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TRANSFORMATION OF ORGANIC COMPOUNDS BY
TRANSITION METAL SALTS IN IONIC LIQUIDS

Miss Piyada Taboonpong

A Dissertation Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy Program in Chemistry
Department of Chemistry
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Thesis Title	TRANSFORMATION OF ORGANIC COMPOUNDS BY TRANSITION METAL SALTS IN IONIC LIQUIDS
By	Miss Piyada Taboonpong
Field of Study	Chemistry
Thesis Advisor	Assistant Professor Warinthorn Chavasiri, Ph.D.

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ปิยะดา ตะบูนพงศ์ : การแปลงสารอินทรีย์ด้วยเกลือโลหะแทรนซิชันในของเหลวไอออนิก (TRANSFORMATION OF ORGANIC COMPOUNDS BY TRANSITION METAL SALTS IN IONIC LIQUIDS) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร.วรินทร ชวศิริ, 154 หน้า.

ได้ค้นพบระบบการสังเคราะห์รูปแบบใหม่ที่สะดวกและให้ผลิตภัณฑ์ในปริมาณสูงสำหรับการแปลงสารอินทรีย์ที่หลากหลาย ผ่านออกซิเดชันของสารประกอบอินทรีย์ที่หลากหลายโดยการใช้รีเอเจนต์ผสมระหว่าง 1-เฮกซิล-3-เมทิลอิมมิดาโซเลียมโบรไมด์ ([hmim]Br) และเกลือโลหะแทรนซิชัน เช่น เหล็ก(III)คลอไรด์ (FeCl$_3$) และคอปเปอร์(II)คลอไรด์ (CuCl$_2$) ปฏิกิริยาออกซิเดชันของแอลกอฮอล์กับการใช้ของผสมเหล็ก(III)คลอไรด์และ1-เฮกซิล-3-เมทิลอิมมิดาโซเลียมโบรไมด์ ในระบบที่มีเทอร์-บิวทิลไฮโดรเพอร์ออกไซด์ (TBHP) ให้สารประกอบคาร์บอนิลในปริมาณสูง พบว่าสารกลุ่มไพมารีและเซกันดารีเบนซิลิกแอลกอฮอล์ว่องไวต่อระบบตัวเร่งปฏิกิริยาผสมที่เลือกมาก ให้กรดคาร์บอกซิลิกและคีโทนเป็นผลิตภัณฑ์ตามลำดับ และไม่พบผลิตภัณฑ์อื่นเกิดร่วม สำหรับปฏิกิริยาการเกิดสารแอโรมาติกของสารไซคลิก ทั้งไซคลิกไฮโดรคาร์บอนและเฮเทอโรไซคลิกเอมีนให้ผลิตภัณฑ์ที่ต้องการได้ด้วยระบบตัวเร่งของเหลวไอออนิกร่วมกับเกลือคอปเปอร์(II)คลอไรด์ ผลที่สุดคือพบว่าระบบตัวเร่งที่พัฒนาขึ้นมีคุณสมบัติในการนำกลับมาใช้ซ้ำได้ ส่วนปฏิกิริยาดีไฮโดรจีเนชันของสารเฮเทอโรไซคลิกเอมีนด้วยระบบตัวเร่งปฏิกิริยาผสมของเหล็ก(II)คลอไรด์ (FeCl$_2$) กับไดเมทิลซัลฟอกไซด์ (DMSO) ให้ผลิตภัณฑ์แอโรมาติกเอมีนที่ต้องการในปริมาณสูงโดยผ่านกระบวนการที่เกี่ยวข้องกับอนุมูลอิสระ ในระบบตัวทำละลายอินทรีย์ดีกว่าในของเหลวไอออนิก

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PIYADA TABOONPONG: TRANSFORMATION OF ORGANIC COMPOUNDS BY TRANSITION METAL SALTS IN IONIC LIQUIDS. ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 154 pp.

A new, convenient, and high yielding synthetic protocol for transformation *via* oxidation process of various organic compounds using a combination of 1-hexyl-3-methylimidazolium bromide ([hmim]Br) and a transition metal salt, such as $FeCl_3$, and $CuCl_2$ is uncovered. The oxidation of alcohols utilizing $FeCl_3$/[hmim]Br in the presence of *tert*-butyl hydroperoxide (TBHP) afforded the corresponding carbonyl compounds in high yields. Primary and secondary benzylic alcohols seem to be reactive substrates for conversion to the desired carboxylic acids and ketones, respectively, without by-products formed. For aromatization of cyclic dienes catalyzed by $CuCl_2$ coupled with TBHP in [hmim]Br, cyclic hydrocarbons yielded highly amount of the expected aromatic substances under short reaction time, while heterocyclic amines furnished the expected heteroaromatics in moderate yield. Consequently, the developed catalytic system of a transition metal salt/[hmim]Br displayed the reusability in this methodology. For the dehydrogenation of *N*-heterocycles, $FeCl_2$/DMSO combination under oxygen atmosphere offered the corresponding *N*-heteroaromatic products in good yields *via* radical involving process, the catalytic system operated better under conventional organic solvents than ionic liquids.

Department: Chemistry   Student's Signature ....

Field of Study: Chemistry   Advisor's Signature ....

Academic Year: 2016

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

α	alpha
δ	chemical shift (NMR)
°C	degree of Celsius
γ	gamma
%	percent
A°	angstrom
ACN	acetonitrile
$AgNO_3$	silver nitrate
Al_2O_3	aluminium oxide or alumina
anh	anhydrous
aq	aqueous solution
BQ	1,4-benzoquinone
Bz	benzoyl
Bn	benzyl
BPO	benzoyl peroxide
br s	broad singlet (NMR)
DABCO	1,4-diazabicyclo[2.2.2]octane
CCl_4	carbon tetrachloride
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
DCE	dichloroethane
DCM, CH_2Cl_2	dichloromethane

DMA	dimethylacetamide
DMF	dimethylformamide
DMP	Dess–Martin periodinane
cm	centimeter
cm^{-1}	unit of wavelength
conc.	concentrated
$Cu(OAc)_2$	copper(II) acetate
d	doublet (NMR)
dd	doublet of doublet (NMR)
DDQ	2,3-dichloro-5,6-dicyanoquinone
DMSO	dimethylsulfoxide
eq, equiv	equivalent
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram (s)
h	hour (s)
hv	light
HPLC	high performance liquid chromatography
Hz	hertz
IBX	2-iodoxybenzoic acid
J	coupling constant
$KMnO_4$	potassium permanganate
$LiPF_6$	lithium hexafluorophosphate
M	molar

m	multiplet (NMR)
MB	mass balance
m.p.	melting point
mg	milligram (s)
min	minute (s)
mL	milliliter
mm	millimeter
mmol	millimole
MS	molecular sieve
MW	microwave irradiation
$NaBF_4$	sodium tetrafluoroborate
NaBr	sodium bromide
$NaIO_4$	sodium periodate
$NaSO_4$	sodium sulfate
NBS	*N*-bromosuccinimide
(+)-NMDPP	neomenthyldiphenylphosphine
NMR	nuclear magnetic resonance
$NaNO_2$	sodium nitrite
N.R.	no reaction
IL (s)	ionic liquid (s)
p-	para position
PCC	pyridinium chlorochromate
ppm	part per million
PTLC	preparative thin layer chromatography

q	quatet (NMR)
quant.	quantitative
quint	quintet (NMR)
RT	room temperature
s	singlet (NMR)
SM	starting material
t	triplet (NMR)
THF	tetrahydrofuran
TBHP	tert-butylhydroperoxide
TLC	thin layer chromatography
TPPTS	tris(3-sulfophenyl)phosphine trisodium salt
TsOH	*p*-toluenesulfonic acid
UV	ultra violet
VO(acac)$_2$	vanadyl acetylacetonate

CHAPTER I

INTRODUCTION
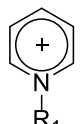
1.1 Stage of the Problem

Nowadays, the requirements of organic compounds in both laboratory and industry are in high demands. A lot of organic molecules are naturally occurring substances; however, some of them still need to be prepared [1, 2]. Therefore, the understanding of the relationship between numerous functional groups and methods of transformation is essential. In general, five major reactions including substitution, addition, elimination, oxidation, and reduction are recognized in organic synthesis. Among reagents used in those reactions, some cause problems due to reagent toxicity, harsh condition process, non-recyclability of catalysts or reagents, and troubling from using organic solvents which are volatile, toxic, and non-recoverable. Alternatively, ionic liquids (ILs) have been developed for those reactions as new reliable catalysts or reagents.

1.2 Ionic Liquids

An ionic liquid (IL) is an organic compound with the combination of ions only between a large organic cation and either an organic or inorganic anion. Generally, ILs are liquid at room temperature (melting point < 100 °C); however, both of their physical and chemical properties can be designed depending on the variation between the two ion components. In the past decade, numerous developed ILs are synthesized based on common cations and anions as shown in Table 1.1 [3]. According to the literature [1.3], ILs can be used as multifunctional compounds in catalytic reactions such as catalyst, co-catalyst, support or ligand, and solvent. As solvent, ILs not only can support catalyst; especially transition metal salts, but also act as catalyst themselves.

Table 1.1   Most common cation and anion components for general ILs

Cations	Anions
R_1 $\overset{+}{N}$ R_2 $\quad$ R_1 $\overset{+}{P}$ R_2 R_3 $\quad$ R_4 $\qquad$ R_3 $\quad$ R_4 (ammonium) $\qquad$ (phosphonium) R_1 $\overset{+}{S}$ R_2 $\qquad$ (+) ring R_3 $\qquad\qquad$ $\overset{|}{N}$ $\qquad\qquad\qquad$ R_1 (sulfonium) $\qquad$ (pyridinium) R_1-N $(+)$ N-R_2 (imidazolium)	$Cl^-/[AlCl_3]$ $[Cl]^-$, $[Br]^-$, $[I]^-$ $[NO_3]^-$, $[SO_4]^{2-}$ $[CF_3COO]^-$, $[CF_3SO_3]^-$, $[CH_3SO_3]^-$ $[BF_4]^-$ $[PF_6]^-$ $[(CF_3SO_2)N]^-$
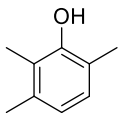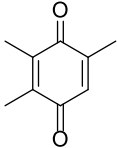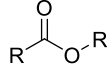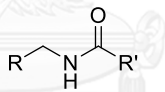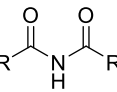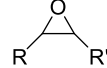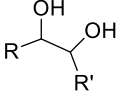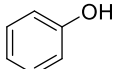
1.3   Reactions in ILs

ILs as one class of solvents are remarkable in organic synthesis, particularly approaching to green chemistry. It is due to their properties including chemical and thermal stability, nonflammability, non-volatility, ILs can be considered as environmental friendly compounds better than traditional organic solvents. In synthesis, many studies have applied ILs as solvents with several organic reactions based on common ILs. Moreover, ILs in some of following reactions can act as both solvents and catalysts in the same reaction.

1.3.1   Oxidation

Numerous organic compounds can be converted into other functional groups via oxidation in various ILs. Some examples of those reactions are displayed briefly in Table 1.2 [4].

Table 1.2   Example reactions involving oxidations in ILs

Type of substrate	Example of SM	Product
Alcohol	RCH_2OH RCHOHR'	RCHO RCOR'
Phenol[a]		 quinone
Thiol[b]	RSH RSR'	RS-SR RSOR'
Carbonyl compound[c]	 aldehyde ketone	 carboxylic acid ester
Oxime[d]		
Imide[e]		
Alkene - Epoxidation[f] - Dihydroxylation[g] - Wacker-Type reaction[h]	 	
Alkane[i]		 or
Benzene[j]		

[a] [5]; [b] [6, 7]; [c] [8, 9]; [d] [10]; [e] [11]; [f] [12]; [g] [13]; [h] [14]; [i] [15]; [j] [16]

1.3.2 Transition-Metal Catalyzed Reactions

In organic chemistry, many transition-metal catalyzed reactions concerning carbon-carbon bond formation have been operated in ILs. These reactions are examples of those.

- Heck reaction [17]

$R = H, OMe, NO_2$

51% to 99%
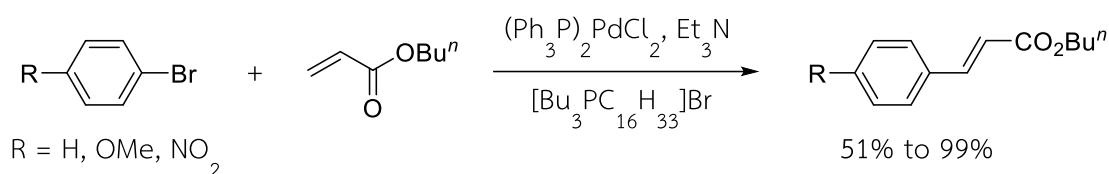
- Suzuki coupling [18]

81%
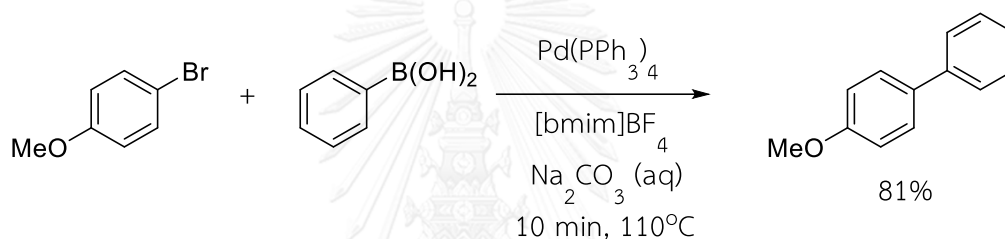
- Trost-Tsuji coupling [19]

90%

- Sonogashira coupling [20]

$$ArI \quad + \quad \equiv\!\!-R \xrightarrow[\substack{[bmim]PF_6 \\ piperidine}]{PdCl_2(PPh_3)_2} Ar\!\!-\!\!\equiv\!\!-R$$
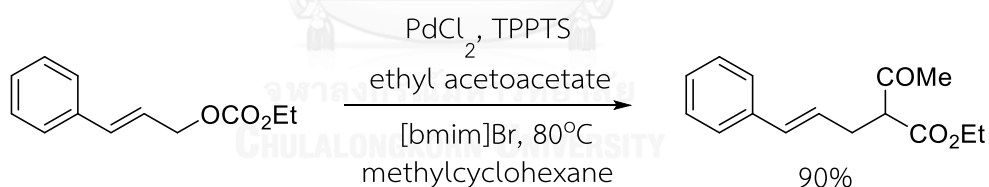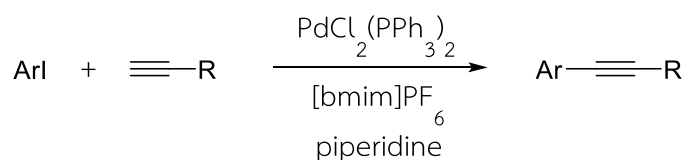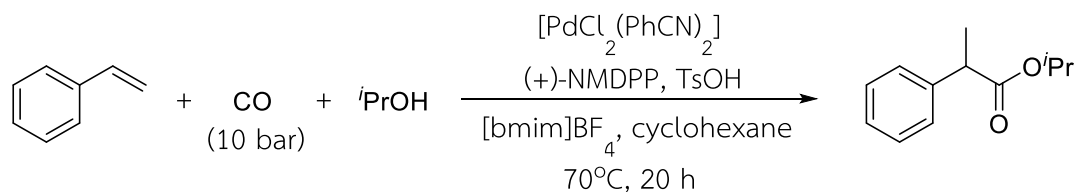
- Carbonylation [21]

- Carbonylative polymerization [22]

- Hydrogenation [23]

96% conversion   98% selectivity
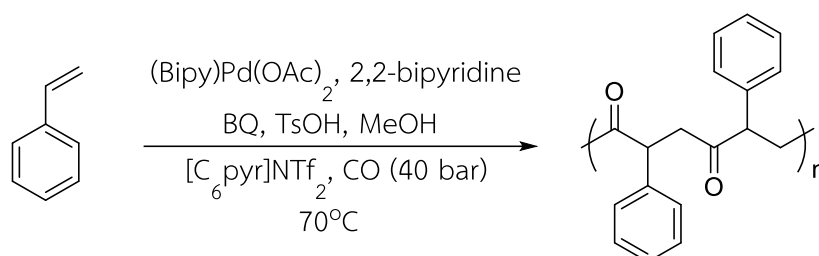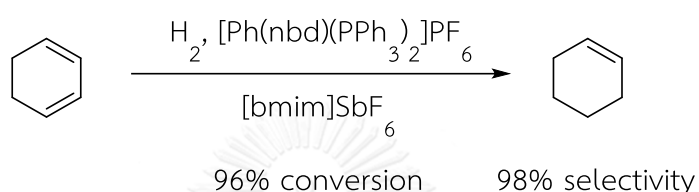
1.3.3   Other Organic Reactions

Except from oxidations, and carbon-carbon bond forming reactions, there are other reactions utilizing ILs. Some reports are exhibited in the following information.

- Reduction of aldehydes and ketones [24]

R_1 = Ph, 3-NO$_2$C$_6$H$_4$ 55-99%

R_2 = H, Ph, PhCO, PhCH(OH)

R_1,R$_2$ = CH$_2$(CH)$_3$CH$_2$
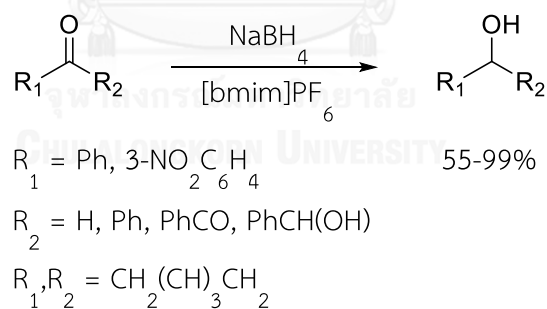
- Diels-Alder reaction [25]

exo:endo = 1:4.5

99%

- Friedel-Crafts reaction [26]
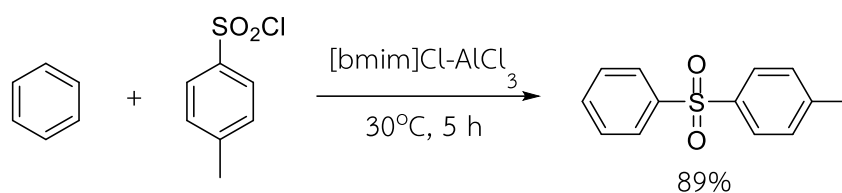
89%

- Beckmann rearrangement [27]

BPy = *N*-butylpyridinium   99%

- Esterification [28]

70-90%

- Fischer indole synthesis [29]

n-BPC = 1-(*n*-butyl)pyridinium chloride   80%
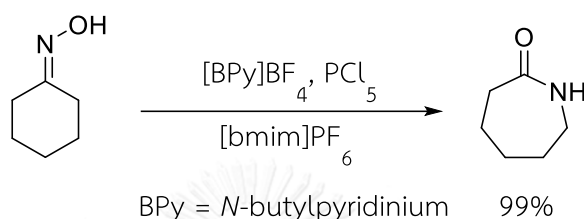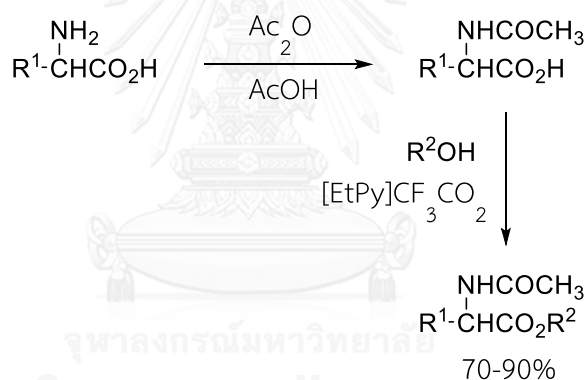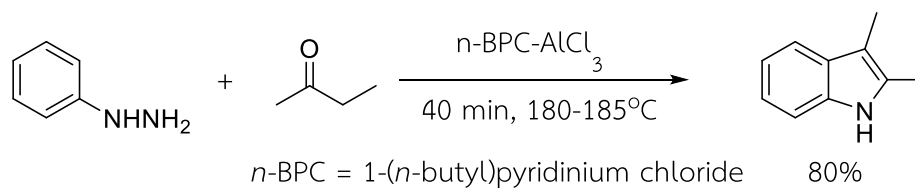
Based on examples of the aforementioned reactions, catalytic oxidations are noticeable because many types of substrates can be transformed *via* oxidation process in ILs. Moreover, their procedures are specifically interesting when ILs as solvents immobilized catalysts, thus leading to reusable catalytic systems.

1.4   Goal of Research

Despite having been reported over a decade on catalytic oxidation, the application of ILs as simple, convenient, and recyclable compounds is still considered as a challenge. The main topic of this work is the methodology for transformation of one functional group to another. Therefore, in this research, utilization of the combination between simple metal salt and IL as a new recyclable catalytic system will be thoroughly investigated for the following oxidation reactions:

1. Transformation of alcohols to carbonyl compounds in ILs

2. Aromatization of cyclic dienes and *N*-heterocyclic compounds in ILs

3. Oxidative dehydrogenation of *N*-heterocycles
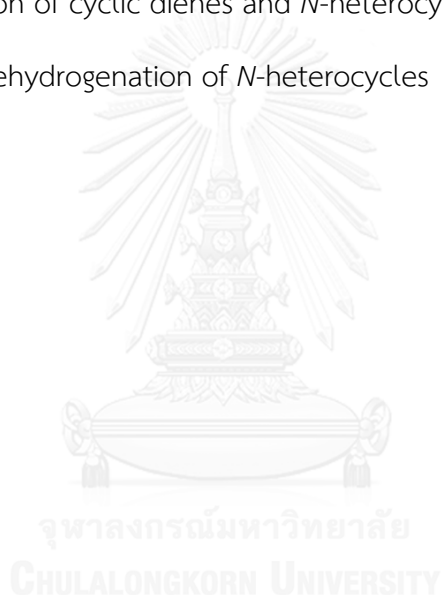
CHAPTER II

OXIDATION OF ALCOHOLS IN IONIC LIQUIDS

2.1 Introduction

A carbonyl functional group is common in numeral classes of organic compounds, as a part of many large organic structures or natural occurring species. Carbonyl compounds are one of the most valuable substrates in chemical and pharmaceutical science [30]. Over these past decades, copious evidences have been found for the development of many methodologies to synthesize those compounds. There are several general methods to prepare carbonyl compounds; especially aldehydes, ketones, and carboxylic acids, from various precursors.

2.1.1 The Synthesis of Carbonyl Compounds

In laboratory, numerous substrates are generally used for the preparation of carbonyl compounds in many manners [31].

- From oxidation of alcohols
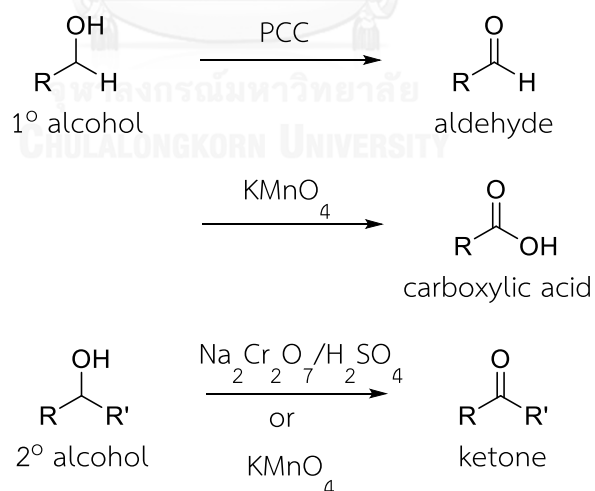
- From oxidation of alkyl benzene
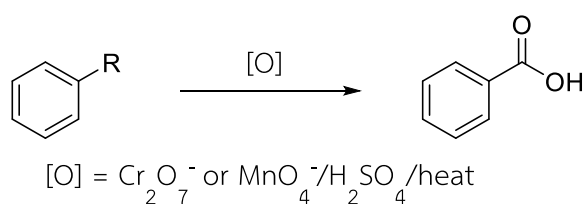
- From Friedel-Crafts acylation

benzene + acyl chloride $\xrightarrow{AlCl_3}$ acyl benzene

- From ozonolysis of alkenes

alkene $\xrightarrow[\text{2. Zn/H}_2\text{O}]{\text{1. O}_3}$ carbonyl compound
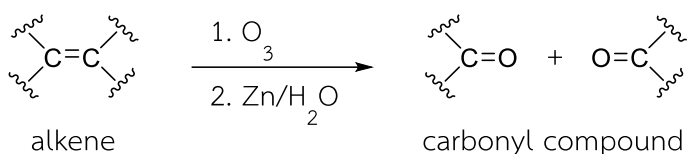
- From reduction of acid chloride

acid chloride $\xrightarrow{\text{LiAlH(O}^t\text{Bu)}_3}$ aldehyde

- From acid chloride to ketone with organometallic reagent

acid chloride $\xrightarrow{R_2CuLi}$ ketone
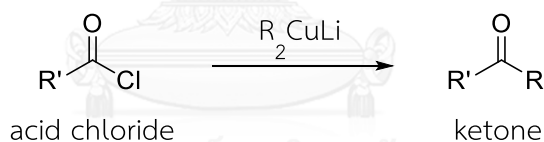
- From hydrolysis of nitriles

$R-C\equiv N \xrightarrow[\triangle]{H_3O^+} R-COOH$
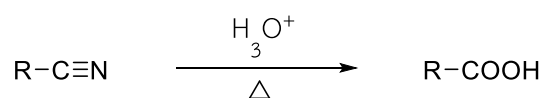
Although, carbonyl compounds can be manipulated from various sources of starting materials, the general and simple protocols mostly stem from the oxidation of alcohols because of the uncomplicated process, the variety and easy procreation and commercial availability.

2.1.2 The Importance of Carbonyl Compounds

Carbonyl compounds can react with various reagents to create many other functional groups such as alkanes, alcohols, imine derivatives, and other carbonyl

substances. Because of the charge different between carbon and oxygen of C=O, this position tends to be attacked by other active species, and then converted into others.

2.1.3 Oxidation of Alcohols with Common Reagents

General oxidants for alcohol oxidation are usually used while considering in terms of their reactivity, and selectivity towards each type of alcohol. Some reagents can control the selectivity of products which are competitively generated between aldehyde and carboxylic acid from the oxidation of primary alcohols (Scheme 2.1) such as chromium [32], ruthenium [32], manganese [32], activated DMSO [33], and hypervalent iodine [34, 35] oxidizing agents.

In accordance with previous works, even though, alcohols could be oxidized to their corresponding carbonyl products utilizing numerous reagents or catalysts, most of them encounter some disadvantages such as using toxic reagents, occurring under severe condition, using non-recyclable reagents or catalysts, requiring organic solvents which have volatility, toxicity, and non-recoverability problems. In order to solve those problems, using ILs has been found to be one of the best solutions.
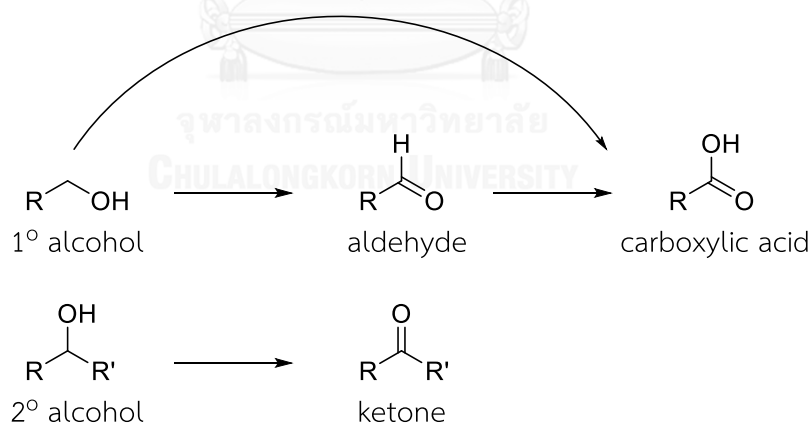
Scheme 2.1 General study for alcohol oxidation

2.2 Literature Reviews

Even though ILs are highly stable and have been evaluated as media for oxidation reactions [36], surprisingly little attention has been focused on carrying out catalytic oxidations in ILs. For oxidation of alcohols, reactions normally require

catalysts, and ILs which mostly used as solvents may have functions to support catalysts; especially transition metal catalysts or act as catalysts themselves.

In alcohol oxidation, the characteristics of ILs can be designed by choosing their components. Thus, different types of ILs show various chemical and physical properties. In case of physical properties such as melting point, viscosity, density, water solubility, etc., can be determined by both cation and anion parts. Solubility, which is one of interesting properties as potential solvents, is considered to play an important role for catalytic process with regard to recycling catalysts being homogeneous or heterogeneous system.

In the past several years, ILs being used for oxidation of alcohols mostly consisted of imidazolium group; especially *N,N*-dialkylimidazolium, on the cation part. The anion part will be the one to contribute to the solubility of various ILs with the same cation. ILs can be divided into two major groups based on solubility in water as water immiscible and soluble ILs.

2.2.1 Oxidation of Alcohols in Water Immiscible Ionic Liquids

The convenient methodology for the preparation of carbonyl compounds from alcohols utilizing non-water soluble ILs has been used in a number of transition metal catalyzed reactions. For example,

Ansari and Gree [37] reported a mild and simple catalyst containing 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) and CuCl for oxidation of primary and secondary alcohols to their corresponding aldehydes and ketones under O_2 atmosphere in [bmim]PF_6. The allylic and benzylic alcohols were converted into their expected products in good yield while aliphatic alcohols were less reactive. Moreover, the IL used as solvent could be reused eight times with slight loss of the product yield.

$$R_1 \overset{OH}{\underset{}{\big|}} R_2 \xrightarrow[\substack{O_2,\ [bmim]PF_6,\ 65^oC}]{\text{TEMPO (5 mol\%), CuCl (5 mol\%)}} R_1 \overset{O}{\underset{}{\|}} R_2$$

$$R_1 = \text{aryls, alkyls} : R_2 = \text{H, alkyls}$$
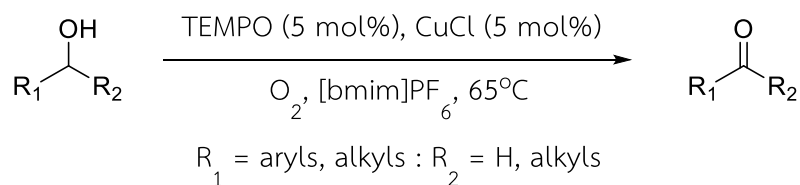
Bianchini and co-workers [38] displayed the oxidation of secondary alcohols catalyzed by methyltrioxorhenium (MTO) and supported MTO (polyvinylpyridine/MTO and polystylene/MTO) as homogeneous and heterogeneous catalysts, respectively with hydrogen peroxide (H_2O_2) in [bmim]PF_6. The heterogeneous system could be used to perform with the same reactions more than one time.
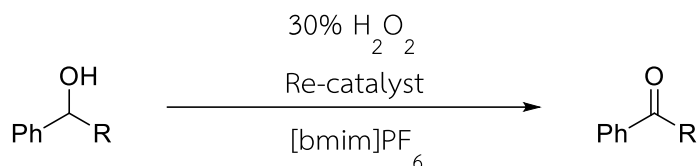
Jiang and Ragauskas [39] showed the oxidation of benzylic alcohols to their desired carbonyl compounds utilizing a modified TEMPO (acetamide-TEMPO), HBr, and H_2O_2 in [bmim]PF_6. The IL containing acetamide-TEMPO could be reused for other cycles with either the same or different substrate.
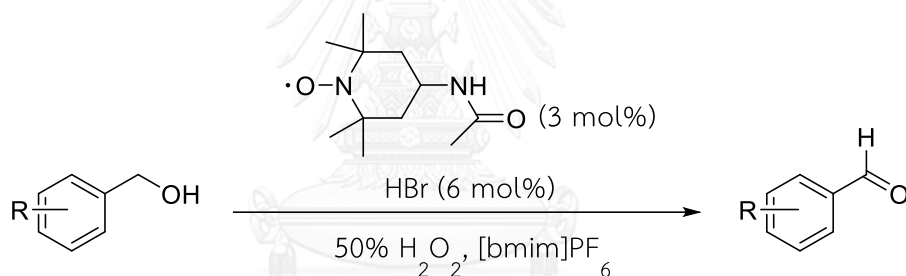
Lei and co-workers [40] developed IL-TEMPO as catalyst which was immobilized in [bmim]PF_6-H_2O in presence of $NaIO_4$ as the external oxidant for the oxidation of benzyl alcohol. The remaining IL carrying the catalyst was able to be reused up to six times.
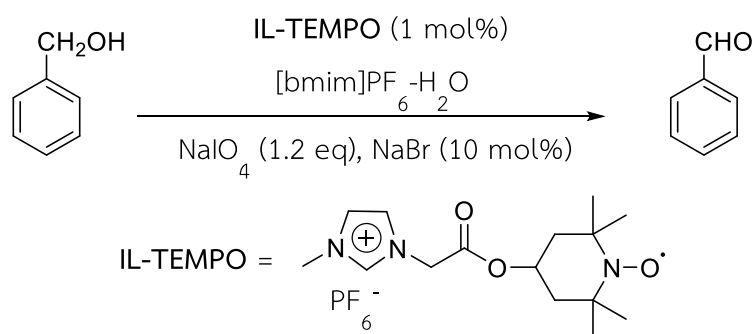
Ragauskas and co-workers [41] studied the catalytic conversions of alcohols into their expected aldehyde or ketone products by using VO(acac)$_2$/DABCO system in [bmim]PF$_6$ under O$_2$ atmosphere. The catalytic system was found to be able to recycle for the oxidation of 4-methoxybenzyl alcohol for three times.
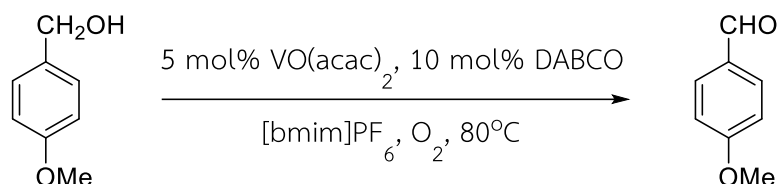
Kumar and co-workers [42] addressed the oxidation of 3,4-dimethyoxybenzyl alcohol catalyzed by iron(III) porphyrin complex (Cl$_8$TAPS$_4$FeCl) and H$_2$O$_2$ in [bmim]PF$_6$. The activity of the catalyst was compared with the reaction with a biocatalyst – horseradish peroxidase (HRP) affording similar results under the same reaction condition.
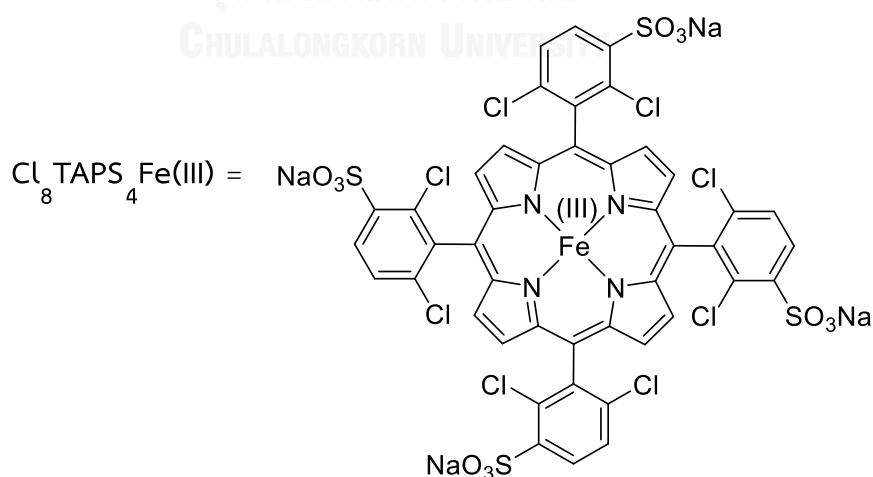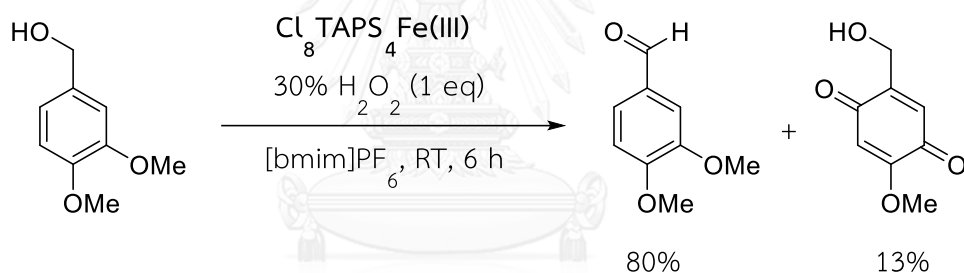
Fan and co-workers [43] described RuCl$_3$-catalyzed oxidation of homopropargyl alcohols to 1,2-allenic ketones in ILs with TBHP.
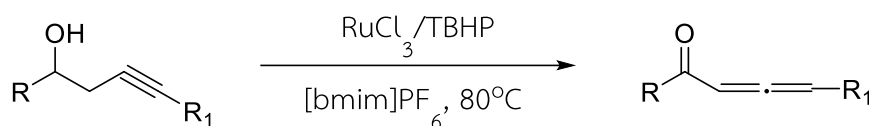
Liu and co-workers [44] developed a supported ionic-liquid catalytic system for oxidation of alcohols. A selected alcohol was also tested for catalyst recyclability.
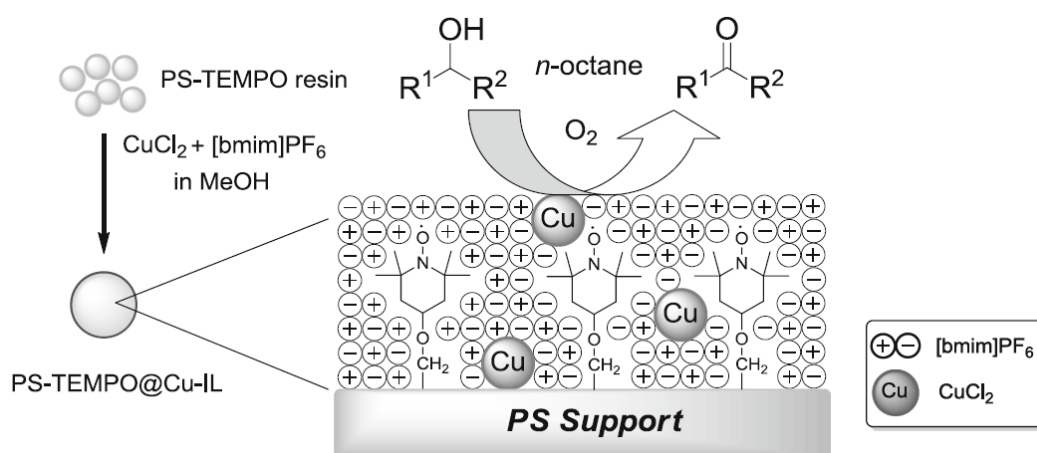
According to the above reviews, there are a lot of reports for alcohol oxidations in water immiscible ILs; especially in [bmim]PF$_6$. Those reactions mostly performed under the condition of using catalysts or ILs which were synthesized with specific designs in order to obtain complicated structures that would have never been reported before; however, the procedures may be complicated. Therefore, the development of new systems for organic transformation by using commercially available catalysts or ILs, or with simple method for their preparations should be concerned.

