results [107], the study on the mixed solvent

systems between CH_3CN and toluene was investigated. However, hexane was found as another alternative solvent for the epoxidation reaction.

In order to study the effect of mixed solvent, four diverse ratios of CH_3CN to toluene were investigated. With ratios of 2:13, 5:10, 10:5 and 13:2, the reactions gave similar results (90-94% yield). Consequently, the only system with the ratio of CH_3CN:toluene (2:13) was chosen to use in further experiments and cobalt complex of ligands **68** and **72** were also evaluated under this optimized condition. [107]

2.8.3 Kinetic Study of Cyclohexene Catalyzed by Co(II) Calix[4]pyrrole (68), Co(II) Benzimidazole (72) and $CoCl_2.6H_2O$

The kinetic study of the epoxidation of cyclohexene by Co (II) calix[4]pyrrole **(68)**, Co(II) benzimidazole **(72)** and $CoCl_2.6H_2O$ were conducted at RT. The results are shown in Figure 2.1.

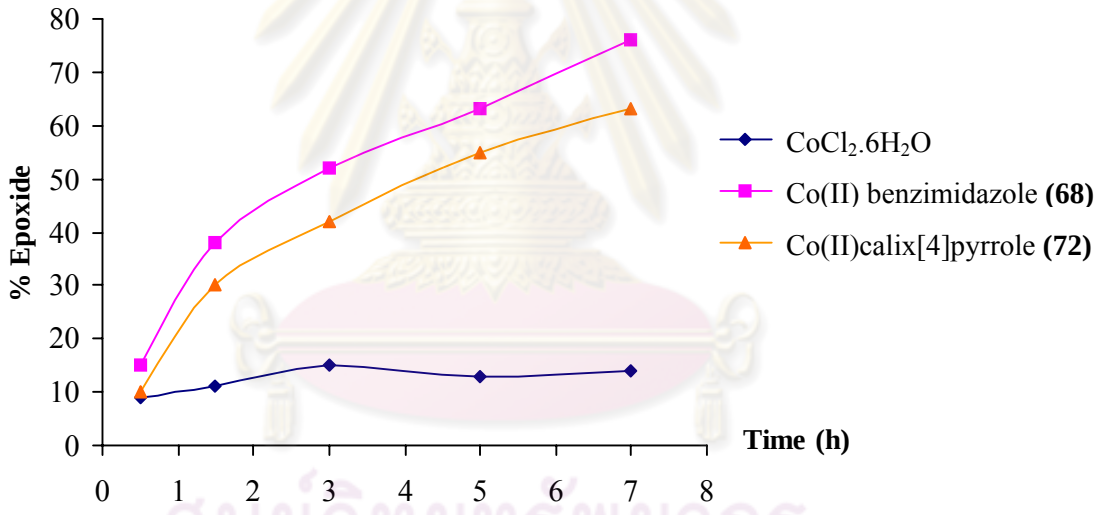


Figure 2.1 Kinetic study on the epoxidation of cyclohexene catalyzed by Co(II) calix[4]pyrrole **(68)**, Co(II) benzimidazole **(72)** and $CoCl_2.6H_2O$

From Fig 2.1, it was found that the rate of the epoxidation of cyclohexene catalyzed by Co(II) benzimidazole **(72)** was faster than those of Co(II) calix[4]pyrrole **(68)** and $CoCl_2.6H_2O$, respectively. The best final yield of cyclohexene oxide was obtained when Co(II) benzimidazole **(72)** was utilized. The half-life of the epoxidation catalyzed by $CoCl_2.6H_2O$, Co(II) benzimidazole **(72)** and Co(II) calix[4]pyrrole **(68)** was approximately 4.0, 2.5 and 3.5 h, respectively. The results showed that Co(II) benzimidazole **(72)** and Co(II) calix[4]pyrrole **(68)** were both

efficient catalysts for this reaction since the reaction in the presence of $CoCl_2.6H_2O$ was very slow and the conversion was < 20%.

2.8.4 Epoxidation of Selected Alkenes Catalyzed by Co(II) Calix[4]pyrrole (68) and Co(II) Benzimidazole (72)

To extend this developed epoxidation system, various alkenes were selected for exploring the selectivity of the reaction. The stereoselectivity of this reaction was focused on the epoxidation of *cis*-stilbene, *trans*-stilbene, norbornene, cholesteryl acetate and cholesteryl benzoate, whereas 4-vinylcyclohexene, (*R*)-limonene, (*S*)-limonene, geraniol, geranyl acetate and ethyl sorbate whose structures contained two different olefinic sites were chosen for regioselectivity study.

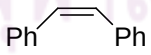
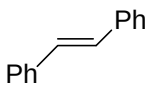
2.8.4.1 Stereoselectivity Study

Stereoselectivity study, one of three selectivity studies in organic reaction is important criterior for the developed reaction that needed to be carefully examined.

***Cis*- and *trans*-stilbenes**

Two isomeric, *cis*- and *trans*-stilbenes were selected as chemical models to perform this selectivity study. The outcome from this study may provide informative data on the mechanism of the reaction. The results are presented in Table 2.3.

Table 2.3 Stereoselectivity study on the epoxidation of *cis*- and *trans*-stilbenes catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**

Entry	Substrate	Catalyst	%Recovery Reactant	% Epoxide		MB
				cis-form	*trans*-form	
1		Co(II) calix[4]pyrrole **(68)**	51	21	25	97
2		Co(II) benzimidazole **(72)**	46	23	28	97
3		Co(II) calix[4]pyrrole **(68)**	50	-	45	95
4		Co(II) benzimidazole **(72)**	45	-	53	98

reaction condition: substrate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde 20 mmol, CH_3CN:toluene 2:13 mL, rt, 24h

From Table 2.3, it was observed that in the case of *cis*-stilbene, the use of either cobalt(II) calix[4]pyrrole **(68)** or cobalt(II) benzimidazole **(72)** yielded

comparable isolated yields of the desired products, a mixture of *cis*- and *trans*-stilbene oxide, even more oxidant was used (20 mmol). The detection of *cis*-epoxide could be accomplished by ^{1}H-NMR spectroscopy. In the ^{1}H-NMR spectrum (Fig 2.2), the aromatic protons were observed around δ_H 7.16-7.42. Fortunately, the most characteristic peaks for *cis*- and *trans*-stilbene oxides distinguishly appearred at different chemical shifts. To illustrate this, the protons on the carbon connected to the oxygen of an oxirane ring of *cis*-stilbene oxide could be detected at δ_H 4.39 while those belonged to *trans*-stilbene oxide was clearly observed at δ_H 3.91. These observed chemical shifts of the epoxidized products were in good agreement with those obtained from authentic samples synthesized. The quantitative analysis could be accomplished by comparison with the intensity of methyl protons of the known amount of an internal standard, toluene added. Under this condition, the yield of the epoxide was quite low; perhaps because the large size of both substrate and the catalyst involved. That made the steric hindrance occurred. Similar observation was noticed from the epoxidation of *trans*-stilbene. In the latter case, cobalt(II) calix[4]pyrrole **(72)** could be employed as a better catalyst than cobalt(II) benzimidazole **(68)**. The best isolated yield was attained in the case of employing 20 mmol of the oxidant.

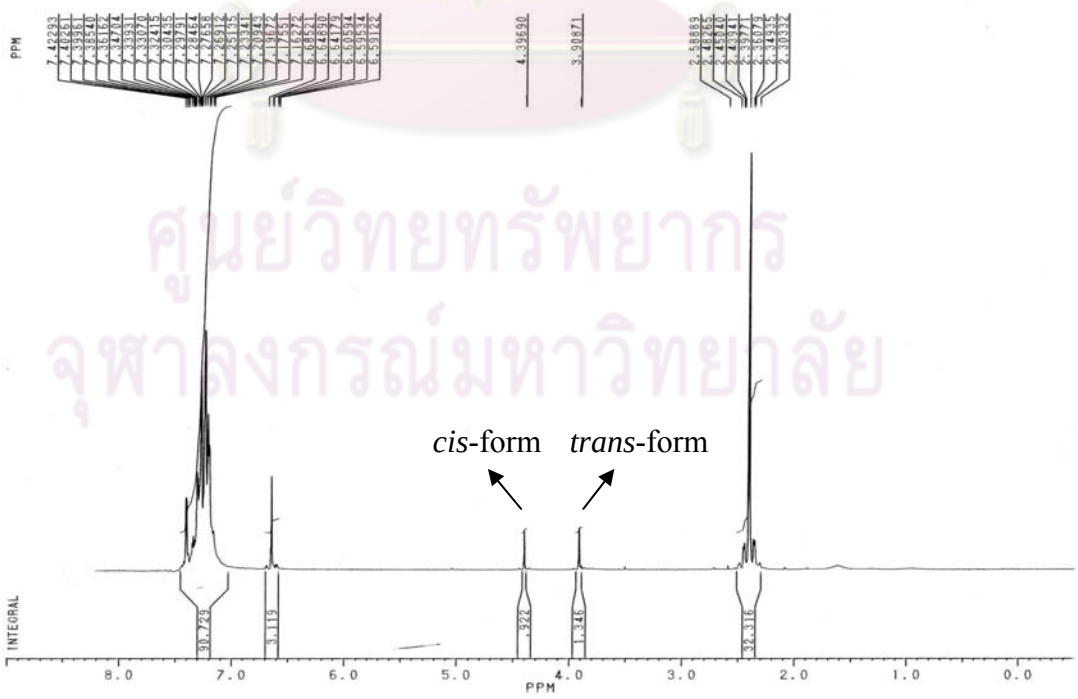
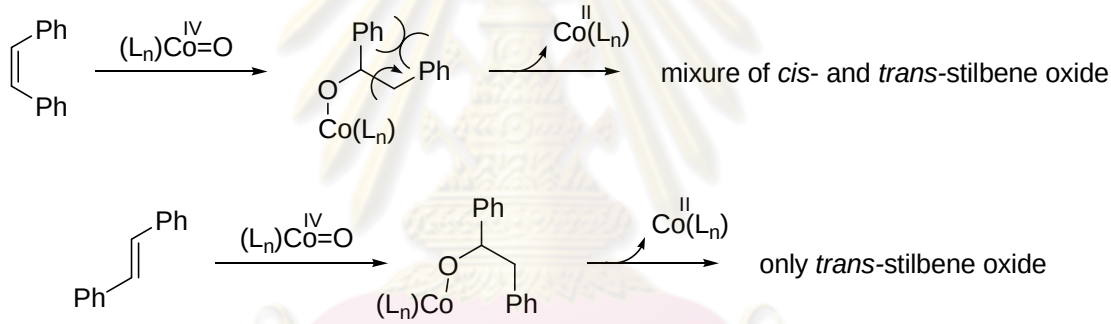


Figure 2.2 The ^{1}H-NMR spectrum of a mixture of *cis*- and *trans*-stilbene oxides

The more important point derived from this experimental fact was that the epoxidation of *trans*-stilbene provided solely *trans*-epoxide whereas the products achieved from the epoxidation of *cis*-stilbene was a mixture of *cis*- and *trans*-stilbene oxides in comparable amount (1:1). This informative data could be used for mechanistic interpretation. The explanation for this observation should derive from the consideration of the intermediate of the reaction formed. The more stable radical intermediate should be a *trans*-form more than the *cis*-one [110]. Thus, in the case of *cis*-stilbene, in an equilibrium stage, the formation of *trans*- radical intermediate derived from the free rotation around C-C single bond from *cis*-one should be occurred simultaneously with the *cis*-radical. This will lead to the observation of a mixture of *cis*- and *trans*-stilbene oxides occurred equally. Whereas the epoxidation of *trans*-stilbene took place *via* more stable *trans*-radical intermediate and produced the *trans*-epoxide as the sole product (Scheme 2.3).

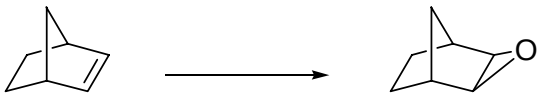


Scheme 2.3 The proposed mechanism of the epoxidation of *cis*- and *trans*-stilbenes

Norbornene

Norbornene was selected as another chemical model for stereoselectivity study. The results of the epoxidation of norbornene catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** are shown in Table 2.4.

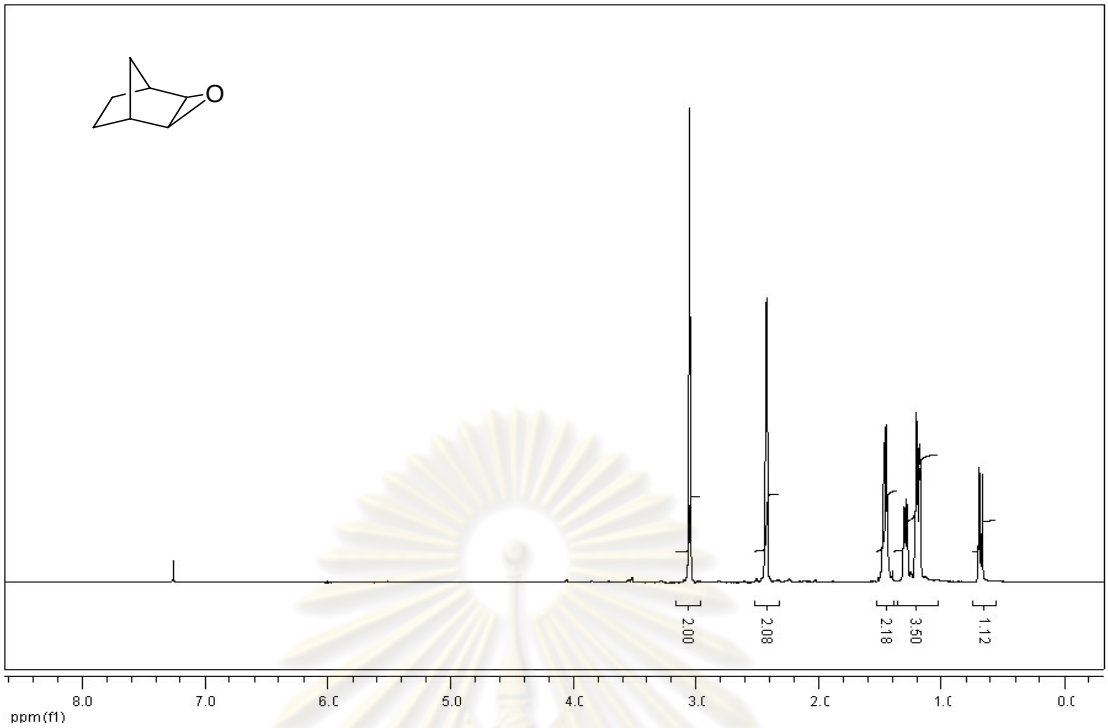
Table 2.4 Stereoselectivity study on the epoxidation of norbornene catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**



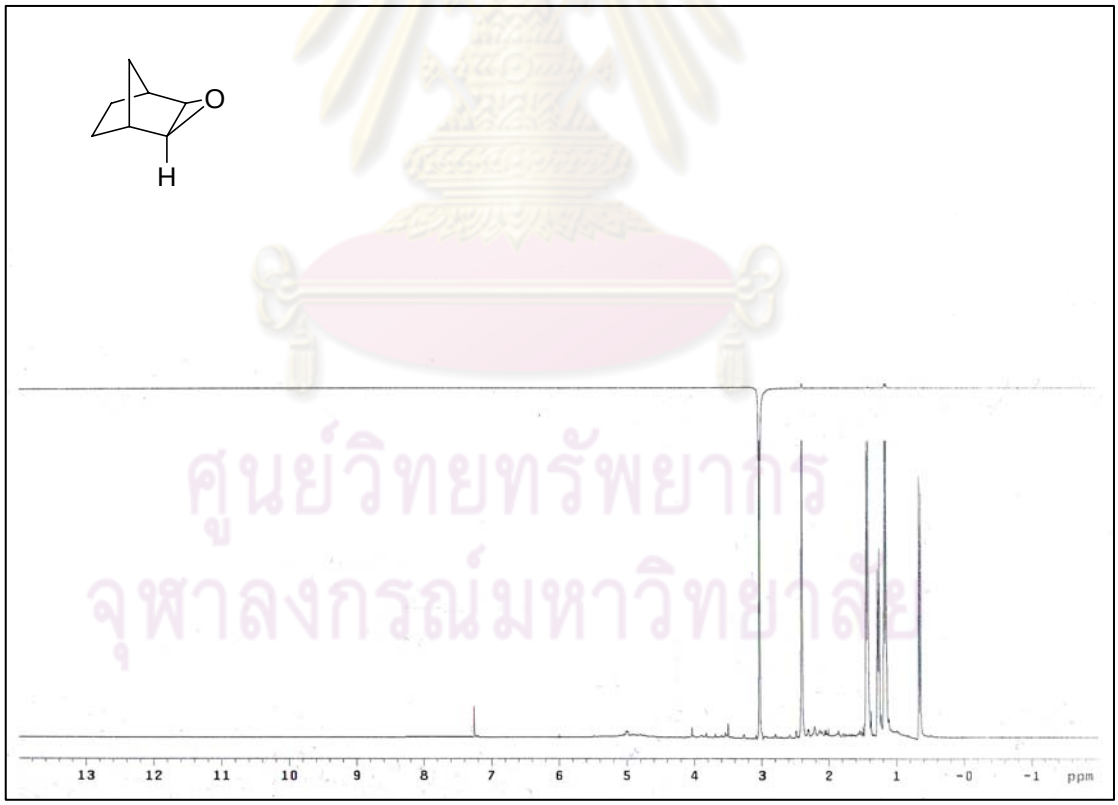
Entry	Catalyst	2-ethylbutyraldehyde (mmol)	%Recovery Reactant	%Yield Epoxide	MB
1	$CoCl_2.6H_2O$	10	45	52	97
2	Co(II) calix[4]pyrrole **(68)**	10	34	72	102
3	Co(II) benzimidazole **(72)**	10	14	88	102
4	Co(II) benzimidazole **(72)**	15	12	86	98
5	Co(II) benzimidazole **(72)**	20	10	85	95

reaction condition: norbornene 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehye x mmol, CH_3CN:toluene 2:13 mL, rt, 24h

From Table 2.4, it was found that under this developed condition, norbornene oxide was observed in moderate yield when $CoCl_2.6H_2O$ was used as catalyst (entry 1). Employing Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**, norbornene oxide could be attained in high yield (entries 2, 3). The increment of the amount of oxidant, 2-ethylbutyraldehyde from 15 to 20 mmol did not affect on the epoxidation reaction (entries 4, 5). The detection of norbornene oxide could be accomplished by ^{1}H-NMR spectroscopy using NOE technique. In the ^{1}H-NMR spectrum (Fig 2.3a), the proton of epoxide was observed at δ_H 3.01. When the proton of the epoxide at δ_H 3.01 was irradiated by NOE technique, all proton signals were not changed. This could confirm that the oxirane ring in norbornene was present in the *exo* form. The spectrum is shown in Fig 2.3b.



(a)



(b)

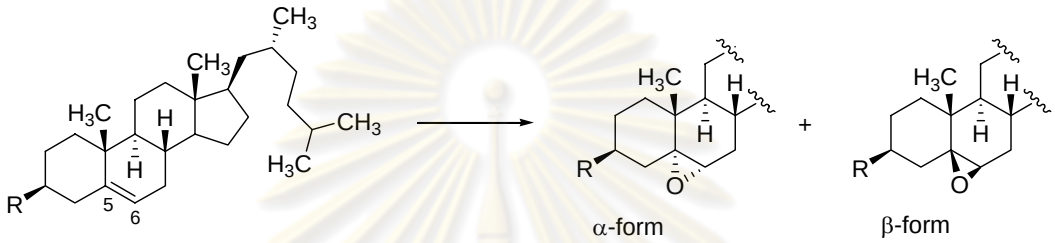
Figure 2.3 (a) The ^{1}H-NMR spectrum of norbornene oxide

(b) The NOE spectrum of norbornene oxide irradiated at δ_H 3.01

Cholesteryl acetate and cholesteryl benzoate

Cholesteryl acetate and cholesteryl benzoate were selected as another two substrate models for stereoselectivity study. These substrates could give informative data on which face of epoxide would be reacted with the actual reagent. The results are presented in Table 2.5.

Table 2.5 Stereoselective epoxidation of cholesteryl acetate and cholesteryl benzoate catalyzed by Co(II) calix[4]pyrrole **(65-71)** or Co(II) benzimidazole **(72)**



Entry	Substrate	Catalyst	% Yield[b]	α–epoxide : β-epoxide[c]
1[a]		-	84	70 : 30
2		**65**	82	50 : 50
3		**66**	95	40 : 60
4		**67**	78	37 : 63
5	CH_3COO—	**68**	91	35 : 65
6		**69**	88	45 : 55
7		**70**	85	35 : 65
8		**71**	80	35 : 65
9		**72**	80	50 : 50
10[a]		-	78	71 : 29
11	PhCOO—	**68**	76	34 : 66
12		**72**	81	50 : 50

reaction condition: substrate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde 10 mmol, $C_2H_4Cl_2$, rt, 24h

[a] substrate 5 mmol, *m*-CPBA 7.5 mmol, CH_2Cl_2, 0°C, 4h

[b] Isolate yield [c] determined by ^{1}H-NMR analysis

Stereochemistries of the epoxidation of 5,6-double bond in cholesteryl acetate were examined as presented in Table 2.5. It was found that the epoxidation catalyzed

by Co(II) calix[4]pyrroles **(65-71)**, afforded the hindered 5,6-β-epoxide as a major product (entries 2-8), whereas Co(II) benzimidazole **(72)** could epoxidize cholesteryl acetate to its oxide in high yield but no pronounced selectivity was observed (entry 9). The ratio of α- and β-epoxides was approximately 1:1. This was indicative that the structure of catalyst, Co(II) benzimidazole **(72)** was not sutible for asymmetric epoxidation. The epoxidation of cholesteryl acetate furnished the corresponding mixture of 5,6-α- and 5,6-β-epoxides in the ratio of 70 to 30 (entry 1). It was interesting to point out that the less hindered 5,6-α-epoxide was obtained as a major product when *m*-CPBA was used. In addition, when acetyl group was changed to benzoate with the objective to increase steric hindrance of the molecule next to the double bond, no effect on the ratio of α- and β-epoxides was observed (entries 12-13). Stereochemistries of the products were identified by the chemical shift of the proton at C-6 proton in ^{1}H-NMR at δ_H 2.90 of α-epoxide and at δ_H 3.10 of β-epoxide and the ratios of 5,6-α- and 5,6-β-epoxides were obtained by the integrations of the protons at C-6 ($H_{6\alpha}$ and $H_{6\beta}$) in ^{1}H-NMR spectrum. The result is exhibited in Fig 2.4.

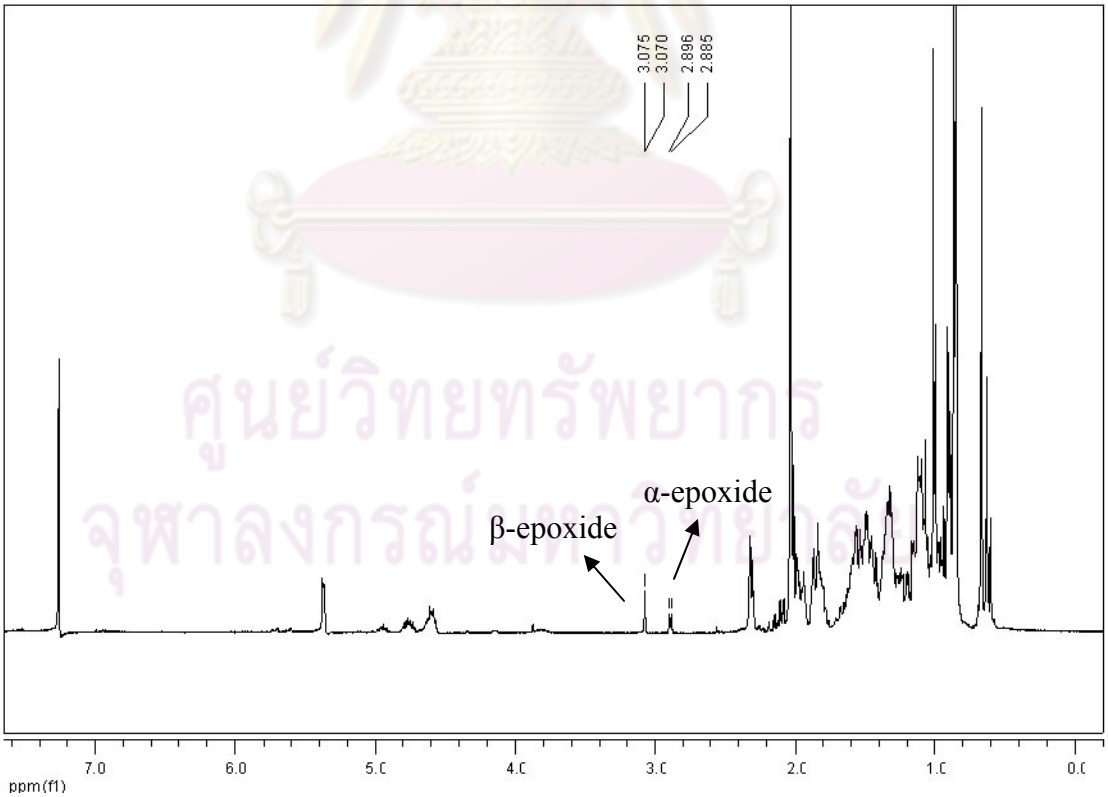


Figure 2.4 The ^{1}H-NMR spectrum of a mixture of α- and β-cholesteryl acetate oxide

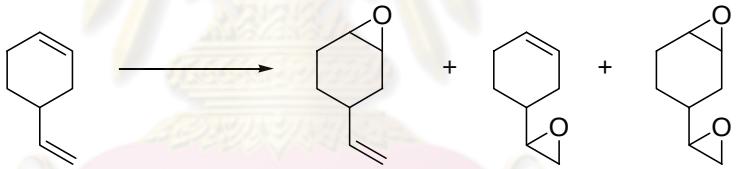
2.8.4.2 Regioselectivity Study

A concern of the direction of chemical reaction to take place involved in the regioselectivity study. Catalyst plays an important role in this regard. 4-Vinyl cyclohexene, (*R*)-limonene, (*S*)-limonene, geraniol, geranyl acetate and ethyl sorbate were selected as a model for studying this purpose. Regioselective studies were carried out utilizing Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** as catalysts.

4-Vinylcyclohexene

4-Vinylcyclohexene was selected as a chemical model to observe regioselectivity of the reaction. Comparative studies were carried out utilizing Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** as catalysts. The results are presented in Table 2.6 and Figs 2.5 and 2.6.

Table 2.6 Regioselective epoxidation of 4-vinylcyclohexene catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**



(78) **(79)** **(80)**

Entry	Catalyst	%Recovery Reactant	%Yield Epoxide (**78:79:80**)	MB
1[a]	-	40	65 (20:1:0)	105
2	Co(II) calix[4]pyrrole **(68)**	20	84 (12:0:1)	104
3	Co(II) benzimidazole **(72)**	20	84 (12:0:1)	104
4[b]	Co(II) calix[4]pyrrole **(68)**	31	63 (7.8:1:0)	94
5[b]	Co(II) benzimidazole **(72)**	20	73 (7.8:1:0)	103
6[c]	Co(II) calix[4]pyrrole **(68)**	16	80 (7:0:1)	96

reaction condition: 4-vinylcyclohexene 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde 10 mmol, CH_3CN:toluene 2:13 mL, rt, 24h

[a] 4-vinylcyclohexene 5 mmol, *m*-CPBA 7.5 mmol, CH_2Cl_2, 0°C

[b] CH_3CN was used as solvent

[c] CH_3CN was used as solvent and 2-ethylbutyraldehyde 20 mmol

4-Vinylcyclohexene contained two olefinic bonds: one was endocyclic double bond and the other was a terminal double bond outside the ring. Therefore, it was possible that three isomeric epoxides as 1,2-oxide **78**, 7,8-oxide **79** and 1,2,7,8-diepoxide **80** could be formed. The attempt to purify these three epoxides from the crude product was accomplished *via* silica gel column. These three isolated single isomers were well-confirmed their stuctures by spectroscopic evidence as illustrated in Figs 2.5-2.7. Regioselectivity of the epoxide product was identified by the chemical shift of the oxirane proton in ^{1}H-NMR. The two protons of oxirane ring of 1,2-oxide **78** could be observed at δ_H 3.15 while those of 7,8-oxide **79** were detected at δ_H 2.20, 2.52 and 2.76. For 1,2,7,8-diepoxide **80**, the oxirane protons were clearly detected at δ_H 3.18, 2.65 and 2.46, respectively.