2.2.2 Oxidation of Alcohols in Water Soluble Ionic Liquids

In the past decade, there has been numerous research addressing the alcohol oxidation in water miscible ILs. The ILs mostly contained the combination of N,N-dialkylimidazolium cation ([RMIM]$^+$) and tetrafluoroborate (BF$_4^-$) or halide (Cl$^-$ or Br$^-$) anion. In case of BF$_4^-$ anion IL, 1-butyl-3-methylimidazolium tetrafluoroborate

([bmim]BF$_4$), which was partially soluble in water, was the most effective because it has been used by many reports for the transformation of alcohols. For examples,

Yadav and co-workers [45] exhibited the oxidation of various alcohols in [bmim]BF$_4$ promoting the corresponding products in good yield with IBX and/or DMP as catalysts. The reactions in IL showed a faster reaction rate than using common organic solvents with several times recyclability.

$$R_1R_2CHOH \xrightarrow[\text{[bmim]BF}_4\text{, RT}]{\text{IBX and/or DMP}} R_1R_2CO$$
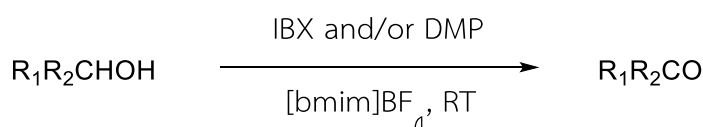
Xia and co-workers [46] showed an efficient catalyst of PhI(OAc)$_2$/Mn(salen) complex in the mixture of CH$_2$Cl$_2$ and [bmim]BF$_4$ for preparation of ketones from secondary alcohols. The complex remaining in the IL could be recovered and reused for five times.

$$R_1R_2CHOH \xrightarrow[\text{DCM/[bmim]BF}_4\text{, RT}]{\text{PhI(OAc)}_2\text{/Mn(salen)complex}} R_1R_2CO$$
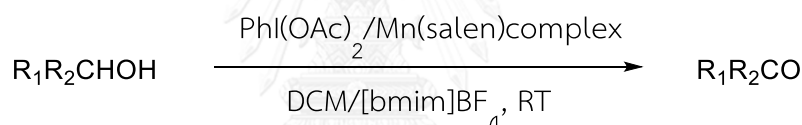
Chhikara and co-workers [47] developed imidazolium decatungstate [bmim]$_4$[W$_{10}$O$_{23}$] as catalyst to oxidize benzylic and secondary alcohols affording the desired products in high yields with H$_2$O$_2$. The catalyst could be reused because of its solubility in IL.
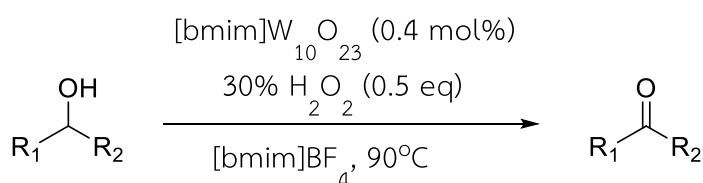
In the similar period, the transformation of alcohols under the condition of using IL as a catalyst to both aldehydes and acids, selectively by controlling H$_2$O$_2$ concentration was investigated [48].
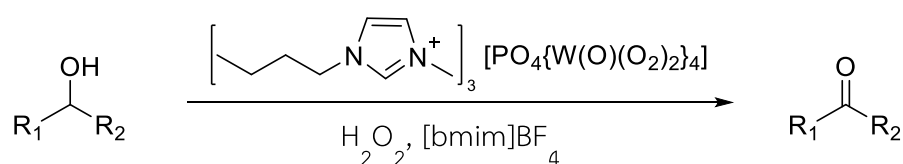
Sain and co-workers [49] reported the primary and secondary alcohol conversion in [bmim]BF$_4$ with H$_2$O$_2$ and catalytic amount of MTO and NaBr at room temperature.

$$R_1R_2CHOH \xrightarrow[\text{[bmim]BF}_4\text{, RT}]{\substack{\text{MTO (1 mol \%), NaBr (5 mol\%)} \\ \text{30\% H}_2\text{O}_2}} R_1R_2CO$$
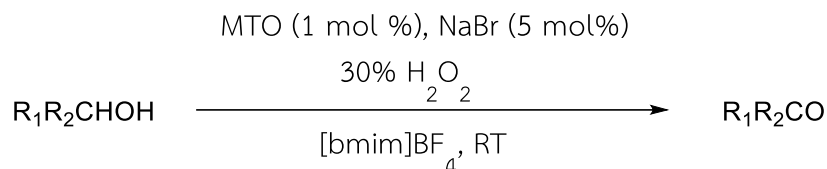
Han and co-workers [50] explored the oxidation of alcohols in [bmim]BF$_4$ with TBHP catalyzed by copper (I) amino acid Schiff base to afford their corresponding carbonyl products under mild conditions.

$$R_1R_2CHOH \xrightarrow[\text{[bmim]BF}_4\text{, RT, 1 h}]{\text{(1 mol\%), TBHP}} R_1R_2CO$$
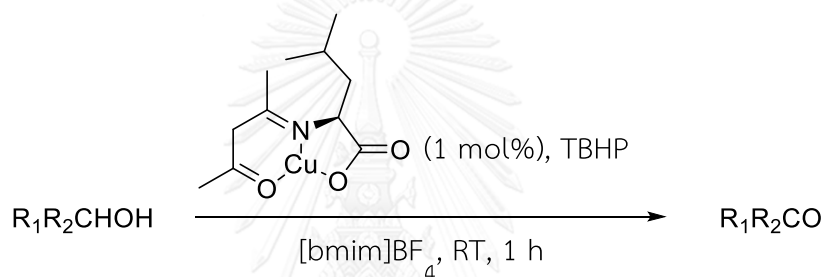
Lee and co-workers [51] displayed a low-reactivity iodide catalyst activated with lithium carbonate (Li$_2$CO$_3$) for the preparation of carbonyl compounds from alcohol oxidation in [bmim]BF$_4$.
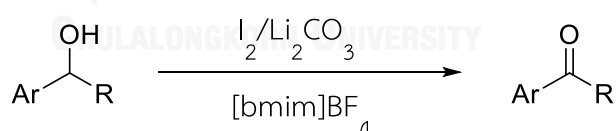
Kim and co-workers [52] addressed the oxidation of benzylic alcohols using trichloroisocyanuric acid (TCCA) in a mixture of [bmim]BF$_4$ and H$_2$O. This reaction clearly explained that TCCA was activated by IL because the substrate was intact under the condition without IL.
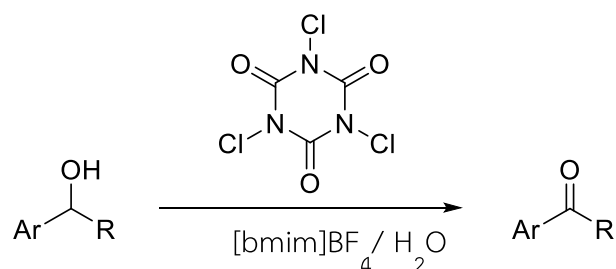
In accordance to some examples from relating records, the oxidations in [bmim]BF$_4$ led to the formation of the corresponding ketones in excellent yields; however, most of those reactions showed some disadvantages. The reactions not only required catalysts which normally had complicated structures or specific transition metal complex; but also, adding co-catalysts was necessary in many conditions. Then, later or around similar time, using halide as anion part was found to be able to avoid those problems in some cases. For instance,

Zheng and co-workers [53] reported the usage of IBX in a mixture of 1-butyl-3-methlimidazolium chloride ([bmim]Cl) and water for the oxidation of alcohols under mild condition. The desired carbonyl compounds were isolated from the reaction by extracting with organic solvents in good yields. Controlling amount of IBX reagent could provide one or two hydroxyl-group conversion on dihydroxy substrates.
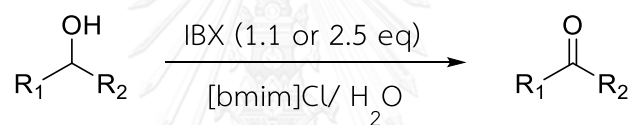
Later, similar research was displayed by Chhikara *et al.* [54]. 2-Iodoxybenzoic acid (IBX) was immobilized in [bmim]Br as catalyst for the oxidation of 17α-methylandrostan-3β,17β-diol (**1**) to generate a well-known 2-oxasteroid which is widely used as anabolic drugs. Applying 1.2 equiv of IBX only provided the ketone product (**2**) around 80% yield, while large amount of IBX with longer reaction time generated α,β-unsaturated ketone (**3**) as the major product. Other cyclic secondary alcohols were also investigated resulting in the same trend of the model transformation.
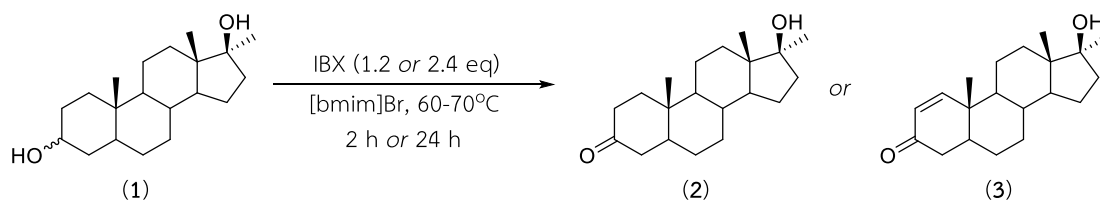
Yadav and co-workers [55] exhibited an example of the reaction using IL to promote one-pot oxidative conjugate addition of TMSCN to Baylis-Hillman adducts. The IL-[bmim]Br and IBX catalyst was used to generate the first step that would constantly lead to the final product. The reaction was also treated with NaNO$_3$ and

acidic IL-[Hmim]HSO$_4$ to study the scope of the reaction with various substrates. After product isolation, ILs could be recycled at least four times for the same reaction.
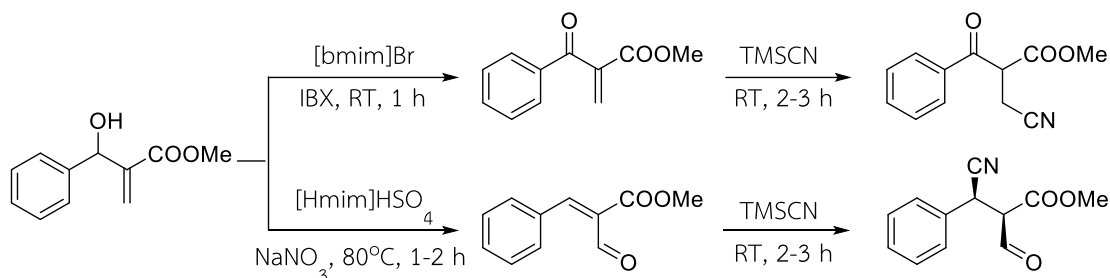
Shaabani and co-workers [56] described the oxidation of alkyl arenes and alcohols catalyzed by NaBrO$_3$ in [bmim]Br. Generally, sodium bromate could not be used alone for oxidation with conventional solvents, the reaction should be in acid condition or required co-reactants to activate BrO$_3^-$. IL was easily recovered and reused for the next cycles, while the catalyst was lost after the whole process.
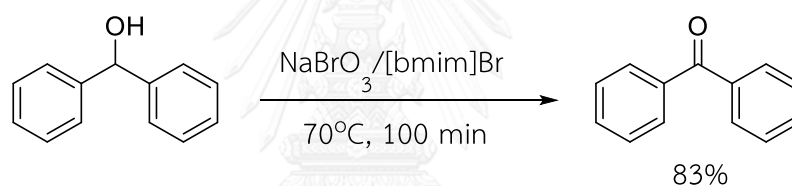
Sharma and co-workers [57] demonstrated unique chemoselective oxidation of aryl alcohols/acetates catalyzed by recyclable catalyst with the combination of *Candida antarctica* lipase B (CAL-B) and 1-hexyl-3-methylimidazolium bromide ([hmim]Br) to activate H$_2$O$_2$ without using any metal catalysts. The catalytic system showed good functional group compatibility under neutral conditions to generate the expected carbonyl compounds from the oxidation of various alcohols and their derivatives with ten times for recyclability.

R$_1$ = H, OMe, OCH$_2$O, NO$_2$, Cl, *etc.*
R$_2$ = H, Methyl, Ethyl, Propyl, *etc.*
R$_3$ = H, COMe
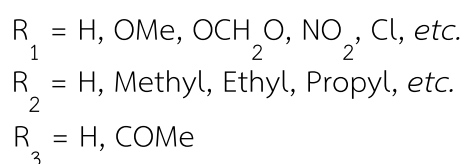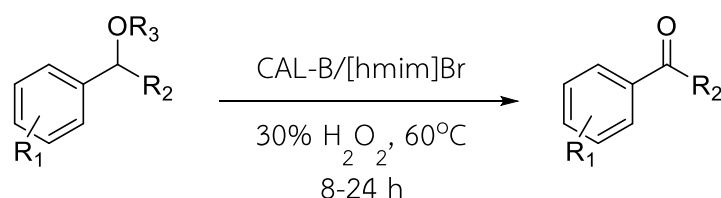
Ramakrishna and co-workers [58] developed a coordination Co(II) complex and NaOCl in 1-ethyl-3-methylimidazolium chloride ([emim]Cl) to oxidize primary and secondary alcohols. Five derivatives of Co(II) complexes were synthesized and applied with various ratio of [emim]Cl/NaOCl to obtain the optimum condition. Those complexes provided little difference on the product yields mostly depending on of their substituents.
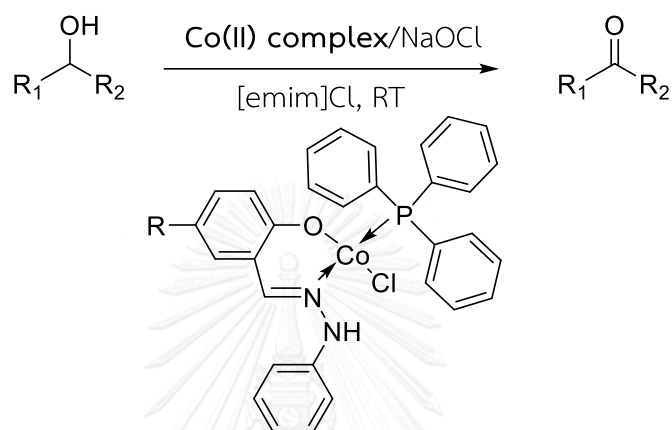
CoL1: R=H, **CoL2**: R=Cl, **CoL3**: R=Br, **CoL4**: R=NO$_2$, **CoL5**: R=OCH$_3$

Sinha and co-workers [59] investigated the oxidation of aryl alcohols utilizing *Pseudomonas mandelii* KJLPB5 and [hmim]Br in H$_2$O$_2$ system. The carbonyl products could be prepared from either direct-oxidation or sequential dehydration-oxidation cleavage which led to the corresponding aryl aldehydes by losing some carbons from aryl alcohols. Even though this biocatalytic system produced moderate yields for direct-oxidation of 2° aryl alcohols, it offered a new biocatalytic process to gain a direct synthesis of a few carbon shorter aryl aldehydes in better yield.
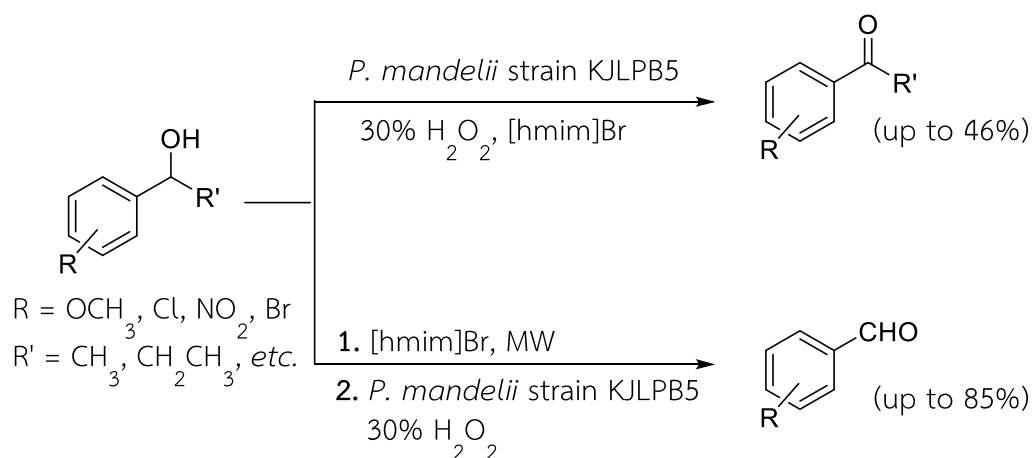
Around the similar period, the same group [60] developed a metal-free chemoselective oxidation of benzyl alcohols with H_2O_2 in [hmim]Br under microwave irradiation. Various alcohols provided different carbonyl products depending on electrophilic factors and nature of substrates. Comparison between benzylic and aliphatic alcohols by carrying out under the same condition, the expected products from benzylic substrates were the only product formed, while the other was intact. It clearly showed that benzylic alcohols were much more reactive than aliphatic ones. Even though this system could provide the target compounds in good yield, unavoidable side products were also found in some cases.
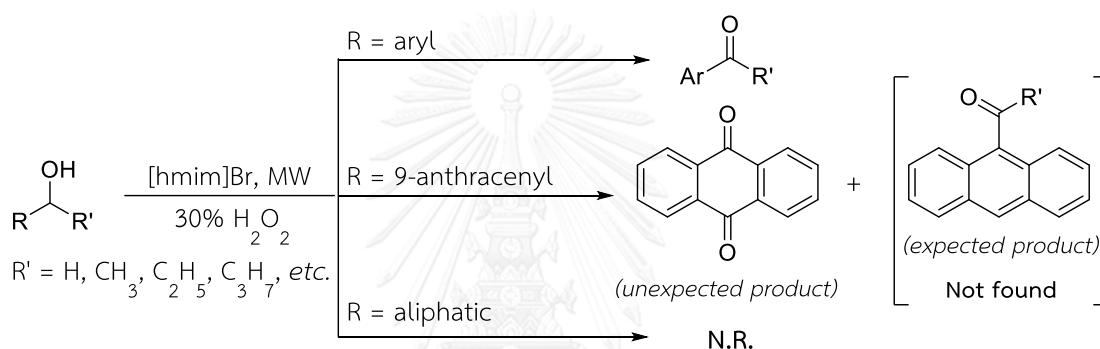
With imidazolium ILs carrying halide anion, commercially available materials or natural substances such as enzymes could be used as catalysts for alcohol oxidations instead of using metal complexes. There are still some problems, for instance, long reaction time still could not be evaded for those biocatalyst reactions due to their nature that will be destroyed at high temperature. Moreover, H_2O_2 was mainly used as indispensably required catalysts; especially transition metal catalysts to initiate the catalytic process [61]. Therefore, to avoid those problematic conditions, using TBHP had been expanded in the oxidation of alcohols in ILs.

Even though, TBHP has been used by many researchers [4, 62], it have never been addressed on the oxidation of alcohols in water soluble ILs, especially in 1-hexyl-3-methylimidazolium bromide ([hmim]Br). Thus, this Chapter is devoted for the alcohol oxidations with TBHP using the combination of [hmim]Br and a simple transition metal salt that could dissolve in IL to allow the possibility of catalyst recycling.

2.3 Scope of This Work

The methodology for the preparation of carbonyl compounds from the oxidation of alcohols utilizing metal salt/ionic liquid will be focused. The objective of this research is to develop a new catalytic system of simple transition metal salt/uncomplicated ionic liquid in the presence of TBHP for alcohol oxidation, and to investigate the optimal condition for the synthesis of the desired ketone. Moreover, the oxidation of various alcohols including primary, secondary, and tertiary ones under developed system would be considered.

2.4 Experimental

2.4.1 Instruments and Equipment

Column chromatography was performed on silica gel (Merck Kieselgel 60, 70-230 mesh). Thin layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel (Merck Kieselgel 60 PF_{254}). Glass plate chromatography was performed on glass 20x20 cm precoated with silica gel (Merck Kieselgel 60, 70-230 mesh). The ^1H and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as an internal reference on the NMR Bruker Advance 400 spectrometer which operated at 399.84 MHz for ^1H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons. The Shimadzu gas chromatography GC-14B (FID CP-Sil 8 column) was employed to determine the quantity of the products.

2.4.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology [63] except for those which were reagent grades. The reagents used for synthesis were purchased from Fluka, Aldrich, and TCI chemical companies or otherwise stated and were used without further purification.

2.4.3 General Procedure

2.4.3.1 Preparation of Alcohol Substrates

To a solution of available ketone (5.10 mmol) in 10 mL of 95% EtOH was gradually added NaBH$_4$ (1.45 mmol) at room temperature. After having been stirred for 20 min, the reaction was quenched by adding 30 mL of water in ice bath, and then 6M HCl was dropped to the solution until it became acidic. After that, the mixture was extracted with Et$_2$O, and dried over anhydrous Na$_2$SO$_4$. After concentration, the corresponding alcohol was obtained as a pure compound or purified by silica gel column chromatography with EtOAc:Hexane (v/v : 3:1)

1-Phenylethanol [64]: light yellow oil; ^{1}H NMR (CDCl$_3$) δ 7.39 (m, 4H), 7.35 – 7.26 (m, 1H), 4.92 (q, J = 6.5 Hz, 1H), 2.00 (s, 1H), 1.52 (d, J = 6.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 145.8, 128.5, 127.5, 125.4, 70.4, 25.1.

1-(4-Methoxyphenyl)ethanol [65]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 7.32 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.87 (q, J = 6.4 Hz, 1H), 3.82 (s, 3H), 1.92 (s, 1H), 1.50 (d, J = 6.4 Hz, 3H); ^{13}C NMR (CDCl$_3$) δ 159.0, 138.0, 126.7, 113.9, 70.0, 55.3, 25.0.

1-([1,1′-Biphenyl]-4-yl)ethanol [66]: pale yellow powder; ^{1}H NMR (CDCl$_3$) δ 7.62 – 7.60 (m, 4H), 7.49 – 7.45 (m, 4H), 7.39 - 7.35 (m, 1H), 4.99 (q, J = 6.4 Hz, 1H), 1.70 (br s, 1H), 1.58 (d, J = 6.5 Hz, 3H); ^{13}C NMR (CDCl$_3$) δ 144.8, 140.9, 140.5, 128.8, 127.3, 127.1, 125.9, 70.2, 25.1.

1-Phenylpropanol [67]: pale brown oil; ^{1}H NMR (CDCl$_3$) δ 7.39 (m, 4H), 7.35 – 7.26 (m, 1H), 4.92 (q, J = 6.5 Hz, 1H), 2.00 (s, 1H), 1.52 (d, J = 6.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 145.8, 128.5, 127.5, 125.4, 70.4, 25.1.

Diphenylmethanol [68]: colorless solid; ^{1}H NMR (CDCl$_3$) δ 7.50 – 7.22 (m, 10H), 5.88 (s, 1H), 1.92 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 143.8, 128.5, 127.6, 126.5, 76.3.

1-(Naphthalen-2-yl)ethanol [66]: colorless solid; ^{1}H NMR (CDCl$_3$) δ 7.98 – 7.80 (m, 4H), 7.59 – 7.40 (m, 3H), 5.09 (m, 1H), 1.96 (br s, 1H), 1.61 (d, J = 6.5 Hz, 3H); ^{13}C NMR (CDCl$_3$) δ 143.2, 133.3, 132.9, 128.3, 127.9, 127.7, 126.1, 125.8, 123.8, 123.8, 70.5, 25.1.

2.4.3.2 Preparation of Water Soluble Ionic Liquids

For bromide anion ILs [59, 60], 1-bromoalkane was gradually added in the mixture of 1-methylimidazole and toluene at room temperature under N_2 atmosphere. The reaction was carried out at 30-35°C for 48 h. After that, the mixture was extracted with EtOAc /Et$_2$O and solvents were removed by evaporation on rotary evaporator at 60 ^{o}C for 24 h. The yield of ILs obtained were above 90%.

1-Butyl-3-methylimidazolium bromide ([bmim]Br) [69]: light yellow liquid; ^{1}H NMR (CDCl$_3$) δ 10.02 (s, 1H), 7.58 (s, 1H), 7.47 (s, 1H), 4.21 (t, J = 7.4 Hz, 2H), 3.99 (s, 3H), 1.77 (quint, J = 7.5 Hz, 2H), 1.30 – 1.18 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR (CDCl$_3$) δ 136.9, 123.8, 122.2, 49.7, 36.6, 32.0, 19.3, 13.3.

1-Hexyl-3-methylimidazolium bromide ([hmim]Br) [59, 60]: light yellow liquid; ^{1}H NMR (CDCl$_3$) δ 10.06 (s, 1H), 7.57 (s, 1H), 7.41 (s, 1H), 4.26 (t, J = 7.4 Hz, 2H), 4.06 (s, 3H), 1.85 (quint, J = 7.7 Hz, 2H), 1.34 – 1.17 (m, 6H), 0.80 (t, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$) δ 137.2, 123.7, 122.0, 50.1, 36.8, 31.0, 30.2, 25.8, 22.3, 13.9.

1-Octyl-3-methylimidazolium bromide ([omim]Br) [70]: yellow liquid; ^{1}H NMR (DMSO-d_6) δ 9.22 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 4.17 (t, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.79 (m, 2H), 1.24 (m, 10H), 0.85 (t, J = 6.5 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 136.4, 123.5, 122.2, 48.8, 35.7, 31.1, 29.3, 28.4, 28.3, 25.4, 22.0, 13.9.

Tetrafluoroborate ILs were synthesized from anion-exchange reaction as follows: the solution of [bmim]Br (1 equiv) and acetone (2 mL/mmol IL) was added 1 equiv of sodium tetrafluoroborate (NaBF$_4$) with continuous stirring and a drying tube, at room temperature during 15 h. After finishing the reaction, NaBr as the by-product was filtered while the product was soluble in acetone. After that, an alumina column was used to completely remove NaBr from the crude product. Finally, solvent was removed *in vacuo* and the IL was obtained.

1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF$_4$) [71]: yellow liquid; ^{1}H NMR (DMSO-d_6) δ 9.08 (s, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 4.16 (t, J = 7.2 Hz, 2H), 3.85 (s, 3H), 1.77 (m, 2H), 1.27 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 136.4, 123.6, 122.2, 48.5, 35.7, 31.3, 18.7, 13.2.

2.4.3.3 Preparation of Water Immiscible Ionic Liquids

The ILs were prepared from anion-exchange reaction between bromide anion IL and lithium hexafluorophosphate (LiPF$_6$) [71]. To a solution of [bmim]Br (19 mmol) in CH$_2$Cl$_2$ was added LiPF$_6$ (21 mmol) and stirred for 24 h. The precipitated chloride salt in the suspension was filtered and the organic phase repeatedly washed with small amount of water while checking the aqueous layer, which should have no chloride salt by adding a concentrated AgNO$_3$ solution. Complete removal of the chloride salt was confirmed by washing the organic phase with further two times of water. The solvent of the upper layer was removed *in vacuo* and then the IL was stirred with activated charcoal for 12 h. After that, the IL was passed through a short alumina column (acidic and/or neutral) to afford a colorless IL, which was dried at 100 $^{\circ}$C for 24 h with 80% yield.

1-Butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF$_6$) [71]: colorless oil; ^{1}H NMR (Acetone-d_6) δ 8.82 (s, 1H), 7.60 (s, 1H), 7.55 (s, 1H), 4.21 (t, J = 7.3 Hz, 2H), 3.91 (s, 3H), 1.79 (m, 2H), 1.25 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR (Acetone-d_6) δ 137.4, 124.8, 123.4, 50.2, 36.6, 32.7, 19.9, 13.6.

2.4.4 Typical Procedure for Oxidation of Alcohols in Ionic Liquids

1-Phenylethanol as a model compound (1.7 mmol) and 2 equiv of TBHP (5.5 M in decane) were added to a 50-mL round-bottom flask containing 1 mL of [hmim]Br and 5.0 mol% FeCl$_3$. After heating at 70 $^{\circ}$C for 2 h, the reaction mixture was extracted with Et$_2$O (3x10.0 mL). The organic layer was washed with distilled water, dried over anhydrous Na$_2$SO$_4$ and then quantified for the product yield with naphthalene as internal standard by GC.

2.4.5 Optimum Conditions Study

2.4.5.1 Effects of Catalysts

This observation was carried out under the condition described in typical procedure. Nine different metal chlorides: copper(I) chloride (CuCl), copper(II) chloride

(CuCl$_2$), nickel(II) chloride (NiCl$_2$), manganese(II) chloride (MnCl$_2$), cobalt(II) chloride (CoCl$_2$), ferrous chloride (FeCl$_2$), chromium(III) chloride (CrCl$_3$), indium(III) chloride (InCl$_3$), and ferric chloride (FeCl$_3$) were examined to compare their effects on the oxidation.

2.4.5.2 Effects of Reaction Time

Following the general procedure, several different reaction times were investigated with 2, 5, 12, and 24 h in order to gain the maximum yield of the ketone product.

2.4.5.3 Effects of Reaction Temperatures

Effects of reaction temperature were studied with four different temperatures: at room temperature ($\sim$ 28 $^{\circ}$C), 70, 80, and 90 $^{\circ}$C.

2.4.5.4 Effects of TBHP Concentrations

In order to study the effects of TBHP concentration under a similar protocol, various amounts of TBHP: 0.0, 2.0, 3.0, 4.0, and 6.0 equiv based on the substrate were observed.

2.4.5.5 Effects of Catalyst Amounts

This investigation was to compare different amounts of catalyst between 1.0, 1.5, and 5.0 mol% of the most suitable catalyst in order to find an appropriate concentration for this catalytic system using the aforementioned method.

2.4.6 Solvent System Comparative Study

This examination was to study the effects of solvent towards the product yield, and also the catalyst by following the optimized conditions. Seven different organic compounds were chosen: Acetonitrile (MeCN), and Decane (C$_{10}$H$_{22}$) as organic solvents, [bmim]Br, [hmim]Br, [omim]Br, and [bmim]BF$_4$ as water soluble ILs, [bmim]PF$_6$ as water immiscible ILs.

2.4.7 Recyclability Study of the Catalytic System

After finishing the reaction, the ionic-liquid residue as the mixture of $FeCl_3$ and [hmim]Br was evaporated to remove all solvents by rotary evaporator at 50 $^{\circ}$C for 2 h. It was reused as the catalytic solvent for the next cycles under the aforementioned optimum condition.

2.4.8 Oxidation of Various Alcohols in Ionic Liquids

General procedure from the oxidation of 1-phenylethanol was performed by using different types of alcohols including primary, secondary, and tertiary ones. Moreover, several substituted benzylic alcohols were also used as starting materials. Some starting materials were quantified, and purified by isolation with NMR and silica gel column, respectively.

2.5 Results & Discussion

The development of a new catalytic system and the exploration of optimum condition for the preparation of ketones from alcohols were thoroughly examined.

2.5.1 Condition Optimizations

Optimum conditions for the preparation of ketones from alcohols utilizing transition metal salt coupled with TBHP in [hmim]Br were explored. Various parameters such as catalysts, reaction time, reaction temperature, TBHP concentration, and amount of catalyst were investigated. 1-Phenylethanol (1 equiv) was chosen as a model under the typical condition: 5 mol% of catalyst, TBHP (2.0 equiv) in [hmim]Br at 70 $^{\circ}$C for 2h. The desired ketone product was quantified by GC using naphthalene as an internal standard.

Acetophenone as the expected product was confirmed its identity by GC. The mixed standards of all possible compounds in the crude reaction: 1-phenylethanol, acetophenone, and naphthalene were analyzed by GC to check their retention times as shown in Figure 2.1.
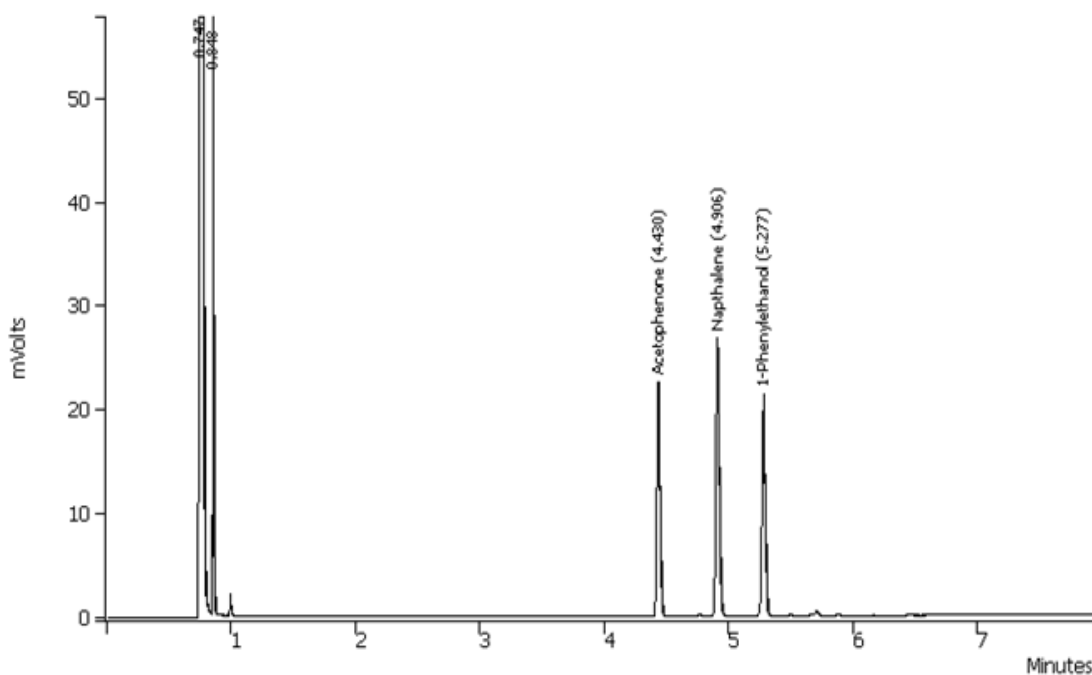
Figure 2.1 GC Chromatogram of mixed standards

2.5.1.1 Effects of Catalysts

Significant differences in the reactivity of alcohols were mainly caused from transition metal catalysts. To prove this assumption, the variation of nine different catalysts was explored and the results are shown in Figure 2.2.

Considering the effects of catalysts on the formation of the ketone, $FeCl_3$ clearly displayed the best result. Even though this was demonstrated that catalyst played an important role for the reaction, the desired product was still detected under the catalyst-free condition. Possible explanation found from the literature is shown in Scheme 2.2.
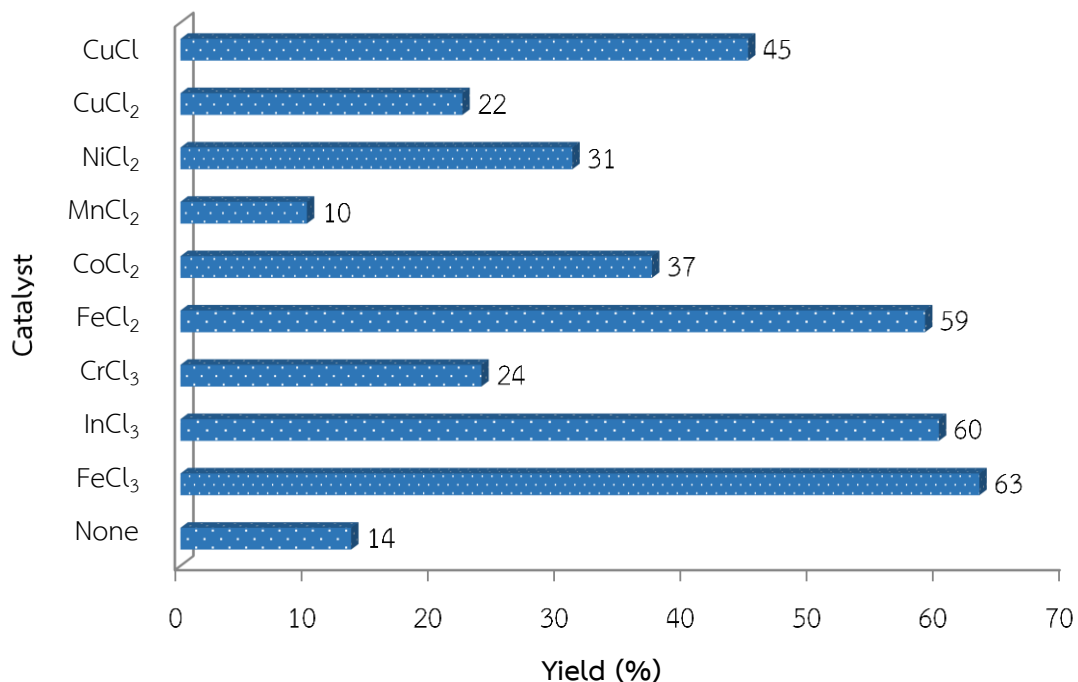
Figure 2.2 Effects of catalysts on oxidation of 1-phenylethanol under the typical procedure

Without using any catalyst, TBHP acting as an initiator under heating (Scheme 2.2 – 1a) generated radical active species and then led to the oxidation of the alcohol *via* a radical process [72]. In contrast, TBHP easily interacted with metal catalyst; especially iron salt (Scheme 2.2 – 1b), and then rapidly produced an "activated oxygen species" in form of high-valent oxenoid iron species ($Fe^V=O$) which subsequently reacted with alcohol before turning into the final ketone product with reduction of iron and/or regenerating Fe^{III} as a consequence [73, 74].

Based on the results, $FeCl_3$ was considered as the most suitable catalyst for further investigation. Besides the yield provided, the iron salt was chosen due to its solubility in [hmim]Br which led to a homogeneous reusable catalytic system while the other salts mostly were insoluble.
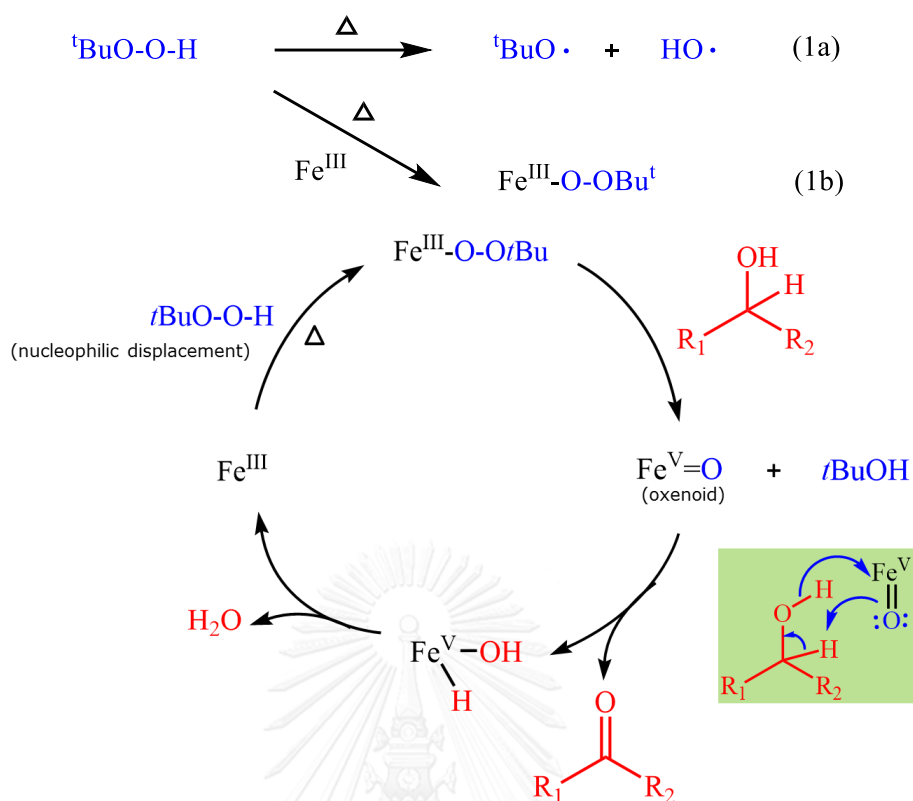
Scheme 2.2 Possible mechanism for the oxidation of 1-phenylethanol with TBHP

2.5.1.2 Effects of Reaction Time

In order to gain the maximum product yield, longer reaction time: 5, 12, and 24 h, was applied to the reaction. The results are displayed in Figure 2.3.
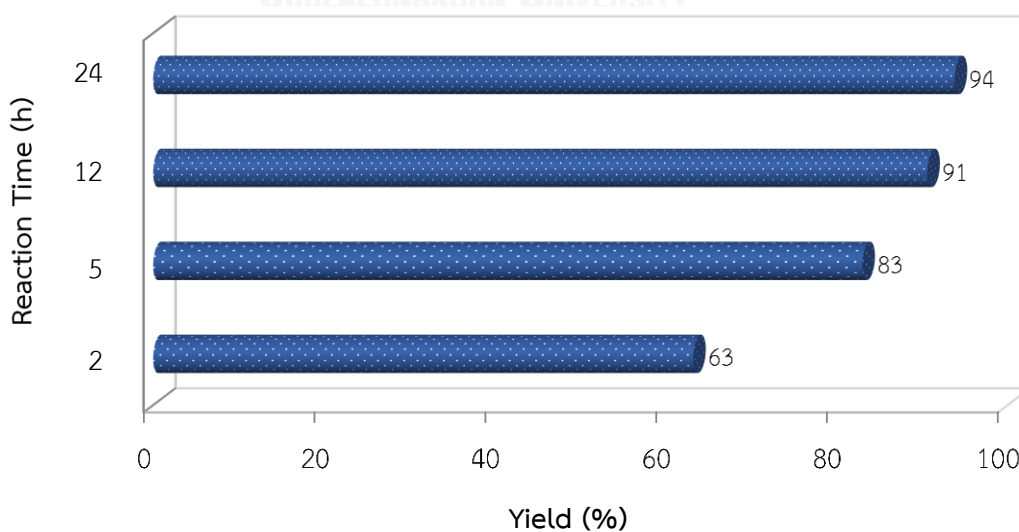
Figure 2.3 Effects of reaction time on the oxidation of 1-phenylethanol under the general method

63% Yield of the desired ketone was detected during two-hour reaction time. Increasing reaction time tended to give higher yield (83% in 5 h); however, the yield did not improve much even after 24 h (almost 100% without any starting material recovery). Twelve hours which was enough to complete the reaction (91%) was not considered as the proper reaction time because it took too long. Similar to operating with 5 h, this reaction time was also too long comparing with previous reports. Therefore, further investigation on the effects of other factors to improve the yield will be carried out within 2 h.

2.5.1.3 Effects of Reaction Temperature

A few different temperatures were applied to the system to provide the maximum yield within short reaction time under the general protocol. The results are presented in Figure 2.4.
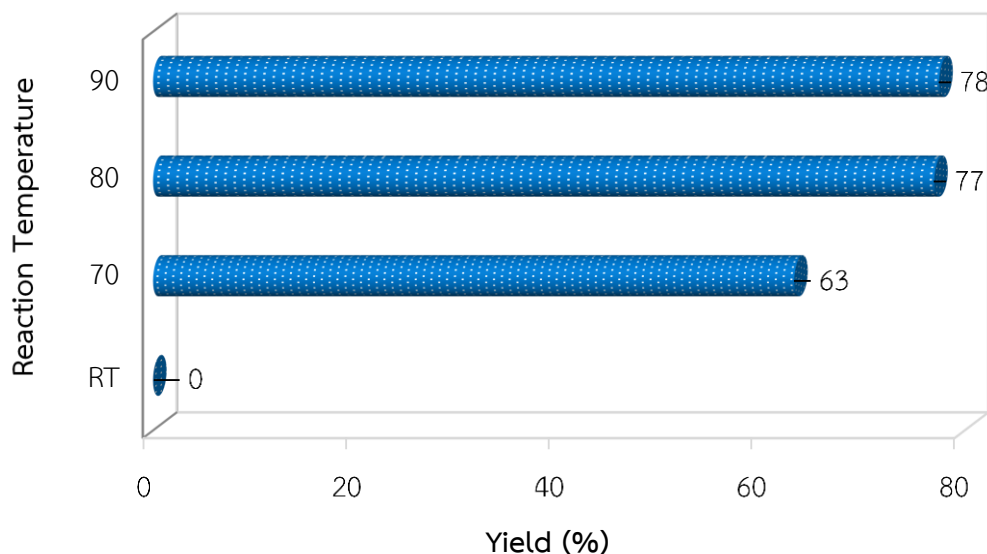
Figure 2.4 Effects of reaction temperature on 1-phenylethanol oxidation

The observation of various reaction temperatures could clearly verify the effect of temperature on the system. When the reaction was carried out at room temperature, the expected product was not obtained. On the other hand, the yields were found to increase at higher temperature (70, 80, and 90 $^{\circ}$C) with the yield up to 78%. This showed that heating was necessary for this reaction to stimulate TBHP

turning into the active species as an initiator for the whole process as mentioned in Scheme 2.2.

Within 2 h, at least 80 $^{\circ}$C was sufficient to transform the alcohol to the desired ketone with no substrate recovery; however, the reaction did not convert completely. This implied that other parameters should have some effects towards the product yield.

2.5.1.4 Effects of Concentration of TBHP

According to previous results, the amount of TBHP should be considered as one of important parameters to increase the yield. The reaction was varied with 0.0, 2.0, 3.0, 4.0, and 6.0 equiv of TBHP based on substrate. The results are shown in Figure 2.5.
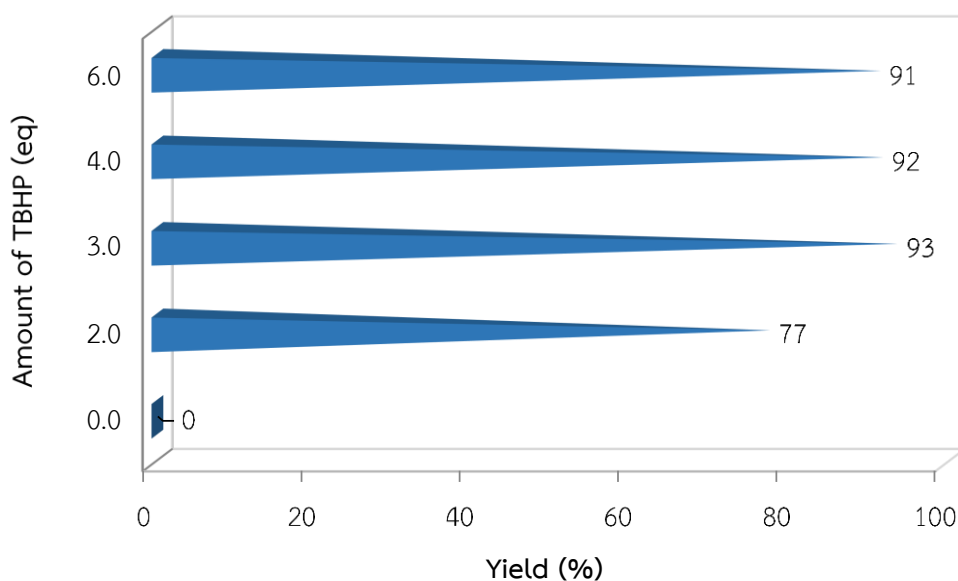
Figure 2.5 Effects of TBHP concentration on the oxidation of 1-phenylethanol

Due to the TBHP coordination with FeCl$_3$ from Scheme 2.2, those results could clearly confirm the role of TBHP as the external oxidant to the reaction system. Without using any TBHP (0.0 equiv) no product formed; while, using higher concentration led to increasing in yield to 77% of the expected product (2.0 equiv of TBHP) with substrate recovery. Increasing TBHP to 3.0 equiv, the yield rapidly increased to 93% with the complete reaction. Adding one more equivalent of TBHP (4.0 equiv)

or doubling the amount (6.0 equiv) did not improve the yield further. Overall, only 3.0 equiv of TBHP as an excess amount was optimal in converting 1-phenylethanol to its ketone product.

2.5.1.5 Effects of Catalyst Amounts

This observation was examined to find an appropriate amount of catalyst that could provide the best product yield with three-catalyst concentrations: 1.0, 1.5, and 5.0 mol% catalyst. The research is displayed in Table 2.1.

Comparing with previous study using 5.0 mol% $FeCl_3$, two less amounts of catalyst were investigated. 1.0 mol% was not enough for the reaction to be complete, while 1.5 mol % gave the same result. Further examination thus on the effect of these different amounts of $FeCl_3$ was explored as shown in Figure 2.6. After 120 min of the whole process, using 5.0 mol% made the reaction finish within 60 min while the completion by 1.5 mol% was 120 min. Considering the $t_{1/2}$ of each reaction, they both offered only a few-minutes difference in a short reaction time, thus either 1.5 or 5.0 mol% of catalyst could be used for this reaction. 1.5 mol% $FeCl_3$ was selected as a minimum amount for this new catalytic system.

Table 2.1   Effects of the amount of $FeCl_3$ on oxidation of 1-phenylethanol in [hmim]Br[a]

$FeCl_3$ (mol%)	Yield (%)[b]	MB (%)
5.0	94	94
1.5	93	93
1.0	83	93

[a] The reactions were conducted with 3.0 equiv of TBHP at 80 °C

[b] GC yield
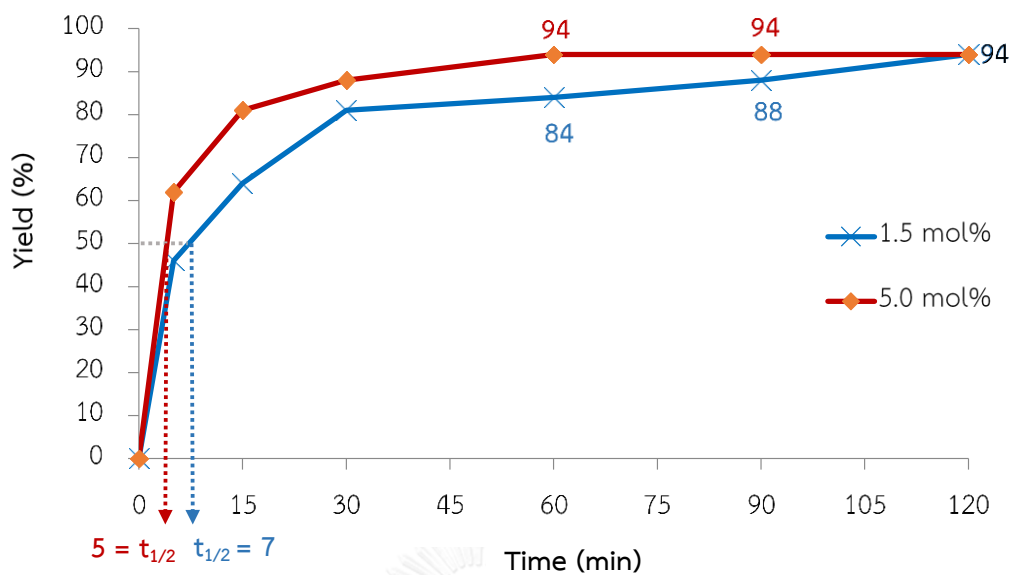
Figure 2.6 The comparative study on the use of 1.5, and 5.0 mol% FeCl$_3$

on the oxidation of 1-phenylethanol

According to all of the above information, the oxidation of 1-phenylethanol was successfully performed under these optimal factors including catalyst, reaction time, reaction temperature, TBHP concentration, and amount of catalyst as described in Figure 2.7.
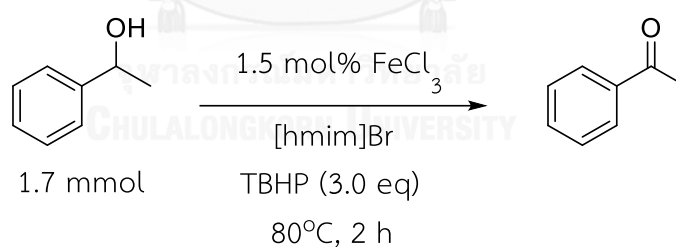
Figure 2.7 Optimum condition for oxidation of 1-phenylethanol in [hmim]Br

2.5.2 Comparative Study of Solvent System

This examination was studied in order to indicate the propose of using [hmim]Br by comparing several organic compounds as solvents under optimized conditions for 1-phenylethanol. The results are displayed in Table 2.2.

Table 2.2   Comparative study of solvent system[a]

Entry	Solvent	Yield (%)	MB (%)	Solubility of $FeCl_3$
1	MeCN	97	97	✖
2	Decane	97	97	✖
3	[bmim]Br	91	91	✓
4	[hmim]Br	93	93	✓
5	[omim]Br	92	92	✖
6	[bmim]BF_4	92	92	✖
7	[bmim]PF_6	90	90	✖

[a] All of the product yields were determined by GC with an internal standard method

Both MeCN (entry 1), which is normally used as one of the best solvents for metal catalyzed alcohol oxidation, and decane (entry 2), which is a solvent system for TBHP solution, led to the complete reaction; however, iron catalyst could not completely dissolve in these solvent systems.

In case of using water soluble 3-alkylimidazolium bromide ILs (entry 3-5), all of them gave only the desired product in excellent yield. Considering the solubility of the catalyst in ILs, $FeCl_3$ could completely dissolve in [bmim]Br (entry 3) and [hmim]Br (entry 4) while it still remained as powder in [omim]Br (entry 5) under the same condition. It was similar to the reaction using [bmim]BF_4 and [bmim]PF_6 (entries 6,7), in which $FeCl_3$ is barely dissolved, the product even though was obtained in high yield. These results showed that different alkyl chains or anions on the cation, and anion parts, respectively, of the ILs could provide different results.

Overall, even though using [bmim]Br generated the same result as [hmim]Br, there have been many reports on the oxidation in [bmim]Br [54-56] over a recent decade. Therefore, this work only focused on a new combination of recyclable catalytic system between $FeCl_3$ and [hmim]Br. Moreover, for those reactions that the catalyst could not dissolve, it was because only a few miligrams of $FeCl_3$ were used, a lot of steps thus should be applied in order to reuse those small amounts of the catalyst.

2.5.3 Recyclability Study of the Catalytic System

Owing to the oxidation process, the remaining ionic liquid, which was the mixture of $FeCl_3$ and [hmim]Br, showed the same color of the metal salt. The same ^1H NMR spectrum as that of the starting system was displayed in Figure 2.8. Therefore, the catalytic system ($FeCl_3$/[hmim]Br) was reused for next cycles in order to assess the recyclability. The results are shown in Figure 2.9.
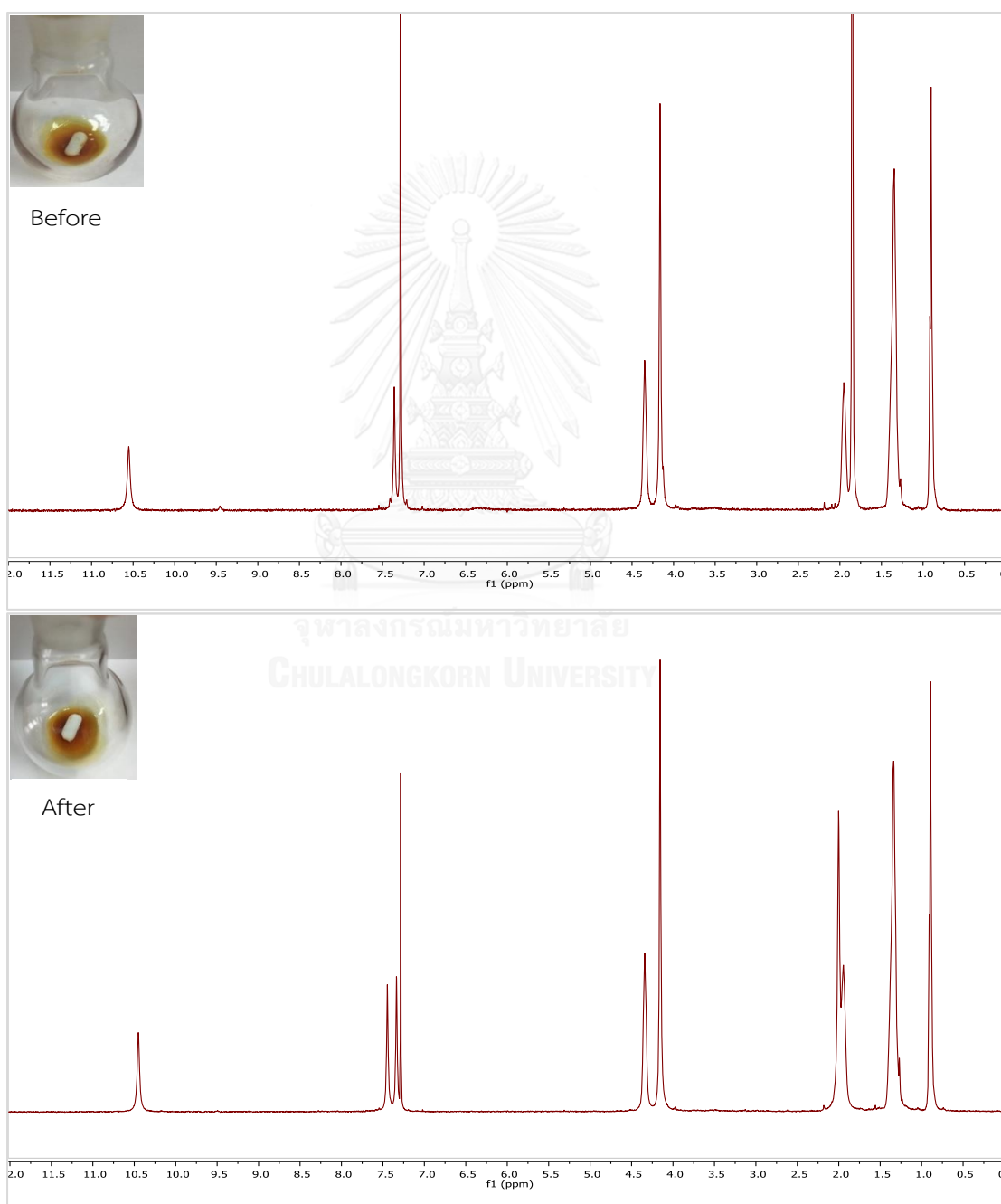
Figure 2.8 The ^1H NMR spectra of the starting and the recovered ILs, respectively.
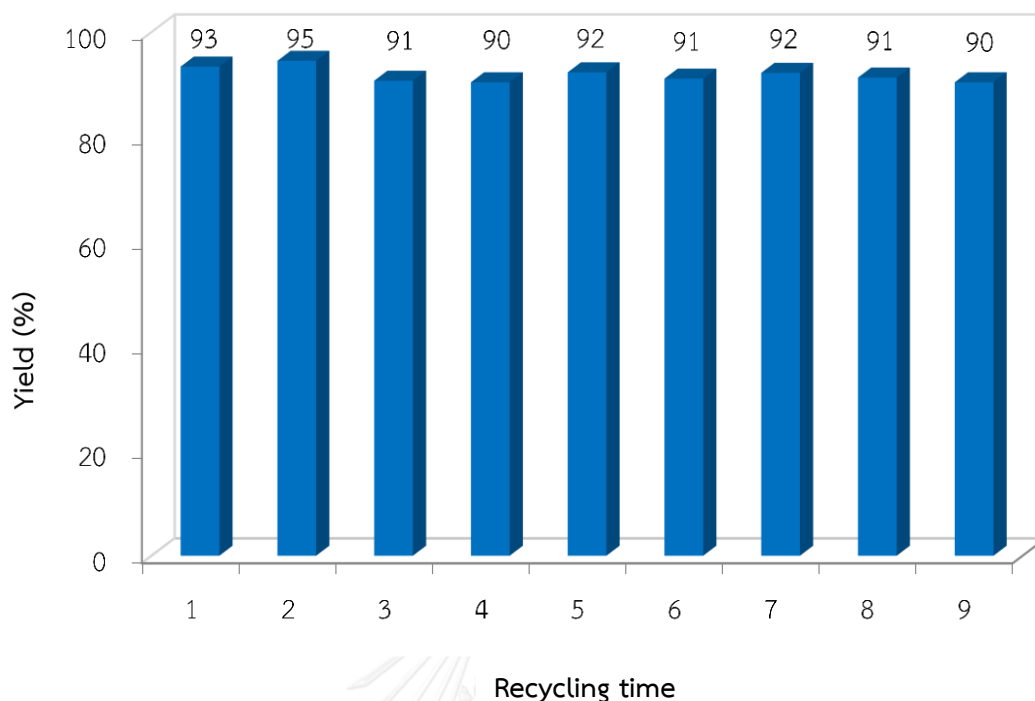
Figure 2.9 The recycling of FeCl₃/[hmim]Br on the oxidation of 1-phenylethanol

under the optimized conditions

Nine reactions were carried out successively under the optimized conditions by using the same catalytic system. The first reaction (1st cycle) generated the desired product in 93% yield without any substrate recovery. Next cycles yielded the only one ketone over 90% (2nd to 8th cycle). Moreover, the last reaction (9th cycle) also provided the expected product in excellent yield. Therefore, those results showed that a new developed catalytic system could be recovered and reused at least nine times without significant loss of the product yield.
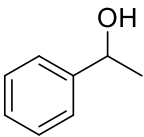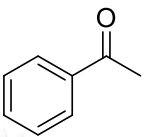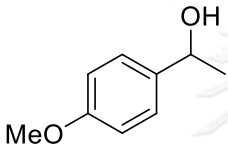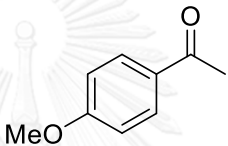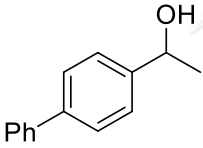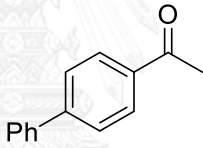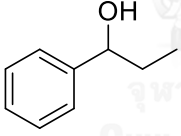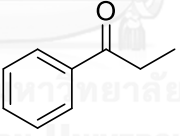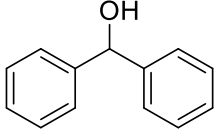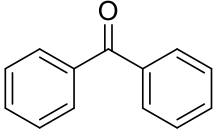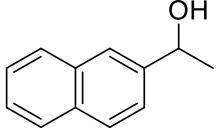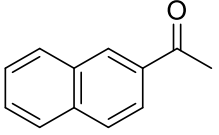
2.5.4 Oxidation of Various Alcohols in Ionic Liquids

The optimal conditions for 1-phenylethanol was further extended to various types of alcohols including primary, secondary, and tertiary ones. The methodology study is summarized in Table 2.3.

Various secondary alcohols could be smoothly and selectively converted to the corresponding ketones in high to excellent yields (entries 1-8). The transformation carried out with 1-phenylethanol (entry 1) completely generated the desired ketone

in excellent yield. This illustrated that the benzylic position had a profound effect to the oxidation under this developed protocol. To confirm the benzylic effect on the oxidation of alcohols, numerous derivatives of 1-phenylethanol were chosen (entries 1-6).
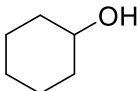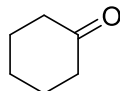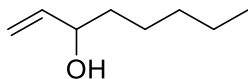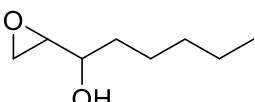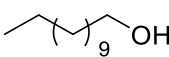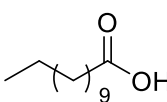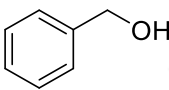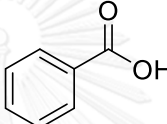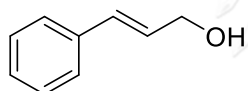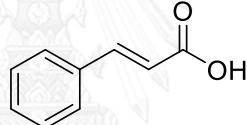
Table 2.3   Oxidation of alcohols with $FeCl_3$/[hmim]Br and TBHP[a]

Entry	Substrate	Product	Yield (%)	MB (%)
1	1-phenylethanol (OH)	acetophenone (O)	93	93
2	MeO–C6H4–CH(OH)CH3	MeO–C6H4–C(O)CH3	90	90
3	Ph–C6H4–CH(OH)CH3	Ph–C6H4–C(O)CH3	92	92
4	1-phenyl-1-propanol (OH)	propiophenone (O)	94	94
5	diphenylmethanol (OH)	benzophenone (O)	90	90
6	1-(naphthalen-2-yl)ethanol (OH)	2-acetylnaphthalene (O)	90[b]	-

[a] All reactions were carried out with substrate (1.7 mmol), 1.5 mol% $FeCl_3$, 6.0 equiv of TBHP (5.5 M in decane) in [hmim]Br (1mL) at 80 °C

[b] Isolated yield

Table 2.3   Continue[a]

Entry	Substrate	Product	Yield (%)	MB (%)
7[c]			82	97
8			40[b]	-
9[c]			38	76
10			quant.	quant.
11			58[b]	-

[a] All reactions were carried out with substrate (1.7 mmol), 1.5 mol% $FeCl_3$, 6.0 equiv of TBHP (5.5 M in decane) in [hmim]Br (1mL) at 80 °C

[b] Isolated yield

[c] 0.85 mmol SM

In case of alcohols bearing substituents on a benzene ring including 4-methoxy-1-phenylethanol (entry 2), and 1-([1,1′-biphenyl]-4-yl)ethanol (entry 3), the substituent groups at *para*-position did not affect this reaction. For those adjacent to the benzylic position including 1-phenylpropanol, and diphenylmethanol (entries 4-5), the alkyl or benzyl group as steric hindrance did not show any effects on the reactions. Similarly, naphthalenic alcohol (entry 6) was also oxidized into the desired ketone in good yield. For other cases, the observation with cyclohexanol (entry 7) did not proceed completely and gave the desired product in only 82% with 17% substrate recovery; while, a secondary allylic alcohol (1-octen-3-ol; entry 8) was transformed to the

epoxide product instead. All of these results confirmed that the benzylic position was obviously a crucial position for the oxidation of alcohols under this catalytic system.

Comparing with secondary alcohols, primary alcohols (entries 9-11) displayed less reactive toward the system except for benzyl alcohol (entry 10) and the corresponding carboxylic acid became prominent. The reaction with 1-dodecanol and cinnamyl alcohol (entries 9, 11) provided the desired acid in low to moderate yields; while benzoic acid was found in quantitative yield under the oxidation of benzyl alcohol (entry 10). This demonstrated that the benzylic effect was predominant the same as that observed in previous reactions with 1-phenylethanol derivatives.

Another independent experiment was conducted to further study on the oxidation of 1,6-hexandiol catalyzed by $FeCl_3$/[hmim]Br.

Surprisingly, not only the expected product (caprolactone) not detected, the starting material also could not be found from GC. Due to the fact that [hmim]Br is water soluble IL; therefore, the substrate, which was also miscible in water, should be able to dissolve in the IL as the consequence. Then, the remaining IL containing $FeCl_3$/[hmim]Br after the extraction process was checked its identity with NMR technique (Figure 2.10).

Comparing the ^{1}H NMR spectra of [hmim]Br before and after doing the reaction, the whole spectrum from Figure 2.10 showed the same spectrum pattern of [hmim]Br as the pure one at δ 10.39, 7.42, 7.32, 4.36, 4.16, 1.94, 1.34, 0.90 ppm; however, four other signals (1, 2, 3, and 4) were also found at δ 6.90 (s, 1H), 3.66 (m, 4H), 1.60 (m, 4H), 1.41 (m, 4H) ppm. Those signals as confirmed by comparing with the literature belonged to 1,6-hexandiol [75]. These results supported the aforementioned prediction about the solubility of the substrate towards [hmim]Br. The hydroxyl part of the substrate could have interaction with the IL as with water, and because of that it was impossible for the substrate to make a contract with the oxidant which was in another layer. As the result, 1,6-hexandiol was intact to this catalytic system.