The epoxidation of 4-vinylcyclohexene by *m*-CPBA was previously reported [12], two products identified were 1,2-oxide **78** and 7,8-oxide **79** in ratio 25:1. In the same experiment when using peroxybenzimidic acid as an oxidant, 1,2-oxide **78** and 7,8-oxide **79** were obtained in ratio 1:1.5. In this work, when *m*-CPBA was used, 1,2-oxide **78** and 7,8-oxide **79** were found in the ratio of 20:1 (entry 1). Employing Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** catalysts manifestly illustrated high regioselectivity on the epoxidation of 4-vinylcyclohexene. From Table 2.6, when a mixture of CH_3CN and toluene was used, 1,2-oxide **78** and 1,2,7,8-diepoxide **80** were obtained in the ratio of 12:1 (entries 2, 3). The formation of the latter was believed to take place by over oxidation of 1,2-oxide **78**. In addition, when CH_3CN was used 1,2,7,8-diepoxide **80** were not observed (entires 4, 5). The ratio of 1,2-oxide **78** and 7,8-oxide **79** was detected in the ratio of 7.8:1. When 2-ethylbutyraldehyde was increased from 10 to 20 mmol, the overoxidation was observed. 1,2-Oxide **78** and 1,2,7,8-diepoxide **80** was obtained in the ratio of 7:1 (entry 6). This result strongly indicated that the regioselectivity of the epoxidation of 4-vinylcyclohexene was greatly depended on the solvent. The mixture of CH_3CN and toluene was suitable for internal alkene epoxidation while CH_3CN was appropriate for the epoxidation of terminal alkene [111]. This observed regioselectivity could be explained by the electron density, the olefinic portion in the ring of cyclohexene had clearly more electron density than that at terminal site; therefore prevailing being epoxidized.

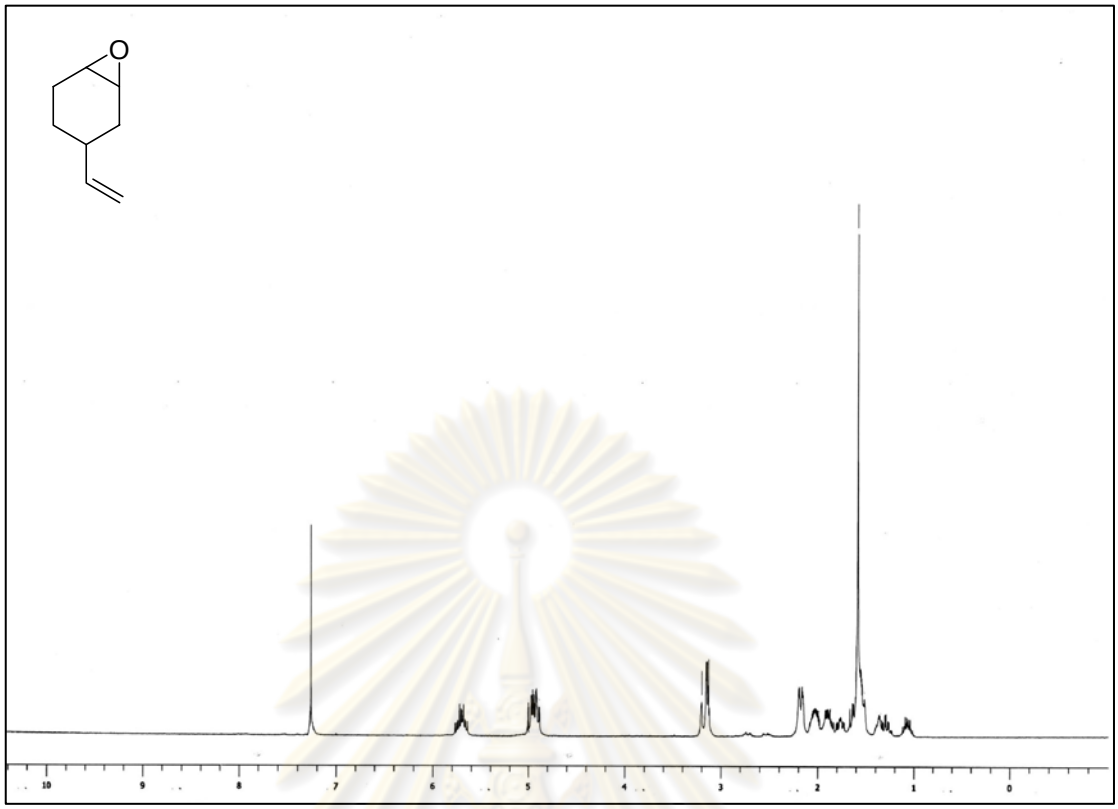


Figure 2.5 The ^{1}H-NMR spectrum of 4-vinylcyclohexene-1,2-oxide **(78)**

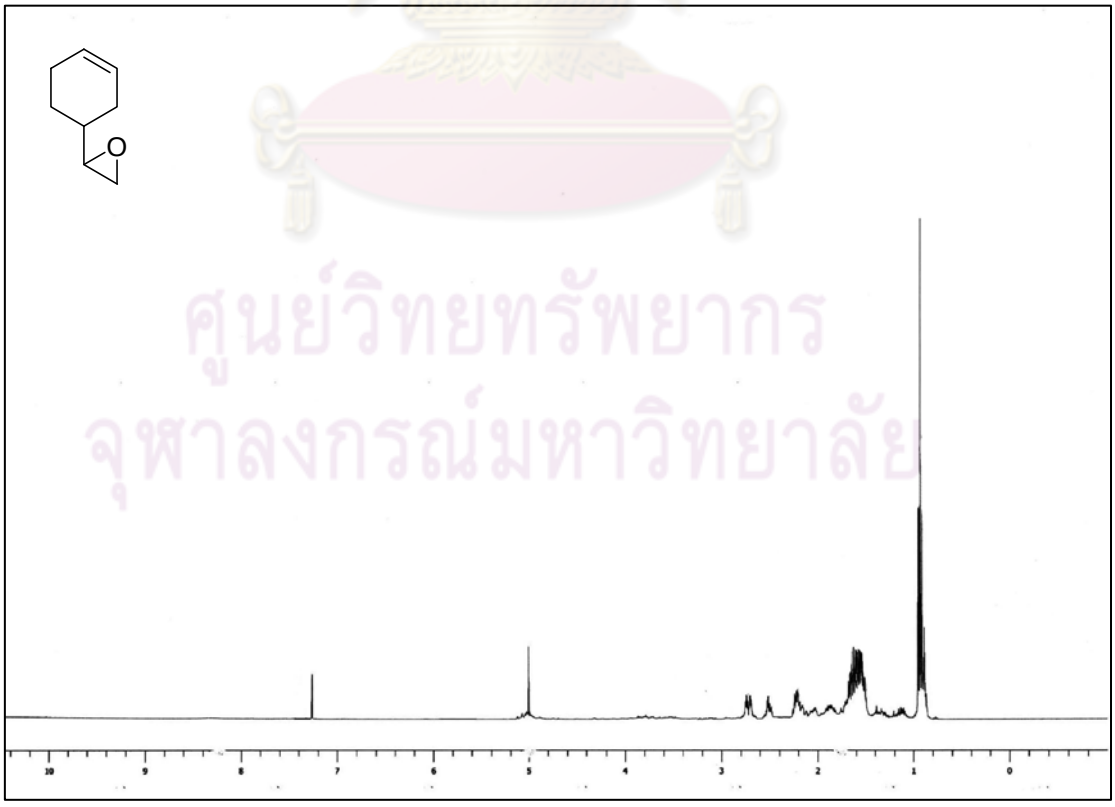


Figure 2.6 The ^{1}H-NMR spectrum of 4-vinylcyclohexene-6,7-oxide **(79)**

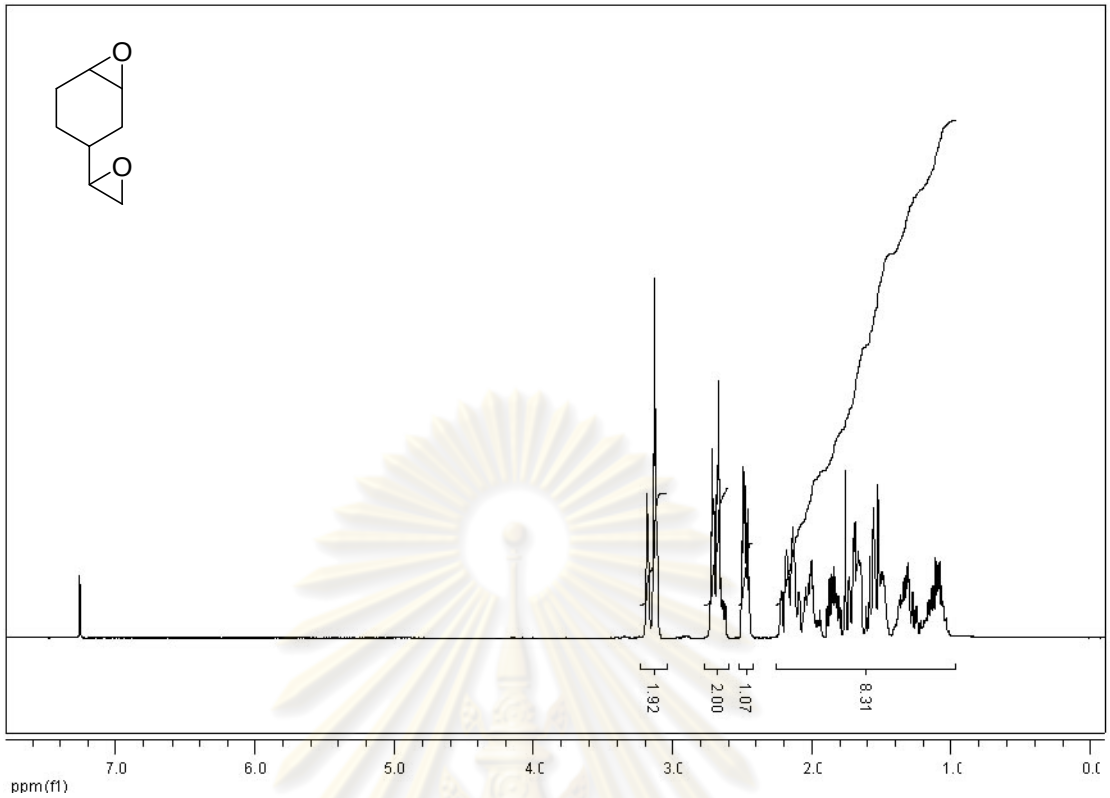
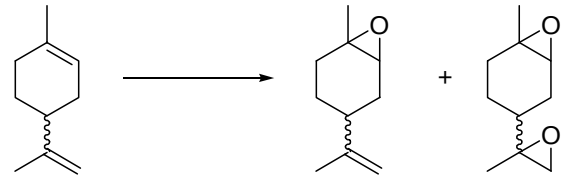


Figure 2.7 The ^{1}H-NMR spectrum of 4-vinylcyclohexene-1,2,7,8-dioxide **(80)**

(*R*)-Limonene and (*S*)-limonene

(*R*)- and (*S*)-limonenes are a natural product containing two double bonds in the molecule. These substrates are interesting as a probe to examine the regioselectivity of double bond. In addition, these substrates could be considered for stereoselectivity study when they were catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** compared with other reagents previously report in literatures. The results are presented in Table 2.7.

Table 2.7 Regioselective epoxidation of limonenes catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**



limonene **(3)** **(81)**

Entry	Substrate	Catalyst	Oxidant (mmol)	%Recovery Reactant	% Yield of epoxide[b]		MB
					3 (*cis* : *trans*)[b]	**81**	
1	*R*-limonene	Co(II) calix[4]pyrrole **(68)**	10	49	48 (1.77:1)	-	97
2	*S*-limonene	Co(II) calix[4]pyrrole **(68)**	10	52	53 (1.75:1)	-	103
3	*R*-limonene	Co(II) calix[4]pyrrole **(68)**	20	0	28 (1.83:1)	78	106
4	*S*-limonene	Co(II) calix[4]pyrrole **(68)**	20	0	30 (1.78:1)	72	102
5	*R*-limonene	Co(II) benzimidazole **(72)**	10	23	75 (1.32:1)	-	98
6	*S*-limonene	Co(II) benzimidazole **(72)**	10	30	72 (1.35:1)	-	102
7[a]	*R*-limonene	-	*m*-CPBA	trace	82 (1:1.45)	trace	82
8[a]	*S*-limonene	-	*m*-CPBA	trace	83 (1:1.40)	trace	83

reaction condition: substrate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde (vary), CH_3CN:toluene, 2:13mL, rt, 24h

[a] substrate 5 mmol, m-CPBA 7.5 mmol, CH_2Cl_2, 0°C 4h

[b] yield and selectivity determined by GC

Table 2.7 shows the catalytic epoxidation of (*R*)- and (*S*)-limonenes. The regioselectivity observed in the epoxidation of (*R*)- and (*S*)-limonenes could be attributed to the effect of the number of substituents in each double bond present in the molecule. For (*R*)- and (*S*)-limonenes, the endocyclic monoepoxide **3** was the most abundant product, which derived from the epoxidation of the more substituted double bond (entries 1-2). In addition, when 2-ethylbutyraldehyde was increased to 20 mmol diepoxide **81** was observed in good yield (entries 3-4). When Co(II) benzimidazole **(72)** was used, epoxide **3** was occurred in higher yield than that obtained from Co(II) calix[4]pyrrole **(68)**, but less regioselectivity. Stereochemistries of *cis*- and *trans*- products were identified by using coupling constants ($J_{trans} > J_{cis}$) in ^{1}H-NMR. All protons of (*R*)- or (*S*)-limonenes were displayed almost at the same chemical shift. The proton of *trans* form of either (*R*)- or (*S*)-limonenes appeared at δ_H

2.98 while that of *cis* form exhibited at δ_H 3.06. The results are presented in Figs 2.8 and 2.9 [112].

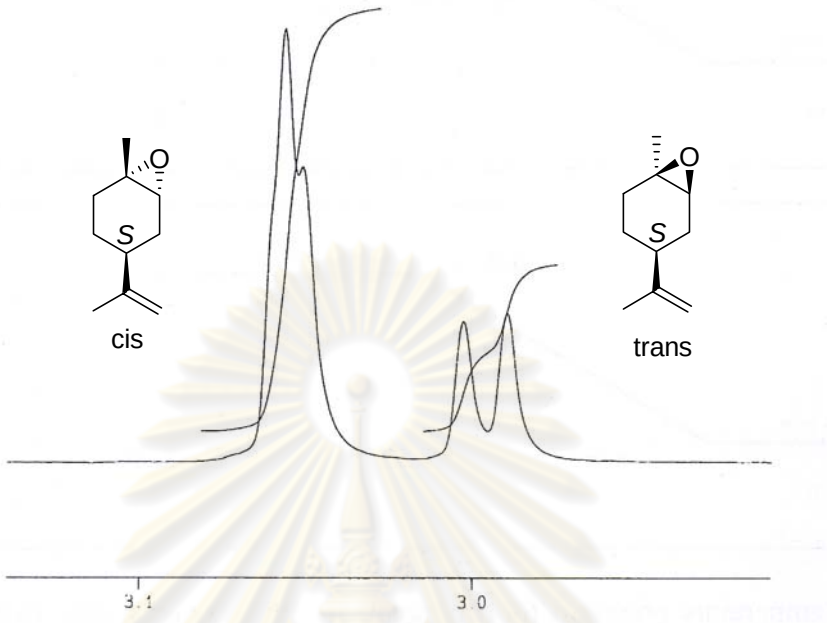


Figure 2.8 The ^{1}H-NMR spectrum of *cis*- and *trans*-(*S*)-limonene oxide

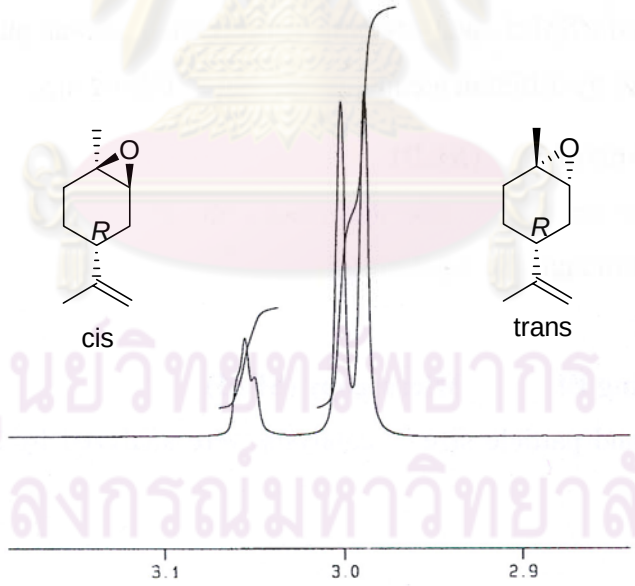


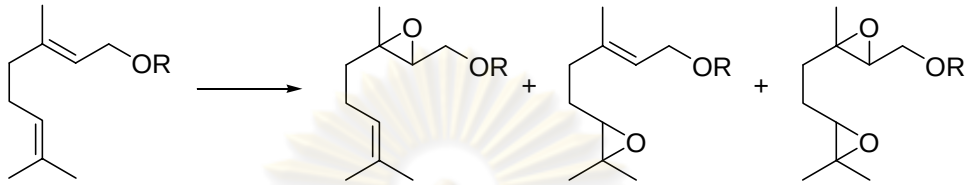
Figure 2.9 The ^{1}H-NMR spectrum of *cis*- and *trans*-(*R*)-limonene oxide

Geraniol and geranyl acetate

Geraniol, a natural monoterpene containing two kinds of double bonds was selected as a model for catalytic epoxidation catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**. In addition, geranyl acetate was selected as a model to

prove whether an acetyl group had direct effect on the epoxidation reaction. The results of the oxidation of this monoterpene and its derivative are presented in Table 2.8.

Table 2.8 Regioselective epoxidation of geraniol and geranyl acetare catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**



(19) **(20)** **(21)**

Entry	Substrate	Catalyst	Oxidant (mmol)	Reactant	% Epoxide[a]			MB
					82	**83**	**84**	
1	R = H	-	-	58	20	25	-	103
2	R = H	Co(II) calix[4]pyrrole **(68)**	10	trace	41	52	-	93
3	R = H	Co(II) calix[4]pyrrole **(68)**	20	trace	-	-	92	92
4	R = H	Co(II) benzimidazole **(72)**	10	trace	40	55	-	95
5	R = OAc	Co(II) calix[4]pyrrole **(68)**	10	trace	trace	90	-	90

reaction condition: substrate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde, CH_3CN:toluene 2:13 mL, rt, 24h

[a] yield and selectivity were determined by ^{1}H-NMR

The catalytic epoxidation of geraniol and geranyl acetate in the presence of Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** gave a mixture of 2,3-epoxide **82** and 6,7-epoxide **83** (entries 2 and 4). In addition, when *m*-CPBA was used, 2,3-epoxide **82** and 6,7-epoxide **83** were obtained in 1:1 ratio (entry 1). Increasing 2-ethylbutyraldehyde to 20 mmol, diepoxygeraniol **(84)** was detected in high yield (entry 3). Interestingly, when a hydroxyl group was protected as an acetyl group, solely 6,7-epoxygeranyl acetate **(83)** was formed in high yield (entry 5). This result confirmed the previous observation on the selectivity of the system that the epoxidation under this developed system selectively not take place at electron deficient C=C position. On the account to the mechanistic point of view, this observed selectivity implied a typical behavior of a hydroperoxy species which reacted faster with more electron rich alkenes [113]. The regioselectivity of the monoepoxy product

was identified by ^{1}H-NMR. The proton signal of 2,3-epoxygeraniol was detected at δ_H 2.95 and that of 6,7-epoxygeraniol was observed at δ_H 2.68 (Figs 2.10, 2.11). From the previous work, Sharpless *et al*. studied the regioselectivity of the epoxidation of geraniol using vanadium-hydroperoxide systems. High regioselectivity for the 2,3-double bond of geraniol was observed. The epoxidation could however be taken place only in the presence of allylic alcohol [46].

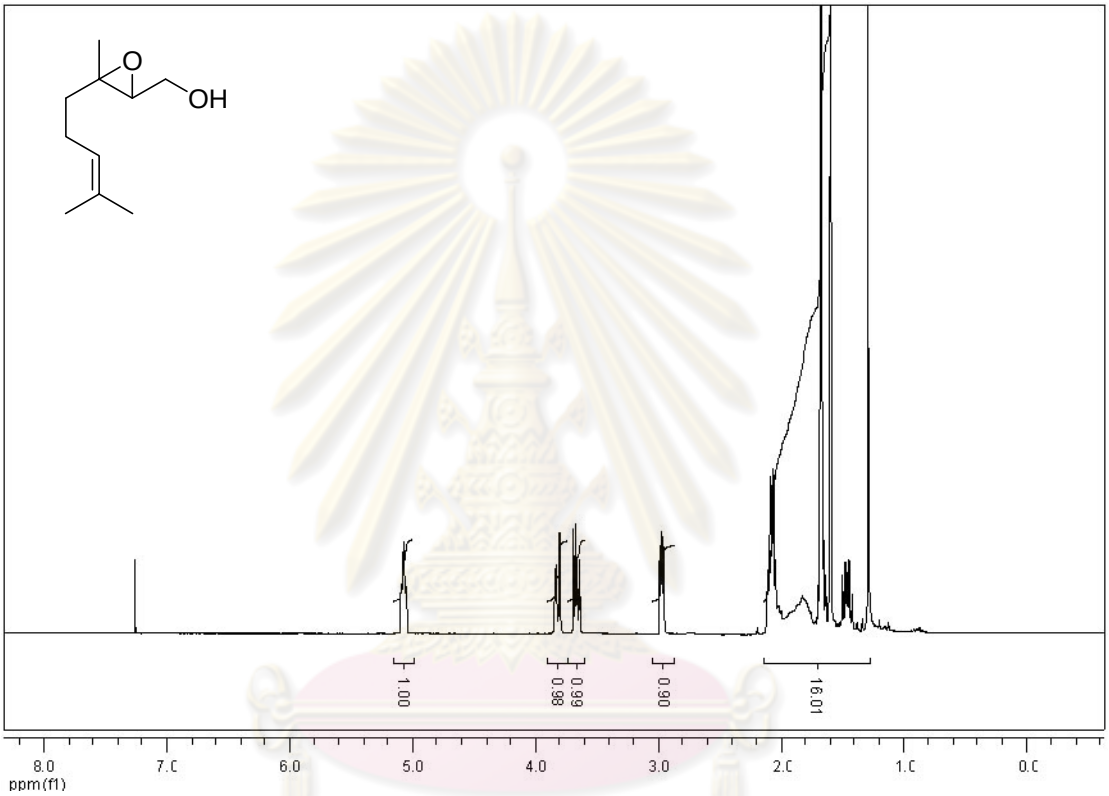


Figure 2.10 The ^{1}H-NMR spectrum of 2,3-epoxygeraniol **(82)**

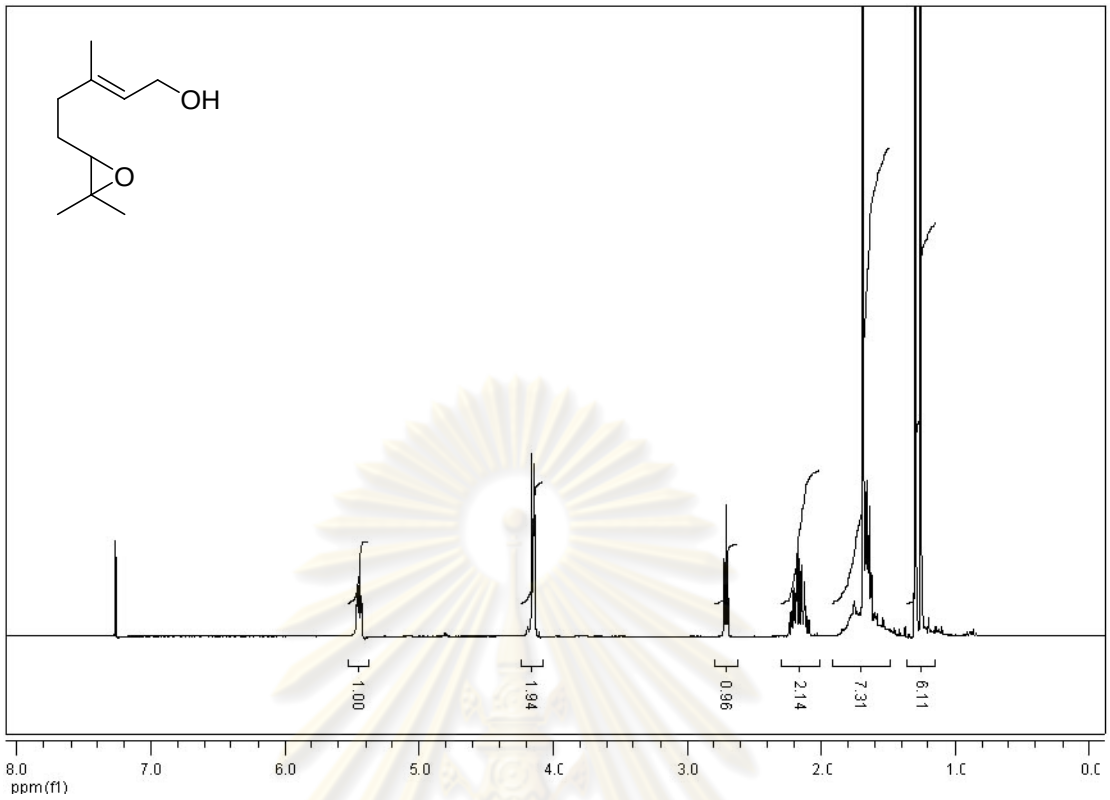
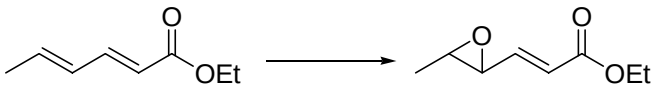


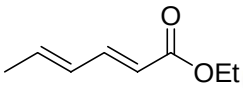
Figure 2.11 The ^{1}H-NMR spectrum of 6,7-epoxygeraniol **(83)**

Ethyl sorbate

In the previous work [107], Buranaprasertsuk *et al.* reported that α, β-unsaturated ketone could not be epoxidized under the system using Co(II) calix[4]pyrrole **(68)** or Co(II) benzimidazole **(72)** as catalyst. To confirm this observation, ethyl sorbate was selected as a substrate. Under the same reaction conditions studied, the results are presented in Table 2.9.