Thus, the investigations for polyhydroxy alcohols would no longer proceed because they should behave in the same manner as the starting model under this developed catalysis.
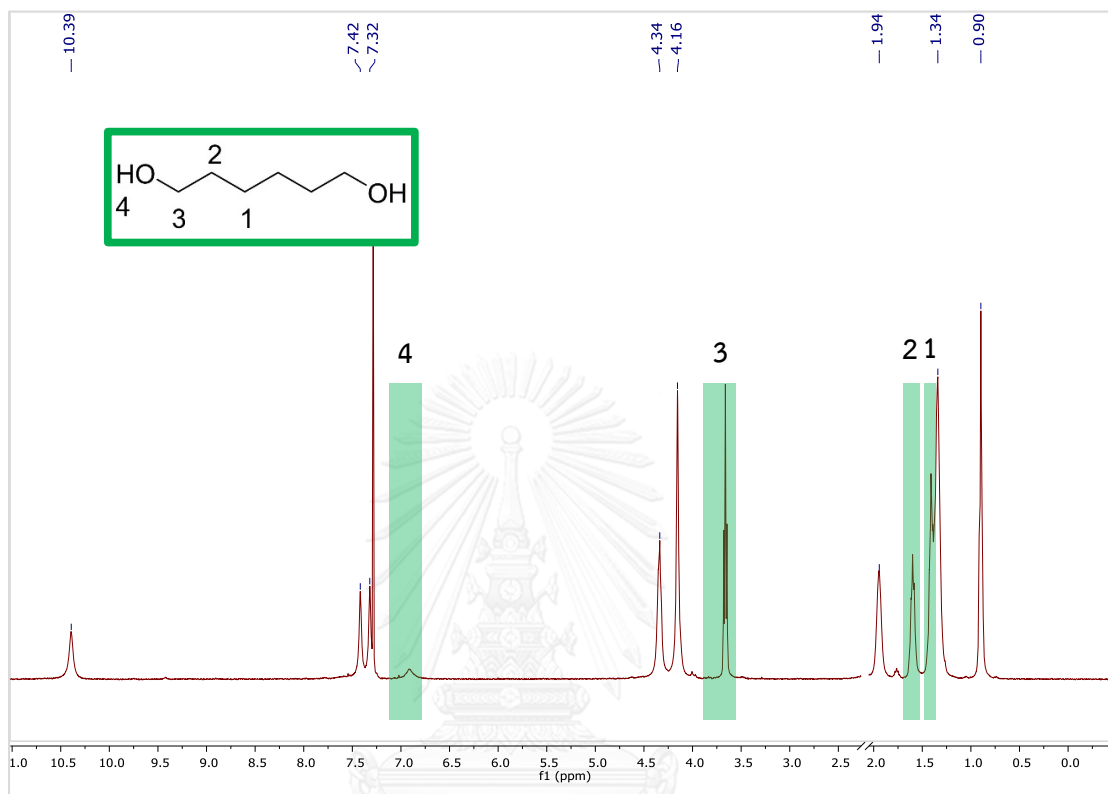
Figure 2.10 The ^{1}H NMR of the remaining IL from the oxidation of 1,6-hexandiol

2.6   Conclusion

The objective of this work is to search for a suitable catalytic system having a recyclability to transform any alcohols into their corresponding carbonyl compounds. The optimum condition of this developed protocol were systematically investigated. This developed methodology was truly displayed to be an excellent and convenient system for alcohol oxidation under recyclable catalytic system that could provide the desired products in high yield.

From this chapter, using alcohol (1 equiv) as substrate, 1.5 mol% FeCl$_3$ and [hmim]Br as a catalytic system at 80°C for 2h was shown to be the best condition for the oxidation of alcohols.

The investigation of several types of alcohols in order to study the scope of the reaction under this developed protocol could be summarized as:

1) Secondary alcohols; especially benzylic types, appear to be the most reactive substrates towards $FeCl_3$/[hmim]Br in the presence of TBHP.

2) Substituents on both of the aromatic ring and those adjacent to the benzylic position of benzylic alcohols have no effects to the oxidation reaction.

3) Secondary aliphatic alcohols are less reactive than the benzylic ones, while the chosen allylic alcohol is transformed to the epoxide product instead.

4) Except for benzyl alcohol, other primary alcohols show less reactivity toward the catalytic system and the major products are the corresponding carboxylic acids.

5) The catalytic system ($FeCl_3$/[hmim]Br) can be easily recovered and reused without any difficult recycling process.

6) Poly-hydroxy alcohols dissolve too well in [hmim]Br, and the transformation cannot proceed.

CHAPTER III

AROMATIZATION OF CYCLIC DOUBLE BONDS

3.1   Introduction

Due to aromaticity, benzene (C_6H_6) being known as the archetypical aromatic compound displays different physical properties, and more stability towards chemical reactions than normal conjugated double bonds [76]. Aromatic compounds not only consist of hydrocarbons (C and H), but also include heteroatom(s) such as nitrogen (N), oxygen (O), and sulfur (S) in the structures being classified as heterocyclic compounds. Figure 3.1 reveals examples of aromatic compounds.

| benzene | naphthalene | chrysene | imidazole | thiophene | furan |
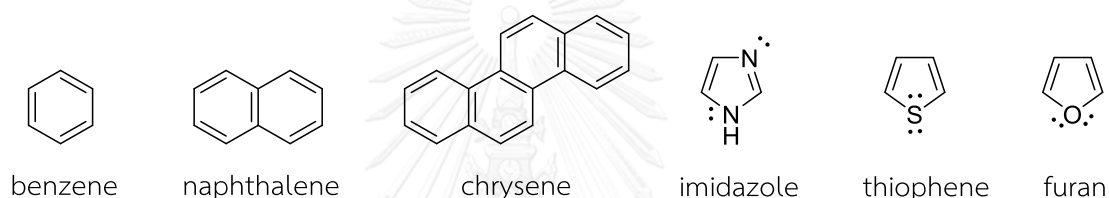
Figure 3.1 Examples of common aromatic compounds

Aromatics are generally found to be parts of naturally occurring substances [77] which normally provide bioactivities. In the past decades, those compounds played essential roles in medicine, pharmaceutical sciences, and manufactures [78]. Some of bioactive compounds used as drugs are shown in Figure 3.2.

| Baicalin | Valium | Claritin | Colchicine |
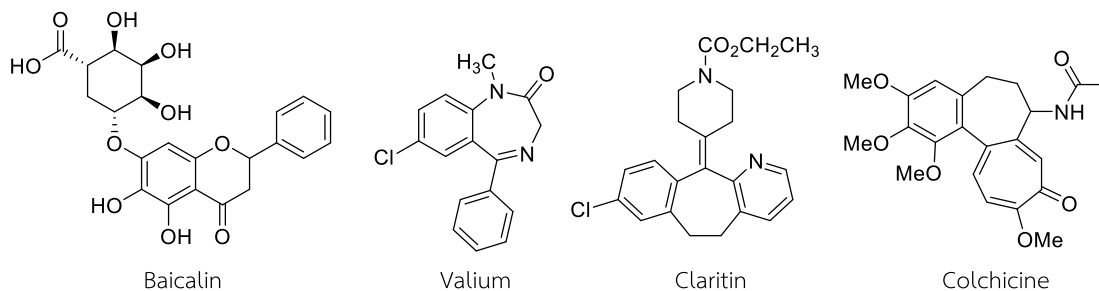
Figure 3.2 Examples of natural drugs containing aromatic compounds

To get the biologically active compounds from either nature sources or organic synthesis [79], not only many processes are involved but also the yields of the final product of those pure compounds should be concerned. Dehydrogenation is one of

those significant reactions for the synthesis as an essential step to gain the target bioactive products.

3.1.1 Introduction to the Preparation of Aromatic Compounds

3.1.1.1 Dehydrogenation

A chemical reaction for organic synthesis involving removal of hydrogen molecule is called dehydrogenation. This reaction is remarkable because even alkanes which have inert functional group can be converted. There is a lot of research using various catalysts for the dehydrogenation of alkanes. For example,

Iridium complexes containing pincer ligand [80] have been developed for alkene synthesis *via* dehydrogenation of alkane substrates since early 1970's.
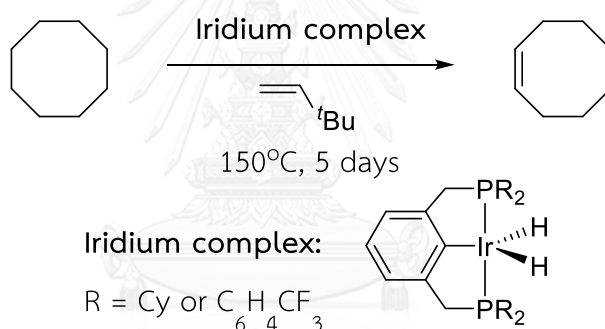
Quinone compounds such as chloranil and 2,3-dichloro-5,6-dicyanoquinone (DDQ) [81] as external oxidizing agents were used in a dehydrogenation step for some parts of steroid synthesis.
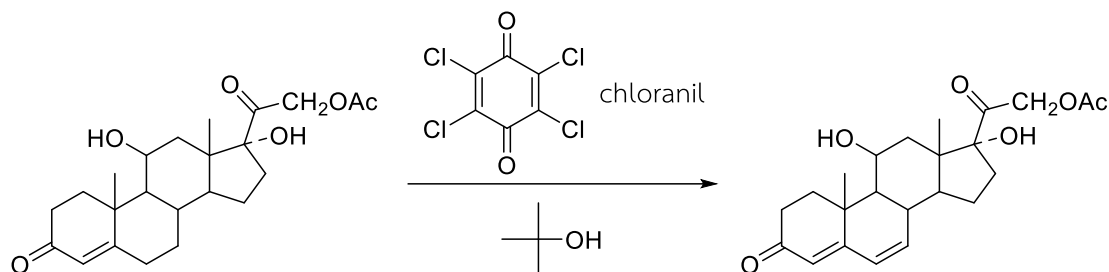
Chromium-based dehydrogenation catalysts being prepared by using alumina support (Cr/Al_2O_3) could be used for dehydrogenation of propane and isobutene to synthesize their desired alkenes as industrial products [82].

Even though these catalysts offered the desired product, a lot of disadvantages still remained such as operating at high temperature, requiring long reaction time. In addition, side-reactions were unavoidable in some cases.
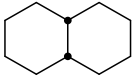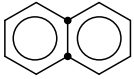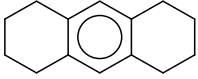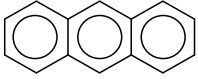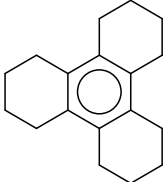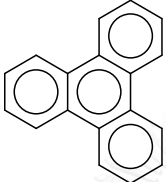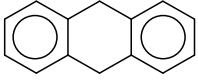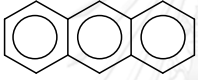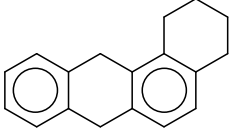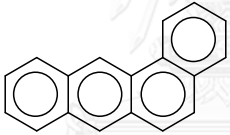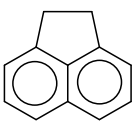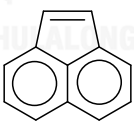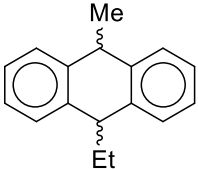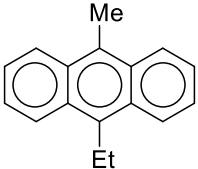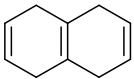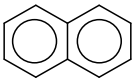
3.1.1.2 Aromatization

The aromatization is a part of dehydrogenation process after removing hydrogen molecule(s) from substrates; especially cyclic compounds, and then the products subsequently turn into aromatics as the most stable products. In the past, a number of research have been developed to synthesize aromatic compounds with numerous catalysts and reagents. Table 3.1 represents some aromatization of polycyclic hydrocarbons with various catalytic systems.

According to Table 3.1 [83], three major groups of catalysts were reported for the aromatization of polycyclic hydrocarbons: single metals, metal complexes, and oxidizing agents. The use of single metals, and metal complexes afforded aromatic products in high yield; however, high temperature and long reaction time were required. Thus, some substrates could not withstand under these conditions, and then generated side products. In case of using oxidizing compounds, long reaction time were spent with stoichiometric amount of catalysts.

With all of these problems, alkenes have been studied as other types of substrates in order to develop new methodologies for aromatization in considering of mild conditions and high productivity.

Table 3.1   Aromatization of various polycyclic hydrocarbons

Substrate	Product	Catalyst	Condition	Yield (%)
a) Single metal catalysts				
		Pt/C	300°C	95
		Pd/C	Reflux, 1 h	100
		Cu	450 – 500°C	-
b) Metal complexes				
		RhCl(PPh$_3$)$_3$	225°C, 15 h	97
		IrCl(CO)(PPh$_3$)$_2$	225°C, 12 h	92
c) Oxidizing compounds				
		p-Chloranil	benzene, 20 h	59
Me ... Et	Me ... Et	TTFA	20 h	85
		NBS, BPO	Reflux CCl$_4$	50

3.2 Literature Reviews

Alkenes, especially appropriate cyclic dienes, are easily aromatized into their expected aromatic products. Many reports have been addressed utilizing various metal catalysts for aromatization of both cyclic hydrocarbons and heterocyclic compounds.

3.2.1 Aromatization of Cyclic Hydrocarbons

Neumann [84] studied hydrocarbon aromatization catalyzed by heteropoly acid, $H_5PMo_{10}V_2O_{40}$ complex. Cyclic dienes were aromatized into their corresponding aromatic compounds in high yield under O_2 atmosphere.
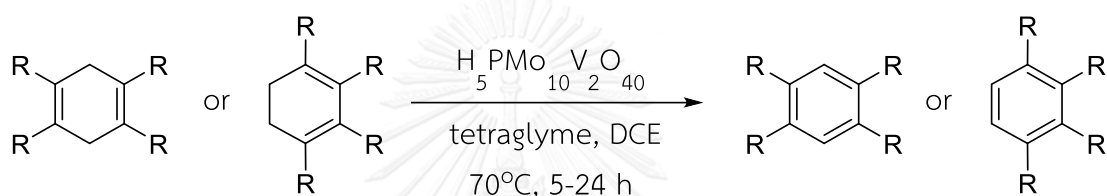
McBride and co-workers [85] reported the preparation of aromatic compounds from 1,4-cyclohexadiene and its derivatives utilizing $KMnO_4$ coated on alumina in acetone. The reactions afforded the expected products up to 95% yield, while 1,3-cyclohexadienes were intact under the developed method.
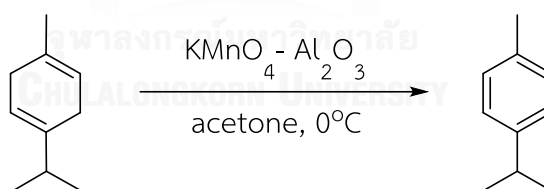
Kasai and co-workers [86] developed a recyclable heterogeneous ruthenium catalyst for aromatization of alkylarenes to give the desired aromatics under O_2 atmosphere. Moreover, the developed system could be used to oxidize other types of substrates into their oxygenated products under alternative solvent system.
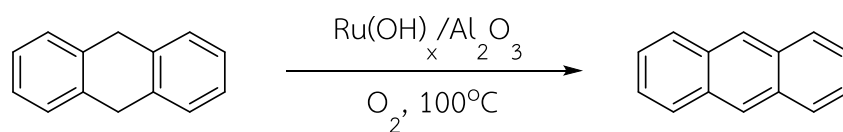
Breton and co-workers [87] exhibited electromediated oxidation to generate alkenone from activated alkenes and dienes catalyzed by TEMPO at controlled

potential in 2,6-lutidine. The aromatized products were the extension of this methodology with cyclohexadiene.
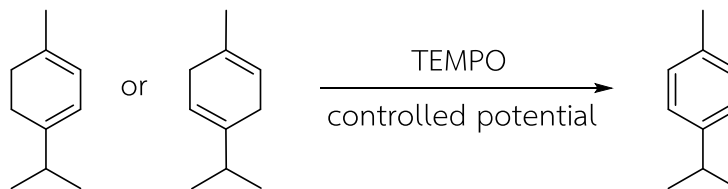
Ichihara and co-workers [88] demonstrated the aromatization of α-terpinene to *p*-cymene by developing a recyclable solid-phase system of FAp disperse phase and vanadomolybdophosphoric acid ($H_{3+n}PV_nMo_{12-n}O_{40}$: PV *n*) under O_2 atmosphere.
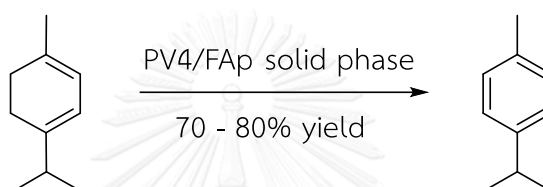
Buranaprasertsuk and co-workers [89] addressed cobalt(II) calix[4]pyrrole complex as a catalyst in the presence of aldehyde/oxygen for alkene epoxidations. *p*-Cymene as an aromatized product could be generated from cyclohexadienes.
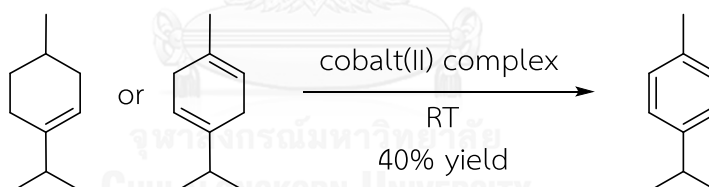
Bercaw and co-workers [90] described palladium(II) trifluoroacetate catalytic system for cyclic-olefin aromatization under O_2 atmosphere.
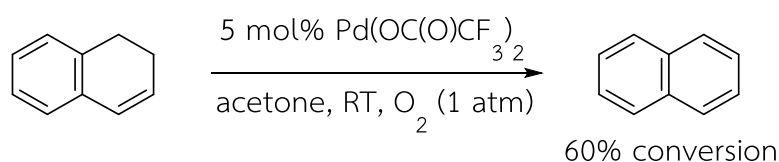
Gusevskaya and co-workers [91] explored copper-catalyzed reactions with or without *p*-benzoquinone (BQ) for aromatization of *para*-menthenic terpenes yielding *p*-cymene with O_2. Using BQ alone provided the expected product in good yield under acidic condition with 80-100 $^\circ$C, 5-10 atm of O_2. On the other hand, using $Cu(OAc)_2$ as

a co-catalyst could make the reaction perform even under atmospheric pressure (1 atm).
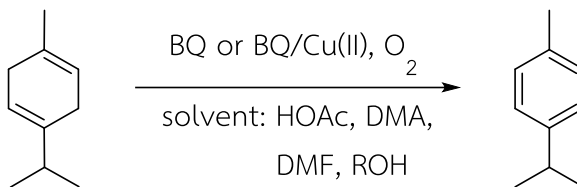
Zhang and co-workers [92] investigated the aromatization of dihydroarenes to their aromatic products utilizing DDQ and $NaNO_2$ with O_2. 9,10-Dihydroanthracene was aromatized to anthracene with 99% conversion under 120 ^{o}C for 8 h.
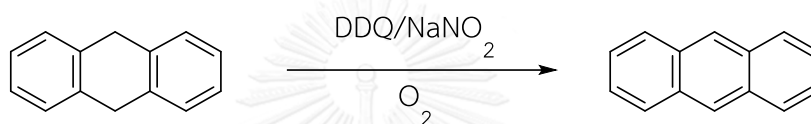
Ngamsomprasert and co-workers [93] developed an efficient catalytic system of copper salt combining with TBHP for aromatization of conjugated and skipped cyclic dienes yielding high aromatic products in short reaction time under mild conditions.
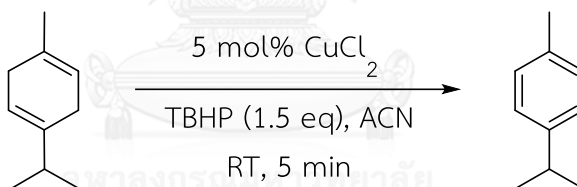
Asikainen and co-workers [94] exhibited the aromatization of γ-terpinene to *p*-cymene under continuous flow reactor with catalyst- and solvent-free system in air. The expected product was found successively in similar yield during 50 h experimental time.
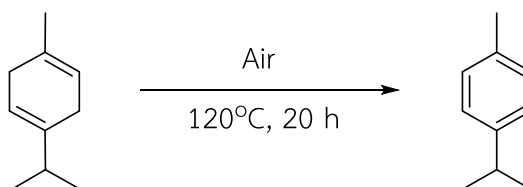
Ronzani and co-workers [95] reported silica-supported sensitizer acting as a catalyst for the oxidation of α-terpinene under UV-Vis. *p*-Cymene was found in all reactions tested. Three photosensitizers (Sens) were used including anthraquinone-2-

carboxylic acid (ANT-COOH), 9,14-dicyanobenzo[b]triphenylene-3-carboxylic acid (DBTP-COOH), and rose bengal sodium salt (RB)
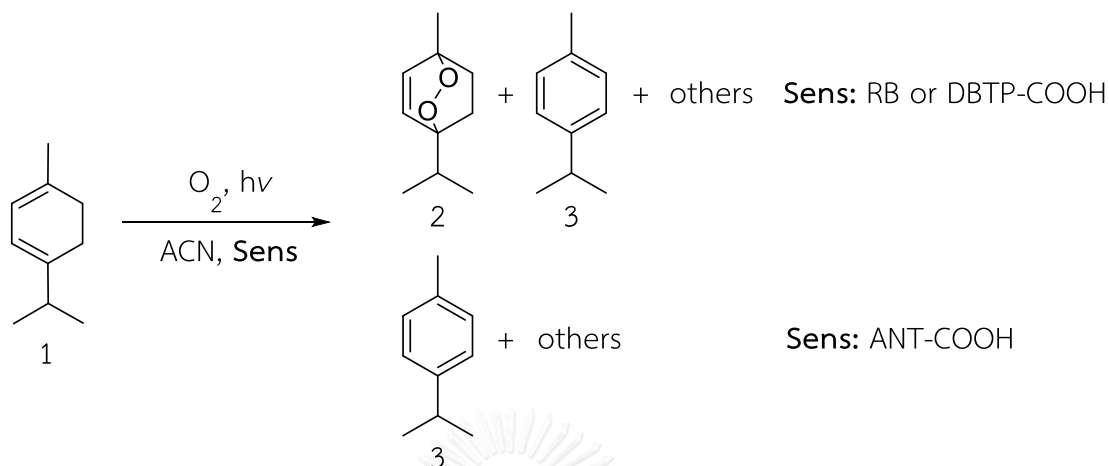
3.2.2 Aromatization of Heterocyclic Compounds

Speier and co-workers [96] studied kinetic and mechanism of the aromatization of indolines to indoles with O_2 by comparing the results between copper(I)-complex and copper(II)-salt catalysts. Using Cu(II)-salt, indole product was generated in 78% yield with high exothermicity in CAN, while 92% of product was obtained using [CuClpy]$_n$ complexes at 25 °C in DCM.
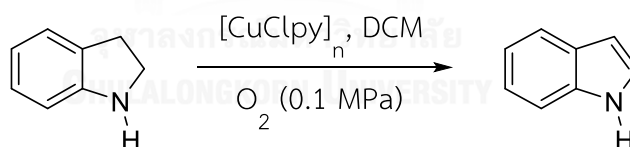
Periasamy and Srinivias [97] reported $TiCl_4$ coupled with Et_3N as a catalytic system for enamine aromatization. Several enamines prepared from cyclohexanone derivatives and various secondary amines were examined under the developed reagent system. The corresponding aromatic amines were obtained in 67-84% yield.
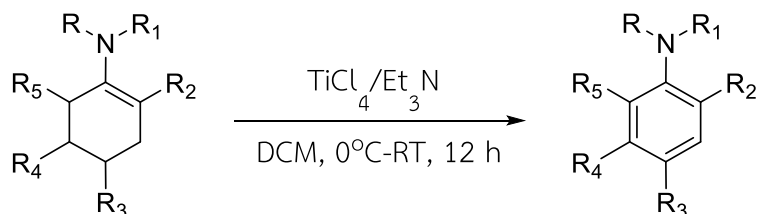
Hara and co-workers [98] demonstrated an efficient hydroxyapatite-bound palladium catalyst (PdHAP) with reusable ability for the transformation of indolines into their aromatized indole products.
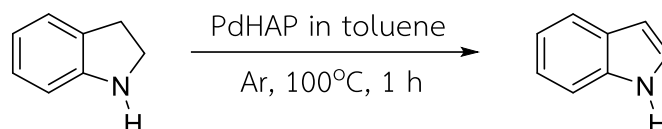
Chandra and co-workers [99] explored the aromatization of α-indoline nucleosides to the desired α-indoles which are parts of natural vitamins catalyzed by manganese dioxide and molecular sieves in benzene or DCM.
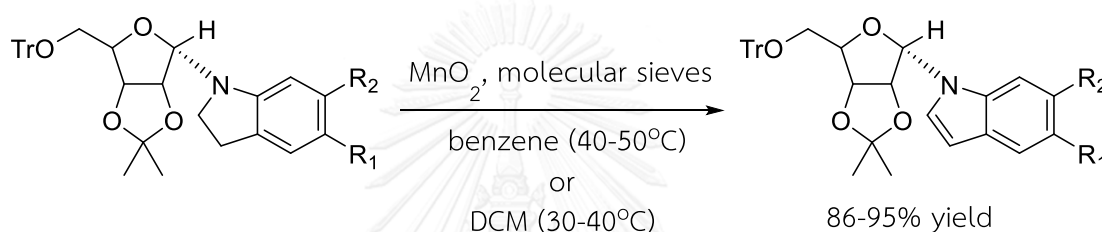
Herevi and co-workers [100] described a catalytic system of ferric perchlorite/acetic acid for Hantzsch oxidation of 1,4-dihydropyridines to synthesize pyridine derivatives. The aromatized products were found with high to excellent yields in a few hours at room temperature.
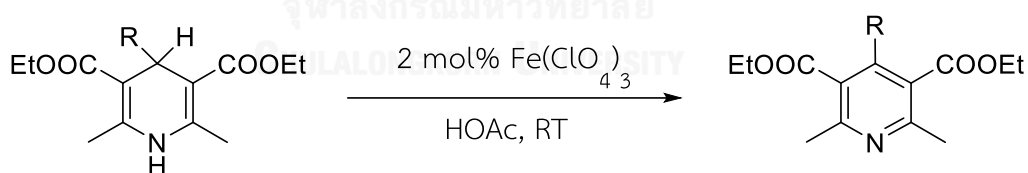
Yamamoto and co-workers [101] displayed the preparation of dihydropyrimidines from the oxidation of dihydropyrimidinones under the catalytic system of copper salt, base, and TBHP. Numeral substrate derivatives were aromatized into their expected products in high yield.
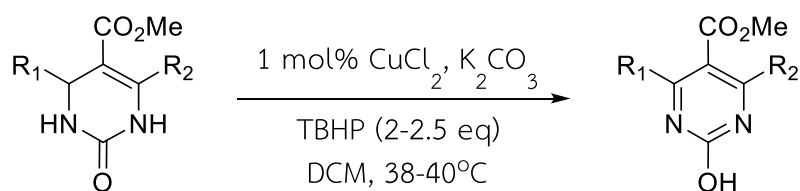
Litvić and co-workers [102] showed Hantzsch-1,4-dihydropyridine transformation into the desired pyridines which were similar to natural occurring substances by treating with iron(III) complex and TBHP.
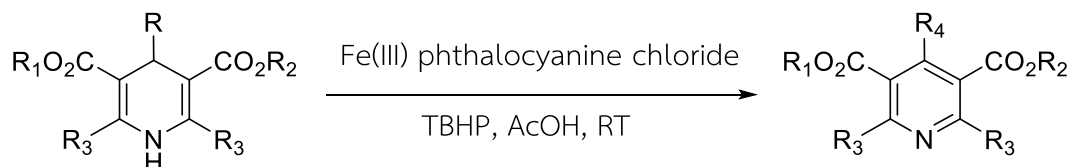
Ramirez and co-workers [103] investigated C-C double bond formation *via* dehydrogenation with Cu(I) and a few co-catalysts in order to prepare numerous heterocycles.
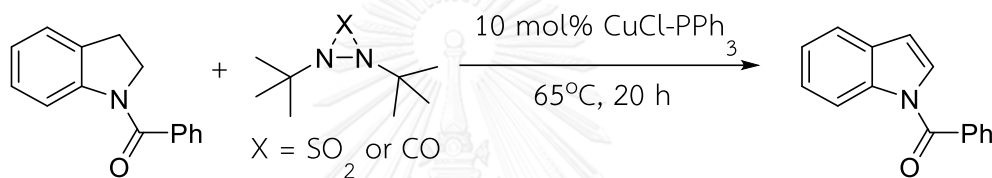
Huang and co-workers [104] addressed imine formation from dehydrogenation of various secondary amines using Cu/TEMPO catalytic system. Heterocycle substrates were oxidized into their aromatized products with excellent yield.
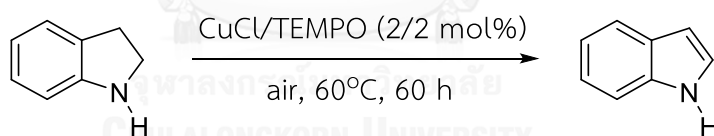
Damodara and co-workers [105] studied the dehydrogenation of amines and alcohols activated by carbon nanoparticles. Copper aluminum hydrotalcite (Cu-ALHT) was reduced into $Cu(0)/Al_2O_3$ which was a recyclable catalyst to prepare various heterocycles from their related dihydro-substrates.
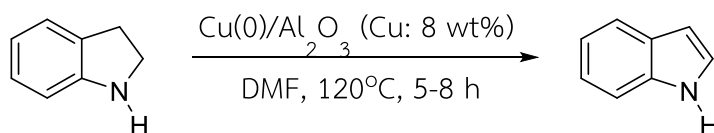
Peng and co-workers [106] demonstrated the preparation of several indoles from Cu(I)-catalyzed aromatization of indoline derivatives under mild conditions with

tert-butylperoxy 2-ethylhexyl carbonate (TBPC) as an external oxidant under electrochemical conditions
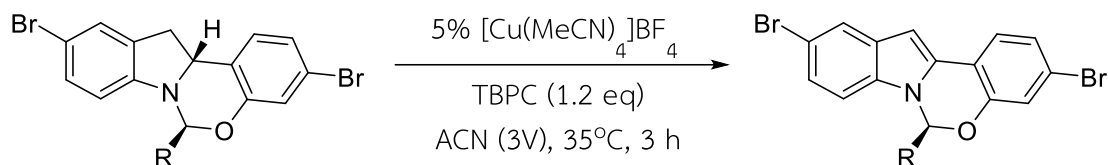
Maier and co-workers [107] explored the oxidative dehydrogenation and mechanistic study of *N*-protected indolines associated with frustrated Lewis pairs (FLPs). Under the best condition, the desired aromatized products were produced in moderate to excellent yield.
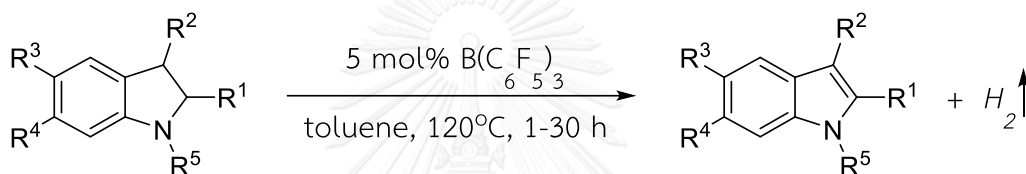
Referring to the aforementioned reports, many systems have been developed to afford aromatic compounds in high yield under mild conditions; however, they still encountered a lot of disadvantages. Some reactions needed to be conducted under low temperature due to high reactivity of catalysts or substrates, while some of them operated with long reaction time to prevent the side effects. In addition, complicated metal complexes for their reactions mostly required many reagents or steps in their preparation. Moreover, some catalysts and oxidants could not be reused in organic solvent system.

Among the above methods, there are a few reports using copper salt coupled with some oxidizing agents; especially TBHP, for the preparation of aromatic compounds *via* aromatization steps to provide some great profiles in terms of operation under mild condition with high product yields for both hydrocarbon and heterocyclic substrates.

3.2.3 Reactions with Copper Salts and TBHP

In this past decades, not only Cu-salt/TBHP system has been used in aromatization reactions, it has also been explored in many other types of chemical reactions.

Tan and co-workers [108] reported the use of Cu-salt/TBHP catalytic system for oxidative coupling between tertiary amines and siloxyfurans to prepare γ-aminoalkyl butenolides. Similar works were demonstrated under the system of rhodium catalysts which were much more expensive than the simple copper salt.
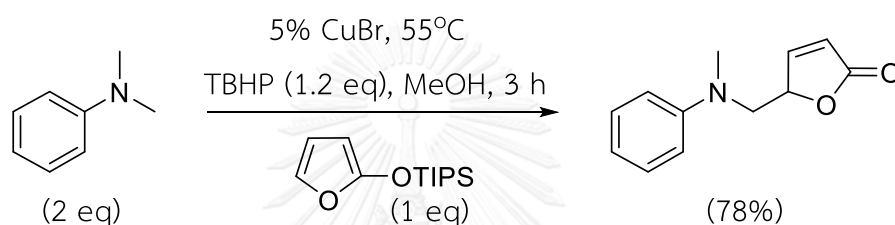
Li and co-workers [109] described Cu complex/TBHP system as a good protocol for the oxidation of Δ^5-steroids at allylic position. The desired enone products were produced up to 99% under the best condition.
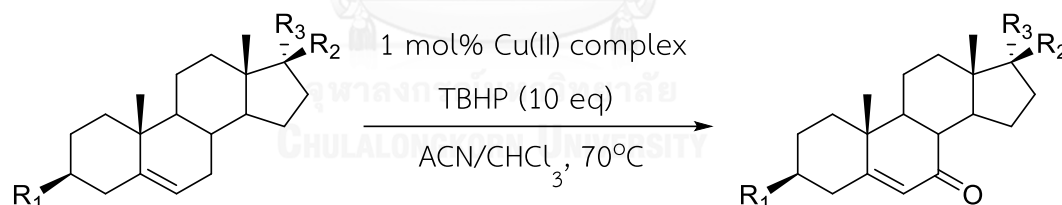
Xie and co-workers [110] exhibited the transformation of tertiary amines to α-amino imides in moderate to high yields involving with three-component congregation and Cu-salt catalyst.
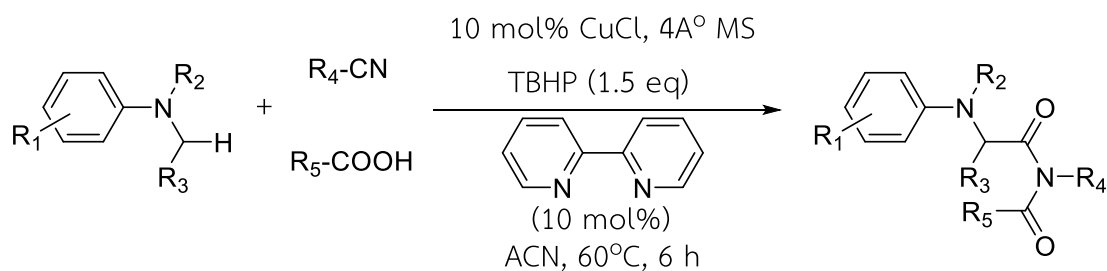
Rayati and co-workers [111] developed Cu(II) Schiff base catalysts for alkene oxidations in the presence of TBHP. Two Cu(II) complexes were synthesized, characterized, and performed in ACN with cyclooctene and styrene affording the corresponding epoxide and benzaldehyde as major products; respectively.

Complex	R	X,Y
Cu{salnptn(3-OMe)$_2$}	OMe	H,H
Cu{hnaphnptn}	H	XY: -CH=CH-CH=CH
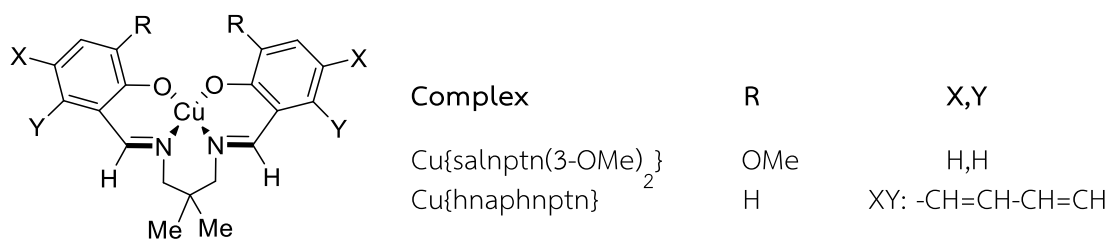
Huang and co-workers [112] presented a dehydrogenative cross-coupling of simple ethers and aryl ketones in the presence of pyrrolidine and TBHP associated with CuBr$_2$ *via* radical process.
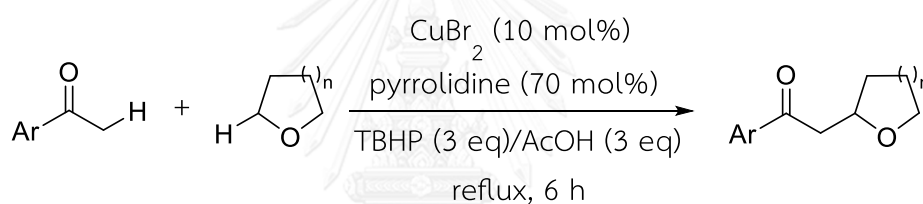
Deb and co-workers [113] explored the formation of naphthols and phenols *via* deaminative oxidation of Betti bases as activated by Cu salt/TBHP system *via* benzoylation or formylation in water.
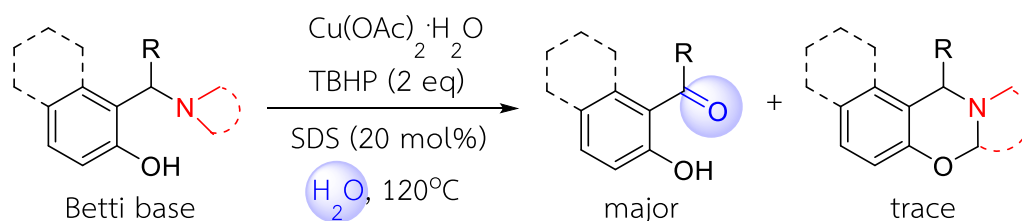
Hossain and Shyu [114] investigated the conversion of arylalkanes to ketones with Cu salts/TBHP in water at room temperature. A few bidentate bipyridine ligands were applied to the reactions in order to optimize this catalytic system. The desired ketones were detected in moderate to excellent yields.
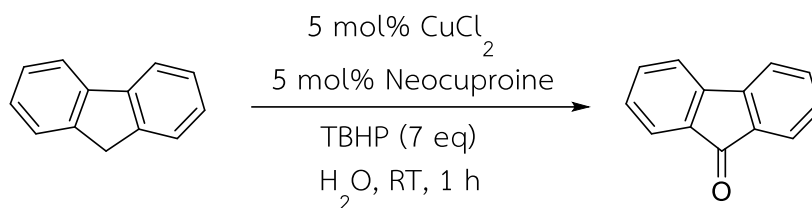
According to previous works relating to Cu salts or complexes associated with TBHP. They mostly operated *via* oxidation process to get the desired final products. In case of aromatization, Cu salt/TBHP system provided excellent product yields under mild condition; however, organic solvents, were necessary for the system. Because of their toxicity, non-recovered ability, and solubility with Cu salt which could not be separated after working-up process for the propose of reuse in next cycle, some developments have been reviewed with the usage of ILs to gain a recyclable catalytic system.

In this past decades, ILs have been used as solvents by many researchers; especially in catalytic oxidations which mainly used H_2O_2 as an oxidizing agent. It is due to the high activation energy of H_2O_2, metal catalysts are necessary for its activation process [107]. Thus, other oxidants such as O_2, and TBHP were applied to reduce the problems. Fortunately, using TBHP showed some benefits referring to the reviews even in organic solvent systems, therefore, it should be a challenge to create a new methodology that have never been reported before for aromatization, of those groups of substrates in ILs.

3.3   Scope of This Work

The methodology for the synthesis of aromatic compounds *via* aromatization of cyclic dienes utilizing metal salt/IL will be focused. The objective of this research is to develop a new catalytic system of simple transition metal salt (Cu salt)/neutral IL in the presence of TBHP for aromatization of cyclic dienes, and to examine the optimal condition to get the maximum yields of the desired products. Moreover, the aromatization of various substrates including conjugated, and skipped dienes, and indoline derivatives under developed protocol would be considered.

3.4   Experimental

3.4.1   Instruments and Equipment

Thin layer chromatography (TLC) was operated on aluminum sheets precoated with silica gel (Merck Kieselgel 60 PF_{254}). Column chromatography was carried out on silica gel (Merck Kieselgel 60, 70-230 mesh) or Alumina oxide (Merck Al_2O_3 - 90 active neutral, 0.063-0.200 mm, 70-230 mesh ASTM). Preparative thin layer chromatography was performed on 20x20 cm precoated with silica gel (Merck Kieselgel 60, GF_{254}).

The ^1H and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) with TMS as internal standard on the NMR Bruker Avance 400 spectrometer which operated at 399.84 MHz for ^1H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons.

The Shimadzu gas chromatography GC-14B (Varian CP-3800) equipped with CPsil8 or BP1 or BP21 column, FID detector, and N_2 as a carrier gas was employed to determine the quantity of the products or the quality of synthesized substrates.

3.4.2   Chemicals

All organic solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades. The reagents and substrates used for synthesis were purchased from Fluka, Aldrich, and TCI chemical companies and were used without further purification. Ionic liquids such as [bmim]Br, [hmim]Br, and [bmim]BF_4 used for this chapter were synthesized with the same method as in Chapter II. *N*-Heterocyclic starting materials were prepared following procedures found in literature, the detail of which will be discussed.

3.5   Aromatization of Cyclic Hydrocarbons

3.5.1   General Procedure

To convert cyclic dienes into their aromatized products, representative experimental process is displayed as follows: a mixture of 1 mL of [hmim]Br and 5 mol% $CuCl_2$ in round-bottom flask was gradually added γ-terpinene as substrate model, and 1.5 equiv. of TBHP (70 % in water). After stirring the reaction mixture at room temperature for 15 min, the mixture was extracted with Et_2O (10.0 mL x 3). Then, the organic layer was washed with distilled water, dried over anhydrous Na_2SO_4, and finally the product was quantified by GC with internal standard method.

3.5.2   Optimization Study

3.5.2.1 Effects of Solvent Systems

In order to find the most suitable solvent for this catalytic system, four solvents: MeCN as an organic solvent, [bmim]Br, [hmim]Br, and [bmim]BF_4 as ILs, were tested under the general condition.

3.5.2.2 Effects of Reaction Time

After choosing the best solvent for the system, various reaction times: 15 min, 30 min, 1 h, and 3 h, were examined to study their effects towards this catalytic system under the above condition to obtimize for more product yield.

3.5.2.3 Effects of TBHP Concentration

To improve the product yield to the maximum, amount of TBHP was varied from 0.0, 1.5, 3.0, 4.5 to 6.0 equiv based on the amount of the substrate.

3.5.3   Aromatization of Several Substrates

To understand the generality of this catalytic system for aromatization of cyclic hydrocarbons, the optimized condition from γ-terpinene aromatization was applied to

other substrates which are examples of conjugated and skipped dienes under the same procedure as the general protocol.

3.5.4 Recyclability of CuCl$_2$/[hmim]Br

After the reaction was complete under the optimum condition, the remaining IL containing CuCl$_2$/[hmim]Br was subjected to reduced pressure evaporator at 50 $^{\circ}$C for 2 h. Then, the IL was reused as a catalytic system for the next cycles of the same reaction in order to study its recyclability.

3.6 Aromatization on Heterocyclic Amines

3.6.1 General Procedure

Following the aromatization of cyclic hydrocarbons, the reaction of indoline, as a model compound, was carried out with the similar steps to the previous reaction using 5 mol% CuCl$_2$, 3.0 equiv of TBHP (70 % in water) in [hmim]Br at room temperature for 15 min. The product yield was quantified by GC with internal standard method.

3.6.2 Preparation of Indoline Derivatives

With the target *N*-subsituted indolines which are mostly commercially unavailable, numerous reactions were chosen to prepare these compounds according to various relating reports.

3.6.2.1 Preparation of 1-Benzylindoline

To a solution of benzyl chloride (200 mmol, 24 mL) in THF (100 mL) was added with a mixture of indoline (180 mmol, 20 mL), and 5M NaOH (30 mL) at room temperature. After stirring for 24 h, the reaction was quenched with water and extracted with Et$_2$O (100 mL x 4). The organic layer was dried over anhydrous MgSO$_4$, and evaporated. Then, the crude reaction was purified by silica gel column using DCM:*n*-hexane (3:7) as mobile phase. The product is known, and its identity was found to be the same as the literature [115].

1-Benzylindoline: light yellow oil; ^{1}H NMR (CDCl$_3$) δ 7.45 – 7.36 (m, 4H), 7.34 – 7.31 (m, 1H), 7.17 – 7.10 (m, 2H), 6.75 (m, 1H), 6.59 (d, J = 7.8 Hz, 1H), 4.31 (s, 2H), 3.38 (t, J = 8.3 Hz, 2H), 3.02 (t, J = 8.3 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 152.3, 138.3, 130.2, 128.5, 128.0, 127.4, 127.2, 124.6, 107.4, 53.9, 53.6, 28.6.

3.6.2.2 Preparation of 1-Boc-indoline

Similar protocol for *N-tert*-butoxycarbonylation of aliphatic amines from a literature was adjusted in order to prepare 1-Boc-indoline as a substrate. To a stirred solution of indoline (2 mmol, 1 equiv.) and Boc$_2$O (2 mmol, 1 equiv.) in DCM (0.4 mL) was gradually added 10 mol% of hexabromoacetone (Br$_3$CCOCBr$_3$) at room temperature. After stirring overnight, the reaction was checked with TLC and then stopped by removing the solvent with reduced pressure evaporator. Then, the crude reaction was isolated by flash column chromatography (SiO$_2$, hexane/ethyl acetate 50:1 to 15:1), and finally the product was confirmed by comparing its identity (^{1}H and ^{13}C NMR) with literature [116].

1-Boc-indoline [117]: pale pink solid; ^{1}H NMR (CDCl$_3$) δ 7.50 - 7.68 (br s, 1H), 7.18 (m, 2H), 6.95 (m, 1H), 4.00 (t, J = 8.3 Hz, 2H), 3.11 (t, J = 8.7 Hz, 2H), 1.60 (s, 9H); ^{13}C NMR (CDCl$_3$) δ 153.0, 142.4, 131.2, 127.3, 124.7, 122.1, 114.7, 81.1, 47.6, 28.5, 27.3.

3.6.2.3 Preparation of 1-Benzoylindoline

At room temperature, to a stirred solution of indoline (1.1 equiv.), Et$_3$N (1.25 equiv.) in DCM (0.5 M) was gradually added benzyl chloride (1 equiv.) resulting in a boiling solution. After stirring for 20 min, the solution was diluted with DCM and then transferred to a separation funnel containing 1N HCl. The organic phase from the extraction was dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The desired product was isolated from the oily residue by flash chromatography with hexane/EtOAc and then purified by recrystallization with n-hexane to afford 80% yield of the pure compound [118].

1-Benzoyl-indoline [119]: white solid; ^{1}H NMR (CDCl$_3$) δ 8.47 – 6.93 (m, 9H), 4.10 (br s, 2H), 3.14 (t, J = 8.2 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 169.0, 142.6, 137.0, 130.3, 128.6, 127.1, 124.9, 123.9, 117.0, 50.6, 28.1.

3.6.2.4 Preparation of 1-Tosylindoline

A mixture of *p*-toluenesulfonyl chloride (TsCl – 2.0 mmol) and indoline (2.0 mmol) in DCM (6.7 mL) was added Et$_3$N (4.0 mmol) dropwise. After stirring at room temperature for 17 h, DCM was removed from the reaction by evaporation. After that the residue was added saturated aqueous NaHCO$_3$, and extracted with EtOAc (x3). The combined organic phases were washed with brine, and dried over anhydrous MgSO$_4$. The solution was concentrated to get the solid residue which were purified afterwards by recrystallization with 95% EtOH. The desired product was confirmed of its structure by comparing its ^{1}H, and ^{13}C NMR with the literature [120].

1-Tosylindoline [121]: pale pink solid; ^{1}H NMR (CDCl$_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.2 Hz, 1H), 7.24 (d, J = 8.2 Hz, 2H), 7.20 (m, 1H), 7.10 (d, J = 7.2 Hz, 1H), 6.99 (m, 1H), 3.93 (t, J = 8.4 Hz, 2H), 2.91 (t, J = 8.4 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 144.0, 142.0, 134.1, 129.6 (x2), 127.7, 127.3 (x2), 125.1, 123.7, 115.0, 49.9, 27.9, 21.5.

3.6.3 Preparation of Indole Derivatives

For using GC with internal standard as quantifying method for the product yield, all of relating indole products which are not commercially available were synthesized by the following methods in order to use them as standards. Moreover, the expected products from their aromatization were also isolated from those reactions to compare with the synthesized indoles.

3.6.3.1 Preparation of 1-Benzylindole

Referring to the literatures about synthesis of 1-benzylindole, most of the reactions required many steps of adding reagents, and also a lot of process for purification of the target product. Therefore, 1-benzylindole in this work was prepared from the isolation of the aromatization which carried out under the general procedure

using 5 mol% CuCl$_2$, 3.0 equiv of TBHP, room temperature for 15 min. The expected product was purified by silica gel column with DCM:*n*-hexane (3:7) solvent system.

1-Benzylindole [122]: yellow oil; ^{1}H NMR (CDCl$_3$) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.31 (m, 4H), 7.26 – 7.15 (m, 5H), 6.63 (d, *J* = 2.9 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (CDCl$_3$) δ 137.6, 136.4, 128.8, 128.3, 127.6, 126.8, 121.7, 121.0, 119.6, 109.7, 101.7, 50.11.

3.6.3.2 Preparation of 1-Boc-indole

Adding DMAP (0.427 mmol, 52 mg), Et$_3$N (5.55 mmol, 0.768 mL), and Boc$_2$O (5.55 mmol, 1.211 mg) to a stirred solution of 1*H*-indole (4.27 mmol) in CH$_2$Cl$_2$ (50 mL) was carefully succeeded at room temperature. After stirring for 24 h, the solvent was removed by reduced pressure evaporator, then the crude reaction was added aqueous solution of NH$_4$Cl (30 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), and dried over anhydrous MgSO$_4$, respectively. Flash column chromatography was used to isolate the expected product from the crude reaction with Et$_2$O:*n*-hexane (5:95) solvent system. The product was identified by ^{1}H and ^{13}C NMR comparing with the previous report [123].

1-Boc-indole: colorless oil; ^{1}H NMR (CDCl$_3$) δ 8.07 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 3.5 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.25 – 7.21 (m, 1H), 7.17 – 7.13 (m, 1H), 6.50 (m, 1H), 1.60 (s, 9H); ^{13}C NMR (CDCl$_3$) δ 149.7, 135.2, 130.6, 125.9, 124.2, 122.6, 120.9, 115.1, 107.2, 28.2.

3.6.3.3 Preparation of 1-Benzoylindole

1-Benzoylindole in this work was isolated from the aromatization of 1-benzoylindoline following the general method using 5 mol% CuCl$_2$, TBHP (6.0 equiv), room temperature for 3 h. The desired product was purified by flash chromatography with EtOAc/*n*-hexane (2/98), and then identified the structure which is identical to the literature with NMR technique.

1-Benzoylindole [124]: pale yellow oil; ^{1}H NMR (CDCl$_3$) δ 8.43 (d, *J* = 8.3 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.66 – 7.54 (m, 4H), 7.46 – 7.31 (m, 3H), 6.64 (d, *J* = 3.7 Hz,

1H); ^{13}C NMR (CDCl$_3$) δ 168.8, 136.1, 134.7, 131.9, 130.8, 129.2, 128.6, 127.6, 124.9, 123.9, 120.9, 116.4, 108.6.

3.6.3.4 Preparation of 1-Tosylindole

1-Tosylindole was isolated from the aromatization of 1-tosylindoline based on the representative method using 5 mol% CuCl$_2$, TBHP (6.0 equiv), room temperature for 18 h. The desired product was purified by PTLC (EtOAc/*n*-hexane = 1/15), and then identified the structure which is identical to the literature with NMR technique.

1-Tosylindole [125]: white solid; ^{1}H NMR (CDCl$_3$) δ 8.01 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.35 – 7.21 (m, 4H), 6.68 (d, *J* = 3.6 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 144.9, 135.5, 134.8, 130.7, 129.8, 126.8, 126.3, 124.5, 123.2, 121.3, 113.5, 109.0, 21.5.

3.6.4 Aromatization Study on Various Starting Materials

General procedure from the aromatization of indoline substrate was examined by using different types of indolines; especially *N*-substituted indolines, to study the scope of this catalytic system. The desired indolines which are not commercially available were synthesized by the aforementioned methods.

3.7   Results and Discussion

A new and efficient recyclable catalytic system was developed and thoroughly investigated on the aromatization of both carbocyclic and heterocyclic dienes. The exploration of optimum conditions for these aromatizations was also fully observed in this chapter.

3.8   Aromatization of Cyclic Hydrocarbons

3.8.1   Condition Optimization

The aromatization of cyclic dienes was investigated in order to find the most suitable conditions using Cu-salt coupled with TBHP in [hmim]Br. Different factors

including solvent system, reaction time, and amount of TBHP were examined. γ-Terpinene (1 equiv) used as a starting model was treated under the typical condition using 5 mol% of $CuCl_2$, TBHP (1.5 equiv) in [hmim]Br at room temperature for 15 min. The expected product was determined by GC using naphthalene as the internal standard.

3.8.1.1 Effects of Solvent System

Four diverse solvents were selected to screen for the best media for the aromatization of cyclic dienes under general conditions. The results are demonstrated in Table 3.2.

Table 3.2   The effects of solvent system[a]
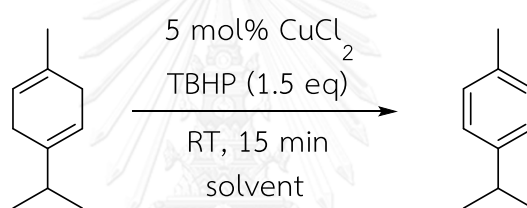
Entry	Solvent	Yield (%)	SM Recovery (%)	MB (%)
1	ACN	quant.	-	quant.
2	[bmim]Br	37	60	97
3	[hmim]Br	32	65	97
4	[bmim]BF$_4$	45	54	99[b]

[a] The product yield was determined by GC with naphthalene as the internal standard.

[b] the catalyst did not dissolve.

Using ACN (entry 1) yielded the expected product in quantitative amount, while the substrate was still remained in the reaction using ILs (entries 2-4). This is mainly due to the solubility of the catalyst, which completely dissolved in ACN; the possibility for the catalyst recovery after the extraction process with Et_2O in order to reuse in next reaction cycles could not possibly happen. Therefore, ILs were examined so that the problem was solved with regard to recycle of catalyst.

Using 1-alkyl-3-methylimidazolium ILs (entries 2-4) afforded the desired product in moderate yield. In case of using water-soluble ILs containing bromide anion (entries 2 and 3), $CuCl_2$ completely dissolved as homogeneous system with ILs. On the other hand, using [bmim]BF_4 (entry 4) showed the remaining of metal salt in the system. Figure 3.3 displays the solubility of Cu salt in those solvents before performing the reactions.

After finishing the reactions, during the extraction process entry 1 showed a homogeneous solution; while entries 2-4 presented heterogeneous with ILs in the lower part. After removing the organic layer the remaining ILs from entries 2-4 displayed the same condition as before for next round of reaction. Therefore, [bmim]Br and [hmim]Br were considered as the solvents of choice because of their solubility with Cu salt.

With the main purpose to develop a new recyclable catalytic system, the $CuCl_2$/[hmim]Br system was chosen because of its capability for oxidation with TBHP (Chapter II), solubility, uncomplicated procedure for the preparation, and none mentions in aromatization of cyclic dienes referring to previous works.

Pure solvent

5 mol% $CuCl_2$

Cu salt/ACN   Cu salt/[bmim]Br   Cu salt/[hmim]Br   Cu salt/[bmim]BF_4
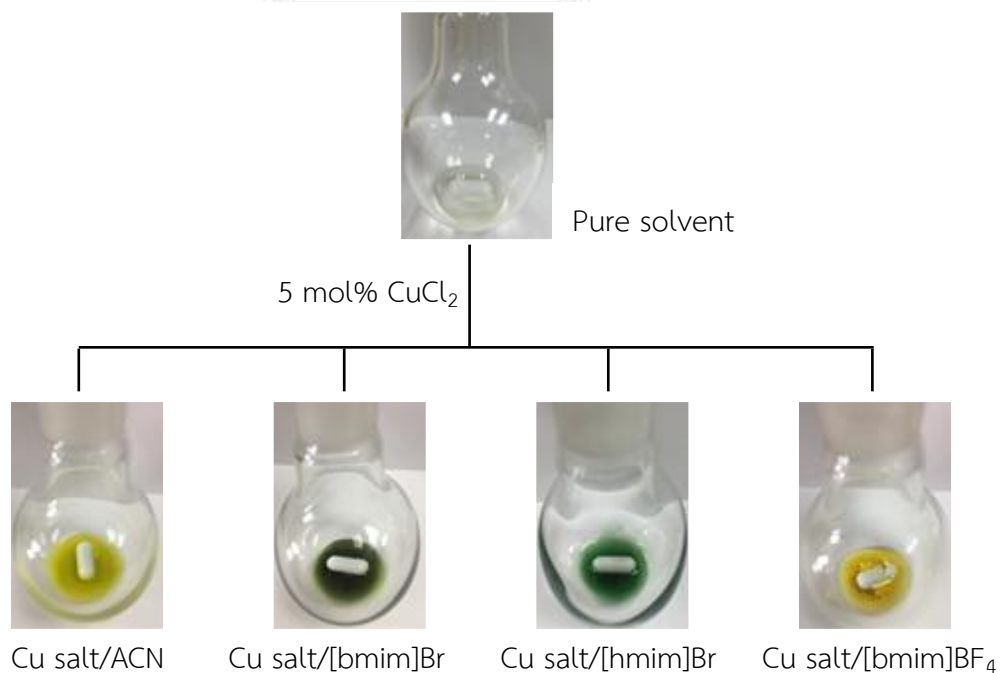
Figure 3.3 The solubility of Cu salt in the above reactions

3.8.1.2 Effects of Reaction Times

      With the intention to improve the product yield using [hmim]Br, the reaction was carried out by varying reaction times to study their effects towards the developed system as presented in Table 3.3.

      The reaction of γ-terpinene for 15 min (entry 1) provided *p*-cymene as the only product in 32% yield. Three longer reaction times were applied (entries 2-4) and found that the longer reaction time, the higher the product yields. Even though the reaction afforded the yield in 85% under the longest reaction time (180 min, entry 4), comparing with the yield at 60 min, not only the yield did not improve, but also the substrate still remained. Therefore, the shortest reaction time (15 min) was selected and other factors were further adjusted to improve the yield.

Table 3.3   The effects of reaction times[a]
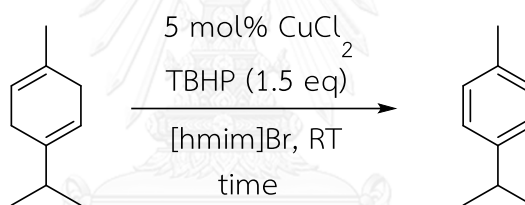
Entry	Reaction time (min)	Yield (%)	SM Recovery (%)	MB (%)
1	15	32	65	97
2	30	75	17	92
3	60	87	11	92
4	180	85	9	94

[a] The product yield was determined by GC with naphthalene as the internal standard.

3.8.1.3 Effects of TBHP Concentration

      Various amounts of TBHP were also applied to the reaction so that the higher yield could be achieved with short reaction time. The results are displayed in Table 3.4.

Amount of TBHP was considered as one of important parameters to improve the product yield. Trace amount of the expected product was found in the system without TBHP (entry 1), while with higher amount of TBHP provided the yield progressively (entries 2-5) with the maximum at quantitative yield. Using TBHP 1.5 equiv (entry 2) gave 32% yield of the product with the substrate recovery. Doubling amount of TBHP (entry 3) increased the yield greatly to more than 91% with a little bit amount of substrate remaining. Adding more concentration of TBHP (entries 4 and 5) made the reaction complete.

Table 3.4 The effects of amounts of TBHP[a]
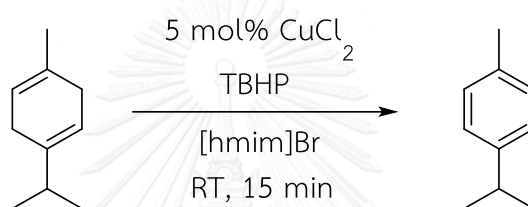
Entry	TBHP (equiv)	Yield (%)	SM Recovery (%)	MB (%)
1	0.0	3	93	96
2	1.5	32	65	97
3	3.0	91	5	96
4	4.5	99	-	99
5	6.0	99	-	99

[a] The product yield was determined by GC with naphthalene as the internal standard.

In summary, 4.5 equiv of TBHP should be enough to complete the reaction; however, in order to make the reaction complete within 15 min with other types of substrates, 6.0 equiv of TBHP should be used in excess. The optimum condition was concluded in Figure 3.4.
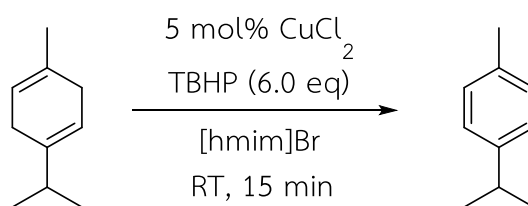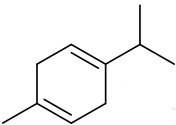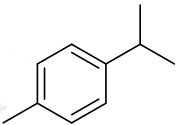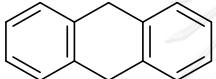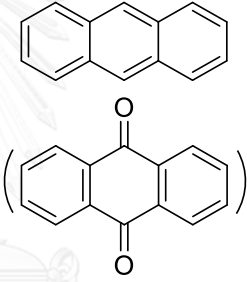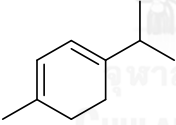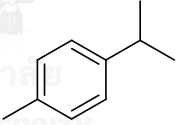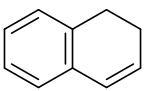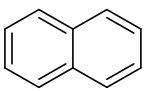
Figure 3.4 Optimum condition for aromatization of γ-terpinene

3.8.2 Variation of Substrates

Under the optimum conditions, other cyclic dienes were investigated in order to extend the scope of this catalytic system. γ-Terpinene and 9,10-dihydroanthracene were chosen as representatives of skipped dienes, while α-terpinene and 1,2-dihydronapthalene were models for conjugated dienes. The results are displayed in Table 3.5.

Table 3.5 Aromatization of conjugated and skipped dienes in [hmim]Br[a]

Entry	Substrate	Product	Yield (%)[b]
1			99
2			14 (72)
3			47
4			55

[a] All reactions were carried out with 1 mmol substrate, 5 mol % CuCl$_2$, 6.0 equiv of TBHP (70% in water) in [hmim]Br, RT, 15 min

[b] All products were quantified with GC by comparing with commercial standards using naphthalene as the internal standard.

In case of skipped dienes (entries 1 and 2), γ-terpinene (entry 1) was aromatized in excellent yield, while 9,10-dihydroanthracene (entry 2) generated the expected anthracene, and a diketone product (anthraquinone) in 14 and 72% yields, respectively. For conjugated dienes, both α-terpinene, and 1,2-dihydronaphthalene

(entries 3-4) produced their expected aromatic compounds in moderate yields which were however in the lower amount than the skipped ones.

Referring to previous work [126] studying on the C-H bond strength of conjugated and skipped dienes, the former required more energy to homolytically break C-H bond than the latter.
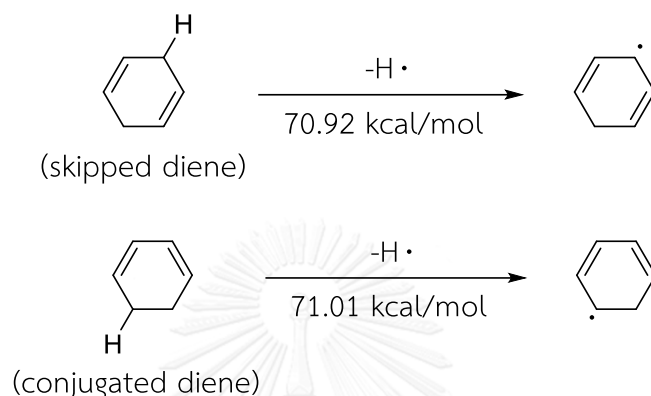
Moreover, based on the earlier report [93], which carried out under the similar conditions in ACN, α-terpinene, and other conjugated dienes required high temperature for their conversions, while skipped ones could be converted at room temperature. According to these results and observations, this should be a reason why conjugated dienes were transformed into their final products in lower yield than skipped ones under the same developed conditions at room temperature. For other reasons, the over oxidation/reaction derived from the excess oxidant may create side reactions. Another possibility was because of the nature of substance such as naphthalene (the product from entry 4), with low sublimating point.

The aromatization of 9,10-dihydroanthracene provided a diketone as a major product with small amount of anthracene. The reaction was further examined trying to adjust some factors to get higher amount of the expected product. Table 3.6 displays various conditions for the aromatization of 9,10-dihydroanthracene.

Conducting the reaction at higher temperature (60 °C) (entry 1), anthracene (**2**) was found in slightly higher yield than at room temperature; however, the diketone (**3**) was still detected as a major product. Thus, using higher temperature did not have much effects on the reaction. When longer reaction times were applied (entries 2-4),

the yields of the products were not different, and the reactions also did not go to completion. Treating the reaction by doubling concentrations of TBHP (entries 5-7), anthraquinone (**3**) was produced in the highest yield of 97% as the only product formed within 6 h (entry 7). Overall, this catalytic reaction of 9,10-dihydroanthracene displayed a competition between aromatization and benzylic oxidation. Figure 3.5 demonstrated possible pathways of both competitive processes of 9,10-dihydroanthracene.

Table 3.6   Aromatization of 9,10-dihydroanthracene (**1**) in [hmim]Br

Entry	TBHP (eq)	Reaction time	Yield (%)[a]	
			2	3
1	6.0	15 min	14 (26)[b]	72 (60)[b]
2		1 h	12	85
3		2 h	7	78
4		3 h	6	88
5	12.0	15 min	6	88
6		1 h	5	87
7		6 h	-	97

[a] GC yield with naphthalene as the internal standard

[b] at 60 °C
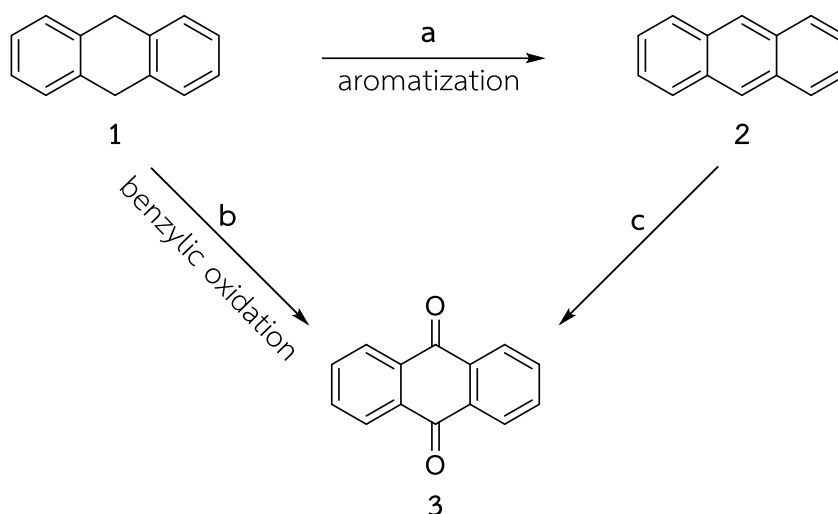
Figure 3.5 Possible pathways of both competitive processes of
9,10-dihydroanthracene (**1**)

Other separate examinations were conducted between those two possible pathways (Figure 3.6). Anthraquinone was synthesized from anthracene under the developed condition (I) in 54% yield. While diphenylmethane could undergo the reaction to generate the corresponding ketone product in 16% yield (II). According to these results, anthracene was converted into anthraquinone faster than benzylic oxidation.
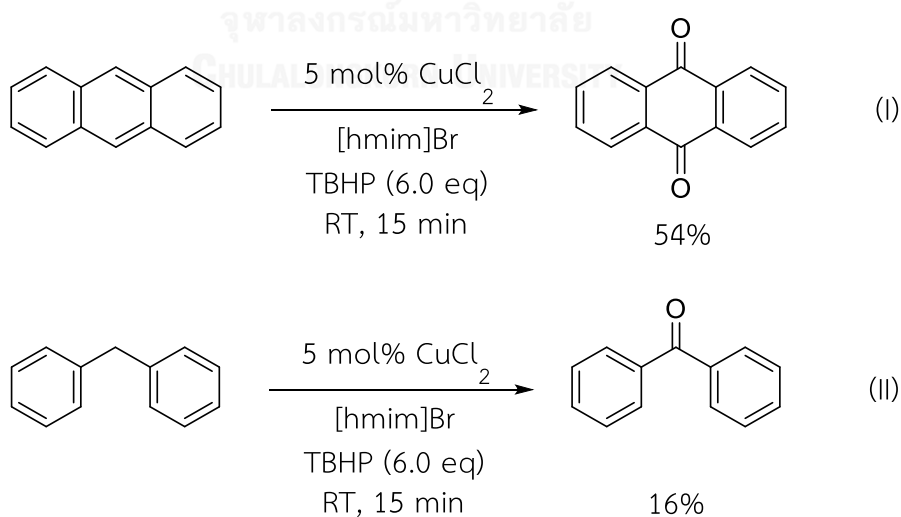
Figure 3.6 Additional experiments for the comparative study

Therefore, anthraquinone was possibly formed *via* pathway **a** to **c** (Figure 3.5). It seemed that the diketone could be rapidly generated from anthracene within short reaction time. It also implied that this system was not suitable for anthracene preparation without any factor adjustments. The condition development for this kind of substrates will be considered as the future work.

3.8.3 Recyclability of the Catalytic System

Continuing from the aromatization process, after extraction step to remove all of possible compounds such as the expected product, and the remained substrate from the reaction mixture, the recovered IL containing Cu salt and [hmim]Br was heated at 50°C under reduced pressure to remove all remaining organic solvents. After that, checking its composition with ^{1}H NMR (Figure 3.7). The crude ILs of both before and after the reaction showed the same color. Their ^{1}H NMR spectra displayed the same spectral patterns. Therefore, it was assumed that the catalytic system was intact after the reaction.