Table 2.9 Regioselective epoxidation of ethyl sorbate catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**



Entry	Substrate	Catalyst	%Recovery Reactant	% Yield Epoxide	MB
1[a]		-	53	45	98
2		Co(II) calix[4]pyrrole **(68)**	40	56	96
3		Co(II) benzimidazole **(72)**	35	60	95

reaction condition: ethyl sorbate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde 10 mmol, CH_3CN:toluene 2:13 mL, rt, 24h
[a] ethyl sorbate 5 mmol, m-CPBA 7.5 mmol, CH_2Cl_2, 0°C, 4 h

From Table 2.9, ethyl sorbate containing two different C=C bonds; one connected to an ester and the other was remoted, was chosen as a new substrate for epoxidation reaction. 4,5-Epoxyethyl sorbate was obtained in moderate yield. The epoxidation was however selectively taken place at the remote double bond while the one next to an ester moiety was intact. This was clearly indicated that the epoxidation prevailly took place at the C=C not adjacent to the electron withdrawing group. All results were confirmed by ^{1}H-NMR. The proton signals of the olefin in ethyl sorbate were detected at δ_H 5.78, 6.19 and 7.24. When the epoxidation occurred at the remote C=C, the proton signals of olefin at δ_H 5.78 and 6.19 were disappeared. The results are displayed in Figs 2.12, 2.13. From the previous work, cationic manganese complex [114] was used to study the regioselectivity epoxidation of this substrate. The mixture of 4,5- and 2,3-monoepoxide was obtained in the ratio of 4:1. This result was clearly indicated the high regioselectivity of this developed reaction.

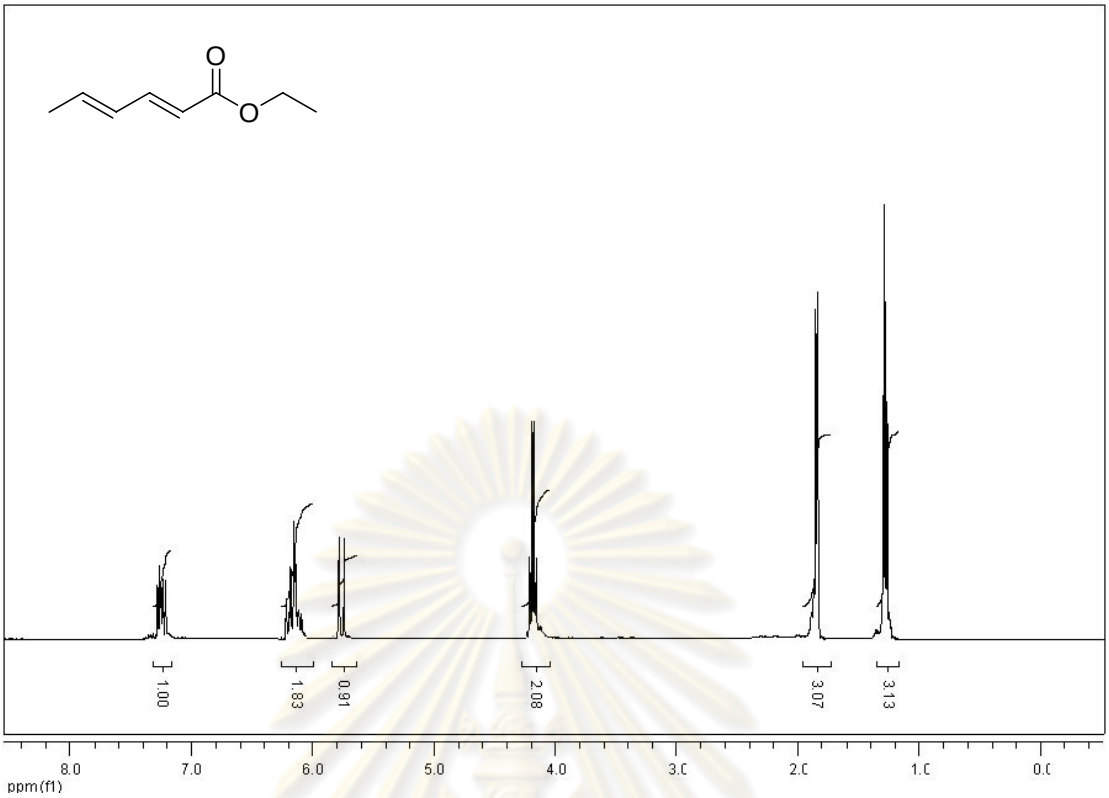


Figure 2.12 The ^{1}H-NMR spectrum of ethyl sorbate

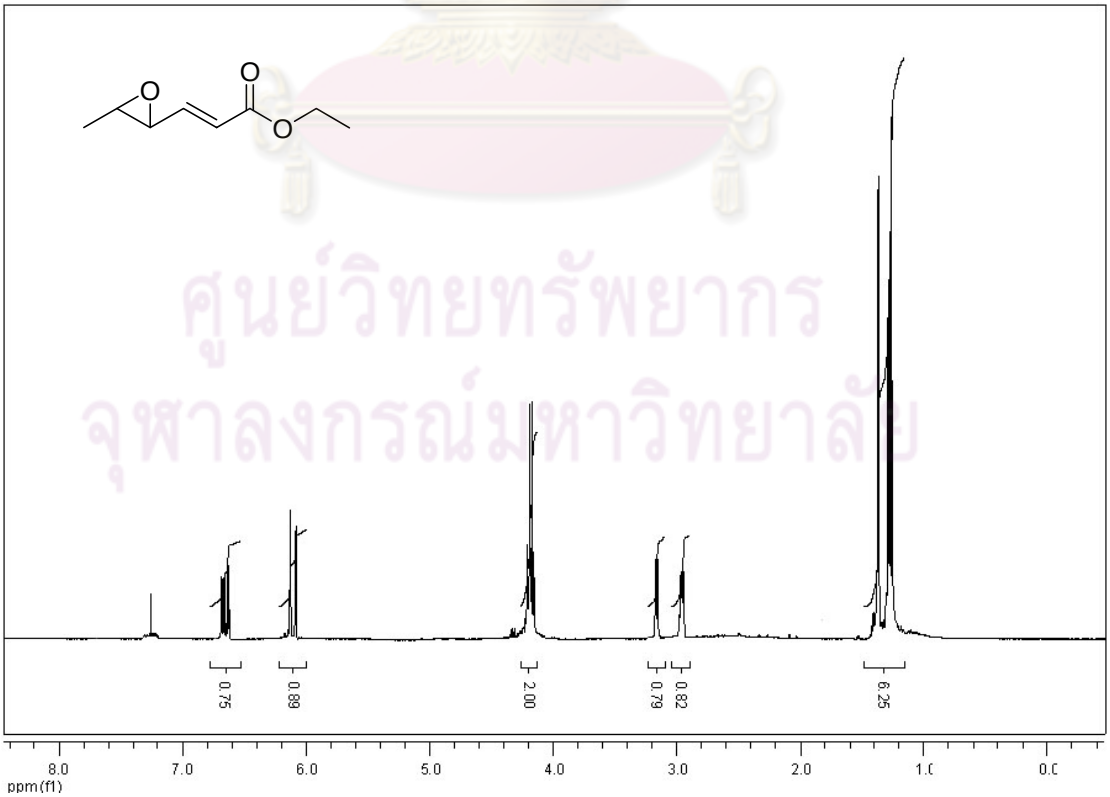


Figure 2.13 The ^{1}H-NMR spectrum of ethyl sorbate oxide

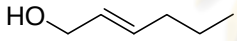
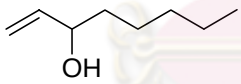
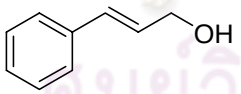
2.8.4.3 Chemoselectivity Study

Following the general epoxidation procedure, a substrate containing two functional groups in the molecules was chosen for chemoselectivity study.

Allylic Alcohol

Certain allylic alcohols including *trans*-2-hexen-1-ol, 3-octen-1-ol and cinnamyl alcohol were selected as models for catalytic epoxidation catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**. All chosen compounds contained an olefinic and a hydroxyl group in the molecules. These substrates could therefore be studied for the effect of hydroxyl group on the epoxidation reaction. The results are displayed in Table 2.10.

Table 2.10 Chemoselective epoxidation of *trans*-2-hexen-1-ol, 3-octen-1-ol and cinnamyl alcohol catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**

Entry	Substrate	Catalyst	%Recovery Reactant	% Yield Epoxide	MB
1		Co(II) calix[4]pyrrole **(68)**	42	60	102
2		Co(II) benzimidazole **(72)**	24	75	99
3		Co(II) calix[4]pyrrole **(68)**	51	45	97
4		Co(II) benzimidazole **(72)**	48	54	102
5		Co(II) calix[4]pyrrole **(68)**	25	74	99
6		Co(II) benzimidazole **(72)**	10	89	99

reaction condition: substrate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde 20 mmol, CH_3CN 15 mL, rt, 24h

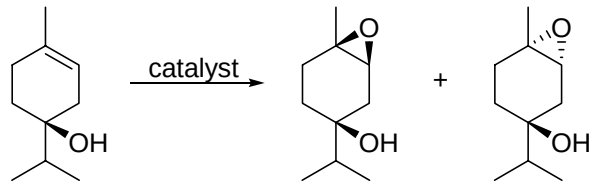
From Table 2.10, Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** could assist the conversion of allylic alcohols to the desired product in moderate to high yield. In this reaction, CH_3CN was used as solvent replacing a mixture of toluene and CH_3CN since the latter gave low to moderate yield. In addition, *trans*-2-hexen-1-ol oxide and 3-octen-1-ol oxide were obtained in moderate yield when Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** were used as catalyst (entries 1-4), whereas cinnamyl alcohol could be epoxidized to cinnamyl alcohol oxide in high yield (entries 5, 6). It is noteworthy at this point that the presence of the hydroxyl

group in the allylic molecule did not interfere the epoxidation occurred at the olefinic site. In addition, this result could give informative data that the hydroxyl group was not oxidized to aldehyde or carboxylic acids. From the previous work, Sharpless *et al.* reported a new chiral epoxidation system that gave uniformly high asymmetric inductions throughout a range of substitution in the allylic alcohol substrate. Upon using of a given tartrate enantiomer, the system seemed to deliver the epoxide oxygen from the same enantioface of the olefin regardless of the substitution pattern. Sharpless' system was found to be suitable for allylic alcohol substrates [115].

Terpinen-4-ol

Terpinen-4-ol isolated from plai oil [116] was selected as a chemical model to observe the chemoselectivity of the system catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**. In addition, this substrate contained two functional groups, thereby interesting to study the stereoselectivity of the epoxide product. The results are presented in Table 2.11.

Table 2.11 Regioselective epoxidation of terpinene-4-ol catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**



cis-form *trans-form*

Entry	Catalyst	%Recovery Reactant	%Yield Epoxide (*cis*:*trans*)	MB
1[a]	Co(II)calix[4]pyrrole **(68)**	38	58 (3.37:1)	96
2[a]	Co(II)benzimidazole **(72)**	40	55 (3.32:1)	95
3[b]	Co(II)calix[4]pyrrole **(68)**	60	41 (2.37:1)	101
4[b]	Co(II)benzimidazole **(72)**	58	44 (2.33:1)	102
5[c]	Co(II)calix[4]pyrrole **(68)**	trace	81 (3.31:1)	81

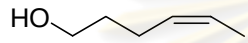
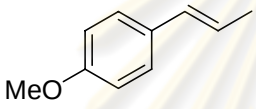
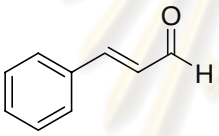
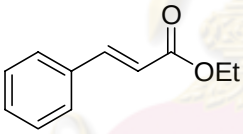
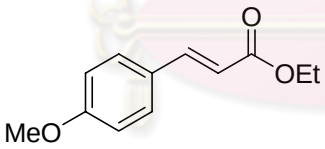
reaction condition: [a]substrate 5 mmol, catlyst 0.05 mmol, CH_3CN:toluene 2:13 mL 2-ethylbutyraldehyde 20 mmol, RT 24h
[b]substrate 5 mmol, catalyst 0.05 mmol, CH_3CN 15 mL, 2-ethylbutyraldehyde 20 mmol, RT 24h
[e]substrate 3 mmol, catalyst 0.05 mmol, CH_3CN:toluene 2:13 mL 2-ethylbutyraldehyde 20 mmol, RT 24h

From Table 2.11, under the same conditions, when a mixture of CH_3CN and toluene was used as solvent, a mixture of *cis*- and *trans*-epoxides were obtained in moderate yield with diastereomeric ratio at 3.37:1 (entries 1, 2), while using CH_3CN as solvent, the diastereomeric ratio was decreased to 2.37:1 (entries 3, 4). This result indicated that the solvent had dramatically effect on diastereomeric ratio. In addition, when terpinen-4-ol was decreased from 5 to 3 mmol, the yield of terpinen-4-ol oxide was obtained in high yield with the same diastereomeric ratio (entry 5). This result could point out that the hydroxy group was not affected under this epoxidation system. The stereochemistry of *cis*- and *trans*-products was compared with (*R*)- and (*S*)-limonenes.

2.8.5 Epoxidation of Other Alkenes Catalyzed by Co(II) Calix[4]pyrrole (68) and Co(II) Benzimidazole (72)

Other alkenes, namely 4-hexen-1-ol, anethole, cinnamaldehyde, ethyl cinnamate and 4-methoxyethyl cinnamate were selected to epoxidize under this developed epoxidation reaction. The results are presented in Table 2.12.

Table 2.12 Epoxidation of selected alkenes catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**

Entry	Substrate	Catalyst	% Epoxide
1		Co(II) calix[4]pyrrole **(68)**	35, 44[a]
2		Co(II) benzimidazole **(72)**	31, 45[a]
3		Co(II) calix[4]pyrrole **(68)**	74
4		Co(II) benzimidazole **(72)**	70
5		Co(II) calix[4]pyrrole **(68)**	NR
6		Co(II) benzimidazole **(72)**	NR
7		Co(II) calix[4]pyrrole **(68)**	NR
8		Co(II) benzimidazole **(72)**	NR
9		Co(II) calix[4]pyrrole **(68)**	NR
10		Co(II) benzimidazole **(72)**	NR

reaction condition: substrate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde 20 mmol, CH_3CN:toluene 2:13 mL, rt, 24h
[a]CH_3CN 15 mL

From Table 2.12, the epoxidation of *cis*-4-hexen-1-ol catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** furnished the corresponding epoxide in low yield. When the solvent was altered from a mixture of toluene and CH_3CN to CH_3CN, the desired product was increased to 44% and 45%, respectively (entries 1, 2). In addition, anethole, another example of natural product could be epoxidized to anethole oxide in good yield (entries 3, 4).

The epoxidation of cinnamaldehyde, ethyl cinnamate and ethyl 4-methoxy-cinnamate were also carried out to observe the possibility to employ this methodology to synthesize epoxy acid or its ester derivatives. It was nevertheless noticed that the

reaction was not occurred. The ester group of cinnamate displayed as electron withdrawing group decreased the electron density of double bond, therefore rendered the reactivity of the substrate (entries 5-10). It could be summarized at this point that this developed system was not applicable for alkenes connected with electron withdrawing group.

2.8.6 Applications of Developed Epoxidation Reaction to Terminal Alkenes

The reaction of alkene with peroxy acid to produce epoxides has been known. It provides the most convenient method for the preparation of epoxides. Oxygen atom transferred from a peroxy acid to an alkene is facilitated by electron donating substituents on the carbon-carbon double bond, and electron withdrawing groups on the peroxy acid [117]. The epoxidation of terminal alkenes was nevertheless less reported because of their less reactivity. Only a few reports such as the system using 30% H_2O_2 under halide-free conditions, and catalytic systems consisted of Na_2WO_4 dihydrate, (aminomethyl)phosphoric acid and methyltri-*n*-octylammonium hydrogensulfate in a 2:1:1 molar ratio were among those limited examples. Therefore, the epoxidation of terminal alkenes are challenging to explore.

The attempt to apply the developed epoxidation reaction employing Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** for terminal alkenes was conducted. Various parameters are explored to optimize the epoxidation reaction. This present work concentrates on the amount of the oxidant, 2-ethylbutyraldehyde. 1-Dodecene was chosen as a chemical model.

2.8.6.1 The Effect of the Amount of 2-Ethylbutyraldehyde on the Epoxidation of 1-Dodecene Catalyzed by Co(II) calix[4]pyrrole (68) and Co(II) benzimidazole (72)

The amount of the oxidant is another important parameter that needed to be studied. The effect of 2-ethylbutyraldehyde was examined and the results are presented in Table 2.13.

Table 2.13 The effect of the amount of 2-ethylbutyraldehyde on the epoxidation of 1-dodecene catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**

Entry	Catalyst	2-Ethylbutyraldehyde (mmol)	% Recovery Reactant	% Yield Epoxide	MB
1	Co(II) calix[4]pyrrole **(68)**	10	41	58	99
2	Co(II) calix[4]pyrrole **(68)**	15	32	65	97
3	Co(II) calix[4]pyrrole **(68)**	20	25	74	99
4	Co(II) calix[4]pyrrole **(68)**	25	51	50	101
5	Co(II) calix[4]pyrrole **(68)**	30	51	48	99
6	Co(II) benzimidazole **(72)**	10	41	62	103
7	Co(II) benzimidazole **(72)**	15	32	71	103
8	Co(II) benzimidazole **(72)**	20	25	80	105
9	Co(II) benzimidazole **(72)**	25	47	65	102
10	Co(II) benzimidazole **(72)**	30	49	55	104

rection condition: 1-dodecene 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde X mmol, CH_3CN 15 mL, rt, 24h

Under the standard conditions, the utilization of 2-ethylbutyraldehyde 20 mmol provided the highest yield of the desired product in both catalytic systems (Table 2.13, entries 3, 8). When the amount of 2-ethylbutyraldehyde was increased from 20 mmol to 25 or 30 mmol, the percent yield of 1-dodecene oxide was invariant. This result indicated that 2-ethylbutyraldehyde 20 mmol was suitable for this substrate.

2.8.6.2 Comparative Kinetic Study on the Epoxidation of Cyclohexene, 1-Dodecene and 1-Methylcyclohexene Catalyzed by Co(II) Calix[4]pyrrole (68) and Co(II) Benzimidazole (72)

To extend the scope of the epoxidation of alkenes catalyzed by Co(II) complexes, various alkenes included cyclohexene, 1-dodecene and 1-methyl cyclohexene were investigated for comparison. The results are presented in Fig 2.14.

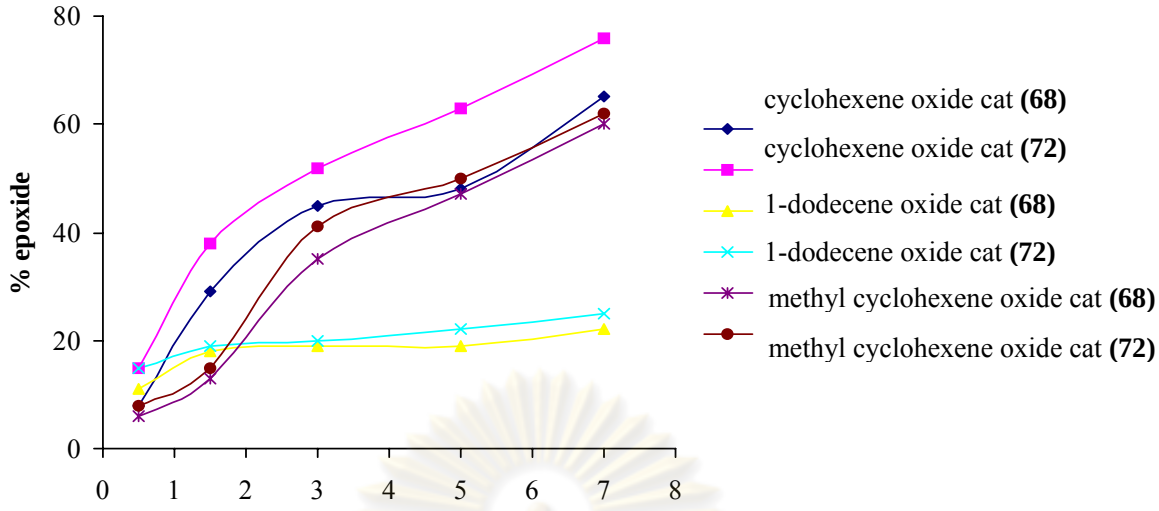


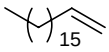
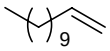
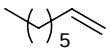
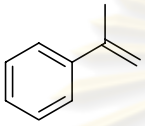
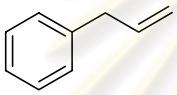
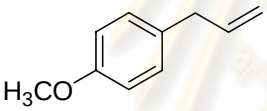
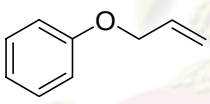
Figure 2.14 Comparative kinetic study on the epoxidation of cyclohexene, 1-dodecene and 1-methylcyclohexene catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**

From Fig 2.14, the rate of the epoxidation of 1-methylcyclohexene was found to be faster than those of cyclohexene and 1-dodecene, respectively. This could be explained that 1-methylcyclohexene was trisubstituted alkene possessed higher electron density than other substrates tested. This observation also implied that the active site of catalyst should be electrophilic in character. The half-life of the epoxidation reaction of cyclohexene, 1-dodecene and 1-methylcyclohexene catalyzed by cobalt(II) calix[4]pyrrole **(68)** and cobalt(II) benzimidazole **(72)** were approximately 3, >7 and 3.5 h.

2.8.6.3 Epoxidation of Selected Terminal Alkenes Catalyed by Co(II) calix[4]pyrrole (68) and Co(II) benzimidazole (72)

Certain terminal alkenes were selected as a chemical model for catalyric epoxidation using Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** as catalyst. The results are presented in Table 2.14.

Table 2.14 Epoxidation of terminal alkenes catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**

Entry	Substrate	Catalyst	% Epoxide
1		Co(II) calix[4]pyrrole **(68)**	41
2		Co(II) calix[4]pyrrole **(68)**	74
3		Co(II) benzimidazole **(72)**	80
4		Co(II) calix[4]pyrrole **(68)**	32
5		Co(II) benzimidazole **(72)**	30
6		Co(II) calix[4]pyrrole **(68)**	59
7		Co(II) benzimidazole **(72)**	61
8		Co(II) calix[4]pyrrole **(68)**	35
9		Co(II) benzimidazole **(72)**	40
10		Co(II) calix[4]pyrrole **(68)**	NR
11		Co(II) benzimidazole **(72)**	NR
12		Co(II) calix[4]pyrrole **(68)**	NR
13		Co(II) benzimidazole **(72)**	NR

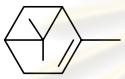
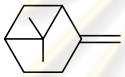
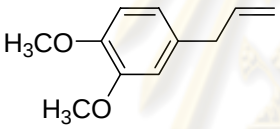
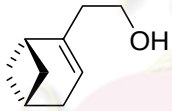
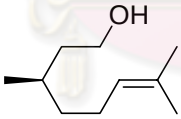
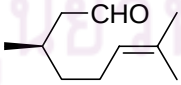
reaction condition: substrate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde 20 mmol, CH_3CN 15 mL, rt, 24h

The results of the epoxidation of terminal alkenes are presented in Table 2.14. The first group, aliphatic terminal alkenes such as 1-octadecene, 1-dodecene and 1-octene were chosen. The desired epoxides were obtained in better yield from 41% to 91% for the compound having less carbon atoms in the molecule (entries 1-5). This result indicated that the reactivity was directly dependent upon the steric hindrance [118]. The second group consisted of aromatic terminal alkenes such as α-methyl-styrene, allylbenzene, 4-methoxyallylbenzene and allylphenyl ether. The moderate yield of α-methylstyrene oxide and allylbenzene oxide was obtained when α-methyl-styrene and allylbenzene was used as a substrate respectively (entries 6-9). In addition, 4-Methoxyallylbenzene and allylphenyl ether could not convert to their epoxide (entries 10-13). The main reason for less activation was depended on the steric hindrance of the substrate.

2.8.7 Applications of the Developed Epoxidation Reaction to Natural Products

Six natural products namely α-pinene, β-pinene, eugenol methyl ether, nopol, citronellol and citronellal were selected as a model for catalytic epoxidation using Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**. The results are presented in Table 2.15.

Table 2.15 Epoxidation of natural products catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**

Entry	Substrate	Catalyst	% Epoxide
1		Co(II) calix[4]pyrrole **(68)**	74
2		Co(II) benzimidazole **(72)**	77
3		Co(II) calix[4]pyrrole **(68)**	NR
4		Co(II) benzimidazole **(72)**	NR
5		Co(II) calix[4]pyrrole **(68)**	trace
6		Co(II) benzimidazole **(72)**	trace
7		Co(II) calix[4]pyrrole **(68)**	68
8		Co(II) benzimidazole **(72)**	55
9		Co(II) calix[4]pyrrole **(68)**	83
10		Co(II) benzimidazole **(72)**	61
11		Co(II) calix[4]pyrrole **(68)**	NR
12		Co(II) benzimidazole **(72)**	NR

reaction condition: substrate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde 20 mmol, CH_3CN:toluene 2:13 mL, rt, 24h

The attempt to use both Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** for the epoxidation of natural products was conducted. α-Pinene was found to smoothly transform to α-pinene oxide as a major product in good yield 74% and 77% (entries 1, 2), respectively. No other rearranged product was observed. Nonetheless, the epoxidation of β-pinene and eugenol methyl ether catalyzed by these two cobalt complexes was not successful under this particular conditions (entries 3-6). This was

because, as discussed earlier, more substituted alkenes were more reactive than less substituted alkenes towards this reaction. Nopol oxide was obtained in moderate yield 68% and 55% (entries 7, 8). In addition, citronellol could convert to citronellol oxide in high yield (entries 9, 10) whereas citronellal oxide was not occurred under the same optimal conditions (entries 11, 12). It could be noted that under this particular conditions, the aldehyde in citronellal was not oxidized to carboxylic acid because only citronellal was observed in GC chromatogram.

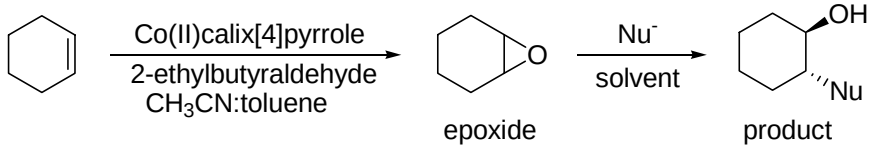
2.8.8 Applications of the Developed Epoxidation for One-Pot Synthesis

A one-pot synthesis is a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical reactions in just one reactor. This is much desired by chemists because of avoiding a lengthy separation process and purification of the intermediates. This would save time and resources while increasing chemical yield.

Cyclohexene

Cyclohexene was first selected as a chemical model to study one-pot synthesis to halohydrin and azido compounds. This reaction can in fact be separated into two steps. First, the epoxidation of cyclohexene using Co(II) calix[4pyrrole **(68)** as a catalyst for 8 h. The second step, a nucleophile was attacked. The results are presented in Table 2.16.