Owing to the above observation, the catalytic system was reused at that stage to study the recyclability by carrying out the reaction of γ-terpinene under the optimum in several cycles, repeatedly. Figure 3.8 presents the recyclability study of this catalytic system.
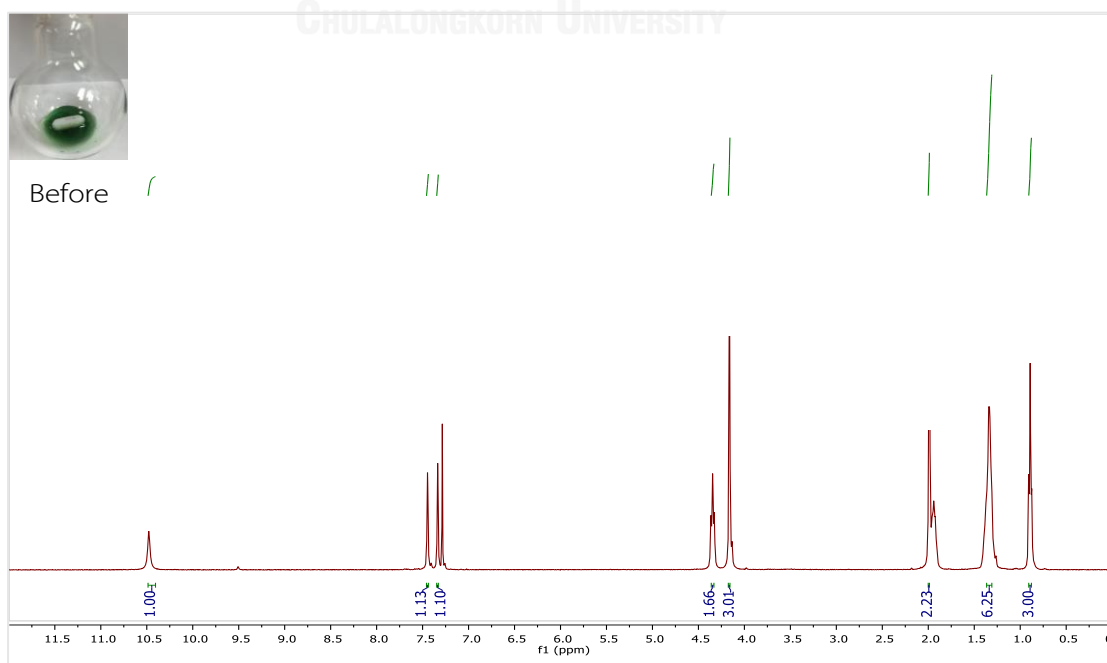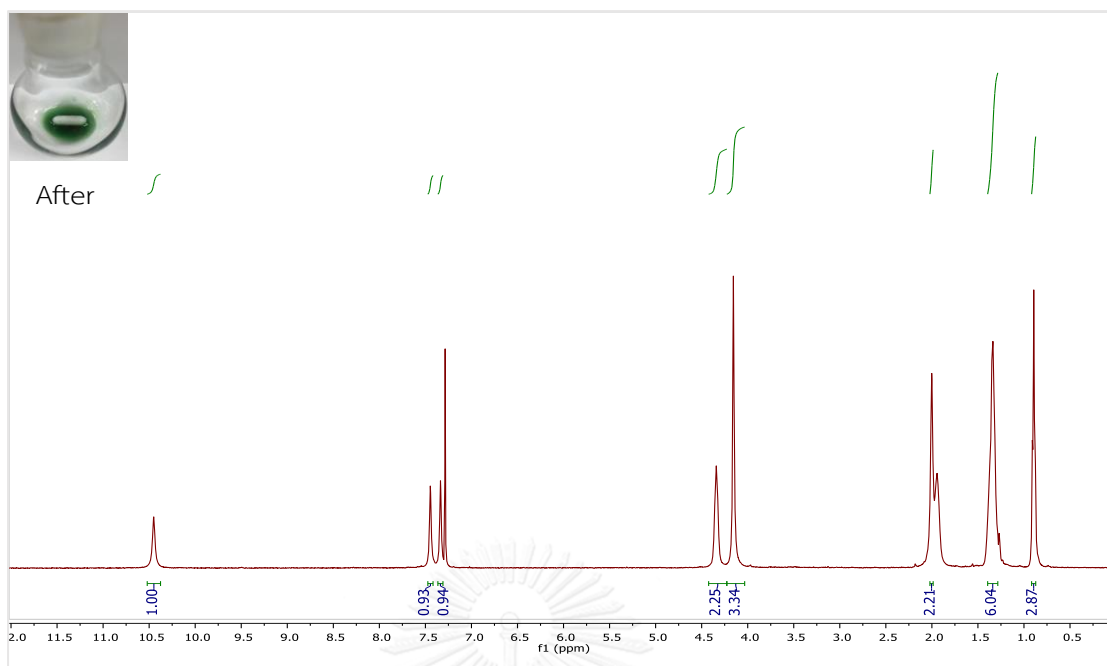
Figure 3.7 Comparative ^{1}H NMR spectrum between the mixture of CuCl$_2$/[hmim]Br before (top) and after (bottom) the reaction
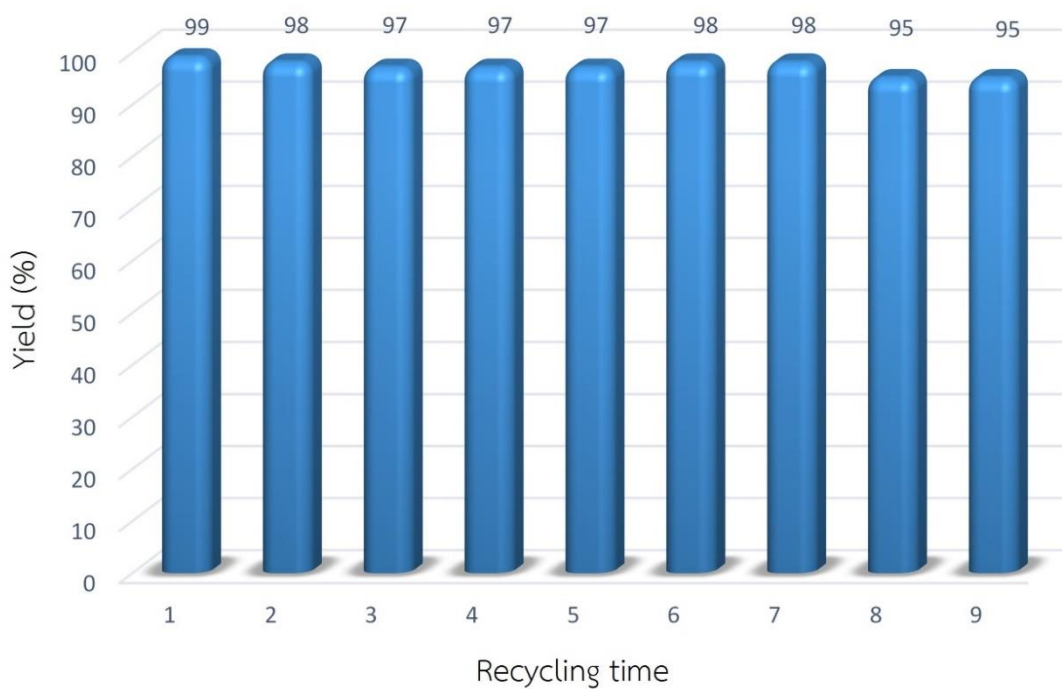
Figure 3.8 Recyclability study of CuCl$_2$/[hmim]Br for aromatization of γ-terpinene under the optimized condition

Numerous reactions with the same catalytic system were conducted successively based on the optimization. The 1st cycle afforded the desired product in

excellent yield with 99% as the only compound formed. Next cycles (2nd to 8th) provided the expected products with almost identical yields as the previous cycle. Last but not least, the 9th cycle generated the product in very excellent efficiency (95%). In conclusion, this new catalytic system (CuCl$_2$/[hmim]Br) displayed a recyclability because it could be reused at least nine times without any remarkable losses of the product yield.

3.9   Aromatization of Heterocyclic Amines

In accordance with a new recyclable catalytic system previously described for the aromatization of cyclic hydrocarbons, further examination with heterocyclic amines were selected. The aromatization plan is shown in Scheme 3.1.

PG = Protecting Group
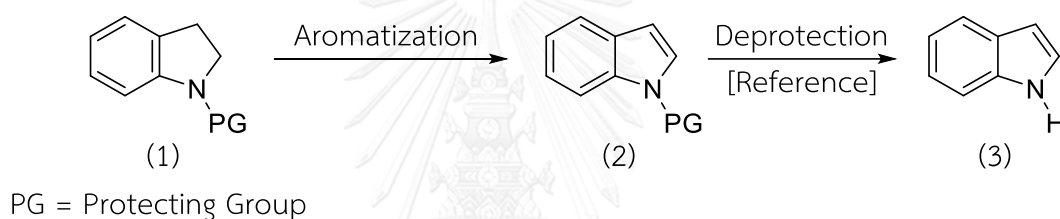
Scheme 3.1 Aromatization process

3.9.1   Aromatization of *N*-substituted indolines

With the same catalytic protocol, several indoline derivatives were examined and the results are collected in Table 3.7.

The corresponding aromatic product (1*H*-indole) was detected as the sole product in moderate yield (39%) from the reaction of indoline (entry 1). While the reaction was operating, the reaction mixture changed rapidly from green into dark-brown with the releasing of some heat. That may cause loss of the product yield on account of overreaction to form pyrrole polymerization [127-129]. With that result, the *N*-unprotected amine was too reactive even in short reaction time, then it would be difficult to distinguish the reactions between their derivatives which had different substituent on the core structure. Thus, *N*-substituted indolines were synthesized.

N-substituted indolines were prepared from the reactions between indoline and a variety of protecting groups to deactivate amines as presented in Scheme 3.1.

Table 3.7   Aromatization of *N*-substituted indolines in [hmim]Br[a]

Entry	Substrate	Product	Yield (%)[b]
1			39
2			65 (9)[c]
3[d]			40 (45)[e]
4[d]			24 (43)[e]
5[d]			0 (40)[e]

[a] General condition: substrate (1 eqiuv), 5 mol% $CuCl_2$, 3.0 equiv of TBHP, room temperature for 15 min in [hmim]Br

[b] GC yield by confirming the products with the references

[c] 1*H*-Indole

[d] Using 6.0 equiv of TBHP for 30 min

[e] The best yield of each reaction

Based on the results obtained from Table 3.7, under the same condition 1-benzyl (-Bn) indoline (entry 2) afforded the corresponding aromatic in higher yield than the unprotected one; however, 1*H*-indole was unexpectedly produced in a detectable amount. It may probably owe to a competitive process of the substrate de-protection which constantly took place in the same reaction.

In contrast, other *N*-substituents (entries 3-5) were affected on the reactions by transforming substrates into their expected indoles as sole products in the absence of the indole product. These protecting groups: *tert*-butyloxycarbonyl (*t*-Boc), benzoyl (-Bz), and *p*-toluenesulfonyl (-Ts) groups are virtually stable under any oxidizing agents. So, this developed system should be able to generate the corresponding aromatics as major products without any competitive reactions; especially de-protection. Moreover, the substituent stabilities could be used to explain different efficiencies of the reaction. Due to their electron-withdrawing effect, the latter indolines were non-reactive under the developed system (entries 3-5). Later, the reactions were modified by using more amount of either TBHP or reaction time. With doubling both TBHP amount and reaction time concurrently could afford the expected products in detectable yields except entry 5 with tosyl group. With longer reaction time more than 2 h, the maximum yields (entries 3-5) were around 40%.

3.10   Conclusion

3.10.1 Aromatization of Cyclic Hydrocarbons

This work aims to search for a new recyclable catalytic system to transform cyclic hydrocarbons; especially conjugated and skipped dienes into their corresponding aromatic products. Simultaneously, this develop protocol was also thoroughly investigated in order to obtain the optimum condition. This new methodology demonstrated an interesting and convenient system for aromatization under recyclable catalytic system that could provide the desired products in acceptable yields comparing with previous reports.

Using a cyclic-diene substrate (1 equiv), 5.0 mol% $CuCl_2$ and [hmim]Br with TBHP (6.0 equiv) at room temperature ($\sim$28°C) for 15 min was the best conditions for the aromatization. Overall investigations are summarized:

1) Conjugated dienes appear to be quite reactive towards $CuCl_2$/[hmim]Br catalyst in the presence of TBHP more than $CuCl_2$/TBHP system which normally required external heat to activate the reaction.

2) Skipped dienes, especially γ-terpinene, are smoothly transformed into the corresponding aromatic products in excellent yield under the developed method.

3) Polycyclic-skipped dienes containing sp^3 carbon at benzylic position such as 9,10-dihydroanthracene, afford diketone as sole product generating from further oxidation of the corresponding aromatic compound which is quite reactive towards this catalytic system.

4) The catalytic system ($CuCl_2$/[hmim]Br) can be easily reused without any difficult recycling process.

3.10.2 Aromatization of Heterocyclic Amines

The scope extension of $CuCl_2$/[hmim]Br with TBHP system was conducted with heterocyclic amines which has never been prepared under any IL systems.

Continuing from the developed conditions of the aromatization of cyclic hydrocarbons, typical condition was using 5.0 mol % $CuCl_2$ in [hmim]Br with TBHP (3.0 equiv) at room temperature for 15 min.

The examination of some examples of heterocyclic amines for their aromatization is concluded as followings:

1) Unprotected amines such as indoline are too reactive towards this protocol and afford 1*H*-indole in moderate yields.

2) *N*-substituted heterocycles are transformed into their corresponding indoles in acceptable yields under the developed method.

Finally, though the developed protocol could not generate the target molecule (1*H*-indole) constantly in high yield, it could be prepared according to Scheme 3.1 from the aromatization of *N*-substituted substrates within short reaction time. In addition, the corresponding aromatized products were easily separated from their crude reactions by solvent extraction. These products could be used as substrates for the next step.

3.11   Application of metal salt/[hmim]Br to other reactions

In accordance with using [hmim]Br coupled with transition metal salt for oxidation of alcohols (Chapter II) and aromatization (this Chapter), these reactions provided the desired products in good yield under the developed protocols. Other types of substrates were considered in order to apply this kind of catalytic system *via* oxidation process in regards to a new recyclable catalytic system.

Oxidative coupling reaction is one of important protocols in organic synthesis for the formation of a new carbon-carbon bond between two either identical or different compounds. Phenolic compounds which are normally found as parts of naturally occurring compounds are also naturally transformed in the biosynthesis of bioactive substances *via* oxidation process [130].

3.11.1 Literature Reviews on Phenolic Coupling

Over this past decade, many reports have reviewed oxidative coupling of phenolic compounds. Most of these reactions were catalyzed by a variety of metal catalysts and/or oxidizing agents to the desired coupling products.

Tanaka and co-workers [131] investigated oxidative coupling of *p*-cresol with dichromate in aqueous solution. In the process, three products: dimeric (1) and trimeric (2) cresols, and dimeric ketone (3), were produced in similar yields with their previous work. Possible mechanism was proposed to occur *via* one-electron transfer.
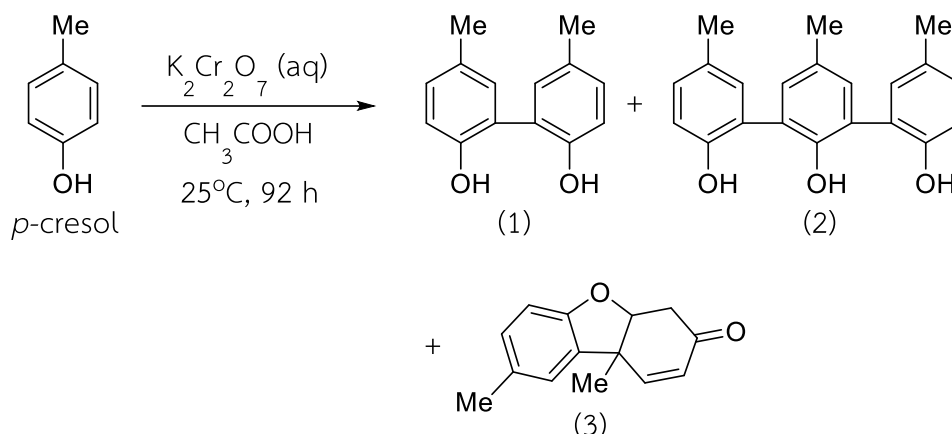
Brussee and co-workers [132] explored the oxidative coupling of 2-naphthol with copper(II) amine complexes. Various amines were observed as one of factors to gain the highest yield of binaphthol.

Pietikäinen and Adlercreutz [133] studied the enzyme-catalyzed oxidation of *p*-cresol in both organic and water media with horse-radish peroxidase (HRP) and H_2O_2. This reaction generated many products from low-molecular-weight to polymer depending on the reaction conditions.
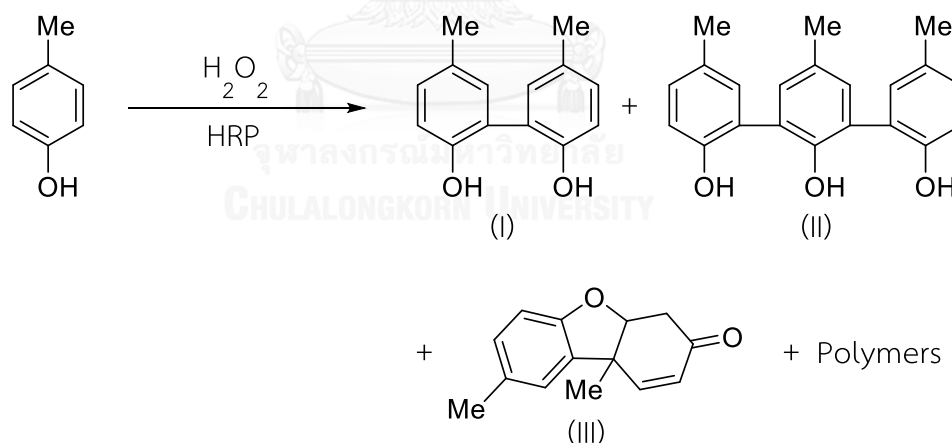
Hovorka and co-workers [134] demonstrated oxidative cross-coupling of several 2-naphtol derivatives with high selectivity catalyzed by Cu(II)-amine complexes.

Noji and co-workers [135] developed a new catalytic system for the synthesis of binaphthol derivatives under CuCl-amine complex from 2-naphthol coupling reactions in air or O_2 atmosphere.

Asakura and co-workers [136] displayed the controllable distribution of the products from p-cresol oxidative coupling by adjusting concentration of $FeCl_3$ in water. Generally, the substrate generated three main coupling products.

o-o direct-link dimer (2) Pummerer's ketone (3)

o-o direct-link trimer (4)
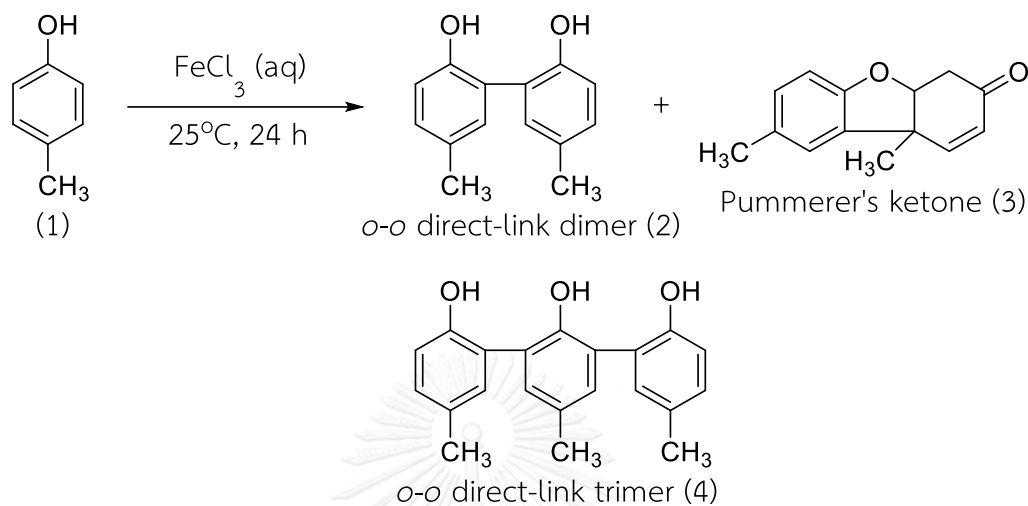
Hu and co-workers [137] presented the binaphthol synthesis from aerobic oxidative coupling of 2-naphthol with CuCl(OH)(TMEDA) catalyst in DCM. The product as a racemic mixture could be separated into pure enantiomer from the crude reaction by a modified method.

Love and Bills [138] described the preparation of 1,2-binaphthol (BINOL) from oxidation of 2-naphthol with iron(III) chloride supported on alumina by heating at 90 °C for 30 min. The developed method could be applied to many substrates which afforded the expected products in high yields and good quality without using any organic solvents.

a R = R' = H
b R = H, R' = Br
c R = CO$_2$Me, R' = H
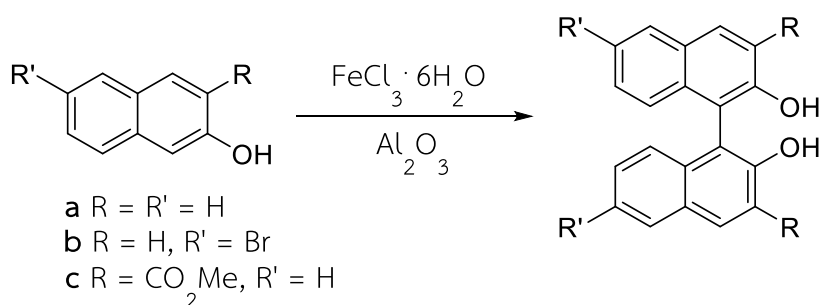
Yadav and co-workers [139] demonstrated a recyclable catalytic system for oxidative coupling of β-naphthols with RuCl$_3$/[bmim]PF$_6$ system under O_2 atmosphere.

The recovered IL containing ruthenium salt could be reused successively for three to four times with slightly decreasing of the product yield.
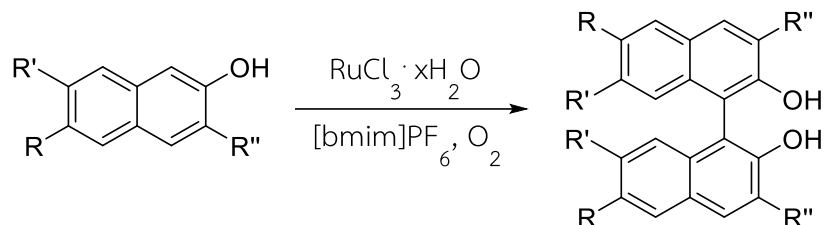
Egami and Katsuki [140] reported the oxidative coupling of 2-naphthols catalyzed by various iron complexes in air. With some chiral ligands, reactions provided the desired products with high enantioselectivity.
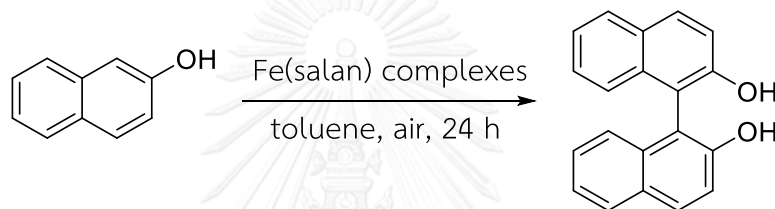
Based on the above examples, p-cresol and 2-naphthol derivatives were explored. Various metal catalysts; especially Fe(III) and Cu(II) salts, were examined. Though these catalysts could provide the desired coupling products, their reactions required long reaction time, high temperature, volatile or toxic organic solvents, and stoichiometric amounts of reagents. To address these problems, some reactions utilized ILs for the recyclability of the catalytic systems. For p-cresol, there have never been reports for the coupling reactions in ILs; however, the reaction provided many coupling products that may be uncontrollable. Therefore, the coupling reaction of 2-naphthol utilizing the developed catalytic system of metal salt/[hmim]Br was focused.

3.11.2 Scope of This Work

The oxidation of phenolic compounds to the desired coupling products under a recyclable catalytic system between the combination of metal salt and [hmim]Br will be concerned. The optimization of this catalytic system will be described and then applied to other compounds.

3.11.3 Experimental

All instruments, equipment, and chemicals were performed or prepared according to Chapter II and the above mentioned part of this chapter without further modification. For product purification, semi-preparative HPLC was performed on Waters 600 controller with Water 2996 photodiode array detector, column C_{18} (250 mm x 4.6 mm x 5 μm).

3.11.4 General Procedure

A typical process for phenolic coupling of 2-naphthol was conducted as follows: to a 50 mL round-bottle flask containing a mixture of a metal salt and [hmim]Br was gradually added 2-naphthol. Then, the mixture was stirred at room temperature for 24 h. Next, the reaction was extracted with Et_2O (3x10 mL) to remove all compounds from the crude reaction. The organic layer was washed with DI water, $NaHCO_3$, and dried over anhydrous Na_2SO_4, respectively. After evaporating all organic solvents, the crude mixture was analyzed by NMR or purified by silica gel column. Semi-preparative HPLC was operated using solvent system of 70% MeOH + 30% H_2O with flow rate of 2 mL/min to obtain pure compounds.

3.11.5 Results & Discussion

3.11.5.1 Preparation of 1,1′-Bi-2-naphthol

Initially, the target product (BINOL) was prepared in accordance with the similar process as afore-mentioned [141]. The full steps for the preparation of the target compound are shown below:

To a hot aqueous solution of 2-naphthol (25 mmol in 150 mL of water) in 250 mL, two-necked, round-bottled flask connecting to the reflux condenser was gradually added with solution of $FeCl_3$ (7g) in water 15 mL with vigorous stirring. After refluxing for 5-10 min, the hot suspension was filtered, and washed with boiling water until the filtrate turned colorless. Then, the residue was left to dry and re-crystallized with

toluene. The synthesized bi-naphthol was confirmed of its identity by NMR technique by comparing with literature data.

1,1′-Bi-2-naphthol [142]: colorless crystal; ^{1}H NMR (CDCl$_3$) δ 8.01 (d, J = 8.9 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.42-7.39 (m, 4H), 7.34 (d, J = 7.6 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 5.09 (s, 2H). ^{13}C NMR (CDCl$_3$) δ 152.8, 133.4, 131.4, 129.5, 128.40, 127.5, 124.2, 124.0, 117.8, 110.9.

3.11.5.2 Reactions on 2-naphthol substrate

Based on previous reviews, DCM was found to be a suitable solvent for coupling reactions. Thus, some experiments were conducted in DCM, and [hmim]Br as solvents without any catalysts. The results were compared to explain their effects as shown in Figure 3.9.
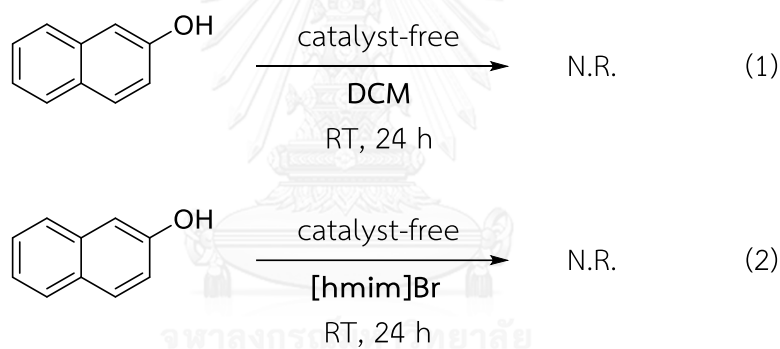
Figure 3.9 Catalyst-free experiments on 2-naphthol

Operating reactions in both DCM (1) and [hmim]Br (2) afforded only the substrate recovery. The catalysts should thus be an important factor for this reaction. The reactions with FeCl$_3$ and CuCl$_2$ were carried out under the same standard method. Table 3.8 displays coupling reaction of 2-naphthol with metal salts in [hmim]Br.

Table 3.8   Phenolic coupling of 2-naphthol with metal salt in [hmim]Br[a]
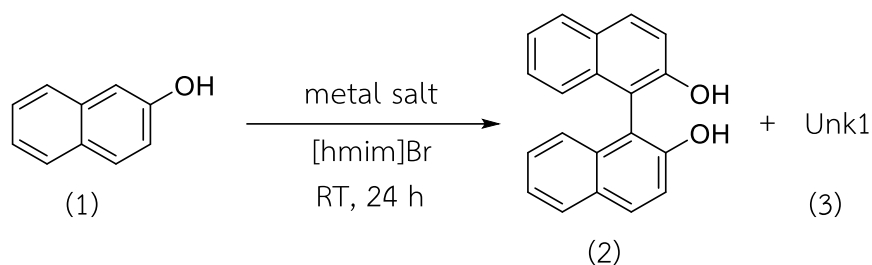
| Entry | Metal salt | | Temperature (°C) | Results[c] | | |
	Type	Amount (eq)		SM Recovery (1)	BINOL (2)	Unk1 (3)
1[b]	FeCl$_3$	1	RT	-	✓	-
2		1	RT	✓	-	-
3		1	90	✓	-	✓
4		2	RT	✓	-	-
5[b]	CuCl$_2$	1	RT	✓	✓	-
6		1	RT	-	-	✓
7		1	90	-	-	-
8		2	RT	-	-	✓
9		0.16	RT	✓	-	✓

[a] General condition: substrate (1 equiv), metal salt (1 equiv), room temperature (28 °C) for 24 h in [hmim]Br

[b] DCM

[c] The result was analyzed by checking with the ^{1}H NMR and TLC of the crude mixture to identify the products: ✓ detectable amount, ─ trace or not found

For iron(III) chloride (entries 1-4), in DCM (entry 1) the reaction generated only bi-naphthol which could be clearly identified from the ^{1}H NMR spectrum as shown in Figure 3.10.
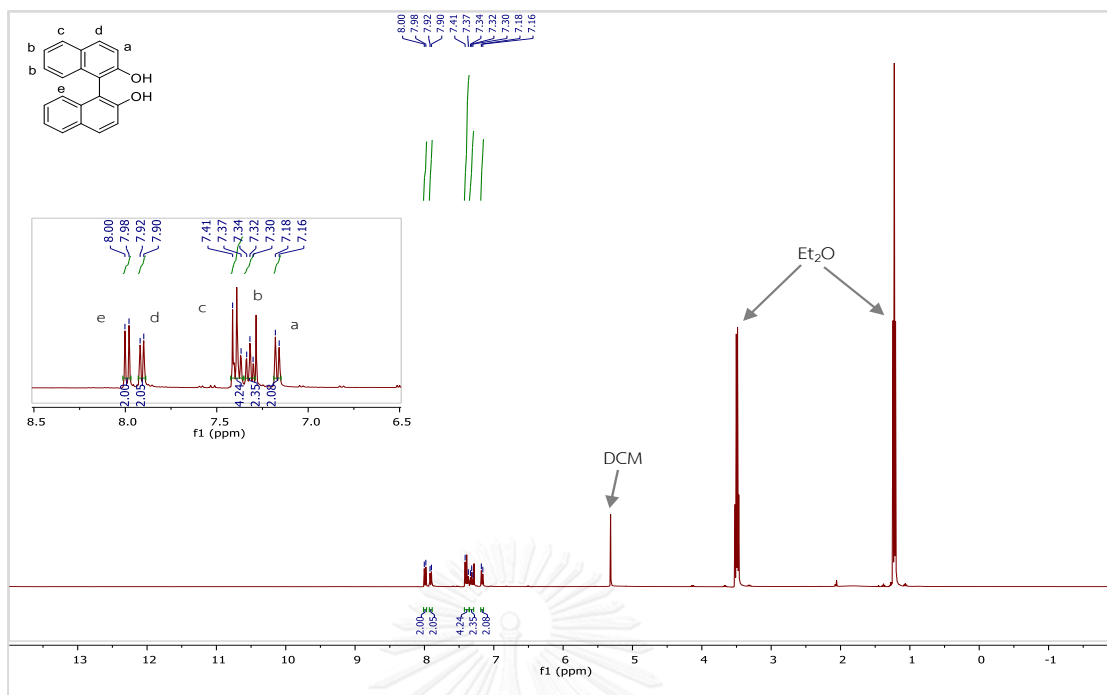
Figure 3.10 The ^{1}H NMR spectrum of the crude mixture from Table 3.8, entry 1

In contrast, the reaction with [hmim]Br (entry 2) afforded only the substrate recovery. The ^{1}H NMR spectrum of the crude reaction is presented in Figure 3.11.
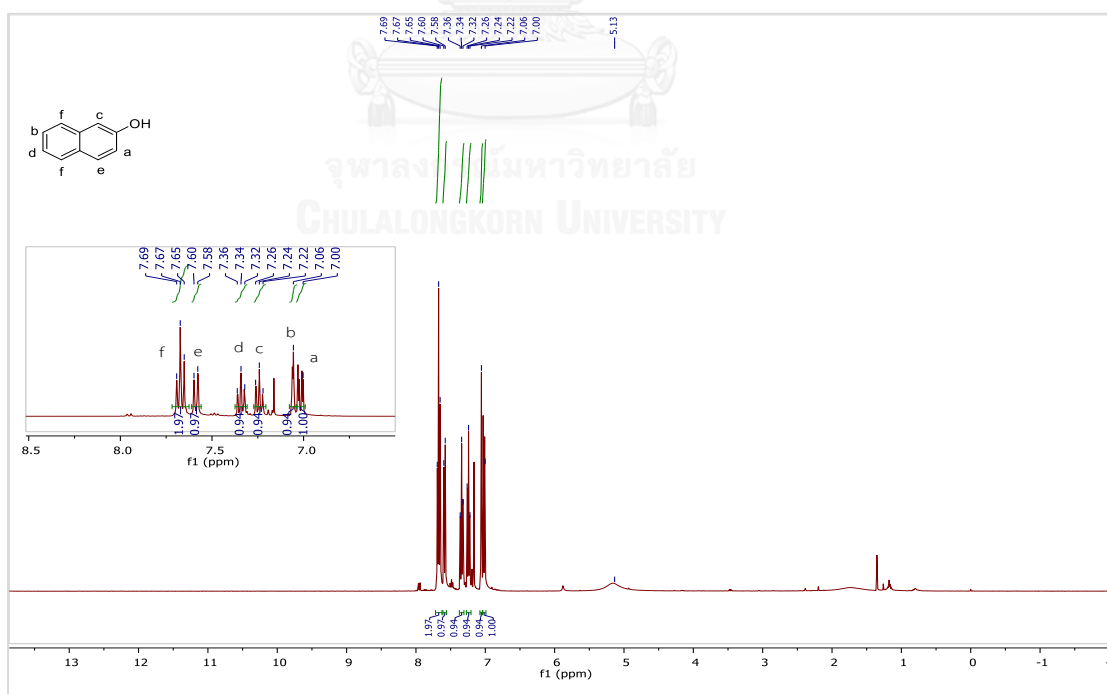
Figure 3.11 The ^{1}H NMR spectrum of the crude reaction from Table 3.8, entry 2

Then, after treating the reaction at higher temperature (entry 3) there was an unknown compound (Unk1) with a little bit different NMR patterns around aromatic region (δ 8.5 to 7.0 ppm) (Figure 3.12). Simultaneously, the reaction at room temperature using twice amounts of the catalyst (entry 4) provided only the substrate recovery. From all results (entries 1-4), $FeCl_3$ was not suitable as a catalyst for coupling reaction of 2-naphthol in [hmim]Br system because it could not generate the target product in either at room or higher temperatures. Moreover, after roughly analyzing the ^{1}H NMR of Unk1 compared with other possible products in previous works [143], Unk1 was not related to any of those possible ones (Figure 3.13). Therefore, no further investigation on the reaction was performed.
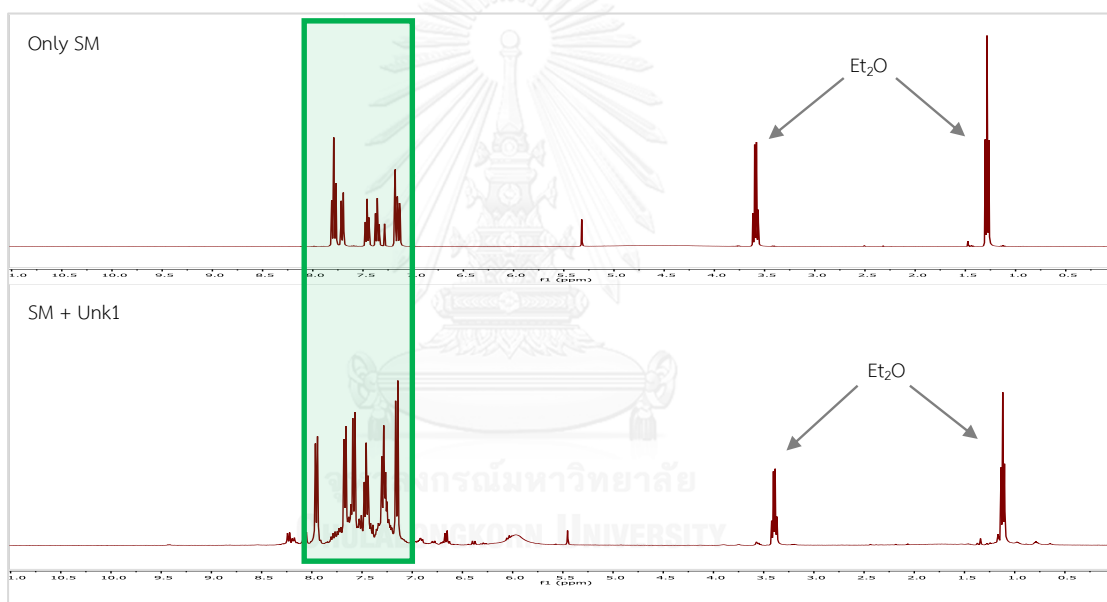
Figure 3.12 Comparison of the 1H NMR spectra between no reaction (top) and the incomplete reaction (entry 3) (bottom)
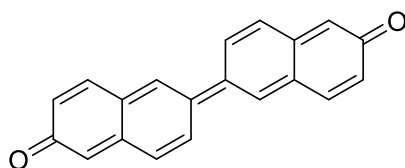
(*E*)-*6H,6'H*-[2,2'-binaphthaleneidene]-6,6'-dione
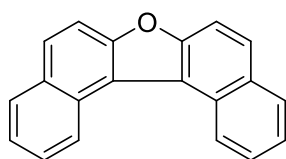
dinaphtho[2,1-*b*:1',2'-*d*]furan

(DNF)
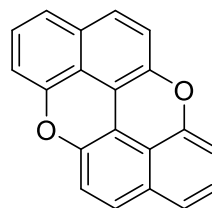
(2,8');(8,2')-dioxo-1,1'-binaphthyl

(DOB)

Figure 3.13 Other possible products from previous works

Continuing with the reactions using CuCl$_2$ (entries 5-9), in DCM and 1 equiv of the catalyst (entry 5), the reaction produced bi-naphthol while the substrate still remained in the mixture. On the other hand, in [hmim]Br system (entry 6) an unknown product was found as the sole product which was the same as that from the reaction using FeCl$_3$ (entry 3). With some unidentified impurities and due to the fact that all reactions were performed in small scale, the isolation of all major compounds will be carried out later in large scale process. When heat was applied (entry 7), a lot of impurities were detected. The developed condition may be too extreme for any products to remain in the system. Doubling the catalyst (entry 8) also offered solely Unk1 while reducing to 0.16 equiv (entry 9) provided mixtures.