Table 2.16 One-pot synthesis of halohydrin and azido compound from cyclohexene



Entry	Substrate	Catalyst	%Recovery		Product	MB
			Reactant	Epoxide		
1[a]	cyclohexene oxide	$CrCl_3.6H_2O$	0	-	100[a]	100
2[a]	cyclohexene oxide	$CrBr_3.6H_2O$	0	-	100[a]	100
3[b]	cyclohexene oxide	NaN_3	0	-	100[b]	100
4[c]	cyclohexene	cat **(68)** + $CrCl_3.6H_2O$	trace	0	95[c]	98
5[c]	cyclohexene	cat **(68)** + $CrBr_3.6H_2O$	trace	0	95[c]	95
6[d]	cyclohexene	cat **(68)** + NaN_3	trace	64	32[d]	106
7[e]	cyclohexene	cat **(68)** + NaN_3	trace	20	80[e]	100

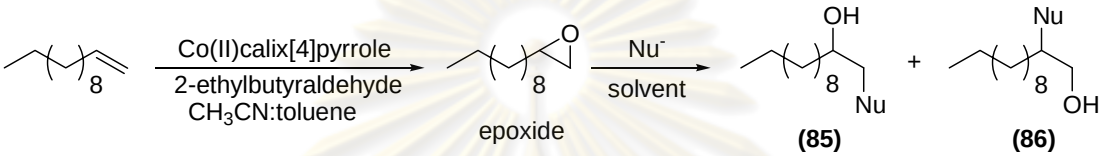
reaction condition:[a]substrate 1 mmol, $CrCl_3.6H_2O$ 1 mmol, THF 5 mL, RT 30 min
[b]substrate 1 mmol, NaN_3 1.5 mmol, $CH_3CN:H_2O$ 4.5:0.5 mL, reflux 6h
[c]substrate 5 mmol, Co(II)calix[4]pyrrole **(68)** 0.05 mmol, CH_3CN:toluene 2:13 mL 2-ethylbutyraldehyde 10 mmol RT 8h and then $CrCl_3.6H_2O$ 4 mmol, THF 5 mL, RT, 2h
[d]substrate 5 mmol, Co(II)calix[4]pyrrole **(68)** 0.05 mmol, CH_3CN:toluene 2:13 mL, 2-ethylbutyraldehyde 10 mmol, RT 8h and then NaN_3 7.5 mmol, $CH_3CN:H_2O$ 9:1 mL reflux 6 hr
[e]substrate 5 mmol, Co(II)calix[4]pyrrole **(68)** 0.05 mmol, CH_3CN:toluene 2:13 mL 2-ethylbutyraldehyde 10 mmol, RT 8h and then NaN_3 7.5 mmol, Bu_4NBr 10% of NaN_3 $CH_3CN:H_2O$ 9:1 mL reflux 6 hr

From Table 2.16, cyclohexene oxide was reacted with $CrCl_3.6H_2O$, and $CrBr_3.6H_2O$ resulting in the formation of holohydrin in excellent yield (entries 1, 2). When NaN_3 was used as a nucleophile, the desired product was also obtained in excellent yield (entry 3). The attempt to perform one pot reaction directly from the parent alkene to the desired product was studied. Cyclohexene was first treated with Co(II) calix[4]pyrrole **(68)**. When cyclohexene oxide was completely occurred, a nucleophile was added to the reaction. It was found that when $CrCl_3.6H_2O$ and $CrBr_3.6H_2O$ were used as a nucleophilic source, chloride can be attacked to the epoxide ring providing *trans*-chlorocyclohexanol and *trans*-bromocyclohexanol in the excellent yield (entries 4, 5). In addition, when NaN_3 was used as nucleophile, *trans*-2-azidocyclohexanol was obtained in low yield (entry 6). This was mainly because NaN_3 was not dissolved in this media. In the presence of tetrabutylammonium bromide (Bu_4NBr) as a phase transfer catalyst, the azidocyclohexanol was obtained in high yield (entry 7).

1-Dodecene

1-Dodecene was used as another substrate for one-pot synthesis to halohydrin. When 1-dodecene was completely converted to 1-dodecene oxide, the subsequent step of ring opening was conducted by the addition of halogen source. This model is interesting to study the regioselectivity of the system by observing what site of the oxirane ring would be attacked either at more or less steric hindrance position. The results are presented in Table 2.17.

Table 2.17 One-pot synthesis of halohydrin from 1-dodecene



Entry	Substrate	Catalyst	%Recovery		Product **85:86**	MB
			Reactant	Epoxide		
1	1-dodecene	cat **(4)** + $CrCl_3.6H_2O$	15	-	82 (4.76:1)	97
2	1-dodecene	cat **(4)** + $CrBr_3.6H_2O$	trace	-	87 (4.66:1)	92

Reaction condition: substrate 5 mmol, Co(II)calix[4]pyrrole **(4)** 0.05 mmol, CH_3CN 15 mL, 2-ethyl-butyraldehyde 20 mmol, RT 24h and then $CrX_3.6H_2O$ 4 mmol, THF 5 mL, RT 2h

From Table 2.17, under the standard conditions, 1-dodecene could be converted to 1-dodecene oxide in excellent yield in the first step. The addition of $CrCl_3.6H_2O$ or $CrBr_3.6H_2O$ produced halohydrin **85** as a major product while halohydrin **86** was obtained as a minor one in the ratio of 4.76:1 and 4.66:1, respectively (entries 1, 2). This result indicated that a nucleophile favored to attack at the less steric hindrance of the oxirane ring.

2.8.9 Epoxidation of *N*-benziridine-*tert*-butylamine Catalyzed by Co(II) Calix[4]pyrrole (68) and Co(II) Benzimidazole (72)

Oxygenation of various aldimines with tetrabutylammonium monoperoxysulfate produced the corresponding *E*- or a mixture of *E*- and *Z*-oxaziridines with very high yield and good to excellent selevtivities (75-100%) within 20 min to 10 h in CH_3CN at RT. The *E/Z* isomer ratio critically depends on the stereo-electronic nature of the substituents in the oxaziridines, solvent, and the presence of Lewis acids and bases [119].

N-benziridine-*tert*-butylamine was selected as a chemical model for studying the epoxidation of imine catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**. The results are presented in Table 2.18.

Table 2.18 Epoxidation of *N*-benziridine-*tert*-butylamine catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)**

E-isomer

Entry	Catalyst	%Recovery Reactant	% yield Product	MB
1	Co(II)calix[4]pyrrole **(68)**	70	31	101
2	Co(II)benzimidazole **(72)**	72	34	106

reaction condition: substrate 5 mmol, catalyst 0.05 mmol, 2-ethylbutyraldehyde 20 mmol, solvent 15 mL, RT, 24h

The results presented in Table 2.18 illustrate the high efficiency and 100% selectivity of this oxidation system. Oxidation of *N*-benziridine-*tert*-butylamine gave 2-*tert*-butyl-3-phenyl-1,2-oxaziridine as a product. It is known that the oxidation of aldimines with bulky *tert*-butyl substituent on the nitrogen site (entries 1, 2) gave *E*-oxaziridine isomer as a major product. This result was confirmed by ^{1}H-NMR, the proton signal of oxaziridine was observed at δ_H 4.81 compared with the previous work [120].

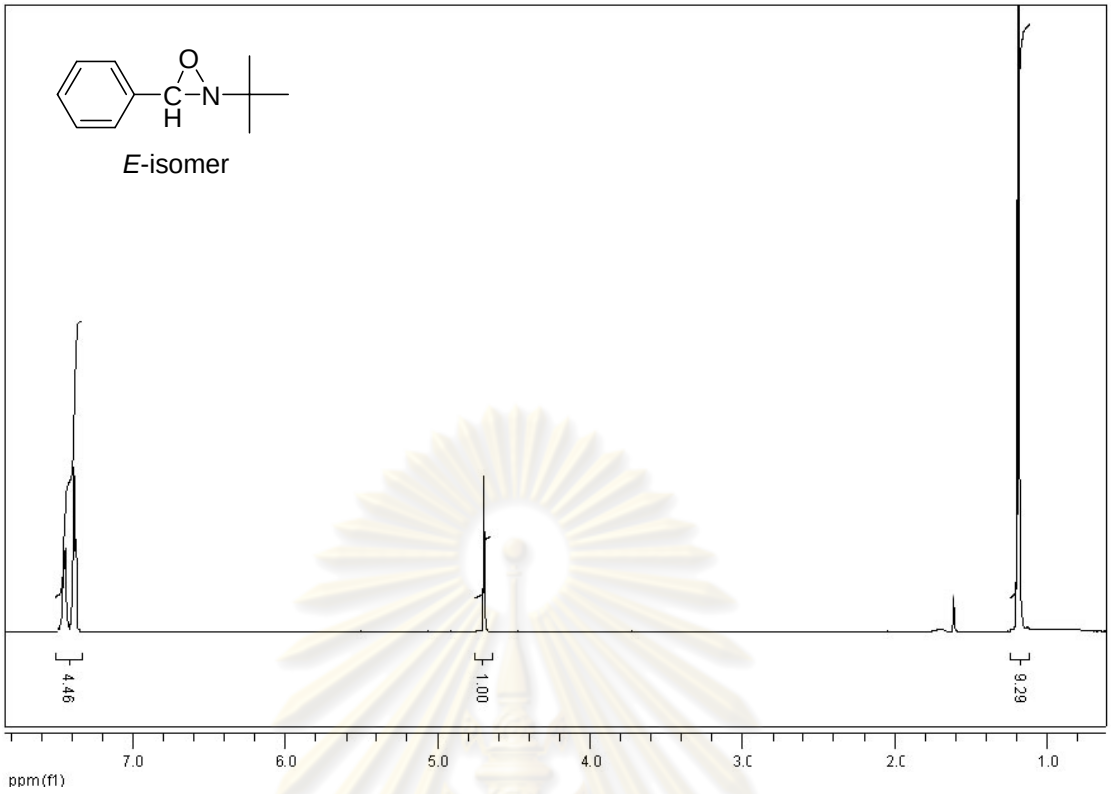
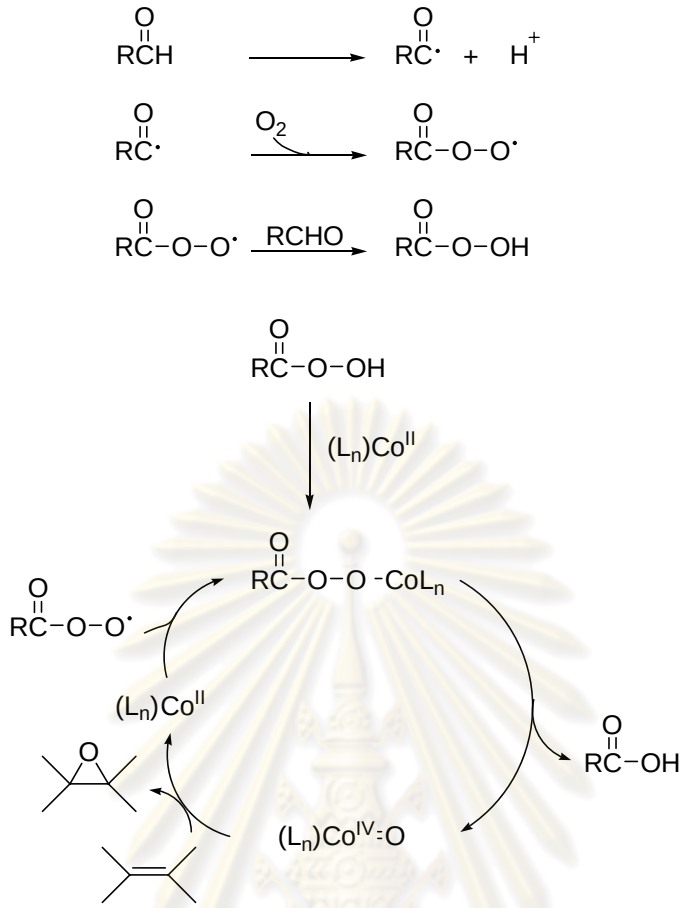


Figure 2.15 The ^{1}H-NMR spectrum of 2-*tert*-butyl-3-phenyl-1,2-oxaziridine

2.8.10 Proposed Mechanism for Co(II) Calix[4]pyrrole (68) and Co (II) Benzimidazole (72) Catalyzed Epoxidation of Alkenes

For the mechanistic pathway (Scheme 2.4), the mechanistic pathway to take place similar to that addressed in previous literature [34]. The cobalt complex played two major roles. First, it reacted with aldehyde to generate an acyl radical ($RC(O)^{\bullet}$). The acyl radical then reacted with dioxygen to give an acylperoxy radical ($RC(O)OO^{\bullet}$). The acylperoxy radical acted as a carrier in a chain mechanism by reacting with another aldehyde molecule to give the peroxyacid, thereby generating another acyl radical. Oxygenation of substrate was assumed to occur *via* reactive high-valent cobalt oxo intermediates, which were produced by the reaction of the peroxy acid with cobalt catalysts which then reacted with the alkene in a fashion analogous to that observed previously for metal complex-catalyzed reactions of peroxy acids with alkenes.



Scheme 2.4 Proposed mechanism for Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** catalyzed epoxidation of alkenes

2.9 Conclusion

The purposes of this research were to screen for the catalytic capability of thirteen synthesized cobalt complexes in cyclohexene epoxidation. It was observed that certain cobalt(II) complexes displayed impressive preliminary catalytic results. The study was carried out in the homogeneous catalytic system. From this research, the epoxidation of cyclohexene was disclosed exploying a catalytic system of 1 mol% of cobalt(II) calix[4]pyrrole **(68)** or cobalt(II) benzimidazole **(72)** with oxygen in the presence of 2-ethylbutyraldehyde 10 mmol using the mixture of CH_3CN:toluene (2:13 mL) as solvent at RT for 24 h. The excellent yield of cyclohexene oxide was obtained. Eventhough these two cobalt catalysts were previously synthesized and reported, the use as catalysts for epoxidation of alkene has never been addressed. Therefore, this is the first report on the utilization of these two complexes in catalytic aspects. In addition, the optimum conditions for the epoxidation of alkenes catalyzed by cobalt

complexes, solvent effect, stereoselectivity, regioselectivity and chemoselectivity studies of these developed systems were thoroughly examined.

The results from the epoxidation reaction of α, β-unsaturated carbonyl compound could point out that alkenes connecting with electron withdrawing group such as cinnamaldehyde, ethyl cinnamate, 4-methoxyethyl cinnamate and anethole were not applicable for epoxidation.

According to the stereoselectivity, regioselectivity and chemoselectivity investigation, the epoxidation of *cis*-stilbene catalyzed by Co(II) calix[4]pyrrole **(68)** and Co(II) benzimidazole **(72)** gave a mixture of *cis*- and *trans*-stilbene oxides in approximately 1:1 ratio. However, the epoxidation of *trans*-stilbene under the same conditions obliged only *trans*-stilbene oxide product. In addition, the *exo*-norbornene oxide was obtained as a major product under the epoxidation system. For cholesteryl acetate and cholesteryl benzoate, these catalysts revealed the possibility to epoxidize at the β-face. These results provide a useful information for mechanistic interpretation. The highly regioselective reaction of this developed system could be observed from the experiment of 4-vinylcyclohexene, (*R*)-, (*S*)-limonenes, geraniol, geranyl acetate and ethyl sorbate.

The epoxidation of terminal alkenes favored the attack at less steric site or having electrophilic moiety in the molecule which would increase the reactivity. Electron withdrawing group made terminal alkenes low electron density and limited its reactivity for oxygen transfer.

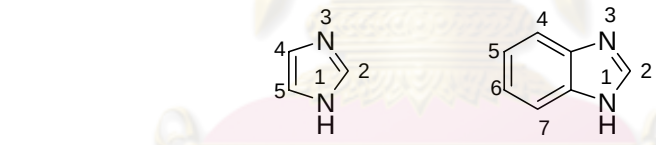
Halohydrin and azido compounds could be manipulated from alkenes by one-pot synthesis. Under the epoxidation system, alkene could be converted to epoxide in excellent yield in the first step. The next step, a nucleophile such as Cl^-, Br^- and N_3^- could be added to the epoxide formed. The halohydrin and azido compounds were achieved in excellent yield.

CHAPTER III

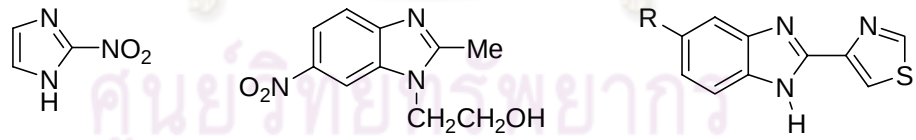
INTERMOLECULAR COUPLING OF DIAMINES WITH AROMATIC ALDEHYDES TO BENZIMIDAZOLES

3.1 Introduction

The imidazole nucleus (A) is found in many important natural products, histidine and purines. The integral part of the structure [121] found in vitamin B_{12} is 5,6-dimethyl-l-(α-D-ribofuranosyl)benzimidazole. In phamacuticals, the imidazoles and benzimidazoles have been interested for the discovery of a new antibacterial **87** [122], a trichomonacide **88** [123]**,** and anthelmintic agents *e.g.* 2-(4-thiazolyl)benzimidazole thiabendazole **(89a)** and cambendazole **(89b)** has added impetus to investigations in these areas.



A B



87 **88** **89a, R=H**
b, R=NHCO$_2$-*i*-Pr

3.2 Synthesis of Benzimidazoles

3.2.1 From Reaction of *o*-Arylene Diamine with Carbonyl-Containing Compounds, Imidates and Miscellaneous Compounds

Benzimidazoles could be synthesized by the reaction between *o*-arylene diamines and carboxylic acids or their derivatives. In general, Philips-type [124] reactions, the heating of the diamine with carboxylic acid in HCl has been applied. For aromatic acids, this method is difficult [125], also for polyphosphoric acid [126].

3.2.2 From *o*-Nitroarylamines and *o*-Dinitroarenes

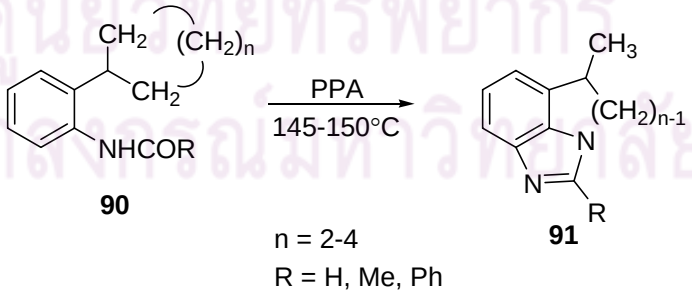
In order to develop benzimidazole syntheses, many methods have been studied from *o*-nitroarylamine or *o*-dinitroarene within a single step. The formation of benzimidazoles involved heating nitroarenealcohol mixtures in gas phase.

The reduction between ferrous oxalate [127] or trialkyl phosphate [128] and *N*-alkyl- and *N*,*N*-dialkyl-*o*-nitroarylamines produces benzimidazoles. Recently, the reactions of *N*,*N*-dialkyl-*o*-nitroarylamines yielding benzimidazoles and their 1-oxide derivatives have been addressed [129]. The acid-catalyzed cyclization of *N*-(*o*-nitroanilino)-substituted aliphatic amines to *N*-aminobenzimidazoles has also been reported [130].

A fair yield of benzimidazoles is received from the reactions under reflux conditions in aqueous HCl. However, benzotriazole and benzotriazole *N*-oxide formation [129] totally succeed in the reaction with benzimidazole formation, but polyphosphoric acid is a requirement.

3.2.3 From *o*-(*N*-Acylamino and aroylamino)arylamines and -Nitrobenzenes

o-(*N*-acylamino and -aroylamino)arylamines and –nitrobenzenes could be used as starting materials. *N*-substituted heterocycles of type **90** has been used in the preparation of tricyclic derivatives **91** by heating with polyphosphoric acid which involved skeletal rearrangement. Using piperidine derivatives (**90**, R = Me; n = 3) an one side and acetyl derivatives (**90**, R = Me) on the other side the product of benzimidazoles has been obtained in a good yield.

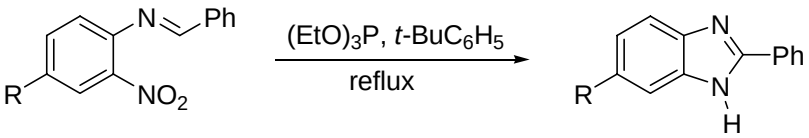


90 **91**

n = 2-4
R = H, Me, Ph

3.2.4 From *N*-Benzylidene-2-nitro- and 2-Azidoanilines

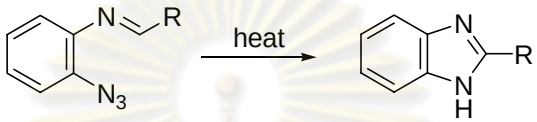
The conversion of 2-phenylbenzimidazoles **(92a.b)** from *N*-benzylidene-2-nitroaniline derivatives **(93a.b)** has been done by reductive cyclization with triethyl phosphite. The higher yield could be achieved by Weidenhagen aldehyde method [131].



92 **93**

a, R = H (47% yield)
b, R = Me (33%)

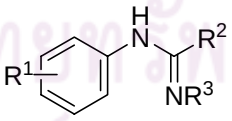
The formation [132] of 2-aryl and 2-hetarylbenzimidazoles has been done by thermolysis of anils from *o*-azidoaniline **(94)**. However, this procedure does not provide high yield.



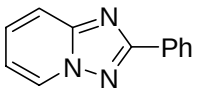
94 **95**

3.2.5 From Amidines and Related Compounds

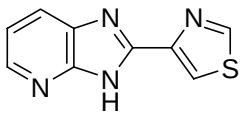
After the hydroxyl derivatives **96a** react with benzenesulfonyl chloride in pyridine or triethylamine under anhydrous conditions, benzimidazoles has been formed. These procedures have been reported by Partridge and Turner [133]. Yield of more than 60% has been obtained, so this method is generally used to synthesis derivatives with substituents in the aryl ring. A variety of derivatives benzimidazoles has been synthesized from the present amidines **96b** by oxidation with sodium hypochlorite under basic conditions. This method was developed by Grenda, *et al*. it is more directly to obtain high yields. Moreover, this method was applied in the synthesis of a triazole derivative **(97)** and an imidazopyridine **(98)**.



96a, R^1 = alkyl, alkoxy, Cl; R^2 = Ph; R^3 = OH
b, R^1 = H; R^2 = 4-thiazolyl, Ph, Et; R^3 = H
c, R^1 = H; R^2 = 4-thiazolyl, Ph, Et; R^3 = Cl



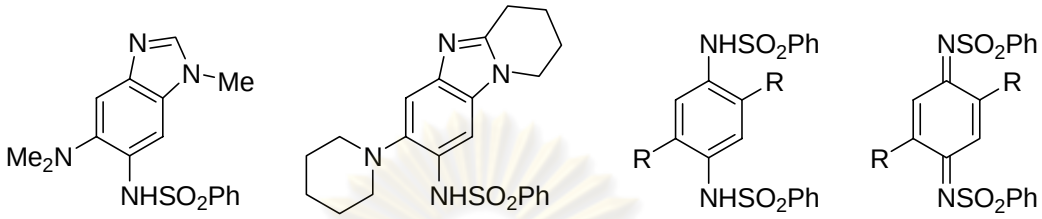
97



98

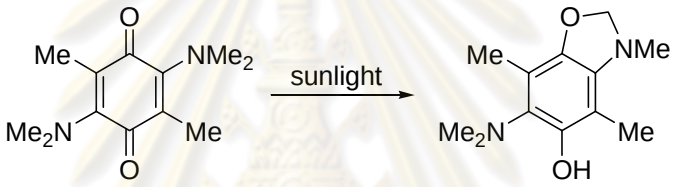
3.2.6 From Quinone Derivatives

The reactions of benzimidazole derivatives **(99a,b)** [134] with disulfonamides **(100a,b)** start in the explosion to the sunlight of quinine dibenzenesulfonimides **(101a,b)**; respectively. These reactions mechanism are believed to be the conversion [135] of analog quinine derivatives **(102)** to benzoxazolines **(103)**.



99a **99b** **100** **101**

a, R = NMe_2
b, R = 1-piperidyl

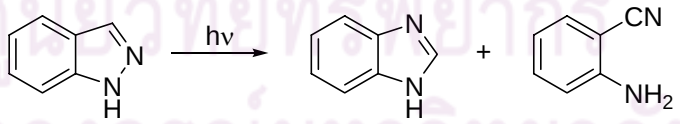


102 **103**

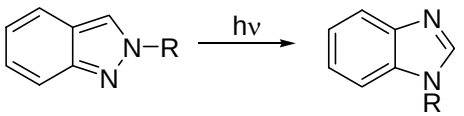
3.2.7 From Heterocyclic Compounds

From Five-Membered Ring Heterocycles

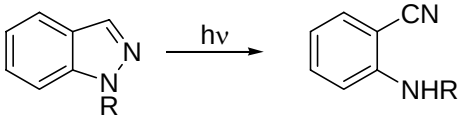
The productivities of benzimidazole and 1-allyl derivatives [136] are induced on the position of the substituent in the heterocyclic ring the photolysis of imidazoles. Therefore, with the absence of the substituent, benzimidazole is formed in low yield, so as the forming of 2-aminobenzonitrile.



(27%) (trace)

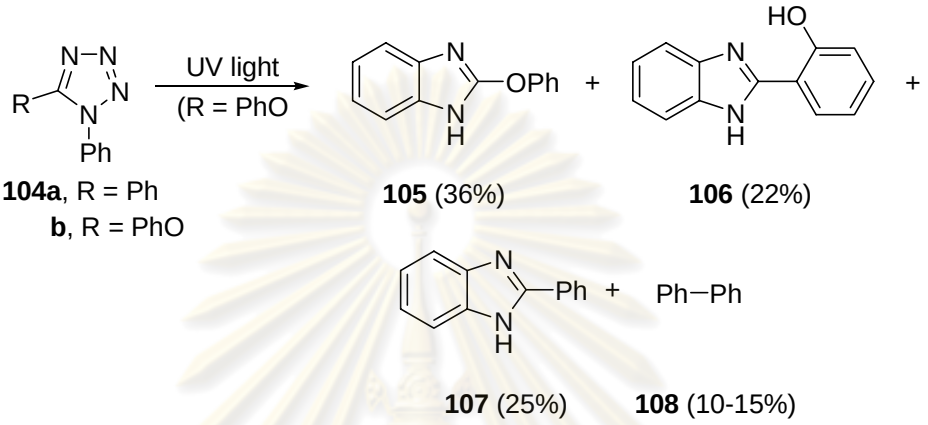


(73-96% for
R = alkyl,
aralky, aryl



R = Me (34%)
R = $PhCH_2$ (10%)

Moriarty and Kliegman [137] reported the photolysis of 1,5-diphenyltetrazole **(104a)** to produce 2-phenylbenzimidazole. The photolysis of tetrazoles has been reported such as the formation of 2-phenoxybenzimidazole which used in the photolysis of 5-phenoxy-1-phenyltetrazole **(104b)** in CH_3CN, therefore compound **(105-108)** were obtained [138] in the photolysis of the tetrazole **(104b)** using benzene as a solvent.



104a, R = Ph
b, R = PhO

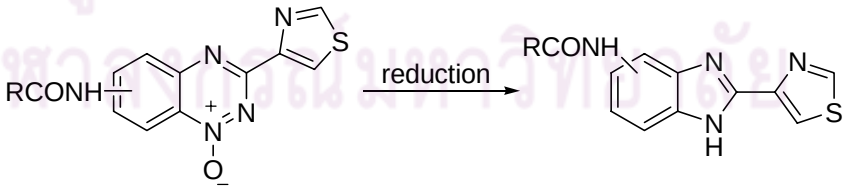
105 (36%) **106** (22%)

107 (25%) **108** (10-15%)

From Six-Membered Ring Heterocycles

100% and 50% Yield of benzimidazole and its 1-methyl derivative have been obtained respectively [139]. These products are produced by the reaction between *o*-phenylenediamine or *N*-methyl-*o*-phenylenediamine with *s*-triazine at the temperatures just over the synthesis of a variety of heterocycles such as other benzazoles, inidazolines, tetrahudropyrimidines and purines. However, the approach has not been ensured.

The reduction of benzotriazine-1-oxide **(109)** with zinc/acetic acid or platinum oxide in ethanol produces 2-(4-thiazolyl)benzimidazoles **(110)** [140].