The system with [hmim]Br coupled with CuCl$_2$ was not appropriate to generate the target bi-naphthol; however, Unk1 was found as the sole product for this catalytic system with both catalysts. To focus on the identification of Unk1, a reaction was operated in scale up under the above condition in Table 3.8, entry 8. The Unk1 in the crude mixture was isolated and analyzed for its characteristic with NMR. Based on the reference, Unk1 was identified as 1-bromo-2-naphthol as shown in ^{1}H and ^{13}C NMR spectra in Figure 3.14.

1-Bromo-2-naphthol [144]: pale yellow solid; ^{1}H NMR (CDCl$_3$) δ 8.06 (d, J = 8.5 Hz, 1H), 7.79 (m, 2H), 7.60 (t, J = 8.2 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 5.96 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 150.6, 132.3, 129.7, 129.3, 128.2, 127.8, 125.3, 124.1, 117.2, 106.1.
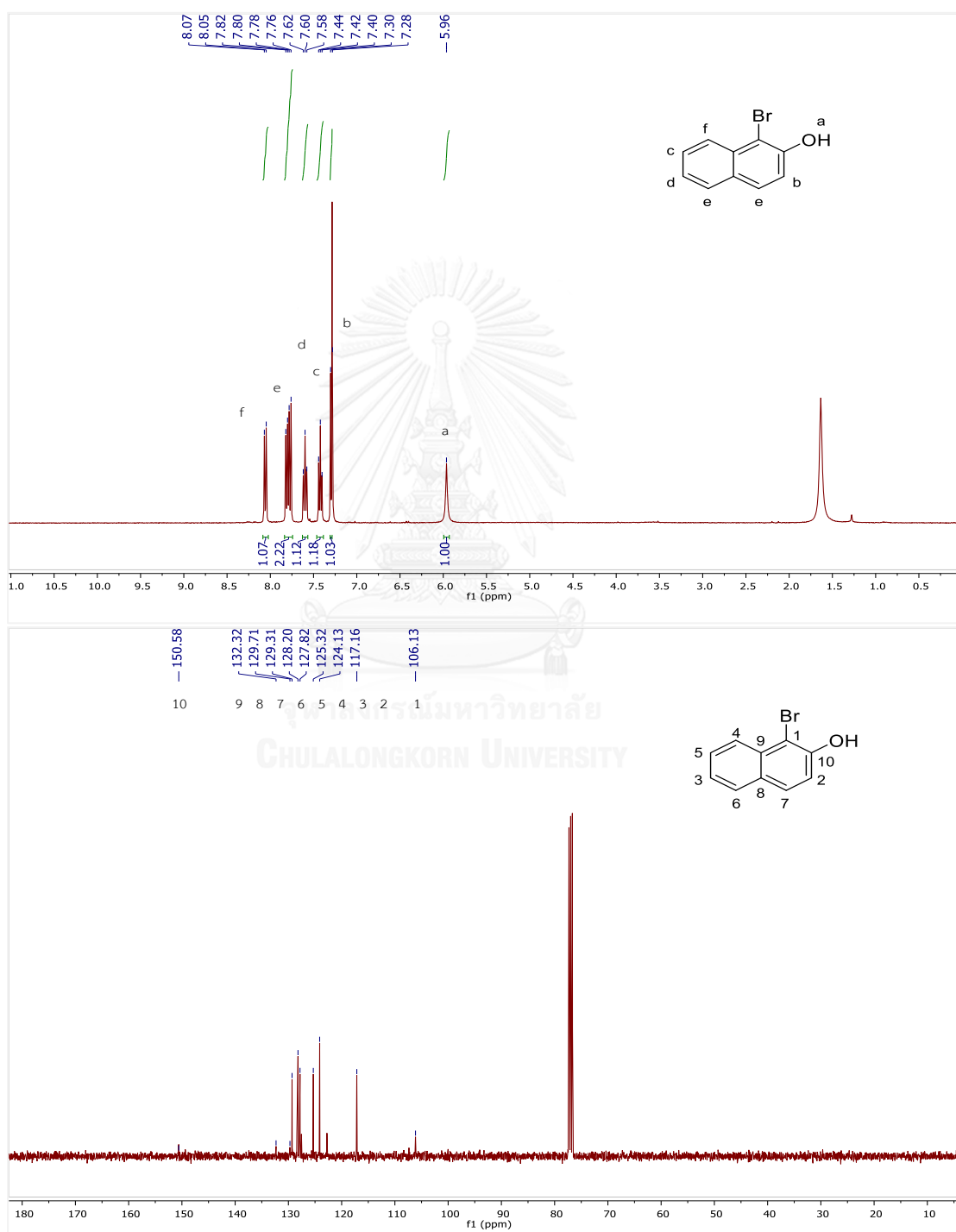
Figure 3.14 The ^{1}H and ^{13}C NMR spectra of 1-bromo-2-naphthol (Unk1)

The reactions which produced 1-bromo-2-naphthol performed under a metal salt/[hmim]Br catalytic system were summarized in Figure 3.15. In this system, [hmim]Br acted as both solvent and a brominating agent. This metal salt/[hmim]Br was unable to oxidize phenolic substrate to their coupling product as firstly presumed.
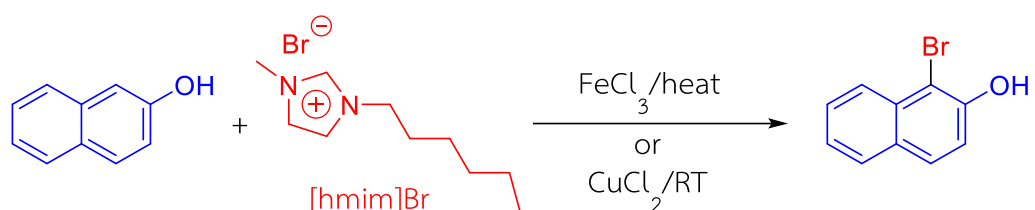
Figure 3.15 Bromination of 2-naphthol

3.11.6 Conclusion

The objective of this part is to apply a developed catalytic system consisting of metal salt/[hmim]Br with phenolic compounds to gain the corresponding coupling products. Unfortunately, the reactions could not produce the target coupling product, instead brominated compounds was attained.

CHAPTER IV

OXIDATIVE DEHYDROGENATION OF *N*-HETEROCYCLES

4.1   Introduction

In this chapter, the overall contents are cooperative work between Dr.Weiyou Zhou and the author being a reprint of the material as it appears in *Synlett*, **2016**, *27*(12), 1806-1809. "A Convenient Procedure for the Oxidative Dehydrogenation of *N*-Heterocycles Catalyzed by FeCl$_2$/DMSO" [145].

Heterocyclic compounds are one of major classes of organic substances. A number of heterocycles are useful as part of both industrial and pharmaceutical products such as nucleic acids, vitamins, and antibiotics in natural occurring compounds, synthetic products for use as drugs, dyes, plastic, and pesticides [146]. There are a lot of methods for the preparation of these heterocycles. Dehydrogenation is an important method for these syntheses. Among these, *N*-heterocycles consisting of at least one nitrogen atom in their rings are found to be interesting according to the previously reported application.

4.2   Literature Reviews

There have been certain reports addressing the dehydrogenation of saturated *N*-heterocyclic compounds to furnish aromatic heterocycles using various catalytic systems.

Yamaguchi and Mizuno [147] presented an efficient Ru catalyst supported on alumina for the transformation of various amines to their corresponding unsaturated products under oxygen atmosphere. This heterogeneous catalytic system could be reused for both aliphatic and cyclic amine oxidations yielding the products in large amount.

$$R\underset{\underset{H}{|}}{\overset{\overset{NH_2}{|}}{C}}H \quad + \quad O_2 \quad \xrightarrow[\text{toluene, 100}^\circ\text{C}]{\text{Ru/Al}_2\text{O}_3} \quad R-C\equiv N \quad + \quad 2\,H_2O$$

1°

$$R_1\underset{\underset{R_2}{|}}{\overset{\overset{NH_2}{|}}{C}}H \quad + \quad 1/2\,O_2 \quad \xrightarrow[\text{toluene, 100}^\circ\text{C}]{\text{Ru/Al}_2\text{O}_3} \quad \underset{R_2}{\overset{R_1}{>}}{=}NH \quad + \quad H_2O$$

2°
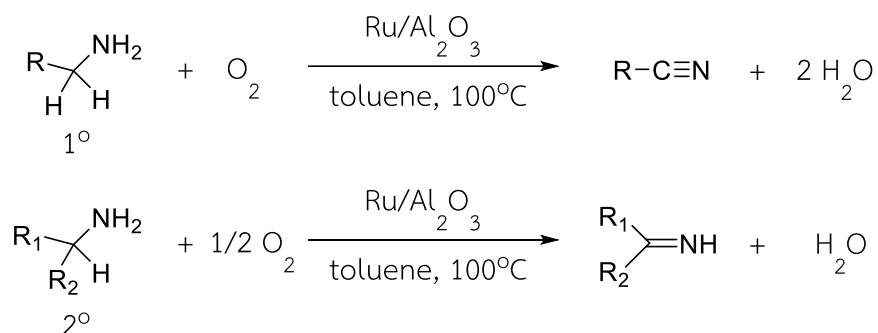
Choi and Doyle [148] developed dirhodium caprolactamate [Rh$_2$(cap)$_4$] complex for catalytic oxidation of secondary amines in the presence of TBHP to prepare imines with high chemo- and regioselectivity.
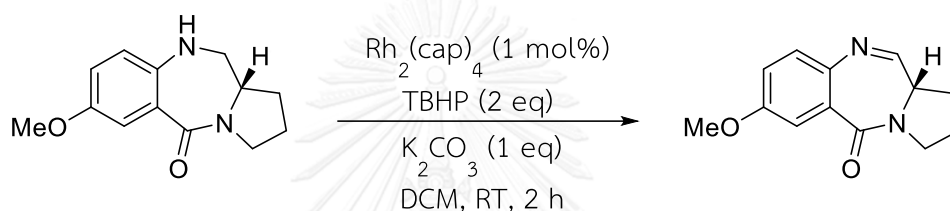
Li and co-workers [149] investigated aerobic oxidation of amines catalyzed by Co$_3$O$_4$-supported ruthenium catalyst. The developed catalyst could be reused even under solvent-free conditions. The reactions of various amines afforded the desired products from moderate to excellent yields at 100-150 °C for 24-48 h.
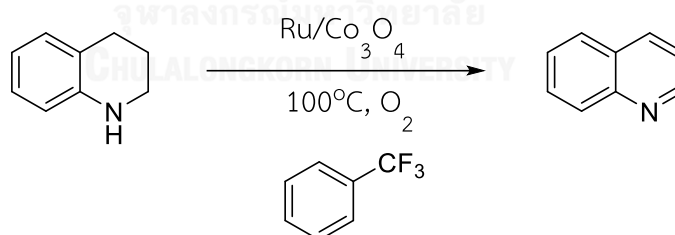
Yamaguchi and co-workers [150] described reversible dehydrogenation-hydrogenation of *N*-heterocycles catalyzed by Cp*Ir complexes. A variety of the substituted complexes was performed with 1,2,3,4-tetrahydroquinoline derivatives to investigate the catalytic performance. The reversible process could be successfully done in the presence of H$_2$ with a different complex comparing with dehydrogenation.
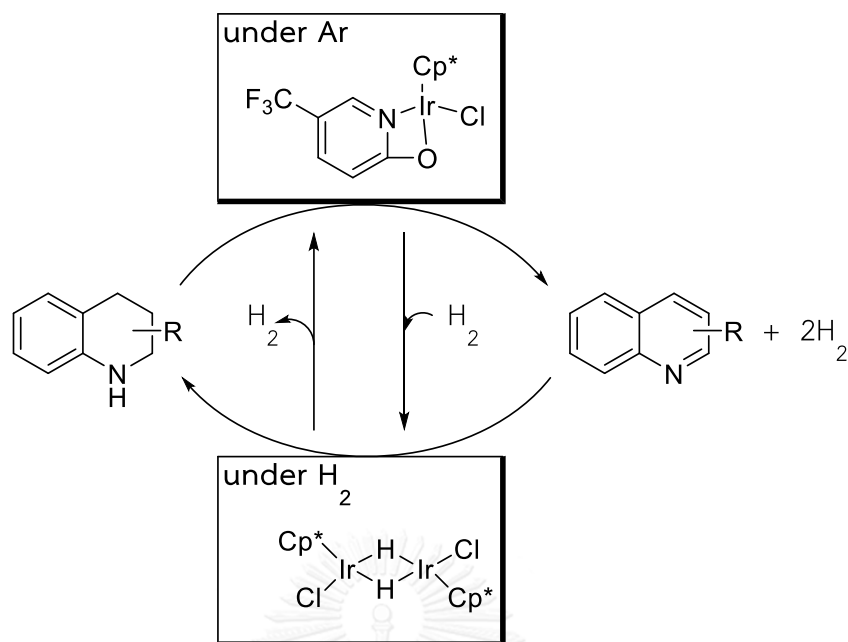
Mikami and co-workers [151] examined tetrahydroquinoline-quinoline reversible dehydrogenation-hydrogenation reaction utilizing a supported carbon nanoparticle catalyst on titania surface (Cu/TiO$_2$).
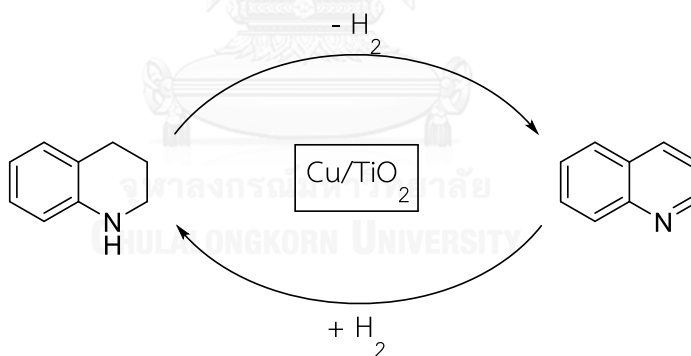
Muthaiah and Hong [152] studied ruthenium-hydride complexes catalyzed the dehydrogenation/oxidation of alcohols and *N*-containing heterocycles to the corresponding ketones and *N*-unsaturated products; respectively. Moreover, the ligand dissociation pathway could be used to explain the mechanism of this catalytic system by the kinetic and NMR investigations.
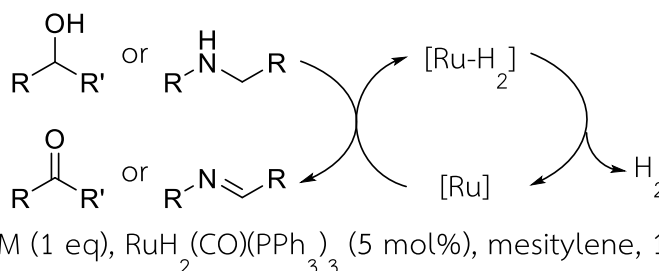
Condition: SM (1 eq), RuH$_2$(CO)(PPh$_3$)$_3$ (5 mol%), mesitylene, 165°C, 24 h

Wu and co-workers [153] demonstrated the oxidant-free dehydrogenation of *N*-heterocycles under iridium complexes. Instead of using any oxidants, 2,2,2-trifluoroethanol (TFE) played important roles towards the reactions because it can activate the catalyst by dissociating some ligands. Several substituted iridium complexes were synthesized and dehydrogenated tetrahydroquinoline to obtain the optimum condition. Various tetrahydroquinoline derivatives were investigated under the developed protocol, and afforded the corresponding quinolines in high yields.
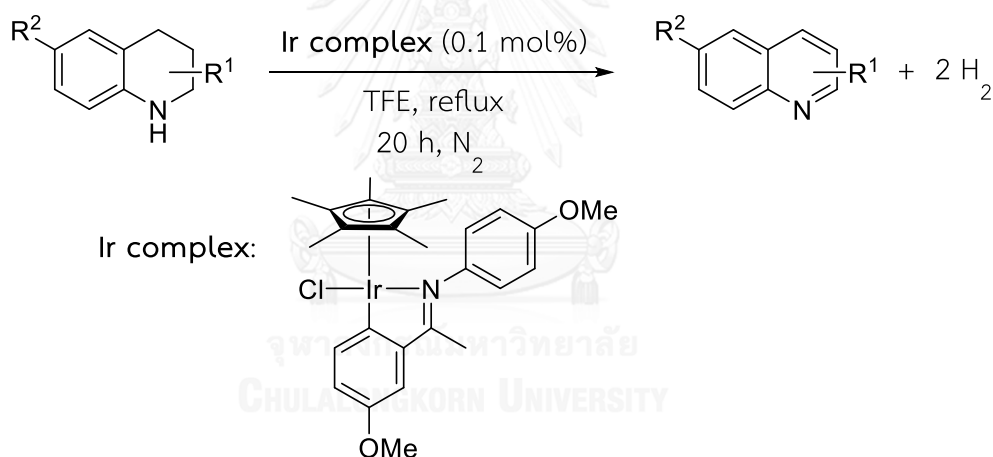
Zhang and co-workers [154] reported iron-catalyzed aerobic oxidation reactions for the preparation of imines from direct transformation of amines under air atmosphere. This catalytic system provided the corresponding imines in high yields from primary, secondary, and benzylamines, while *N*-heterocycles such as 1,2,3,4-tetrahydroquinoline, and indoline were converted in low to moderate yields.
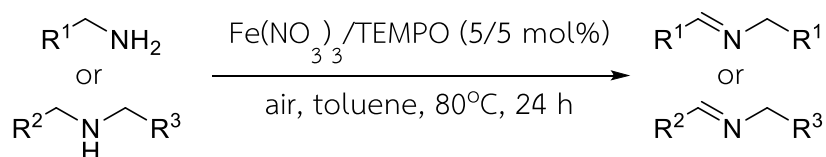
Yao and co-workers [155] presented catalytic dehydrogenation of alkanes and heterocycles utilizing iridium-pincer complex. The developed iridium complex was used for hydrogen transfer process with various parameters to obtain the optimum condition. Numerous heterocycles were investigated under the developed system with adjusting some factors to gain the maximum yield of each substrate.

$$\text{heterocycles} \xrightarrow[\substack{0.2\text{-}10 \text{ mol\% NaO}t\text{Bu} \\ 120^\circ\text{C}, \, p\text{-xylene}}]{\text{Ir-pincer complex (0.1-5 mol\%)}} \text{dehydrogenated heterocycles}$$

1a-p   (1-4 eq)   **2a-p**
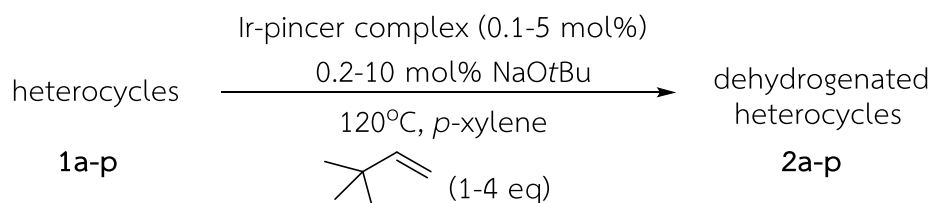
Chakraborty and co-workers [156] disclosed both iron-catalyzed dehydrogenation and hydrogenation of N-heterocycles affording the related products in high yields. The NMR and trapping techniques were used to gain mechanistic insights of the catalytic system. The iron complex with bis(phosphino)amine pincer ligand acted as a hydrogen-transfer compound instead of using external oxidants.

Wendlandt and Stahl [157] observed dehydrogenation of tetrahydroquinolines under O_2 atmosphere or air with o-quinone-based catalysts and Co(salophen) cocatalyst. A number of quinoline derivatives were synthesized successfully under the developed system.

$$R^1 \underset{\overset{|}{H}}{\overset{|}{\bigbox}} \xrightarrow[\substack{5.0 \text{ mol\% Co(salophen)} \\ \text{MeCN, RT, air}}]{2.5 \text{ mol\% [Ru(phd)}_3\text{](PF}_6\text{)}_2} R^1 \overset{|}{\bigbox}$$
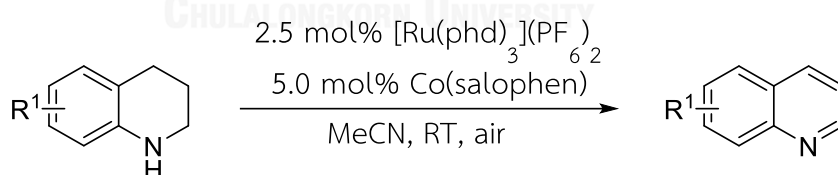
Jawale and co-workers [158] reviewed a nanohybrid catalyst containing rhodium particles supported on carbon nanotubes for dehydrogenation of N-heterocycles in the presence of $tert$-butylcatechol (TBC) as cocatalyst under air and room temperature. Several N-containing substrates were transformed into their dehydrogenated products with excellent yields within 8-12 h in $CHCl_3/H_2O$ (3:1).

Cui and co-workers [159] developed carbon supported iron oxides being immobilized with nitrogen-drop-graphene shells as catalysts (FeO$_X$@NGr-C) for

oxidative dehydrogenation of *N*-heterocyclic compounds. The newly synthesized catalysts were prepared, characterized and applied to investigate their activity and stability in catalytic oxidation of *N*-heterocycles. Twenty-three substrates of substituted tetrahydroquinolines were examined under this new catalytic system.

$$R^2 \text{—} \overset{\displaystyle}{\underset{\underset{H}{N}}{\bigcirc}} \text{—} R^1 \xrightarrow[\substack{\text{air (15 bar), heptane (2 mL)} \\ 100^{\circ}\text{C, 12 h}}]{\text{FeO}_x@\text{NGr-C (0.18 mol\% Fe)}} R^2 \text{—} \overset{\displaystyle}{\underset{N}{\bigcirc}} \text{—} R^1 + 2 H_2O$$
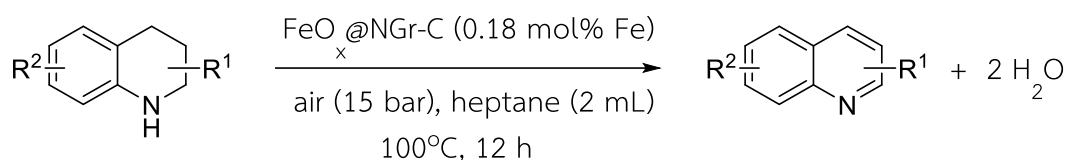
Iosub and Stahl [160] exhibited oxidative dehydrogenation of *N*-heterocycles catalyzed by nitrogen-drop carbon supported cobalt oxides. A variety of substituted 1,2,3,4-tetrahydroquinolines were successfully transformed into their corresponding quinolines in excellent yields. At the same time, other *N*-containing compounds could be converted under the developed system with moderate to high yields.

$$\overset{\displaystyle}{\underset{\underset{H}{N}}{\bigcirc}} \text{—} R^1 \xrightarrow[\substack{\text{MeOH, 60}^{\circ}\text{C} \\ O_2 \text{ (1 atm)}}]{\text{Co}_3\text{O}_4\text{-NGr/C, } K_2\text{CO}_3} \overset{\displaystyle}{\underset{N}{\bigcirc}} \text{—} R^1$$
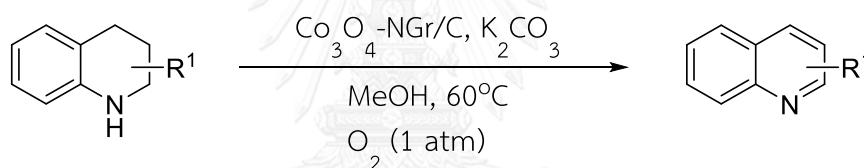
Xu and co-workers [161] described cobalt-pincer catalyst for dehydrogenation-hydrogenation of *N*-heterocycles. The reactions were performed for several days to obtain the maximum yield of the desired products under the oxidant-free condition. Nature of the substrates displayed the most effects to the product yields.
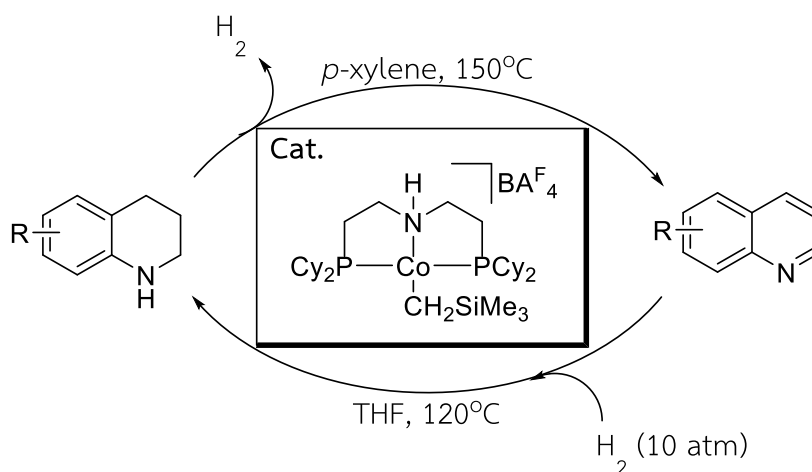
Referring to the reviews, the catalytic systems for the dehydrogenation could be classified into two types as oxidant-free and oxidant-required dehydrogenations. Even though these reactions afforded the desired products in high yields, some disadvantages still could not be avoided such as using expensive metal catalysts (Rh, Ru, Pd, Ir), requiring drastic conditions (high pressure, and high temperature), demanding stoichiometric amounts of reagents, and having many steps for either catalyst preparation or reaction process. Therefore, a catalytic system utilizing a simple metal salt under a simple method is preferable.

Though, iron catalysts have been reviewed in a number of catalytic oxidations [162], only a few examples have been reported in the presence of O_2 as a mild oxidizing agent including the works relating to dehydrogenation. The challenges, thus, are still remained with regards to using inexpensive commercial, and environmentally friendly iron salt under mild conditions with simple steps and high productivity of the desired products.

4.3   Scope of This Work

The methodology study for the preparation of *N*-heterocyclic compounds catalyzed by iron salt coupled with DMSO under O_2 atmosphere will be concentrated. The objective of this research is to develop a simple catalytic system of $FeCl_2$/DMSO to synthesize aromatic *N*-heterocycles from various partially saturated substrates *via* oxidative dehydrogenation process, and to investigate the optimal conditions for the preparation of these aromatic compounds. Moreover, the mechanistic study of the developed system will be conducted to explain the reaction pathway.

4.4   Experimental

4.4.1   Instrument and Equipment

Column chromatography was performed on silica gel (Merck Kieselgel 60, 70-230 mesh). Thin layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel (Merck Kieselgel 60 PF_{254}).

The ^{1}H and ^{13}C NMR spectra were operated in deuterated chloroform (CDCl$_3$) with tetramethylsilane (TMS) as an internal reference on the NMR Bruker Advance 400 spectrometer which operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons. Agilent QTOF 7200 instrument was conducted to obtain High-resolution mass spectra. A Gallenkamp melting point apparatus measured melting points.

4.4.2 Chemicals

The reagents used for synthesis were purchased from Aldrich, and Alfa chemical companies or otherwise stated and were used without further purification. All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades.

4.4.3 General Procedure

4.4.3.1 Preparation of 1,2,3,4-Tetrahydroquinolines

To a solution of a commercially available quinoline (8 mmol) and NiCl$_2$·6H$_2$O (1.4 mmol) in MeOH (30 mL) was added in portions with NaBH$_4$ (32 mmol) while stirring for 30 min under cooling. Then, the mixture was further stirred at room temperature for 30 min. After that, MeOH was removed by reduced-pressure evaporator, and 10% HCl was added to the solid residue. The acid solution was neutralized with concentrated Al(OH)$_3$, extracted with Et$_2$O, and the organic layer was dried with anhydrous MgSO$_4$. After removing the organic solvent, the expected tetrahydroquinoline (> 90%) was obtained and identified by NMR spectral comparison with data in literature [163].

4.4.3.2 Preparation of 1,2,3,4-Tetrahydroquinoxalines

1,2,3,4-Tetrahydroquinoxaline derivatives were synthesized by reduction with the same method as tetrahydroquinoline preparation, and confirmed for their structures with NMR comparing with authentic samples or literature [163].

4.4.3.3 Typical Procedure for Oxidative Dehydrogenation

To a mixture of 1,2,3,4-tetrahydroquinoline (0.5 mmol), $FeCl_2$ (3 mol%), DMSO (0.4 mmol), and *p*-xylene (1 mL) in a Schlenk tube equipped with a magnetic bar was stirred at 110 $^{\circ}$C under O_2 atmosphere using a balloon. After the reaction was complete as monitored by TLC, and cooled to room temperature. The desired product was isolated from the crude reaction by silica gel column (flash chromatography) with hexane/EtOAc 10:1 system. The isolated product was determined of its identity by NMR.

4.4.4   Optimization Study

4.4.4.1 Effects of Iron Catalysts

This investigation was carried out under the condition described in the typical procedure without DMSO for 24 h. Four different iron salts: iron(II) chloride ($FeCl_2$), iron(II) bromide ($FeBr_2$), iron(II) tetrafluoroborate ($Fe(BF_4)_2$), and iron(II) trifluoromethanesulfonate ($Fe(OTf)_2$) were examined to compare their effects on the oxidation.

4.4.4.2 Effects of Solvents

In order to find the most suitable solvent, six organic solvents: ACN, EtOAc, THF, DMF, DMSO, and *p*-xylene, were investigated in the reactions under the general condition for 24 h.

4.4.4.3 Effects of DMSO Concentration

To study the effects of DMSO concentration under a similar protocol to the dehydrogenation, various amounts of DMSO: 0.0, 0.15, 0.3, 0.8, 1.5, and 3.0 equiv based on the substrate were investigated.

4.4.4.4 Effects of Reaction Temperatures

Effects of reaction temperature were studied with three reaction temperatures at 80, 90, and 110 $^{\circ}$C using the typical procedure.

4.4.5 Oxidative Dehydrogenation of 1,2,3,4-Tetrahydroquinoline Derivatives

General procedure from the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline was performed by using several 1,2,3,4-tetrahydroquinoline derivatives in order to study the effects of substituent towards this catalytic system.

4.4.6 Oxidative Dehydrogenation of Other *N*-Containing Compounds

To extend the scope of this catalytic system, numerous *N*-containing compounds besides tetrahydroquinolines were examined under the typical condition.

4.4.7 Mechanistic Study for Oxidative Dehydrogenation

To explain the mechanism of this catalytic system, individual experiments were performed by adding additives and using *N*-methylquinoline as a substrate under the developed protocol.

4.5 Results and Discussion

A convenient catalytic system was developed and thoroughly explored to obtain suitable conditions for the preparation of quinolines from tetrahydroquinolines *via* dehydrogenation under O_2 atmosphere. The explanation on the reaction pathway was also disclosed according to the mechanistic study.

4.5.1 Optimization Study

Numerous *N*-heterocycles prepared from the dehydrogenation of their corresponding partially saturated *N*-heterocyclic compounds were investigated to find the most suitable condition using an iron salt/DMSO system in the presence of O_2. A few different parameters were chosen such as iron salts, solvents, amounts of DMSO, and reaction temperatures. 1,2,3,4-Tetrahydroquinoline (1 equiv) was treated under

the typical condition using 3 mol% of iron salt under O_2 balloon at 110 $^{\circ}$C for 24 h. The expected product was determined by isolation with silica gel flash column chromatography using hexane/EtOAc eluent system.

Quinoline as the desired product was confirmed by NMR. The ^{1}H and ^{13}C NMR spectra of the product is displayed in Figure 4.1.

Quinoline [164]: faint yellow oil; ^{1}H NMR (CDCl$_3$) δ 8.91 (d, J = 4.0 Hz, 1H), 8.15 - 8.11 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H) 7.54 (t, J = 8.0 Hz, 2H), 7.38 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 150.4, 148.2, 136.1, 129.5, 129.4, 127.8, 126.6, 121.1. HRMS calcd for (C$_9$H$_7$N+H$^+$): 130.0657; found: 130.0652.
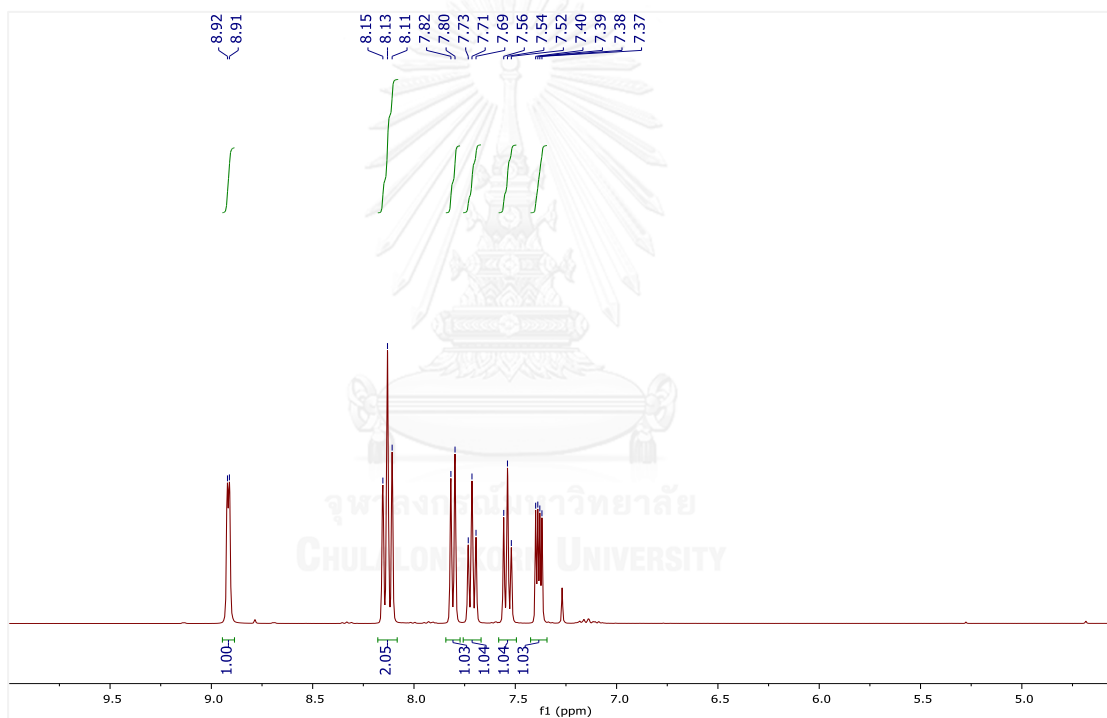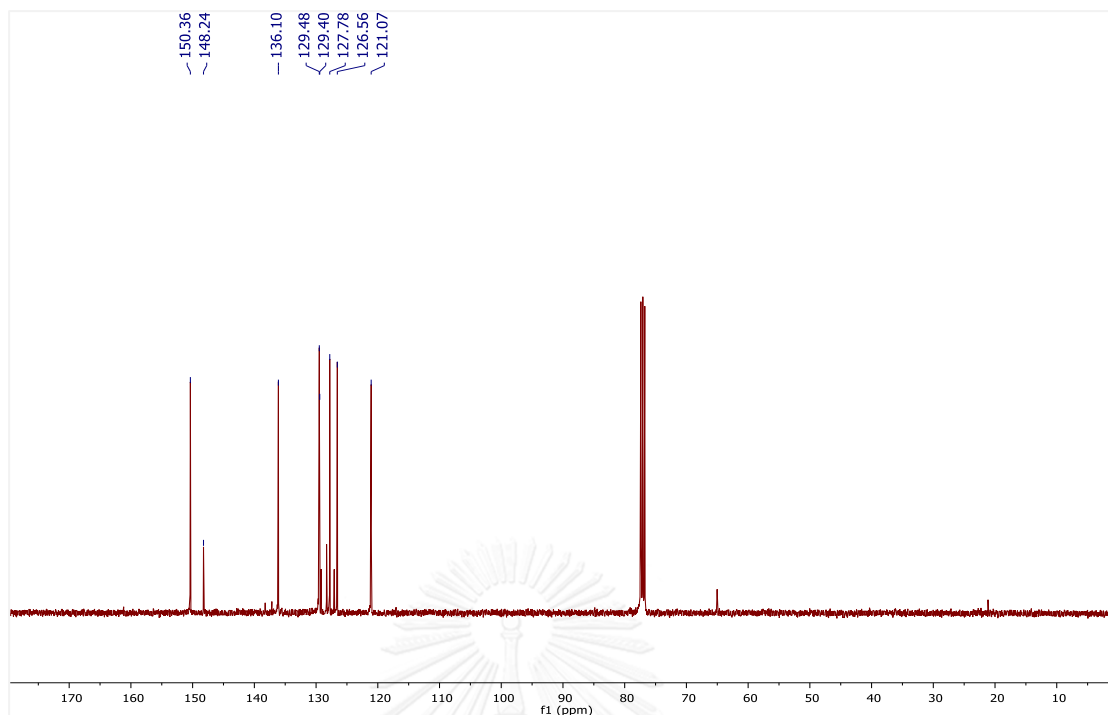
Figure 4.1 The ^{1}H and ^{13}C NMR spectra of quinoline

4.5.1.1 Effects of Iron Catalysts

This screening was to observe the influences of iron salts for the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline in order to find the most suitable catalyst under the optimal condition. Several iron salts containing different anions were chosen and operated at 140 ^{o}C for 24 h in *p*-xylene. Table 4.1 exhibits the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline under a variety of iron salts.