109 **110**

R = Me_2CHO, aryl

3.3 Scope of This Work

The aim of this research can be summarized as follows:

1. To study the parameters such as a ratio of aldehyde and diamine, and solvent that influenced the formation of benzimidazole

2. To apply the developed conditions for benzimidazole synthesis using various aldehydes
3. To study the mechanism of benzimidazole synthesis

3.4 Experimental

3.4.1 Instruments and Equipment

Melting points were measured on Fisher-Johns melting point apparatus and are uncorrected. Spectrometers: the Fourier transform-infrared spectra (FT-IR) were recorded on Nicolet Impact 410 FT-IR spectrometer. The ^{1}H and ^{13}C-NMR spectra were performed in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as an internal reference on the Varian nuclear magnetic resonance spectrometer, model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ^{1}H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons.

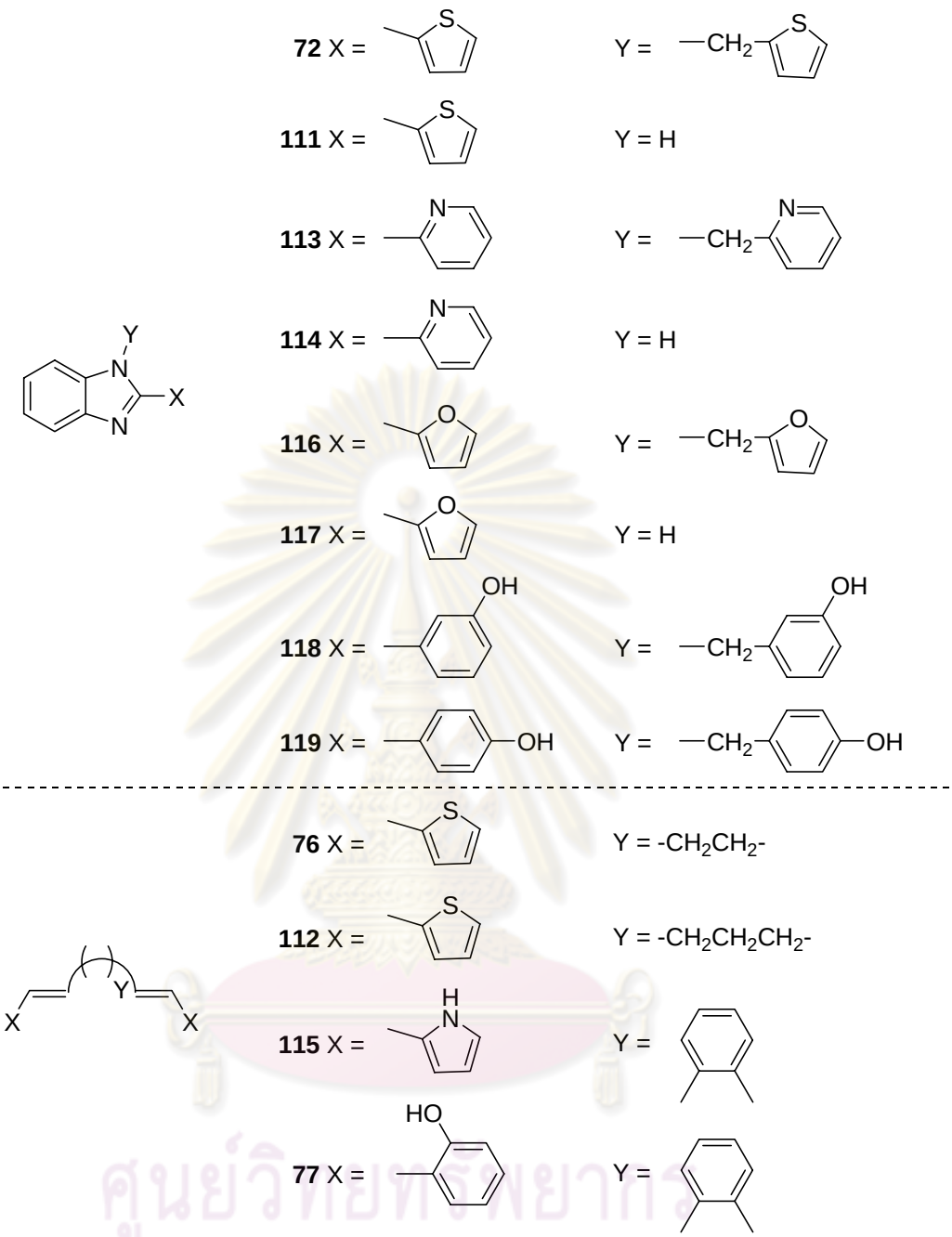
3.4.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades. The reagents utilized for synthesizing the ligands, metal complexes and all alkenes were purchased from Fluka chemical company or otherwise stated and were used without further purification.

3.4.3 General Procedure

3.4.3.1 Preparation of Benzimidazoles

Aldehyde (0.05 mol) was added to a solution of diamine (0.025 mol) in EtOH or toluene (30 mL). The reaction mixture was heated and stirred until a solid occurred. Precipitate was collected by filtration and recrystallized with EtOH.



2-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1H-benzo[*d*]imidazole (72): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.83 (dd, *J* = 6.8 and 1.8 Hz, 1H), 7.51 (dd, *J* = 5.0 and 1.2 Hz, 1H), 7.47 (dd, *J* = 3.8 and 1.2 Hz, 1H), 7.37 (dd, *J* = 7.3 and 1.2 Hz, 1H), 7.29 (m, 2H), 7.23 (dd, *J* = 4.8 and 1.2 Hz, 1H), 7.13 (t, *J* = 4.2 Hz, 1H), 6.94 (t, *J* = 4.4 Hz, 1H), 6.86 (dd, *J* = 3.3 and 1.2 Hz. 1H) and 5.70 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 147.6, 143.0, 138.8, 135.7, 131.8, 129.0, 128.2, 127.2, 125.2, 123.3, 123.0, 119.9, 109.9 and 44.0.

2-(thiophen-2-yl)-1H-benzo[*d*]imidazole (111): ^{1}H-NMR (DMSO-d_6) δ(ppm): 12.93 (br s, -NH), 7.81 (d, *J* = 3.45, 1H), 7.69 (d, *J* = 4.91 Hz, 1H), 7.59 (d, *J* = 6.64 Hz, 1H), 7.48 (d, *J* = 6.64 Hz, 1H) and 7.21 (m, 3H); ^{13}C-NMR (DMSO-d_6) δ(ppm): 147.4, 144.0, 135.1, 134.1, 129.1, 128.7, 127.1, 123.0, 122.1, 118.9 and 111.5.

bis(2-thenylideneimine) *N,N′*-1,2-ethylene (76): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.34 (s, 1H), 7.27 (d, *J* = 4.90 Hz, 1H), 7.25 (d, *J* = 3.57 Hz, 1H), 7.03 (t, *J* = 3.87 Hz, 1H) and 3.90 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 156.0, 142.2, 130.5, 128.7, 127.3 and 60.9.

bis(2-thenylideneimine) *N,N′*-1,3-propylene (112): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.36 (s, 1H), 7.37 (d, *J* = 4.86 Hz, 1H), 7.26 (m, 1H), 7.05 (m, 1H), 3.65 (t, *J* = 6.75 Hz, 2H) and 2.06 (t, *J* = 6.86 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 154.5, 142.5, 130.1, 128.6, 127.3, 58.7 and 31.7.

2-(pyridin-2-yl)-1-(pyridin-2-ylmethyl)-1H-benzo[*d*]imidazole (113): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.55 (m, 2H), 7.89 (m, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.40-7.16 (m, 5H), 7.16 (t, *J* = 6.9 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H) and 6.31 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 157.3, 150.2, 149.7, 149.1, 148.6, 145.9, 142.5, 136.9, 124.6, 123.9, 123.7, 123.1, 122.3, 120.9, 120.0, 110.8 and 51.1.

2-(pyridin-2-yl)-1H-benzo[*d*]imidazole (114): ^{1}H-NMR (DMSO-d_6) δ(ppm): 12.91 (s, 1H), 8.48 (d, *J* = 1.4 Hz, 1 H), 7.71 (m, 4 H), 7.35 (m, 1 H), 7.21 (d, *J* = 1.4 Hz, 2 H); ^{13}C-NMR (DMSO-d_6) δ(ppm): 150.9, 147.4, 148.6, 144.0, 135.0, 124.7, 123.3, 122.0, 121.5, 119.4 and 112.6.

bis(pyrrole-2-carboxaldehyde) *N,N′*-1,2 phenylenediimine (115): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.73 (s, 2H), 7.26 (dd, *J* = 5.6 and 3.5 Hz, 2H), 7.09 (dd, *J* = 5.6 and 3.5 Hz, 2H), 6.42 (d, *J* = 3.3 Hz, 2H), 6.28 (s, 2H) and 6.04 (t, *J* = 2.8 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 150.5, 145.6, 130.8, 126.5, 123.7, 118.9, 117.2 and 109.6.

bis(salicylaldehyde) *N,N′*-1,2 phenylenediimine (77): ^{1}H-NMR ($CDCl_3$) δ(ppm): 13.0 (s, 2H), 8.60 (s, 2H), 7.31 (m, 2H), 7.20 (m, 4H), 7.02 (d, *J* = 13.24 Hz, 2H) and 6.85 (t, *J* = 7.32 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 163.6, 161.3, 142.4, 133.3, 132.3, 127.7, 119.6, 119.1, 118.9 and 117.5.

2-(furan-2-yl)-1-(furan-2-ylmethyl)-1H-benzo[*d*]imidazole (116): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.69 (m, 1H), 7.56 (s, 1H), 7.42 (m, 1H), 7.24-7.14 (m, 4H), 6.52 (s,

1H), 6.20 (d, *J* = 13Hz, 2H) and 5.56 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 149.5, 145.2, 144.0, 142.6, 135.3, 123.3, 123.0, 119.6, 113.0, 112.0, 110.5, 110.0, 108.4 and 41.6.

2-(furan-2-yl)-1H-benzo[*d*]imidazole (117): ^{1}H-NMR (DMSO-d_6) δ(ppm): 12.93 (s, -NH), 7.91 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.18 (d, *J* = 3.0 Hz, 3H) and 6.70 (m, 1H); ^{13}C-NMR (DMSO-d_6) δ(ppm): 146.0, 145.0, 144.1, 134.7, 134.6, 123.1, 122.2, 119.2, 112.7, 111.7 and 110.9.

3-(1-(3-hydroxybenzyl)-1H-benzo[*d*]imidazol-2-yl)phenol (118): ^{1}H-NMR (DMSO-d_6) δ(ppm): 9.81 (s, -OH), 9.44 (s, -OH), 7.70 (d, *J* = 7.1 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.22 (qui, *J* = 7.2 and 5.7 Hz, 2H), 7.15 (s, 1H), 7.08 (m, 2H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 6.47 (d, *J* = 7.5 Hz, 1H), 6.37 (s, 1H) and 5.46 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ(ppm): 158.1, 157.9, 153.7, 143.0, 138.8, 136.3, 131.6, 130.3, 123.0, 122.6, 119.9, 119.6, 117.3, 117.0, 116.4, 114.8, 113.1, 111.5 and 47.9.

4-(1-(4-hydroxybenzyl)-1H-benzo[*d*]imidazol-2-yl)phenol (119): ^{1}H-NMR (DMSO-d_6) δ(ppm): 9.96 (s, -OH), 9.39 (s, -OH), 7.63 (dd, *J* = 6.9 and 1.4 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.39 (dd. *J* = 6.8 and 1.5 Hz. 1H), 7.18 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 2H) and 5.39 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ(ppm): 159.3, 157.1, 154.2, 143.1, 136.2, 131.0, 127.9, 127.5, 122.5, 122.3, 121.2, 119.2, 116.0, 115.9, 111.3 and 47.5.

3.4.4 Study on the Optimized Conditions for Intramolecular Coupling of Diamines and Aldehydes

Effect of Diamines

The coupling of diamines and aldehydes was carried out as described above employing three selected diamines namely 1,2-ethylenediamine, 1,3-propylene-diamine and 1,2-phylenediamine.

Effect of Types of Aldehydes

The coupling of diamines and aldehydes was carried as dercribed earlier except for that 2-furaldehyde, pyrrole-2-carboxaldehyde, 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde and pyridine-2-carboxaldehyde were used.

Effect of Solvents

Several solvents including DMF, CH_3CN, THF, CH_2Cl_2, acetic acid and DMSO were employed for the coupling of thiophen-2-carboxaldehyde and 1,2-phenylenediamine in the coupling of diamines and aldehydes.

3.4.5 General isolation procedure

After the reaction was completed (followed by TLC), benzimidazole products were purified by crystallization.

3.5 Results & Discussion

3.5.1 Synthesis and Characterization of Schiff base and Benzimidazoles

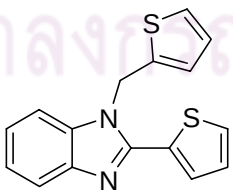
Schiff bases and benzimidazoles were synthesized and confirmed their identities by comparison both physical properties and spectroscopic data with those reported in literature [98].

3.5.2 Optimized Conditions for Intermolecular Coupling of Diamines and Aldehydes

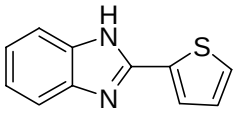
Various parameters are needed to be explored to find the optimized conditions for the synthesis of benzimidazoles such as type of diamine, type of aldehyde and solvent. Thiophen-2-carboxaldehyde was chosen as a chemical model.

Effect of Diamines

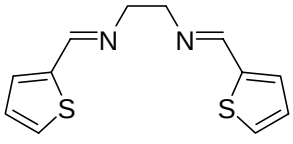
A variety of diamines have been investigated in the coupling of diamines and aldehydes. The results of the utilization of various diamines are presented in Table 3.1.



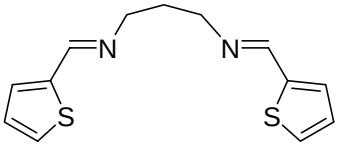
72



111

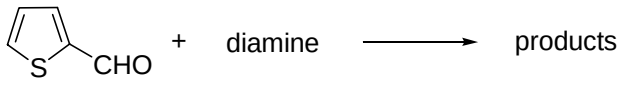


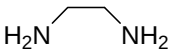
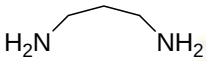
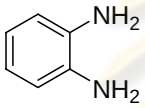
76



112

Table 3.1 Effect of types of amines, ratio of aldehyde to amine, solvent on the coupling of diamines and aldehydes



Entry	Diamine	Ratio of aldehyde:diamine	Solvent	Product	%Yield
1		2:1	EtOH	**76**	78
2		2:1	toluene	**76**	52
3		2:1	EtOH	**112**	83
4		2:1	toluene	**112**	68
5		2:1	EtOH	**72, 111**	86, 3
6		2:1	toluene	**72, 111**	5, 80
7		1:1	EtOH	**72, 111**	trace, 78
8		1:1	toluene	**72, 111**	trace, 74

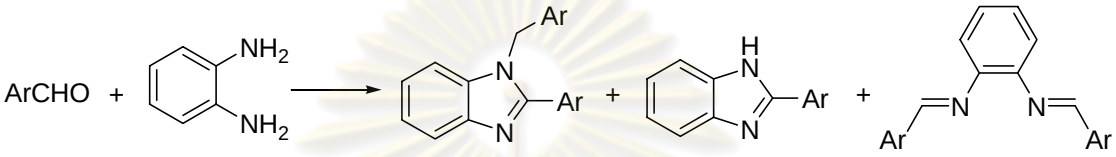
Two different products were observed upon the reaction of thiophen-2-carboxaldehyde and diverse amines. To illustrate this, the reaction of thiophen-2-carboxaldehyde with either ethylenediamine or 1,3-propylenediamine yielded the corresponding Schiff bases. These products were normally attained from the coupling reaction between aromatic aldehyde and diamines (entries 1-4) [98]. The reaction of thiophen-2-carboxaldehyde with 1,2-phenylenediamine however yielded an unexpected product (entries 5-8). This was observed from the ^{1}H-NMR spectrum of the final product, the proton signal of benzimidazole was detected at δ_H 5.70 while that of Schiff base was shown at δ_H 8.3. Based on mechanistic point of view, it could be explained that the most stable cyclic products were preferably formed because of high aromaticity of the final product. In addition, solvents were also directly affected on the structure of product. With a ratio of aldehyde:diamine of 2:1 in EtOH, *N*-substituted cyclic product **72** was detected (entry 5), whereas with the ratio of 2:1 performing in toluene and the ratio of 1:1 in EtOH and toluene (entries 6-8) provided free *N*-substituted cyclic product **111**. Theoretically, the rate of imine formation in polar protic medium as alcohol was faster compared to non-polar solvent as toluene.[98] With 2:1 ratio of aldehyde:diamine in a polar protic solvent, two groups

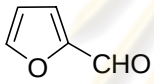
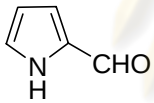
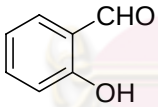
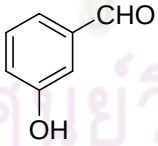
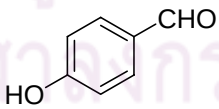
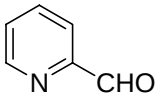
of imine were therefore completely formed with faster rate and provided *N*-substituted cyclic product **72**.

The Effect of Types of Aldehydes

From the experimental conditions described above, several aldehydes were chosen to study the coupling reaction of 1,2-phenylenediamine with various aldehydes. The results are presented in Table 3.2.

Table 3.2 The coupling of 1,2-phenylenediamine with various aldehydes



Entry	ArCHO	Solvent	% Product			
1		EtOH	23	**(116)**	trace	-
2		toluene	5	**(116)**	48 **(117)**	-
3		EtOH	-		-	33 **(115)**
4		toluene	-		-	28 **(115)**
5		EtOH	-		-	80 **(77)**
6		toluene	-		-	75 **(77)**
7		EtOH	92	**(118)**	-	-
8		toluene	90	**(118)**	-	-
9		EtOH	90	**(119)**	-	-
10		toluene	88	**(119)**	-	-
11		EtOH	19	**(113)**	trace	-
12		toluene	trace		34 **(114)**	-

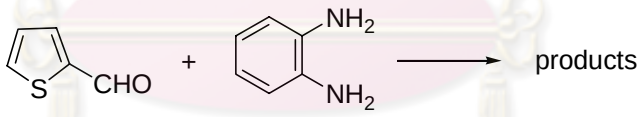
The structures of aldehydes markedly affected on the formation of different types of product occurred *via* intramolecular cyclization. For instance, a mixture of products was attained using furfural-2-carboxaldehyde condensed with phenylene-

diamine (entries 1-2). In addition, when pyrrole-2-carboxaldehyde and salicyaldehyde were used as starting material, a symmetrical Schiff base was formed. This could be explained that the hydroxyl group of salicyaldehyde and NH- group of pyrrole-2-carboxaldehyde could coordinate to the nitrogen atom of 1,2-phenylenediamine thus rendered the formation of a cyclic compound (entries 3-6). When 3- and 4-hydroxy benzaldehydes were used instead of salicyladehyde, benzimidazoles **118** and **119** were obtained in high yield. This was because the distance between the hydroxyl group and nitrogen atom is too far (entries 7-10). Schiff base products were occurred when condensed with ethylenediamine whereas, pyridine-2-carboxaldehyde could be converted to benzimidazoles **113** and **114** because hydrogen bonding could not be formed occurred (entries 11-12).

The Effect of Solvents

From the experimental conditions described above, several solvents were chosen to study the coupling of diamines and aldehydes. The results are presented in Table 3.3.

Table 3.3 The effect of solvent on the coupling of thiophen-2-carboxaldehyde and 1,2-phenylenediamine.



Entry	Solvent	% Product	
		72	**111**
1	DMF	6	45
2	CH_3CN	3	40
3	THF	3	42
4	CH_2Cl_2	5	50
5	CH_3COOH	3	48
6	DMSO	4	53

The effect of solvents on the product formation was also investigated as presented in Table 3.3. Thiophen-2-carboxaldehyde was used to condense with

phenylenediamine. Benzimidazole was obtained in moderate yield and all solvents provided only *N*-substituted cyclic product **111** is a major product. (entries 1-6).

3.5.3 Mechanistic study on the formation of Benzimidazoles

The mechanistic study upon the formation of benzimidazole was conducted by two different experiments: ^{1}H-NMR spectroscopy and by protecting an amino group by Boc-anhydride. The results are presented in Figure 3.1 and Scheme 3.1.

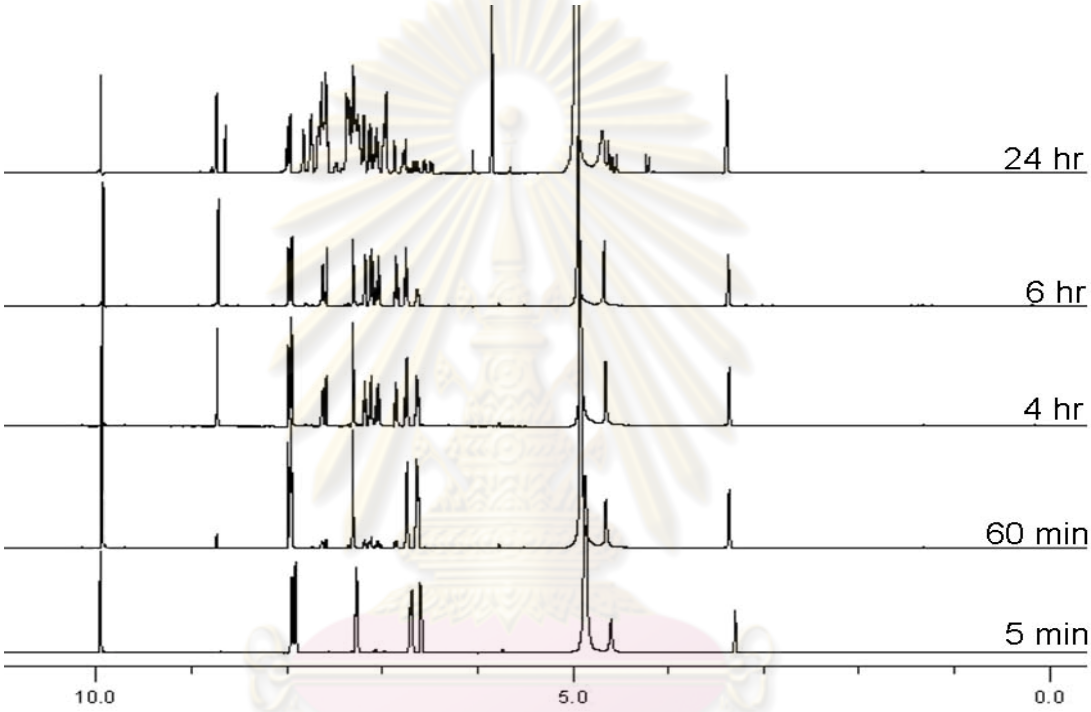
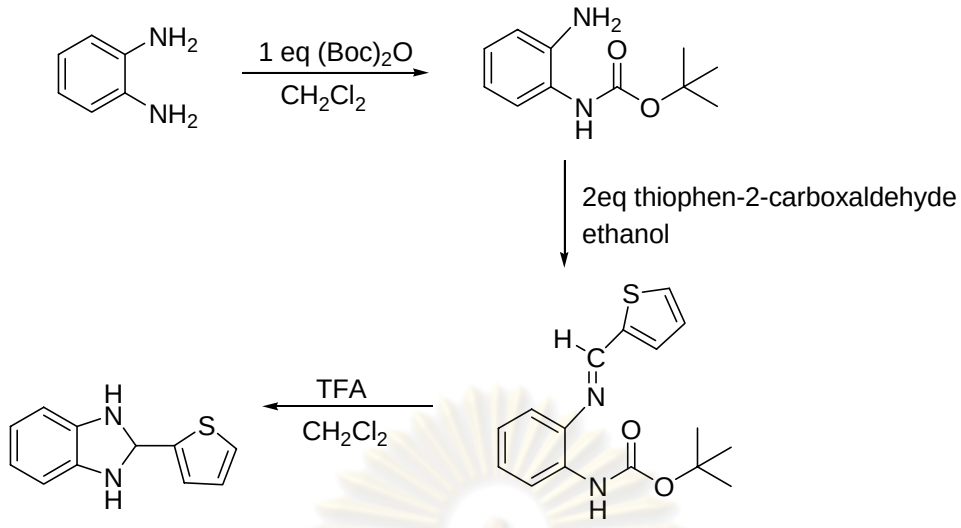


Figure 3.1 ^{1}H-NMR spectra followed the progress of the coupling reaction between thiophen-2-carboxaldehyde and 1,2-phenylenediamine



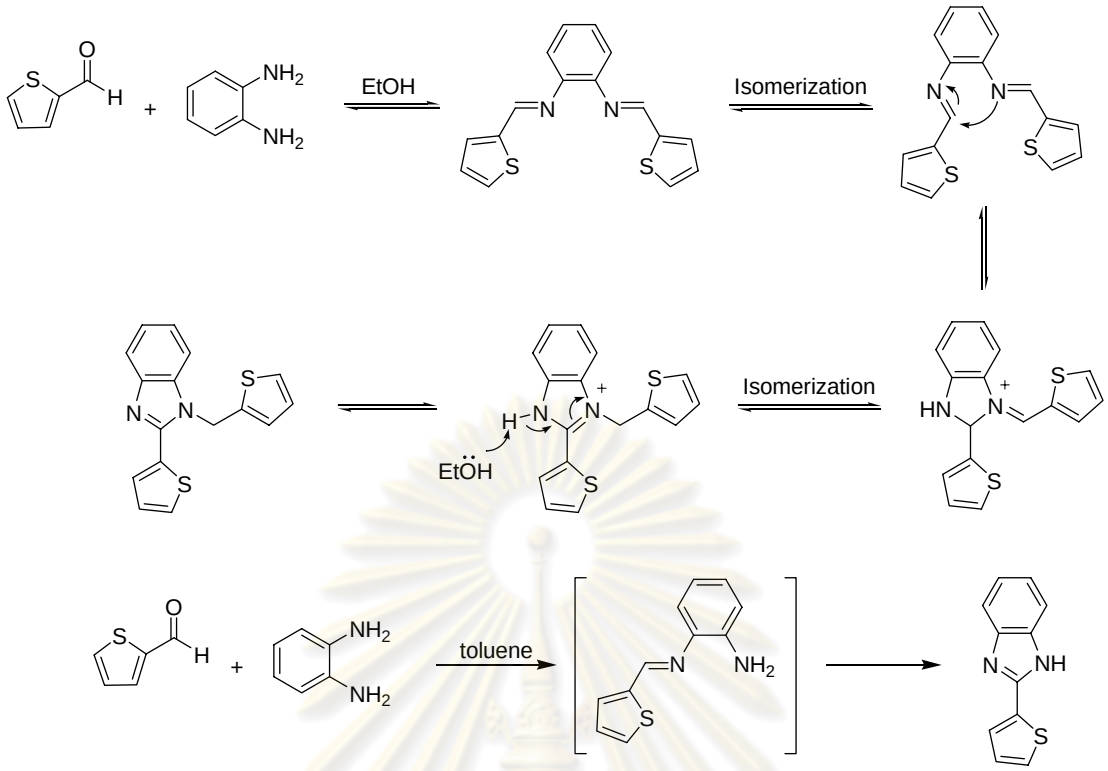
Scheme 3.1 The coupling reaction of thiophen-2-carboxaldehyde and 1,2-phenylenediamine protected by using Boc anhydride

From Figure 3.1 and Scheme 3.1, the mechanism was believed to take place *via* imine and then cyclized. To illustrate this, the reaction followed by ^{1}H-NMR revealed that at 30 min the proton signal of imine was detected at δ_H 8.3, while at 4 h this proton signal was significantly decreased. Another proton signal corresponding to the cyclization product could manifestly visualize at δ_H 5.70. This could be clearly draw a conclusion on the mechanism that imine was formed in the first step and then cyclization product was occurred.

The other approach using a protecting group, the amino group in phenylenediamine was protected by di-*tert*-butyldicarbonate (BOC anhydride) and then allowed to react with thiophen-2-carboxaldehyde. When the reaction was completed, the proton signal of imine was appeared. Later, once the crude product was deprotected by CF_3COOH, the cyclization was occurred.

3.5.4 Proposed Mechanism for Benzimidazoles Synthesis

During the examination of benzimidazole synthesis, the signals of methylene protons at δ_H 5.70 was detected. This clearly indicated that the mechanism should occur *via* an imine pathway. The results are displayed in Scheme 3.2.



Scheme 3.2 Proposed mechanism for benzimidazole synthesis

Furthermore, the mechanism of cyclic formation was also proposed. When EtOH was used as solvent, thiophen-2-carboxaldehyde was condensed with 1,2-phenylenediamine to form diimine. An (*E*)-imine was possibly arranged to form the structure as shown in Scheme 3.2 and then the nitrogen atom of another imine attacked to the carbon atom of (*Z*)-imine to provide five-membered ring of iminium salt. Next, an iminium salt was isomerized followed by proton abstraction to obtain aromatic cyclic compound. When toluene was used as solvent, monoimine was found as an intermediate and then the cyclization product was obtained.

3.6 Conclusion

The objective of this present work is to search for a suitable condition to manipulate Schiff base or benzimidazole. When aliphatic diamine was used, Schiff base was attained in high yield, while using 1,2-phenylenediamine the intramolecular cyclization to benzimidazole was preferentially taken place. In addition, in the case of benzimidazole, two products were formed. Mono-*N*-substituent product was observed when toluene was used as solvent, while di-*N*-substituent product was obtained when EtOH was used as solvent.

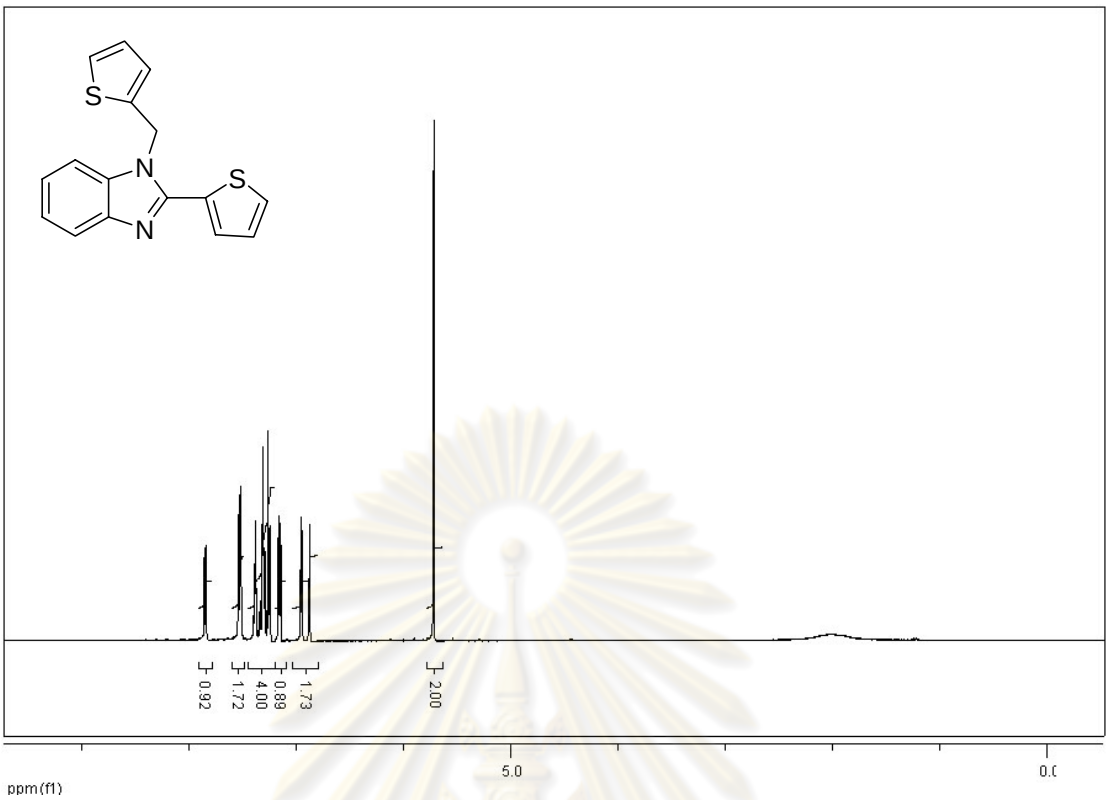


Figure 3.2 The ^{1}H-NMR of 2-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1H benzo-[*d*]imidazole **(72)**

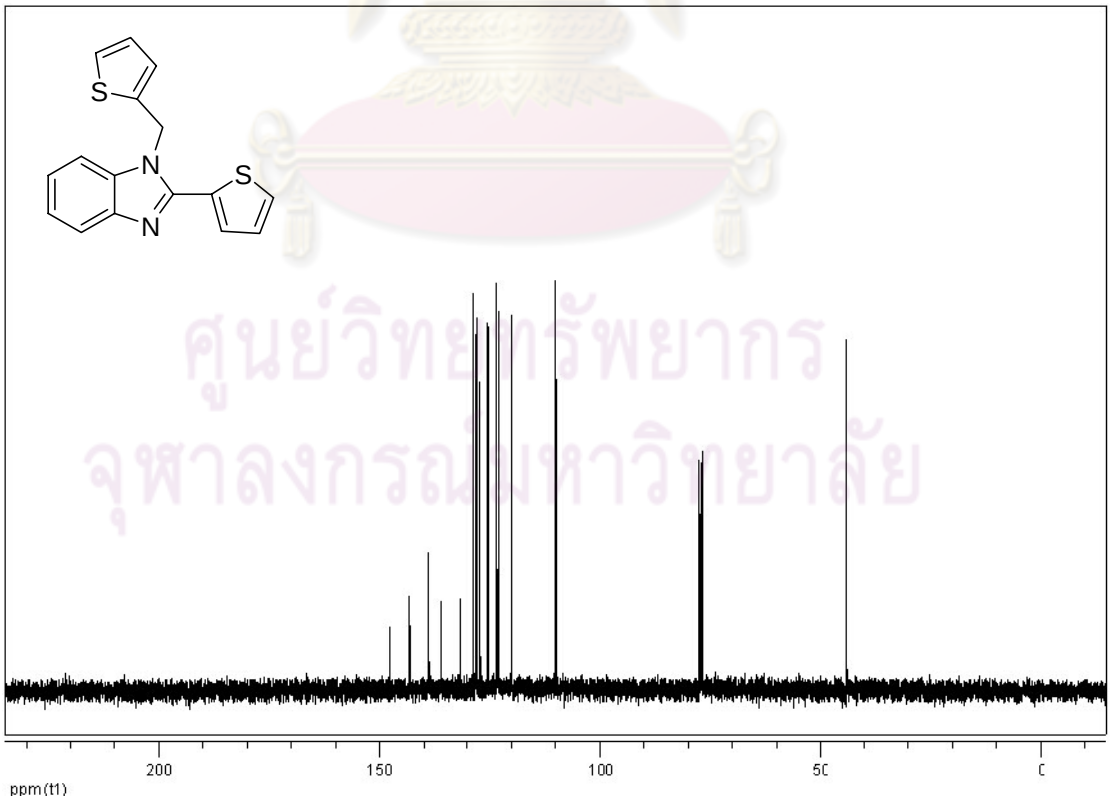


Figure 3.3 The ^{13}C-NMR of 2-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1H-benzo-[*d*]imidazole **(72)**

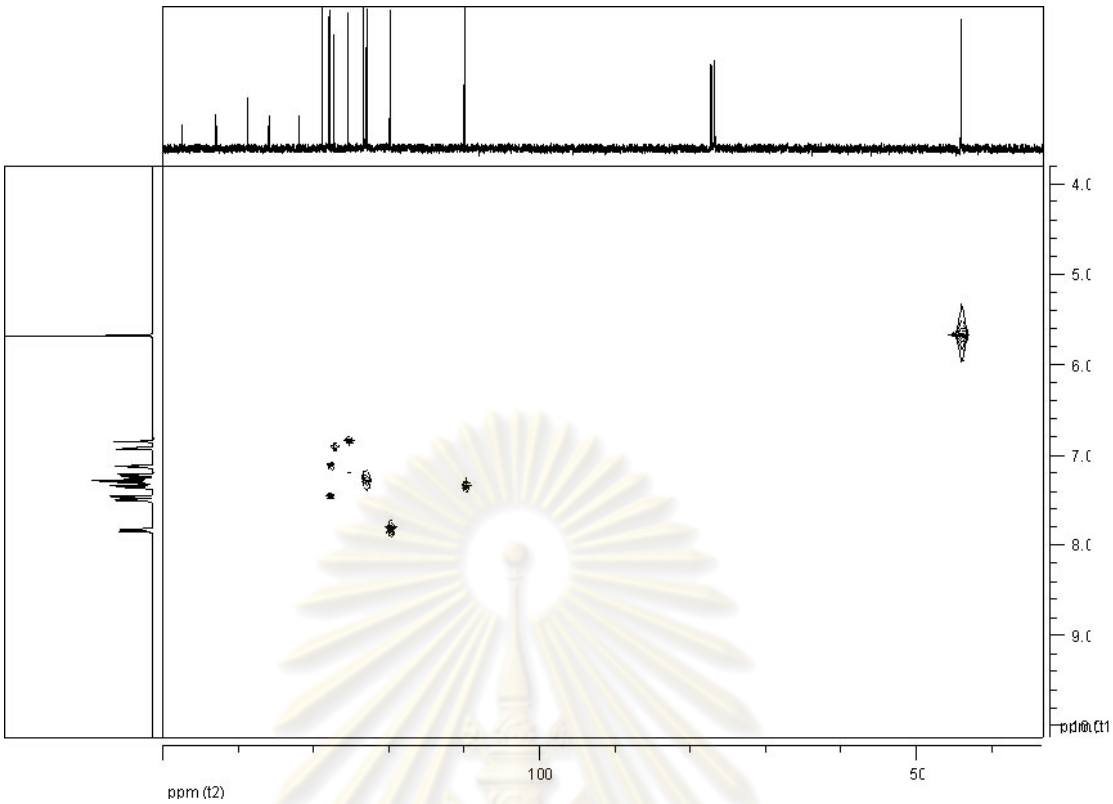


Figure 3.4 The HMQC of 2-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1H-benzo-[*d*]imidazole **(72)**

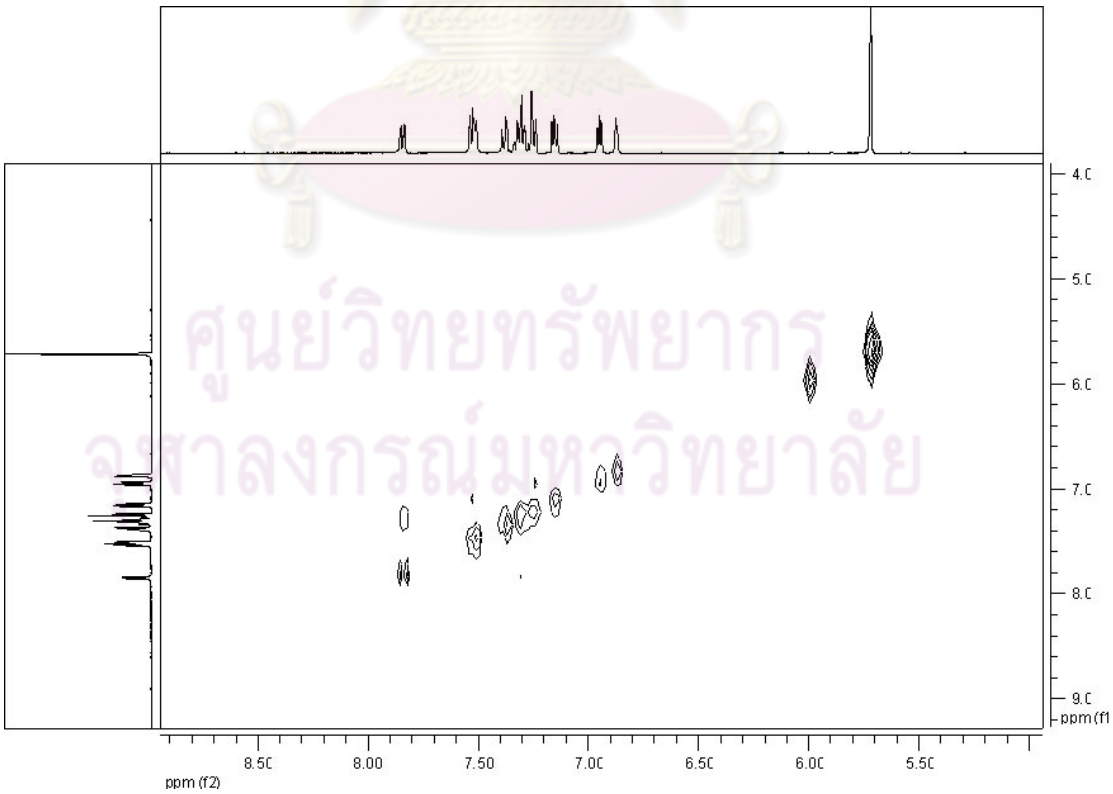


Figure 3.5 The COSY of 2-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1H-benzo-[*d*]imidazole **(72)**

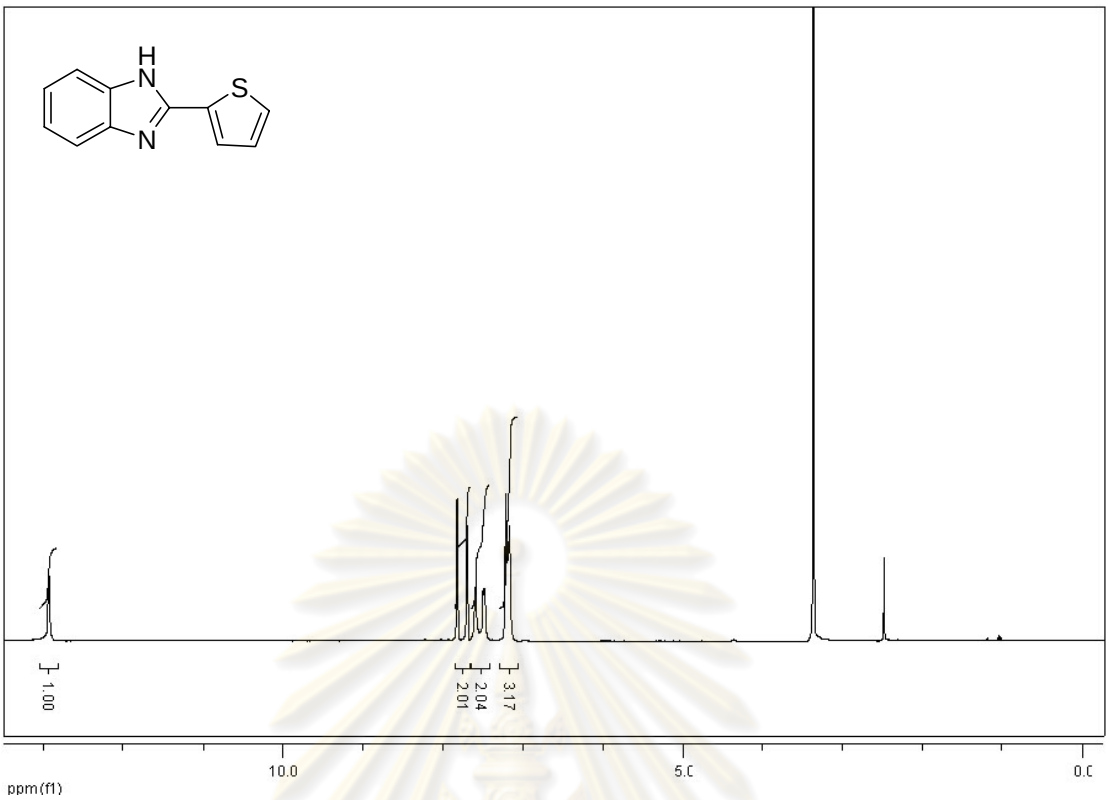


Figure 3.6 The ^{1}H-NMR of 2-(thiophen-2-yl)-1H-benzo[*d*]imidazole **(111)**

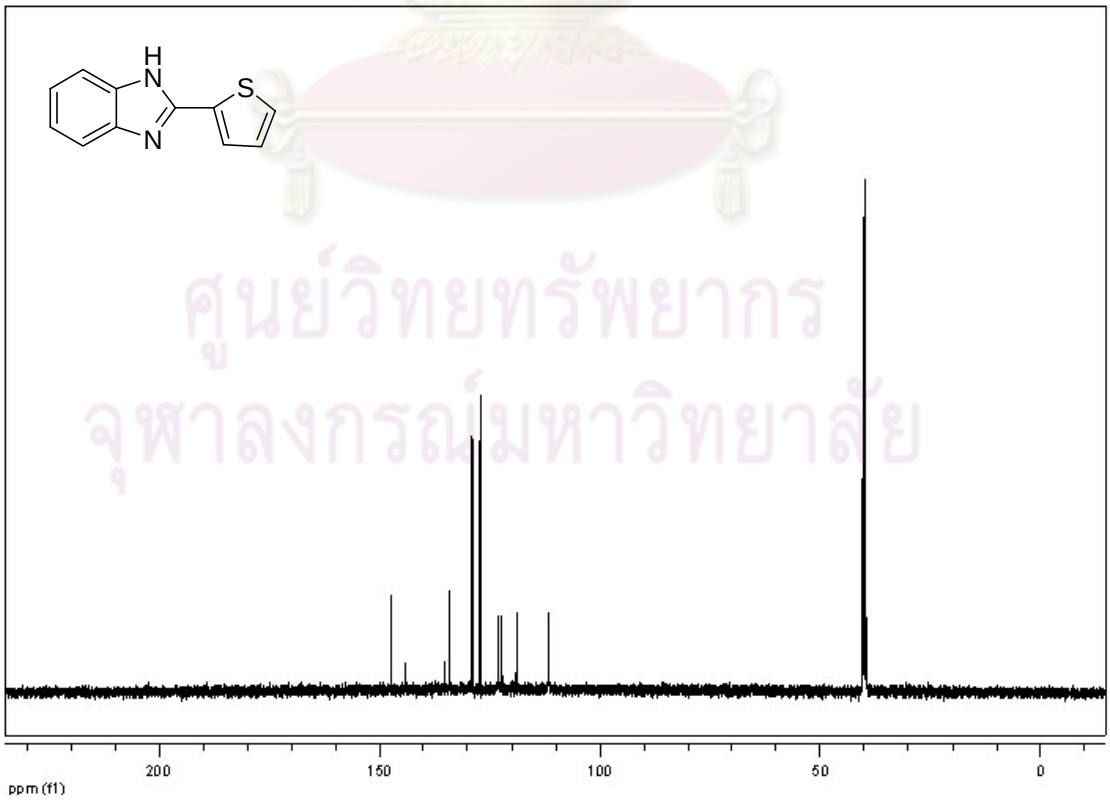


Figure 3.7 The ^{13}C-NMR of 2-(thiophen-2-yl)-1H-benzo[*d*]imidazole **(111)**

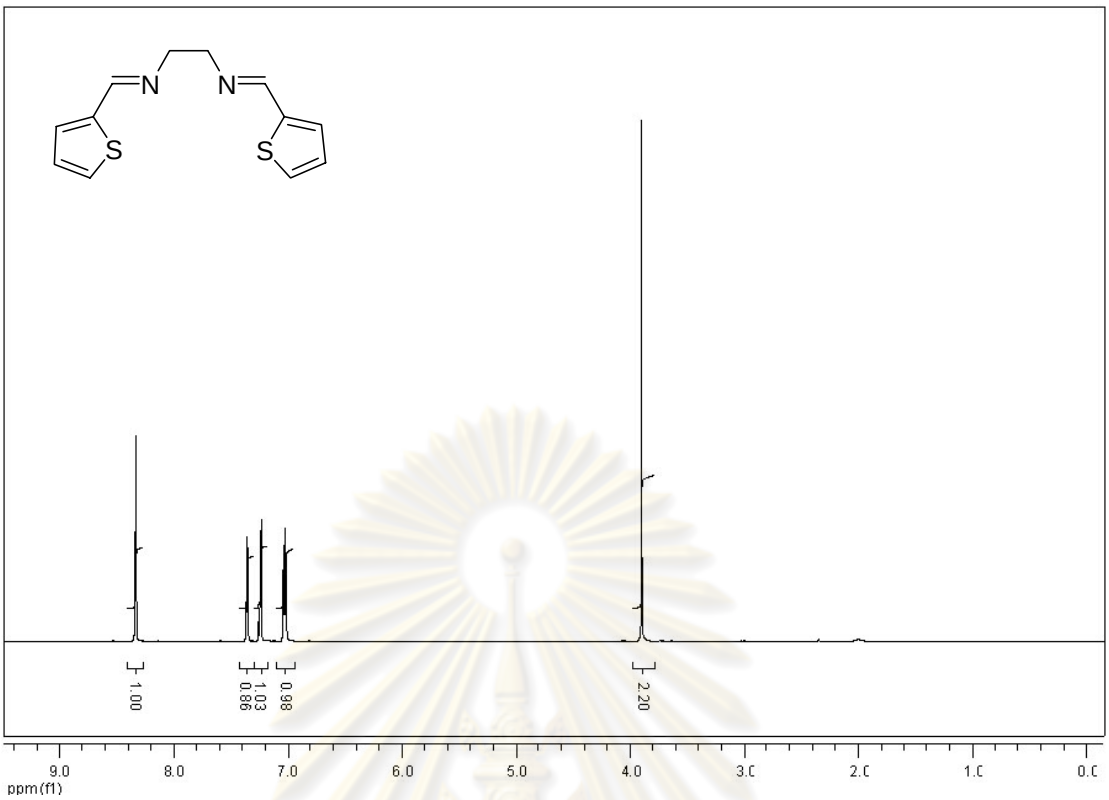


Figure 3.8 The ^{1}H-NMR of bis(2-thenylideneimine) *N,N'*-1,2-ethylene **(76)**

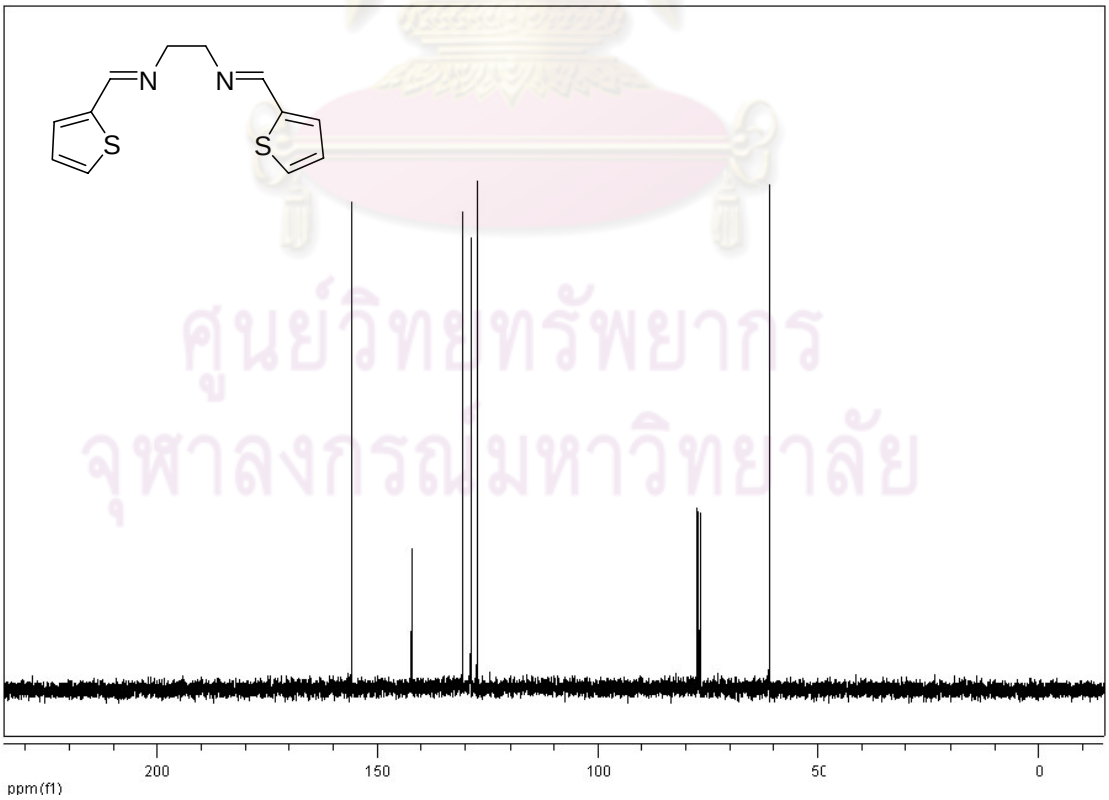


Figure 3.9 The ^{13}C-NMR of bis(2-thenylideneimine) *N,N'*-1,2-ethylene **(76)**

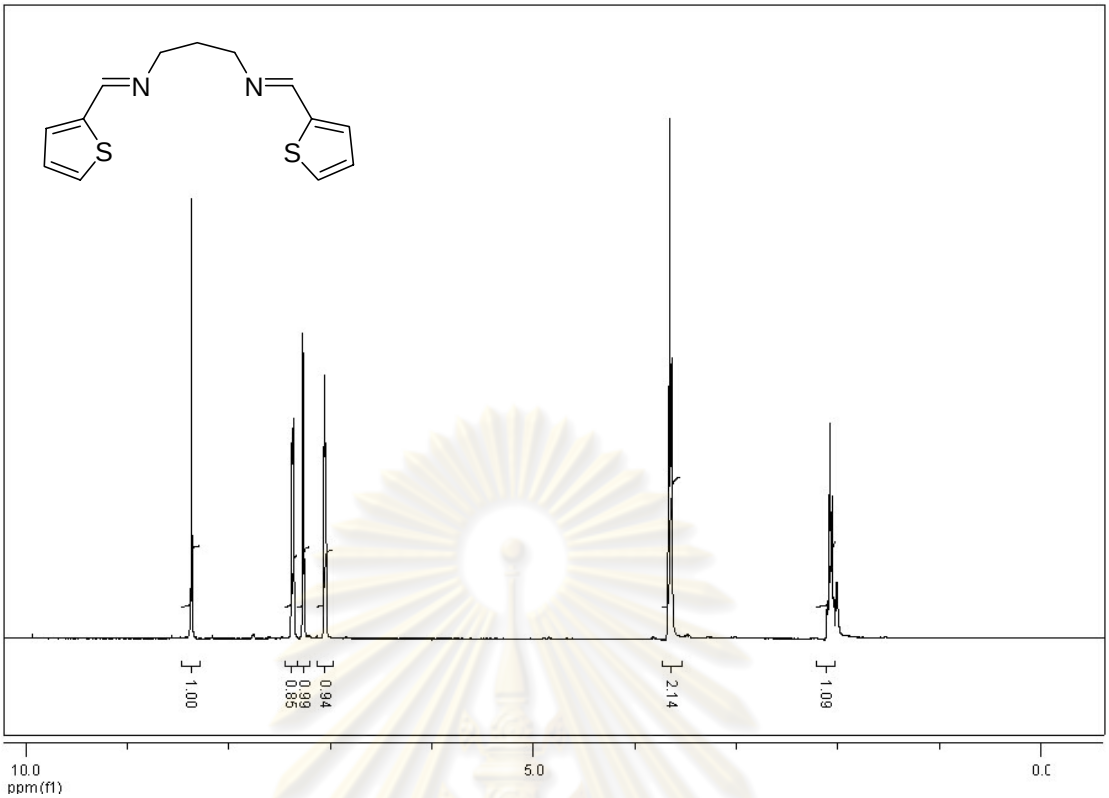


Figure 3.10 The ^{1}H-NMR of bis(2-thenylideneimine) *N,N′*-1,3-propylene **(112)**

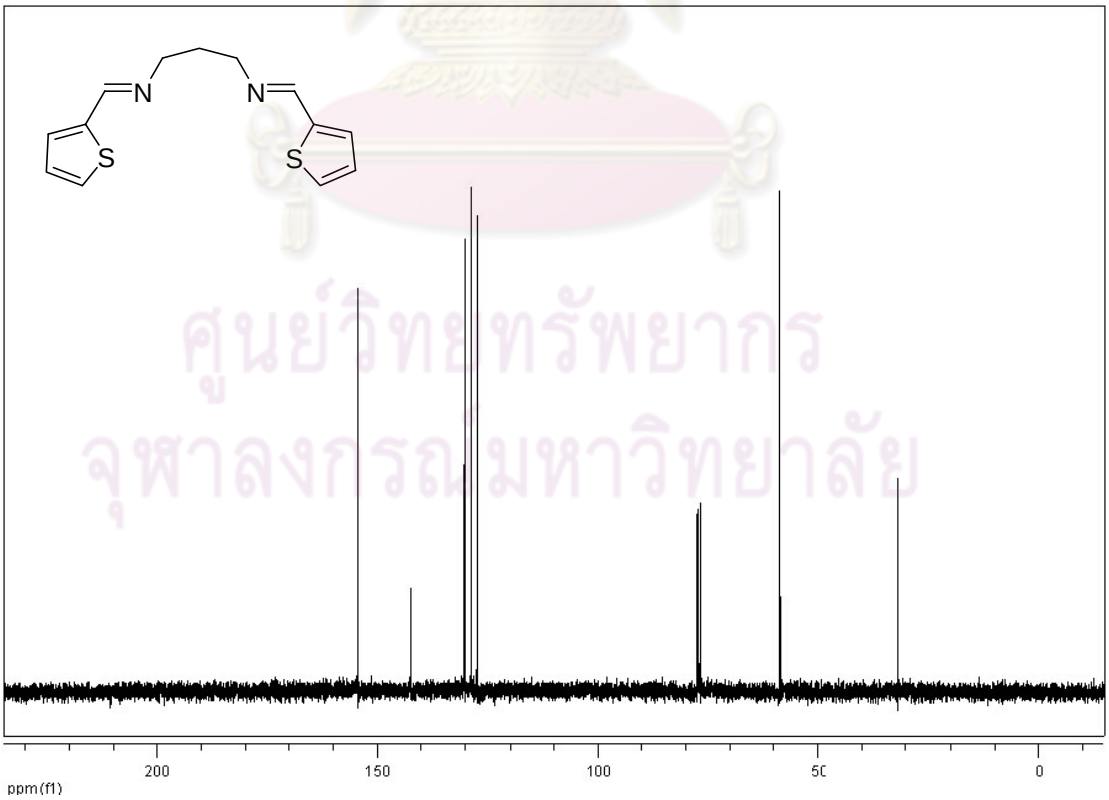


Figure 3.11 The ^{13}C-NMR of bis(2-thenylideneimine) *N,N′*-1,3-propylene **(112)**

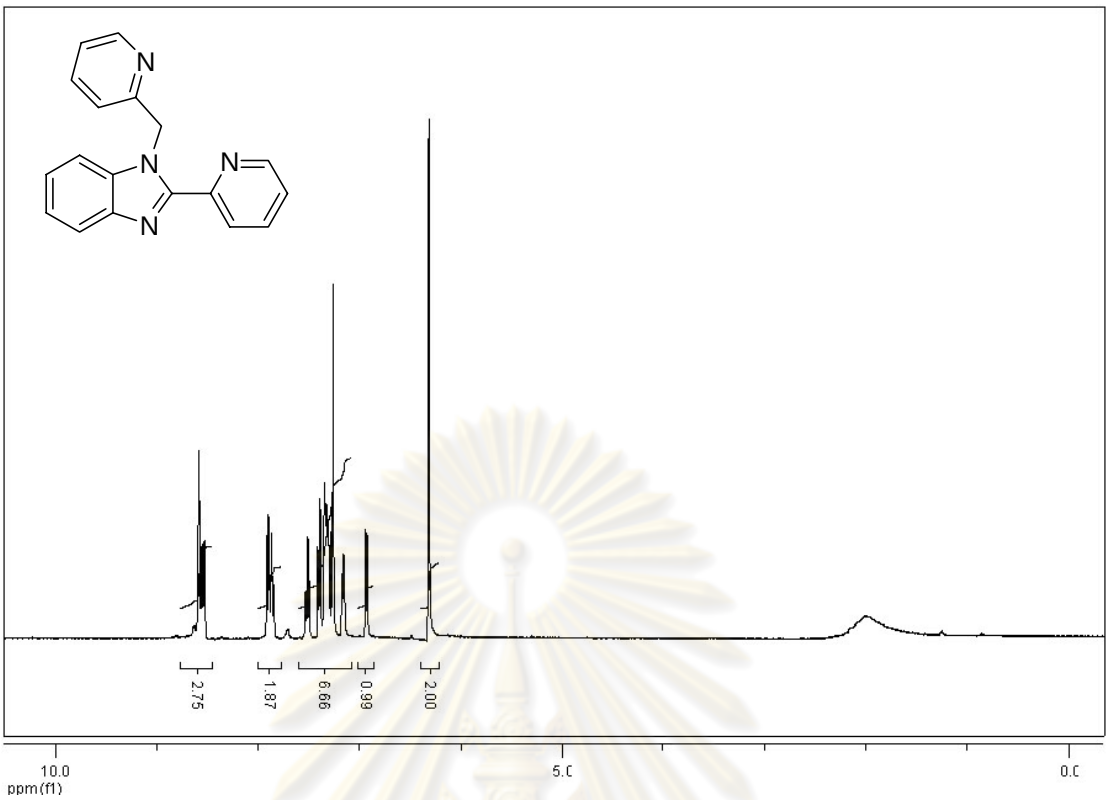


Figure 3.12 The ^{1}H-NMR of 2-(pyridin-2-yl)-1-(pyridin-2-ylmethyl)-1H-benzo-[*d*]imidazole **(113)**

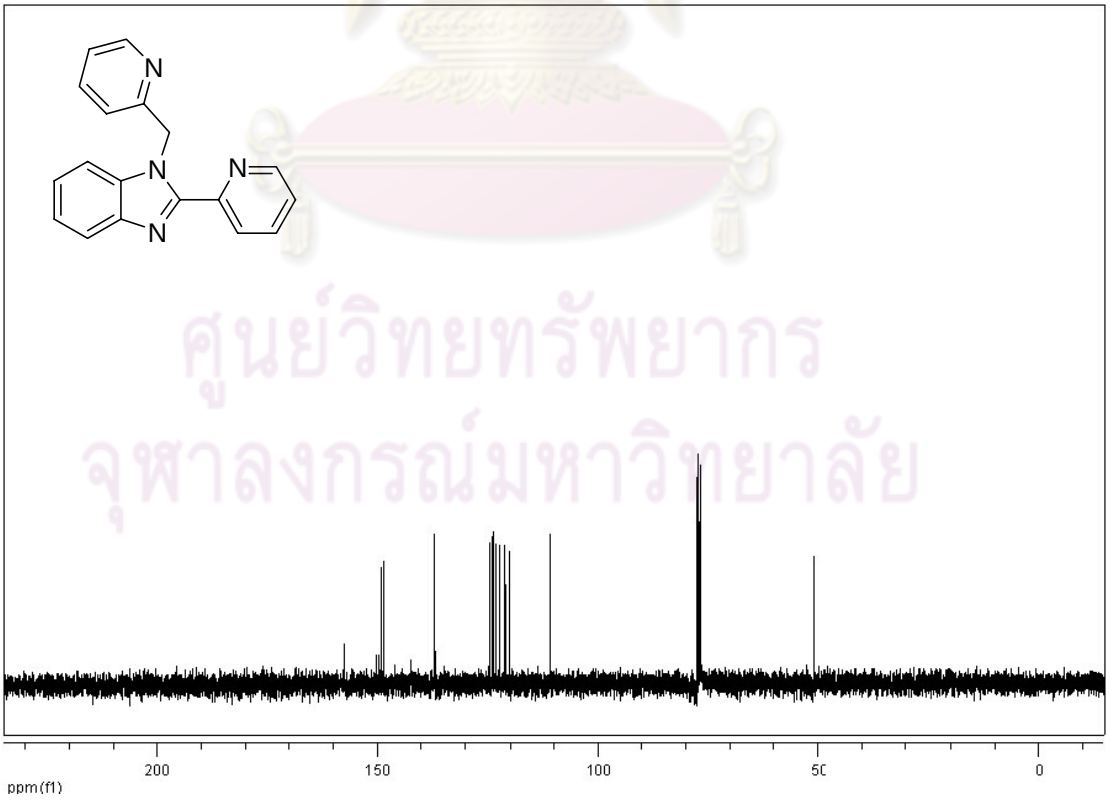


Figure 3.13 The ^{13}C-NMR of 2-(pyridin-2-yl)-1-(pyridin-2-ylmethyl)-1H-benzo-[*d*]imidazole **(113)**

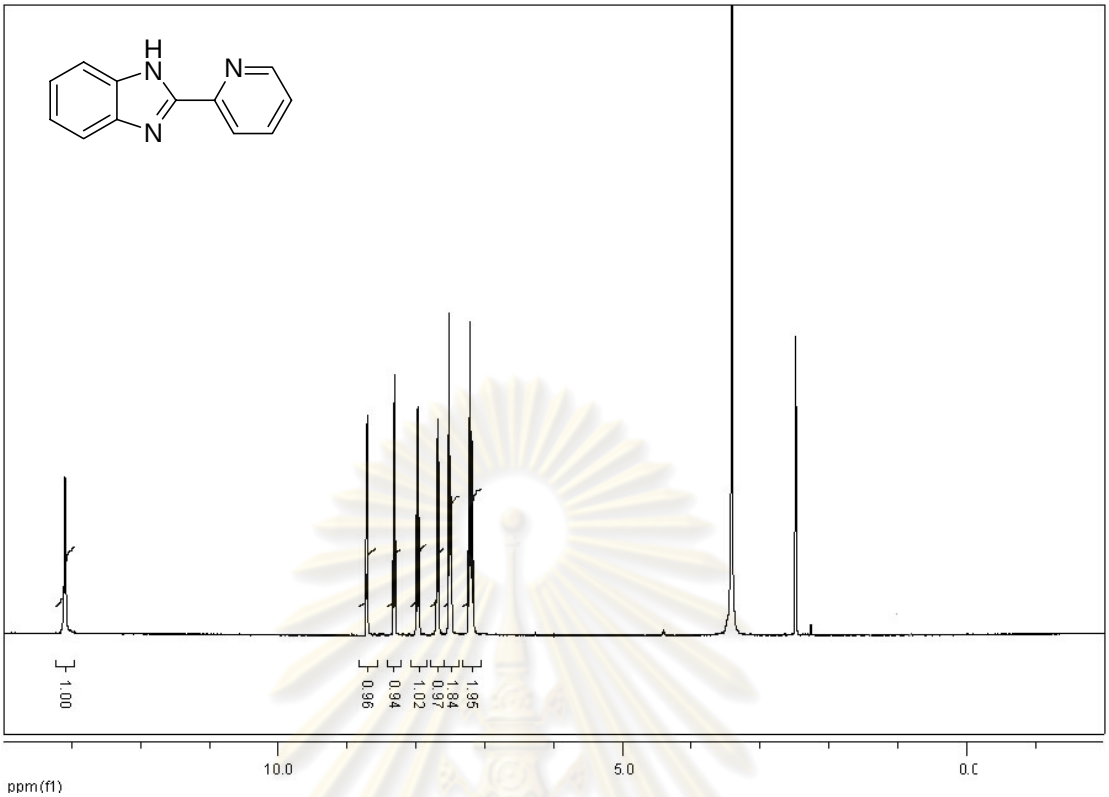


Figure 3.14 The ^{1}H-NMR of 2-(pyridin-2-yl)-1H-benzo[*d*]imidazole **(114)**

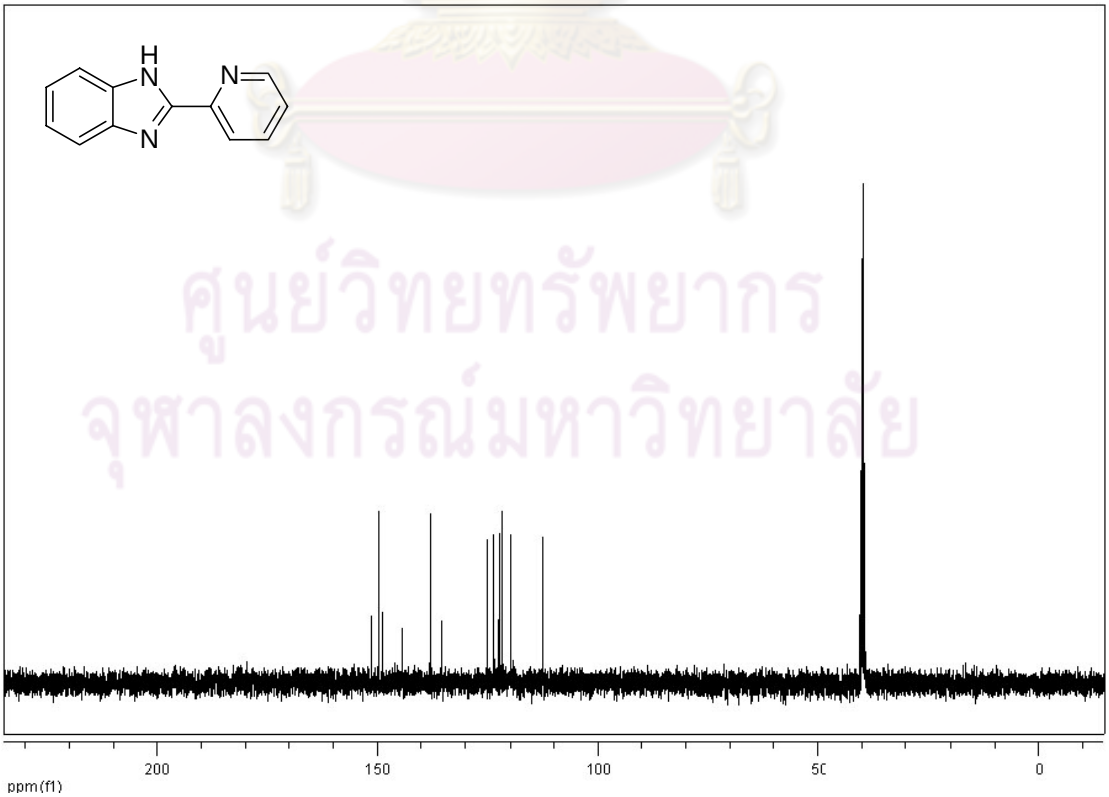


Figure 3.15 The ^{13}C-NMR of 2-(pyridin-2-yl)-1H-benzo[*d*]imidazole **(114)**

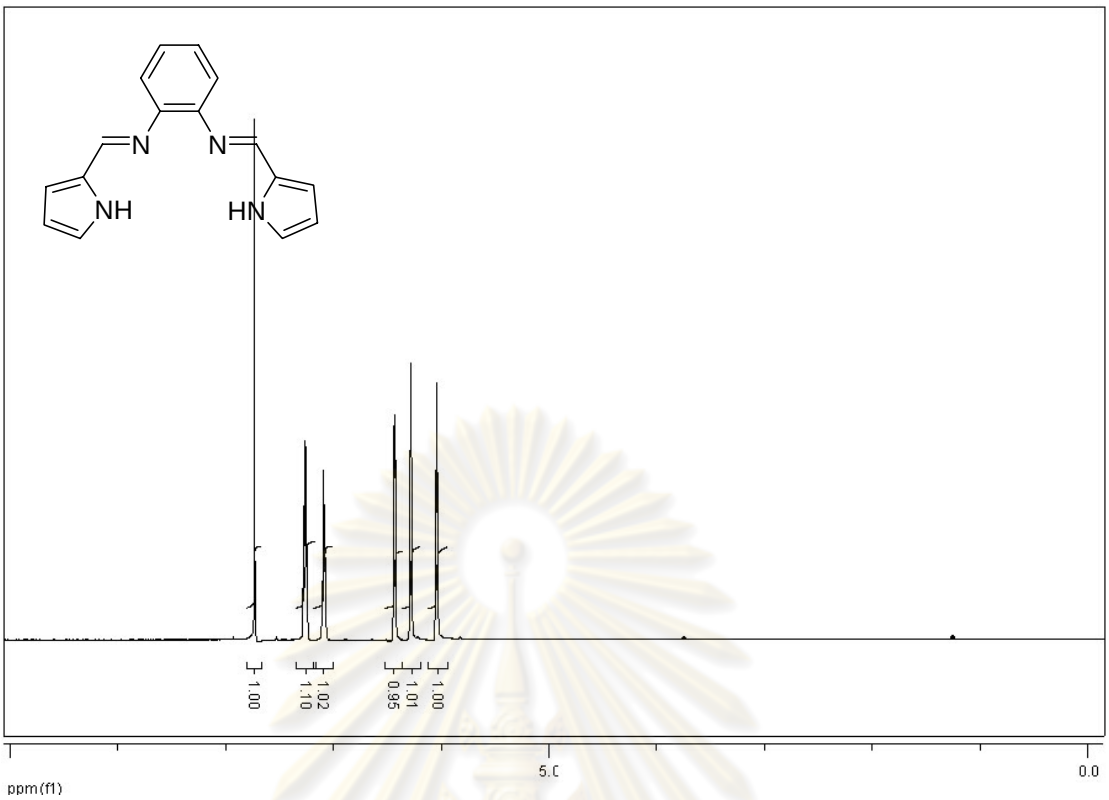


Figure 3.16 The ^{1}H-NMR of bis(pyrrole-2-carboxaldehyde) *N*,*N*′-1,2 phenylene-diimine **(115)**

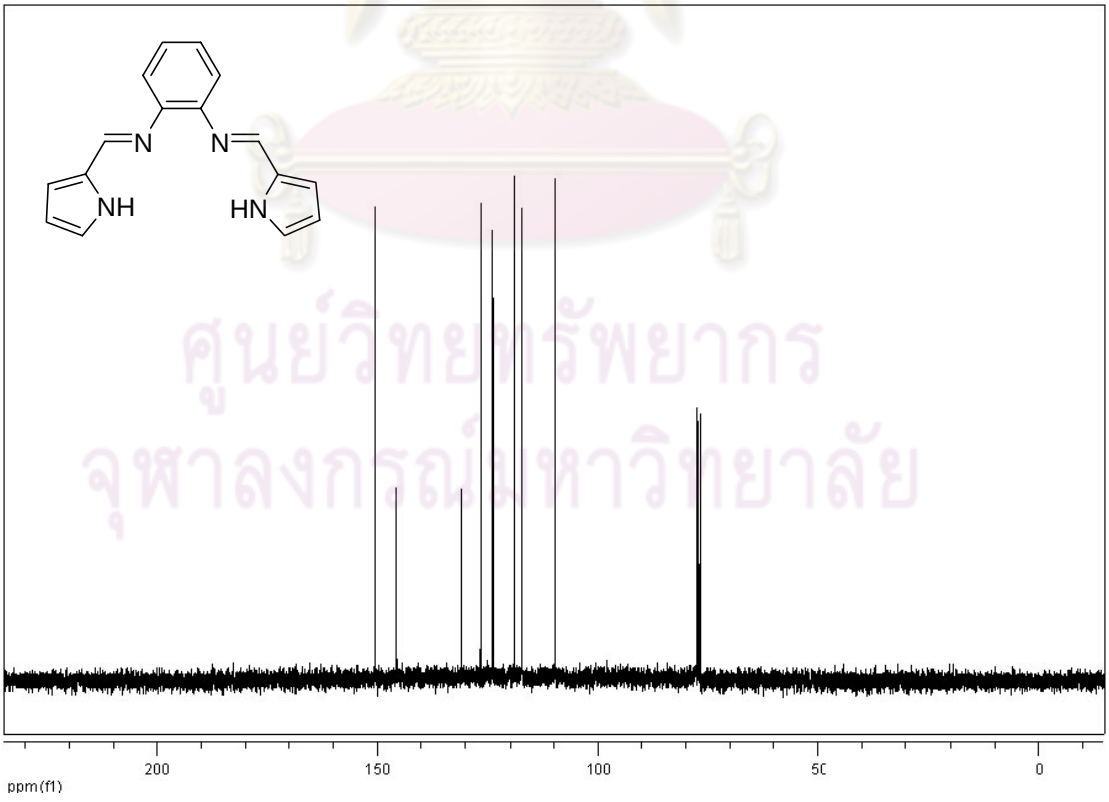


Figure 3.17 The ^{13}C-NMR of bis(pyrrole-2-carboxaldehyde) *N*,*N*′-1,2 phenylene-diimine **(115)**

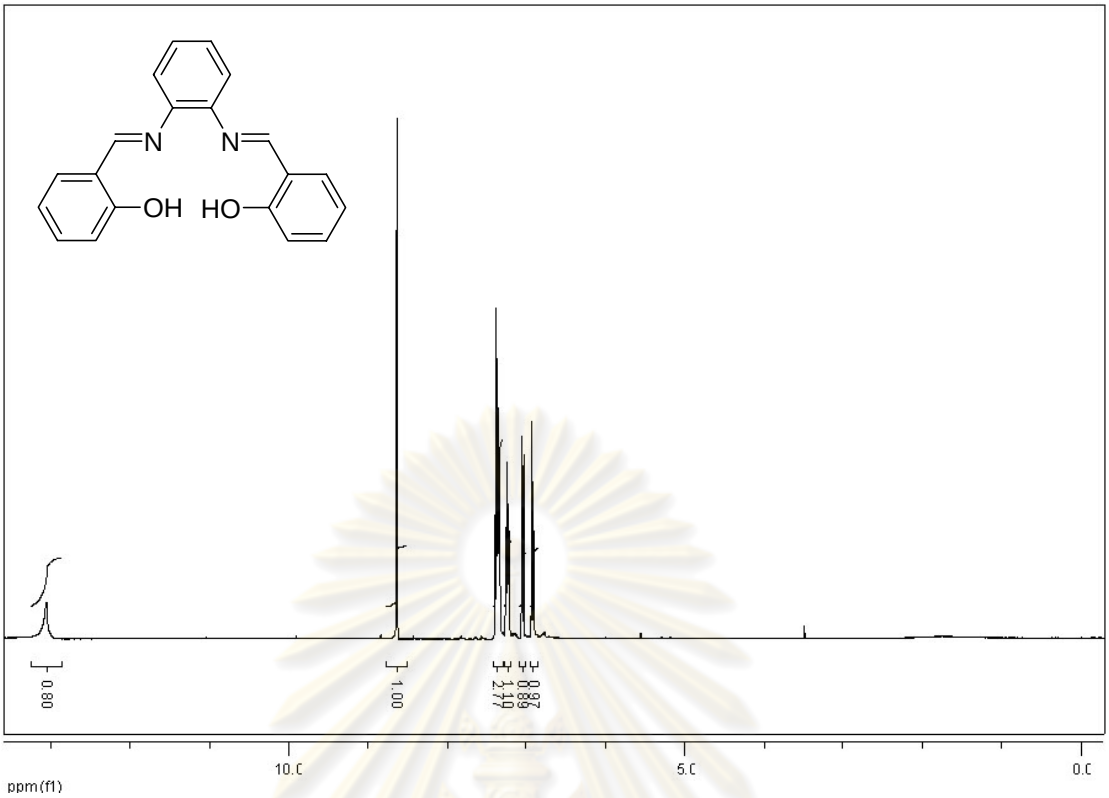


Figure 3.18 The ^{1}H-NMR of bis(salicylaldehyde) *N*,*N*′-1,2 phenylenediimine **(77)**

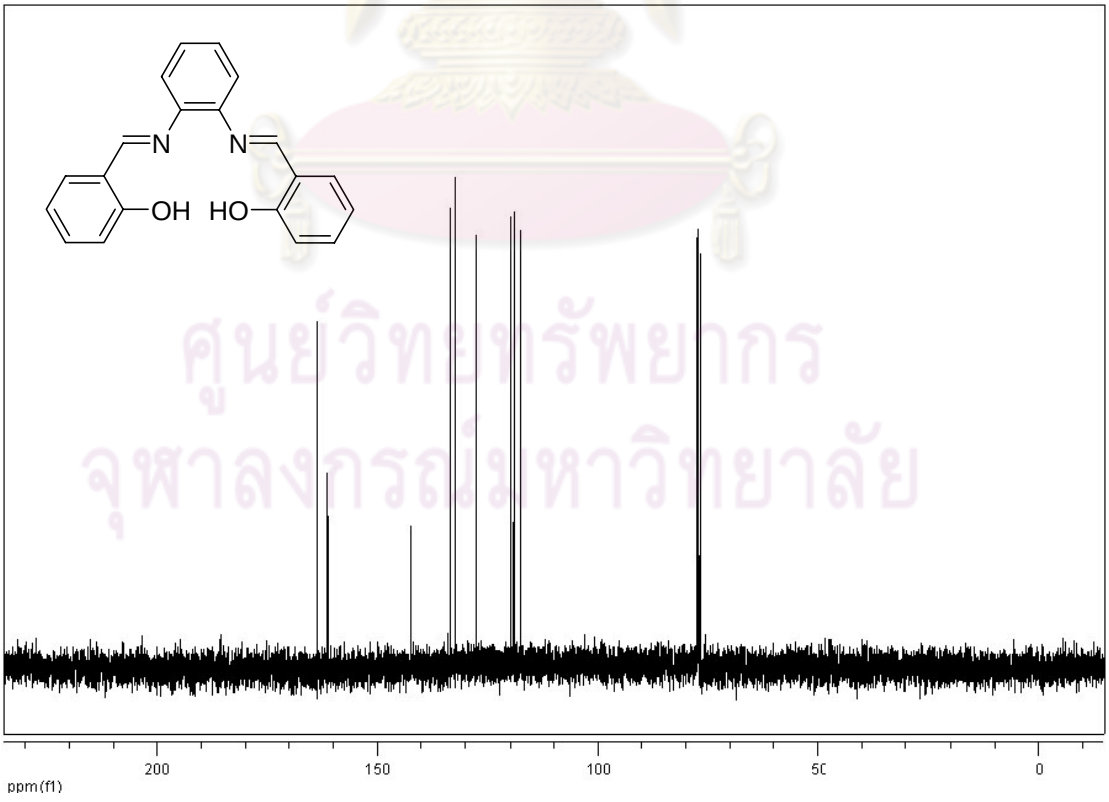


Figure 3.19 The ^{13}C-NMR of bis(salicylaldehyde) *N*,*N*′-1,2 phenylenediimine **(77)**

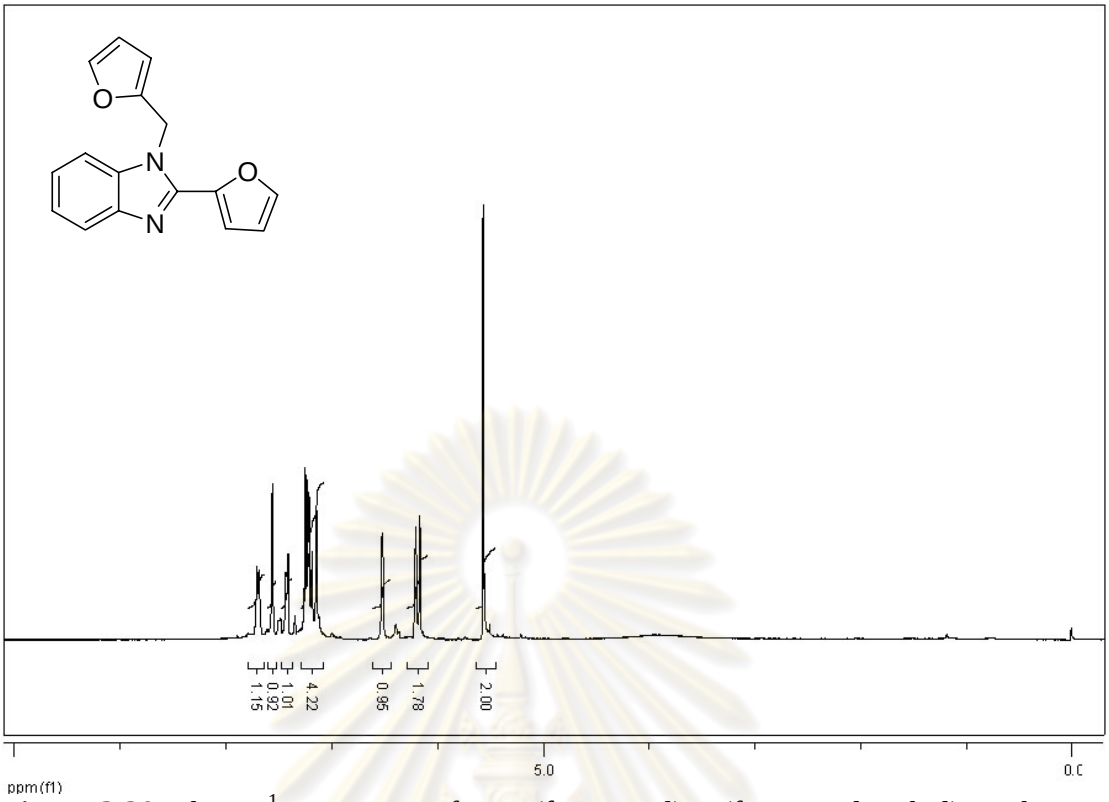


Figure 3.20 The ^{1}H-NMR of 2-(furan-2-yl)-1-(furan-2-ylmethyl)-1H-benzo-[*d*]imidazole **(116)**

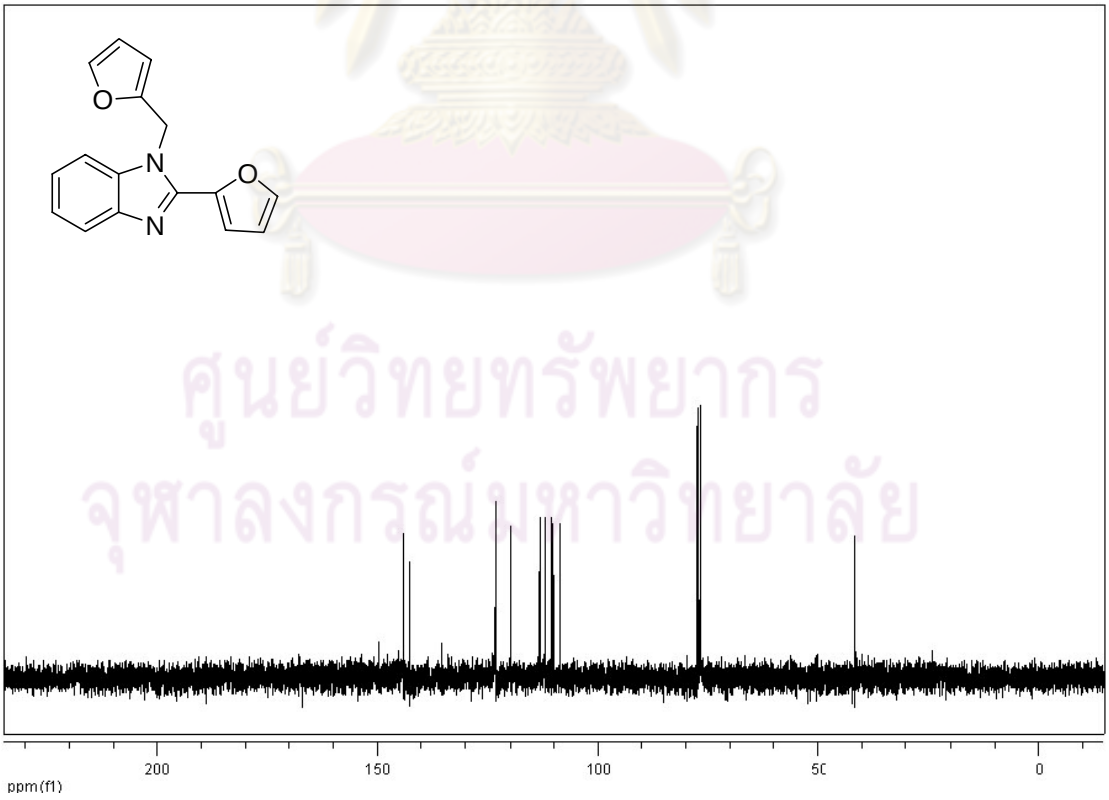


Figure 3.21 The ^{13}C-NMR of 2-(furan-2-yl)-1-(furan-2-ylmethyl)-1H-benzo-[*d*]imidazole **(116)**

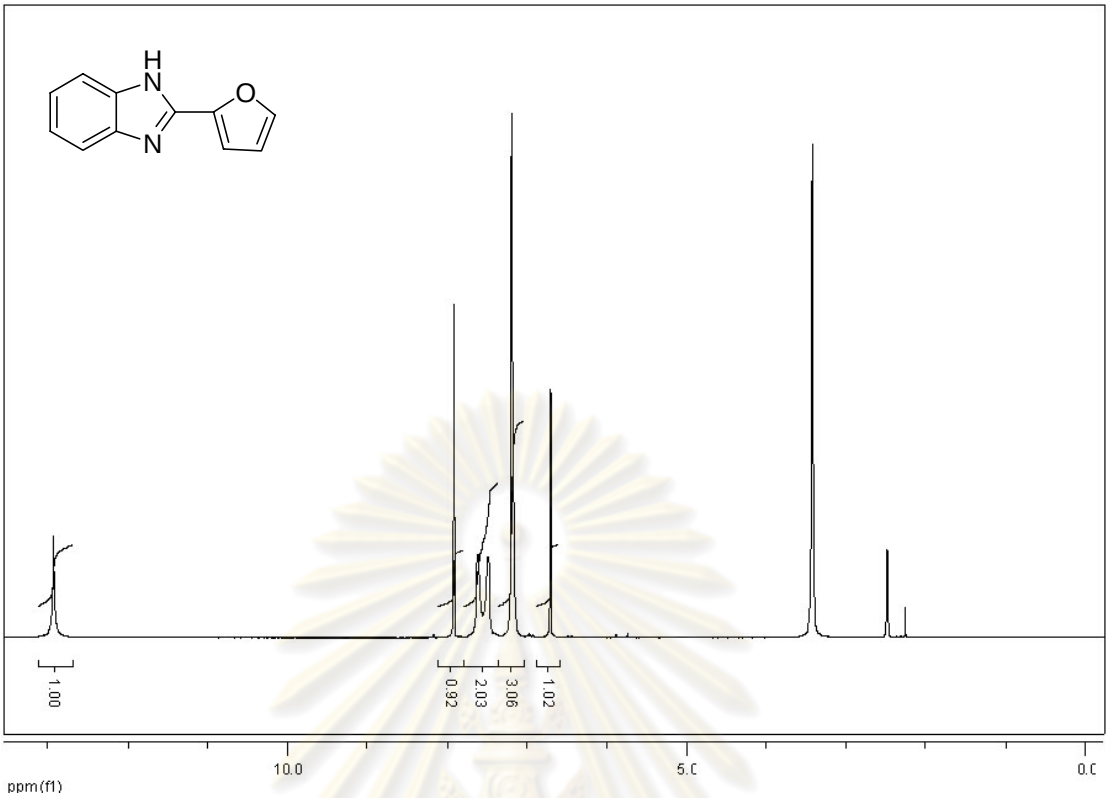


Figure 3.22 The ^{1}H-NMR of 2-(furan-2-yl)-1H-benzo[*d*]imidazole **(117)**

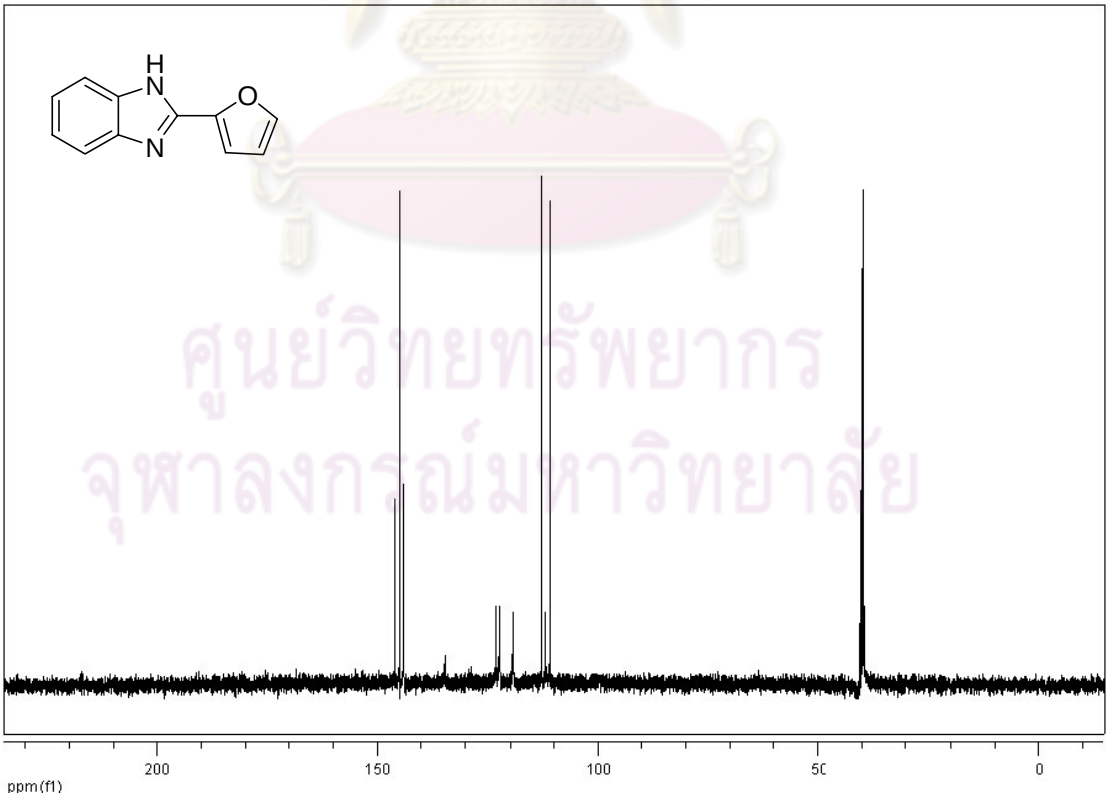


Figure 3.23 The ^{13}C-NMR of 2-(furan-2-yl)-1H-benzo[*d*]imidazole **(117)**

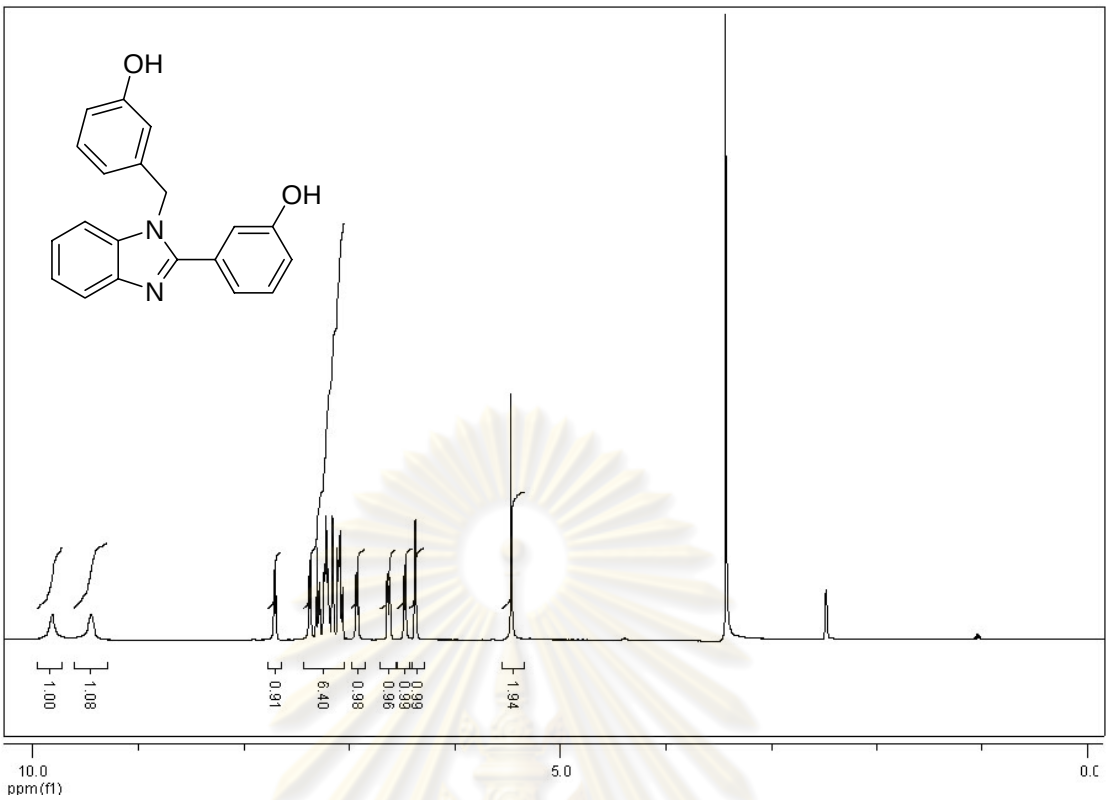


Figure 3.24 The ^{1}H-NMR of 3-(1-(3-hydroxybenzyl)-1H-benzo[*d*]imidazol-2-yl)phenol **(118)**

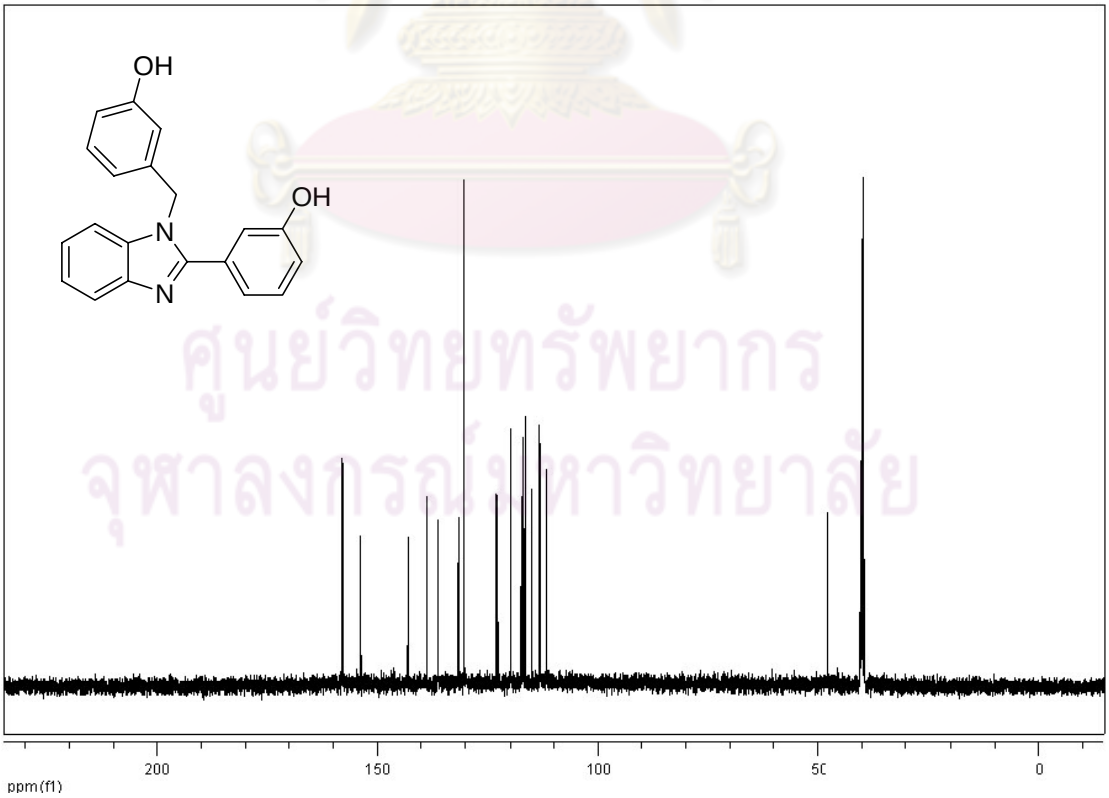


Figure 3.25 The ^{13}C-NMR of 3-(1-(3-hydroxybenzyl)-1H-benzo[*d*]imidazol-2-yl)phenol **(118)**

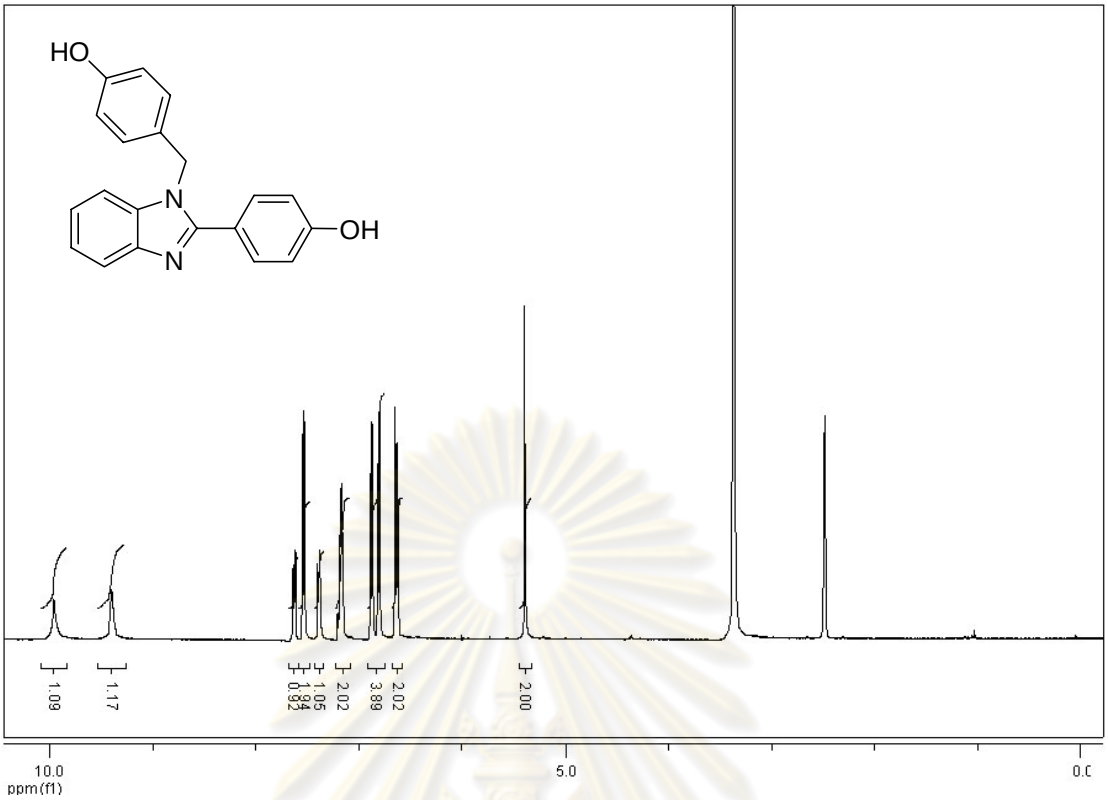


Figure 3.26 The ^{1}H-NMR of 4-(1-(4-hydroxybenzyl)-1H-benzo[*d*]imidazol-2-yl)phenol **(119)**

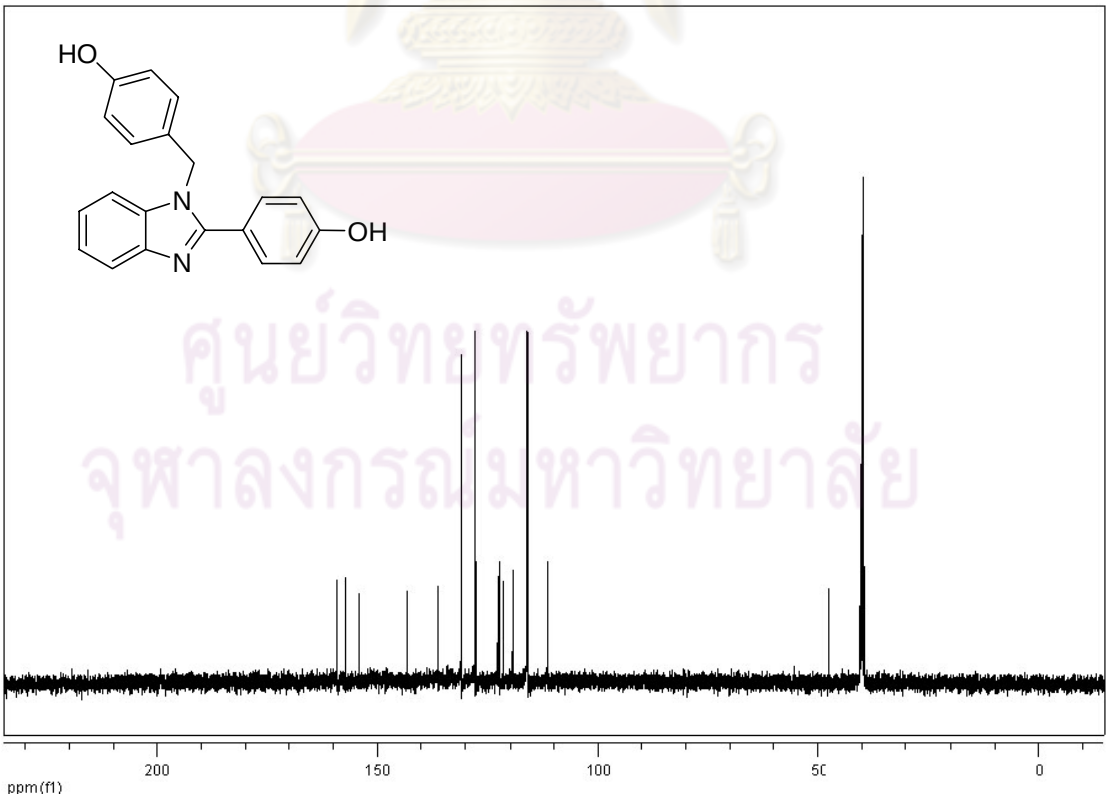


Figure 3.27 The ^{13}C-NMR of 4-(1-(4-hydroxybenzyl)-1H-benzo[*d*]imidazol-2-yl)phenol **(119)**

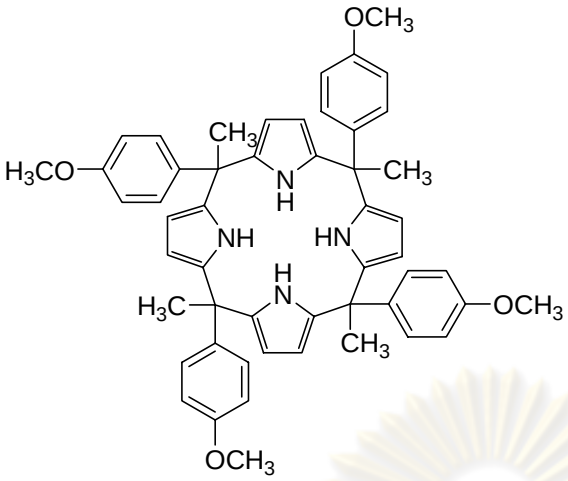
CHAPTER IV

CONCLUSION

This research divides into two parts. The first part involves the epoxidation of unfunctionalized alkenes catalyzed by two new cobalt(II) complexes, namely Dilithium-tetrakis(tetrahydrofuran)-α,β,γ,δ,-tetrakis-(4-methoxyphenyl) tetramethyl-calix[4]pyrrole tetraanion cobalt(II) complex: Cobalt(II) calix[4]pyrrole **(68)** and 2-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1H-benzo[*d*]imidazole cobalt(II) complex: Co(II) benzimidazole **(72)** and the second part concerns with the intermolecular coupling of diamines with aromatic aldehydes to benzimidazoles.

4.1 The Epoxidation of Alkenes Catalyzed by Cobalt(II) Complexes

The main aim of this research is to search for the optimum conditions for the epoxidation of alkenes catalyzed by cobalt(II) complexes. This new catalytic system was applied to the epoxidation of various alkenes. The epoxidation of cyclohexene catalyzed by Co(II) calix[4]pyrrole **(68)** or Co(II) benzimidazole **(72)** with oxygen in the presence of aldehyde in a mixture of CH_3CN and toluene could be fruitfully carried out at RT with high selectivity for the production of cyclohexene oxide. The optimum conditions disclosed were alkene 5 mmol as a substrate, a mixture of CH_3CN and toluene 2:13 mL as a solvent, Co(II) calix[4]pyrrole **(68)** or Co(II) benzimidazole **(72)** 0.05 mmol as a catalyst and 10 mmol of 2-ethylbutyraldehyde in the presence of the oxygen as an oxidant.



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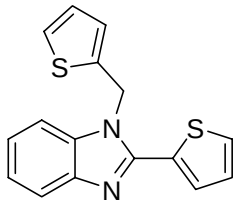

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4.2 The Intermolecular Coupling of Diamines with Aromatic Aldehydes to Benzimidazoles

The goal of this part of the research is to search for the best conditions to synthesize Schiff base and benzimidazole. Schiff bases could be prepared using aliphatic diamine condensed with aldehyde in EtOH, whereas benzimidazoles were derived from aromatic diamine condensed with aldehyde in EtOH or toluene. When toluene was used as solvent, mono-*N*-substituent cyclization was observed while employing EtOH, di-*N*-substituent cyclization was obtained.

4.3 Proposal for the Future Work

This research concerns with the methodology development for the epoxidation of alkenes catalyzed cobalt(II) complexes. The outcome opens many possibilities to deal with future exploration. As mentioned earlier, metal calix[4]pyrrole has never been utilized as a catalyst in organic transformation, therefore the variation of metal from cobalt to chromium or manganese *etc*. may provide other intriguing results in terms of product yield and selectivity. The application of these catalytic systems for asymmetric synthesis is another challenge field of study to be concentrated. This present examination is a profitable example for the epoxidation methodology in crucial chemical reaction nowadays, and may be the one of valuable chemical literature data in the near future.

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VITA

Mr. Pongchart Buranaprasertsuk was born on November 10, 1978 in Bangkok, Thailand. He received a Bachelor Degree of Science in Chemistry at Srinakarinwirote University in 2000 and Master Degree of Science in Chemistry at Chulalongkorn University in 2002. Since 2003, he has been a graduate student studying Organic Chemistry at Chulalongkorn University. During his studies towards the Doctor of Philosophy's Degree, he was awarded a teaching assistant scholarship by Faculty of Science during 2003-2005.

His present address is 133/25 Soi Ratchapralop 12, Ratchapralop Road, Makkason, Ratchatavi, Bangkok, Thailand 10400