With ligand-free conditions, all selected iron compounds offered the corresponding aromatics (entries 1-4) with various yields. FeCl$_2$ (entry 1) provided the highest yield in moderate amount (45 %). Thus, FeCl$_2$ was found to be the most suitable catalyst and was worth carrying out for further examinations to improve the product yield.

Table 4.1   Primary screening on the effects of iron salts to the oxidative dehydrogenation[a]
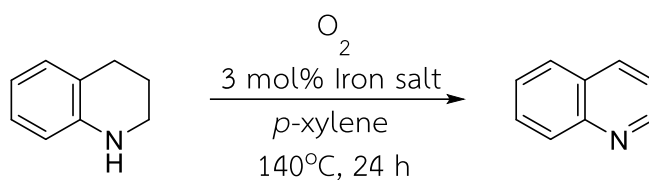
Entry	Iron salt	Yield (%)[b]
1	$FeCl_2$	45
2	$FeBr_2$	26
3	$Fe(BF_4)_2$	8
4	$Fe(OTf)_2$	23

[a] Condition: substrate (0.5 mmol) under O_2 (1 atm), iron(II) salt (3 mol%), solvent (1 mL)

[b] Isolated yields

4.5.1.2 Effects of Solvents

One of major factors on the reaction reactivity was solvent systems. To improve the product yield, numerous organic solvents were explored under the typical procedure with a slightly lower reaction temperature (at 100 $^{\circ}$C) than previous observations (at 140 $^{\circ}$C). The results are displayed in Table 4.2.

With some comparisons between boiling point, and/or polarity of those selected solvents [165] with the product yield (entries 1-6), their relationships varied and could not be useful to explain their effects towards this catalytic system. Using DMSO (entry 6) afforded the product with 100 % conversion, while the substrate was still recovered from other reactions (entries 1-5). Although, using DMSO (entry 6) yielded the product in higher amount than using *p*-xylene (entry 5), the yield was not improved comparing with previous condition (Table 4.1, entry 1). Concurrently, under catalyst-free condition (entry 7) with DMSO the reaction generated unexpectedly the desired product with 23% yield. It could be explained that DMSO itself acted as an oxidizing agent [166] for the dehydrogenation under O_2 atmosphere. The oxidative

dehydrogenation of this kind of substrate was thoroughly re-investigated by adding DMSO in the presence of iron catalyst in p-xylene so that the maximum product yield were obtained.

Table 4.2   Effects of solvents on the oxidative dehydrogenation[a]
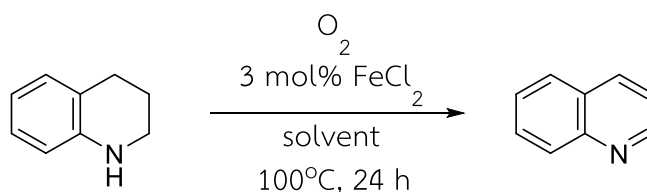
Entry	Iron salt	Solvent	Yield (%)[b]
1	FeCl$_2$	ACN	25
2		EtOAc	12
3		THF	trace
4		DMF	13
5		p-xylene	24
6		DMSO	42
7	-	DMSO	23

[a] Condition: 1,2,3,4-tetrahydroquinoline (0.5 mmol) under O$_2$ (1 atm), solvent (1 mL)

[b] Isolated yields

4.5.1.3 Effects of DMSO Concentrations

This examination was to search for a role of DMSO in this catalytic system. Several different amounts of DMSO were explored for the dehydrogenation of 1,2,3,4-tetrahydroquinoline under O$_2$ atmosphere. The effects of DMSO concentrations are exhibited in Table 4.3.

Under DMSO-free condition (entry 1), the expected product was found only 24 % isolated yield. Though using 3.0 equiv of DMSO (entry 2) clearly increased the yield (41 %), the product amount was not improved compared to the reaction using DMSO (Table 4.2, entry 6 with 42%). Adding more DMSO was not able to increase the yield due to some unidentified effects. Reducing DMSO amounts by using 1.5, 0.8, 0.3 equiv

(entries 3-5, respectively) offered slightly higher yield than previous conditions, on the other hand, using 0.15 equiv of DMSO significantly decreased the yield to only 13 %. As the results, 0.8 equiv of DMSO (entry 4) which provided the highest yield was chosen to be the best amount for this catalytic system with the indication of a synergistic effect between $FeCl_2$ and DMSO in the reaction.

Table 4.3 Effects of DMSO concentrations[a]
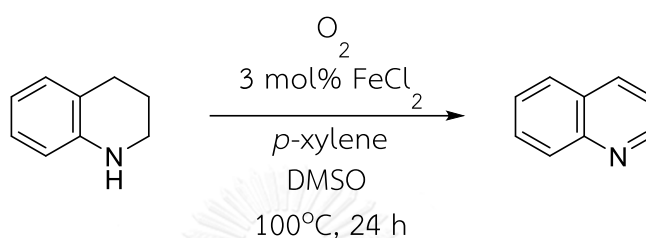
Entry	Amount of DMSO (eq)	Yield (%)[b]
1	0.0	24
2	3.0	41
3	1.5	48
4	0.8	52
5	0.3	46
6	0.15	13

[a] Condition: 1,2,3,4-tetrahydroquinoline (0.5 mmol) under O_2 (1 atm), solvent (1 mL), DMSO (0.0–3.0 equiv))

[b] Isolated yields

4.5.1.4 Effects of Reaction Temperatures

This observation was carried out by varying several reaction temperatures for the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline in order to obtain an optimum condition of this catalytic system. Table 4.4 displays all the results.

At 100 $^{\circ}$C (entry 3), the reaction generated the product with 52% isolated yield. Using reduced temperatures (entries 1-2) produced the expected compound in lower yields (32% at 80 $^{\circ}$C and 42% at 90 $^{\circ}$C) than the previous method. In contrast, conducting the reaction at higher temperature (110 $^{\circ}$C, entry 4) afforded better yields

of the product (65%). Thus, 110°C was the most suitable temperature for this oxidative dehydrogenation.

Table 4.4   Effects of reaction temperatures[a]
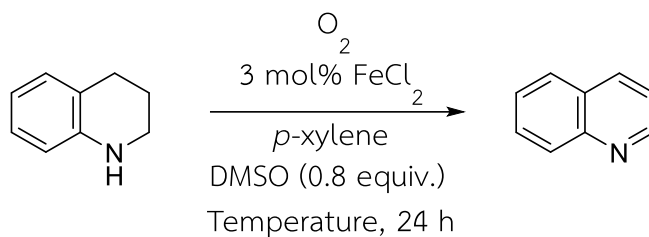
Entry	Temperature (°C)	Yield (%)[b]
1	80	32
2	90	42
3	100	52
4	110	65

[a] Condition: 1,2,3,4-tetrahydroquinoline (0.5 mmol) under O_2 (1 atm), solvent (1 mL), temperature (80-110 °C)

[b] Isolated yields

Referring to all the aforementioned results, the maximum yield was obtained from the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline by using the combination of $FeCl_2$ and DMSO in p-xylene under O_2 atmosphere at 110°C for 24 h. The summary of the optimization is shown in Figure 4.2.
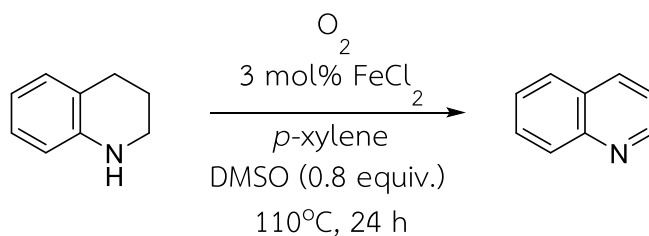
Figure 4.2 The optimum condition for oxidative dehydrogenation of
1,2,3,4-tetrahydroquinoline

4.5.2 Oxidative Dehydrogenation of 1,2,3,4-Tetrahydroquinoline Derivatives
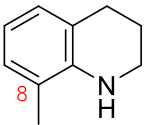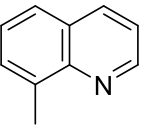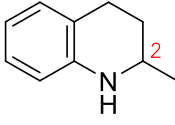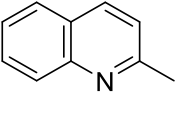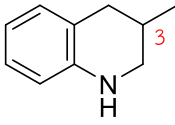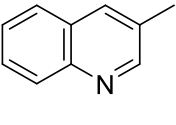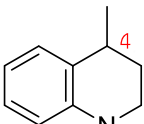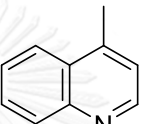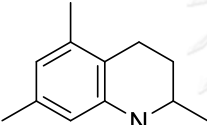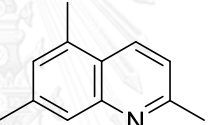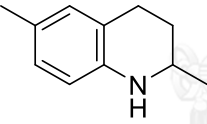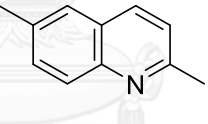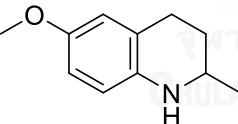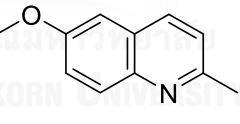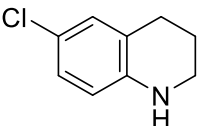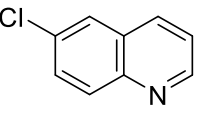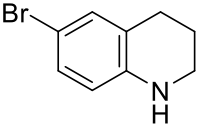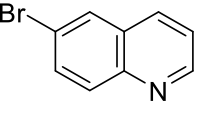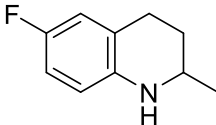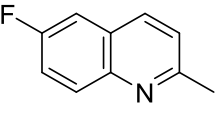
With the optimum condition in hand, a variety of substituted 1,2,3,4-tetrahydroquinolines were further examined under this developed method to study both steric, and electronic effects influences of substituents. Table 4.5 summarizes the oxidative dehydrogenation of these tetrahydroquinolines.

For substrates with the substituent at positions 2, 3, and 4 of non-aromatic ring (entries 2-4) and position 8 of the aromatic ring (entry 1), the reactions afforded the corresponding products in good yields in 65, 82, 75, and 70%, respectively. The results displayed that the substitution at these positions do not have much effects in this catalytic system.

Substrates containing two and three substituents were also investigated (entries 5-13). All reactions provided moderate to good yields (52-81%) of products. Notably, the reactions of substrates containing electron-withdrawing groups (EWG) at 6 position (entries 8-12) needed longer reaction times to reach completion. Then those EWG should have huge effects to the production; however, referring to the product yields which were similar to methyl-substituent substrate, their impacts were not effective towards the conditions used. For 8-chloro-substituted substrate (entry 13), both electronic effects from –Cl at C-8, and steric hindrance at C-2 should have an influence on substrate reactivity because of the longer reaction time.
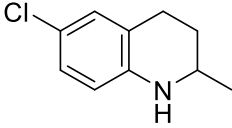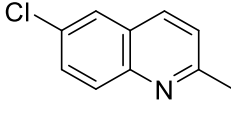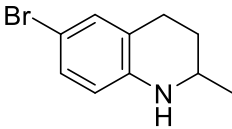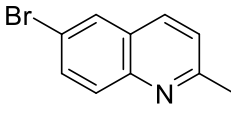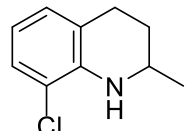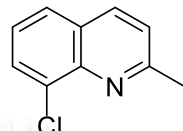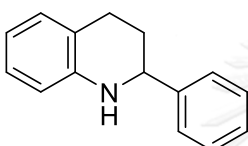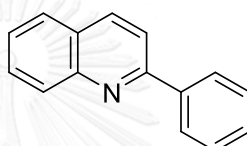
To confirm the assumption, 2-phenyl-1,2,3,4-tetrahydroquinoline (entry 14) was chosen with regards to having a steric group at C-2. Surprisingly, the selected substrate yielded the corresponding product in high yield in relatively short reaction time (8 h). It may be due to the fact that –Ph group affected C-H bond strength at C-2 with their surrounding electrons, and then made electronic effects play more important role than steric hindrance in the oxidative dehydrogenation of these selected substrates.

Table 4.5   Oxidative dehydrogenation of tetrahydroquinolines[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			24	70
2			24	65
3			24	82
4			24	75
5			24	54
6			24	73
7			24	59
8			28	71
9			26	71
10			24	52

[a] Condition: substrate (0.5 mmol), $FeCl_2$ (3 mol%), DMSO (0.8 equiv.), 110 $^{\circ}$C, *p*-xylene (1 mL) under O_2 (1 atm), [b] Isolated yield

Table 4.5   Continue[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
11			24	76
12			30	81
13			40	64
14			8	80

[a] Condition: substrate (0.5 mmol), $FeCl_2$ (3 mol%), DMSO (0.8 equiv.), 110°C, p-xylene (1 mL) under O_2 (1 atm) with TLC monitoring for reaction times

[b] Isolated yield

Furthermore, an individual experiment was performed to gain more data on the effects of the substituent at the 2 position by treating 2-cyclohexyl-1,2,3,4-tetrahydroquinoline (a) with the developed catalytic system under the optimum condition.
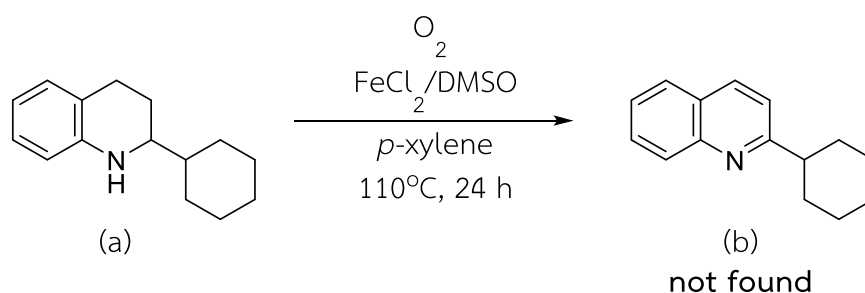
2-Cyclohexylquinoline (b) as the expected product was not detected within 24 h, although it may be found with longer reaction time. Thus, at C-2 steric hindrance of cyclohexyl (-Cy) group could affect the activity of the reaction. This result could obviously verify that the nature of the substituent at C-2 position was the most essential factors influencing the reactivity of this oxidative dehydrogenation, and also

demonstrated that the 2 position is a crucial point or the most active position for this reaction.

8-Methylquinoline [167]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 8.93 (m, 1H), 8.10 (m, 1H), 7.64 (d, J = 4.0 Hz, 1H), 7.54 (m, 1H), 7.43 – 7.35 (m, 2H) 2.82 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 149.2, 147.3, 137.1, 136.3, 129.6, 128.3, 126.3, 125.9, 120.8, 18.2. HRMS calcd for ($C_{10}H_9N+H^+$): 144.0813; found: 144.0813.

2-Methylquinoline [168]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 8.03 – 8.01 (m, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.67 (m, 1H), 7.47 (m, 1H), 7.26 (m, 1H), 2.74 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 158.9, 147.8, 136.2, 129.4, 128.6, 127.5, 126.5, 125.6, 121.9, 25.3. HRMS calcd for ($C_{10}H_9N+H^+$): 144.0813; found: 144.0811.

3-Methylquinoline [169]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 8.75 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.62 (m, 1H), 7.49 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 152.4, 146.5, 134.6, 130.4, 129.1, 128.4, 128.1, 127.1, 126.5, 18.7. HRMS calcd for ($C_{10}H_9N+H^+$): 144.0813; found: 144.0808.

4-Methylquinoline [170, 171]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 8.67 (d, J = 8.0 Hz, 1H), 8.01 (m, 1H) 7.88 (m, 1H), 7.60 (m, 1H), 7.46 (m, 1H), 7.10 (m, 1H), 2.58 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 150.1, 147.9, 144.2, 129.9, 129.1, 128.3, 126.2, 123.8, 121.8, 18.6. HRMS calcd for ($C_{10}H_9N+H^+$): 144.0813; found: 144.0814.

2,5,7-Trimethylquinoline [172]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 8.12 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 2.71 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 158.3, 148.4, 139.2, 133.9, 132.4, 128.5, 125.9, 123.8, 120.7, 25.1, 21.8, 18.4. HRMS calcd for ($C_{12}H_{13}N+H^+$): 172.1126; found: 172.1126.

2,6-Dimethylquinoline [173]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 7.83 – 7.80 (m, 2H), 7.40 – 7.37 (m, 2H), 7.11 (d, J = 8.0 Hz, 1H), 2.61 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 157.9, 146.4, 135.5, 135.3, 131.6, 128.2, 126.5, 126.4, 121.9, 25.2, 21.4. HRMS calcd for ($C_{11}H_{11}N+H^+$): 158.0970; found: 158.0969.

6-Methoxy-2-quinoline [174]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 7.94-7.91 (m, 2H), 7.33 (dd, J = 8.0 and 4.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 3.90

(s, 3H), 2.70 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 157.1, 156.3, 143.9, 135.0, 129.9, 127.3, 122.2, 121.8, 105.2, 55.5, 24.9. HRMS calcd for (C$_{11}$H$_{11}$NO+H$^+$): 174.0919; found: 174.0914.

6-Chloroquinoline [175]: yellow solid, mp. 39-41 °C; ^{1}H NMR (CDCl$_3$) δ 8.79 (dd, J = 6.0 and 1.6 Hz, 1H), 7.95-7.93 (m, 2H), 7.67 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 8.0 and 2.4 Hz, 1H), 7.29 (dd, J = 8.0 and 4.0 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 150.5, 146.6, 135.1, 132.2, 131.1, 130.4, 128.8, 126.4, 121.9. HRMS calcd for (C$_9$H$_6$ClN+H$^+$): 164.0267; found: 164.0264.

6-Bromoquinoline [175]: brown solid, mp. 22-23 °C; ^{1}H NMR (CDCl$_3$) δ 8.92 (d, J = 3.6 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.99-7.97 (m, 2H), 7.78 (dd, J = 8.8 and 0.8 Hz, 1H) 7.42 (dd, J = 8.4 and 4.4 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 150.7, 146.8, 135.0, 132.9, 131.2, 129.8, 129.3, 121.9, 120.4. HRMS calcd for (C$_9$H$_6$BrN+H$^+$): 207.9762; found: 207.9761.

6-Fluoro-2-methylquinoline [176]: yellow solid, mp. 51-53 °C; ^{1}H NMR (CDCl$_3$) δ 8.00 (dd, J = 9.2 and 5.6 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.46-7.41 (m, 1H), 7.36 (dd, J = 8.8 and 2.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 161.1, 158.2, 144.9, 144.9, 135.5, 130.9, 122.7, 119.3, 110.3, 25.1. HRMS calcd for (C$_{10}$H$_8$FN+H$^+$): 162.0719; found: 162.0721.

6-Chloro-2-methylquinoline [177]: white solid, mp. 90-92 °C; ^{1}H NMR (CDCl$_3$) δ 7.94-7.89 (m, 2H), 7.70 (d, J = 2.4 Hz, 1H), 7.58 (dd, J = 8.8 and 2,4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 159.3, 146.2, 135.2, 131.2, 130.2, 129.1, 127.0, 126.1, 122.8, 25.3. HRMS calcd for (C$_{10}$H$_8$ClN+H$^+$): 178.0424; found: 178.0425.

6-Bromo-2-methylquinoline [178]: white solid, mp. 96-97 °C; ^{1}H NMR (CDCl$_3$) δ 7.91 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.72 (dd, J = 8.8 and 2.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 159.5, 146.4, 135.1, 132.8, 130.4, 129.5, 127.6, 122.8, 119.3, 25.3. HRMS calcd for (C$_{10}$H$_8$BrN+H$^+$): 221.9918; found: 221.9920.

8-Chloro-2-methylquinoline [159]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 8.02 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 7.6 and 1.6 Hz, 1H), 7.67 (dd, J = 8.0 and 0.8 Hz, 1H), 7.38 – 7.31 (m, 2H), 2.61 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 160.2, 144.0, 136.5, 132.7, 129.5, 127.8, 126.7, 125.5, 122.9, 25.7. HRMS calcd for (C$_{10}$H$_8$ClN+H$^+$):178.0424; found: 178.0426.

2-Phenylquinoline [179]: white solid, mp. 85-86 °C; ^{1}H NMR (CDCl$_3$) δ 8.12 – 8.07 (m, 4H), 7.78 – 7.71 (m, 2H), 7.65-7.62 (m, 1H), 7.46 – 7.35 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 157.4, 148.3, 139.7, 136.8, 129.8, 129.7, 129.3, 128.9, 127.6, 127.5, 127.2, 126.3, 119.0. HRMS calcd for (C$_{15}$H$_{12}$N+H$^+$): 206.0970; found: 206.0971.

4.5.3 Oxidative Dehydrogenation of Other *N*-Containing Compounds

With the good reactivity of those tetrahydroquinoline derivatives, more investigation on this catalytic system was expanded to other *N*-containing compounds. Several *N*-containing substrates including a few substituted tetrahydroquinolines, tetrahydroisoquinoline, tetrahydroquinoxaline, and indoline were examined based on the typical method under the optimum condition. All results are shown in Table 4.6.
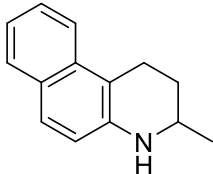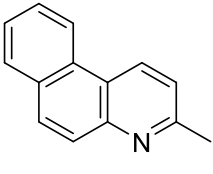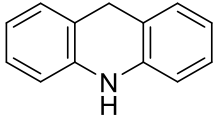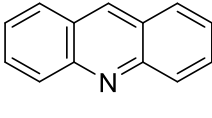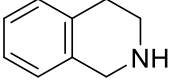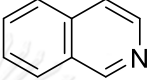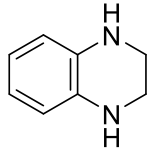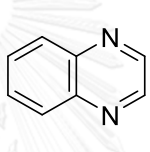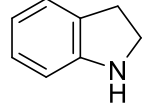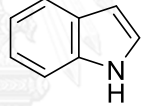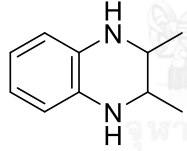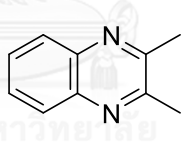
All selected *N*-containing substrates could be smoothly converted into their corresponding unsaturated products under this developed system in moderate to good yields (41-79% isolated yield). Even though most of the products were found in lower yields than previous reports, some of them could be generated in comparable yields such as acridine (entry 2), and quinoxaline (entries 4 or 6).

3-Methylbenzo[f]quinoline [153]: brown solid, mp. 81-83 °C; ^{1}H NMR (CDCl$_3$) δ 8.80 (d, *J* = 8.4 Hz, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 2.4 Hz, 2H), 7.91 (dd, *J* = 7.6 and 1.2 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 2.78 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 158.4, 147.8, 131.8, 130.9, 130.7, 129.7, 128.6, 127.9, 127.0, 126.8, 123.2, 122.4, 121.8, 25.0. HRMS calcd for (C$_{14}$H$_{11}$N+H$^+$): 194.0970; found: 194.0969.

Acridine [153]: yellow solid, mp. 108-109 °C; ^{1}H NMR (CDCl$_3$) δ 8.69 (s, 1H), 8.17 (dd, *J* = 8.8 and 0.8 Hz, 2H), 7.92, (d, *J* = 8.4 Hz, 2H), 7.73 – 7.69 (m, 2H), 7.48 – 7.44 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 149.1, 136.1, 130.3, 129.4, 128.2, 126.6, 125.7. HRMS calcd for (C$_{13}$H$_9$N+H$^+$): 180.0813; found: 180.0815.

Isoquinoline [164]: colorless oil; ^{1}H NMR (CDCl$_3$) δ 9.26 (s, 1H), 8.53 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.59 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 152.5, 142.9, 135.8, 130.3, 128.7, 127.6, 127.2, 126.5, 120.4. HRMS calcd for (C$_9$H$_7$N+H$^+$): 130.0657; found: 130.0659.

Table 4.6   Oxidative dehydrogenation of other *N*-containing compounds[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			24	41
2			20	79
3			24	47
4			26	46
5			34	61
6			24	75

[a] Condition: substrate (0.5 mmol), FeCl$_2$ (3 mol%), DMSO (0.8 equiv.), 110 $^{\circ}$C, *p*-xylene (1 mL) under O$_2$ (1 atm) with TLC monitoring for reaction times, [b] Isolated yield

Quinoxaline [180]: brown solid, mp. 26-27 $^{\circ}$C; ^{1}H NMR (CDCl$_3$) δ 8.78 (s, 2H), 8.07 – 8.03 (m, 2H), 7.73 – 7.69 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 144.9, 143.0, 130.1, 129.5. HRMS calcd for (C$_8$H$_6$N$_2$+H$^+$): 131.0609; found: 131.0612.

1*H*-Indole [181]: white solid, mp. 50-51 $^{\circ}$C ; ^{1}H NMR (CDCl$_3$) δ 8.02 (bs, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H) 7.21 – 7.10 (m, 3H), 6.55 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 135.8, 127.9, 124.2, 122.0, 120.8, 119.8, 111.1, 102.6. HRMS calcd for (C$_8$H$_7$N+H$^+$): 118.0657; found: 118.0658.

2,3-Dimethylquinoxaline [182]: yellow solid, mp. 103-104 °C; ^{1}H NMR (CDCl$_3$) δ 7.98 – 7.96 (m, 2H), 7.66 – 7.64 (m, 2H), 2.71 (s, 6H); ^{13}C NMR (CDCl$_3$) δ 153.4, 141.0, 128.8, 128.3, 23.2. HRMS calcd for (C$_{10}$H$_{10}$N$_2$+H$^+$): 159.0922; found: 159.0923.

4.5.4   Mechanistic Study for Oxidative Dehydrogenation

In order to understand the mechanism of this oxidative dehydrogenation, some extra experiments were conducted under the typical method with some adjustments by adding 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) radical and 2,6-di-*tert*-butyl-1-hydroxytoluene (BHT) to the reactions. The results are displayed in Table 4.7.

Table 4.7   Individual experiments to support the mechanistic study[a]
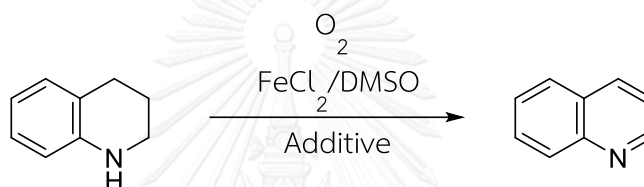
Entry	Additive[b]	Conversion (%)	Yield (%)
1	-	100	65
2	TEMPO	66	45
3	BHT	100	69
4[c]	-	0	0

[a] Condition: 1,2,3,4-tetrahydroquinoline (0.5 mmol), FeCl$_2$ (3 mol%), DMSO (0.8 equiv), *p*-xylene (1 mL) at 110°C for 24 h under O$_2$ (1 atm) with isolated yield of the product

[b] 1.0 mmol

[c] Without O$_2$

Comparing with 65% yield of the isolated product under the additive-free condition (entry 1), the yield was obviously decreased to 45% in the presence of TEMPO (entry 2) while using BHT did not have much effects to the reaction process. Due to the fact that both TEMPO and BHT are known as radical-scavenging reagents, it meant that this catalytic cycle should be involved with radicals in some mechanistic steps during the reaction procedures. In this case, TEMPO as a radical parent was able

to rapidly trap any radical species including those involving mechanistic process. The reaction was consequently inhibited. To verify the involvement of radicals which normally came from O_2 source, the O_2-free reaction was preformed (entry 4) and 0% yield of the product observed. The results indicated that this oxidative dehydrogenation was operated under radical process having O_2 as single-electron sources.

A further examination was carried out by testing *N*-methyl-1,2,3,4-tetrahydroquinoline as substrate under the developed protocol with the optimum condition. No expected product was found under the oxidative dehydrogenation. This demonstrated that the proton at N-H position is crucial for the dehydrogenation process.
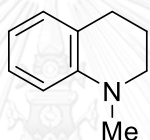
N-methyl-1,2,3,4-tetrahydroquinoline

In the meantime, some additional experiments were also carried out to search for more information on the mechanistic explanation. The reactions proceeded as shown in Figure 4.3.
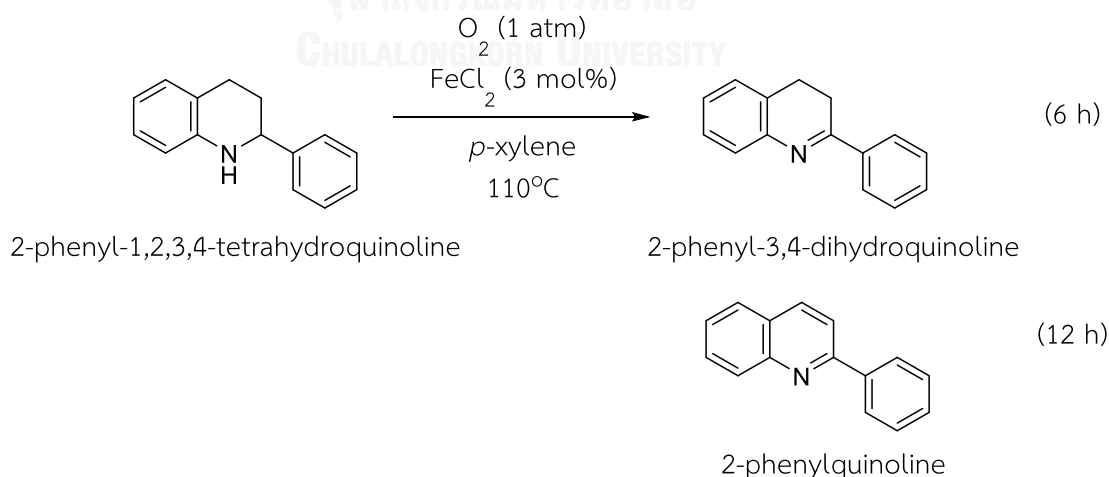
Figure 4.3 Additional supporting experiments for the mechanism study

Based on the previous result, 2-phenyl-1,2,3,4-tetrahydroquinoline (Table 4.5, entry 14) fully yielded the desired product within short reaction time (8 h). The reaction

of the same substrate was re-tested. Surprisingly, 2-phenyl-3,4-dihydroquinoline was found to be the only product formed after 6 h. The same reaction was repeated using longer reaction time (12 h). As expected, 2-phenylquinoline was generated. In summary, 2-phenyl-3,4-dihydroquinoline was inferred as a stable intermediate that could subsequently turn into the final product for this oxidative dehydrogenation process.

According to the results and previous reports [153, 183], a possible mechanism for the oxidative dehydrogenation of *N*-heterocycles utilizing $FeCl_2$/DMSO was proposed in Scheme 4.1. The mechanistic process was to create either imine or enamine as an intermediate that could be finally converted into the desired product.
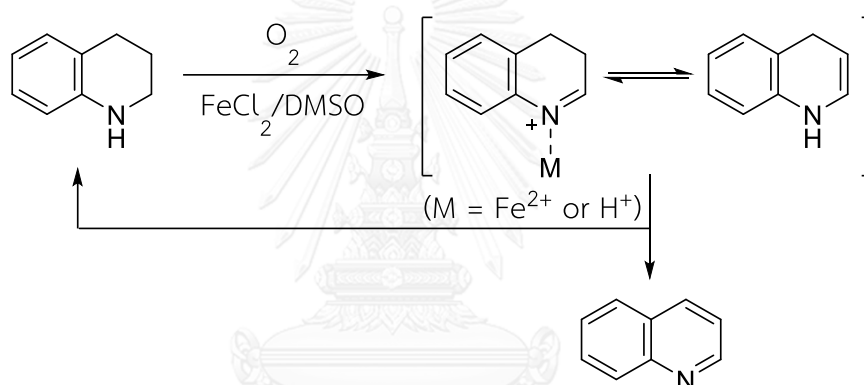
Scheme 4.1 A possible pathway for the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline

4.6   Conclusion

This work aims to search for a valuable catalytic system to transform *N*-heterocycles into their corresponding dehydrogenated products. Meanwhile, optimum condition of this develop method was also systematically observed. This methodology exhibited an excellent and convenient system for the dehydrogenation of partially saturated *N*-heterocycles under O_2 atmosphere with $FeCl_2$/DMSO system that could offer the desired products in acceptable yields compared with previous works. Moreover, the expected products were easily separated from the reaction mixture by only using simple column chromatography technique.

Using selected *N*-heterocycle (0.5 mmol) as substrate, 3.0 mol% FeCl$_2$ and DMSO acting as a co-reagent at 110 $^{\circ}$C for at least 24 h under O$_2$ (1 atm) was found to be the best condition for the oxidative dehydrogenation of *N*-heterocycles.

Various substituted 1,2,3,4-tetrahydroquinolines and other *N*-containing compounds were investigated on their structures consisting of different substituents under the developed protocol and could be summarized below:

1) One or a few substitutions on any positions of tetrahydroquinolines have no effects to this catalytic system.

2) Electron-withdrawing groups as substituents tend to require longer reaction time; however, while products are still afforded in good yields.

3) The reactions of substrates with the substitutions at the 2 and 8 positions required longer reaction time due to both electronic and steric effects.

4) The substrate with phenyl group at the 2 position gives product in good yield implying that electronic effects override the steric hindrance.

A possible mechanistic process was also indicated that O$_2$ is crucial for this FeCl$_2$/DMSO catalytic system.

4.7 Application

With a good reactivity of FeCl$_2$/DMSO system for the oxidative dehydrogenation of *N*-heterocycles, some applications of this catalytic system were investigated.

(a) The oxidative dehydrogenation of aliphatic cyclic amines
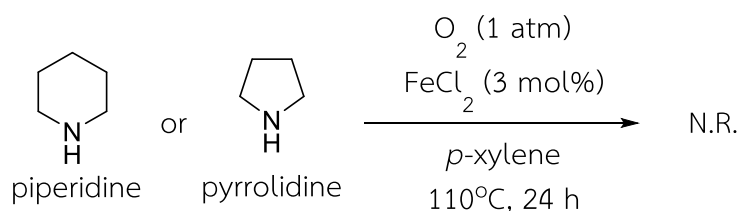
Other *N*-containing compounds with only saturated or single-bond structures were tested based on the optimum condition. Both piperidine and pyrrolidine could

not afford the corresponding products from the reaction condition employed. It may be because the final products from previous experiments were mostly aromatic compounds, therefore, the dehydrogenation process was smoothly proceeded with a potent driving force to get the final most stable products and that made these aliphatic cyclic amines show no reaction towards this catalytic system.

(b) The oxidative dehydrogenation of *N*-heterocycles in ILs

The FeCl$_2$/DMSO system could not be reused or recycled for next reactions. The FeCl$_2$/DMSO system was operated in ILs with regards to obtaining a recyclable catalytic system. The reaction was performed as shown in Figure 4.4.

Condition: substrate (0.5 mmol), FeCl$_2$ (3 mol%), DMSO (0.8 eq), solvent (1 mL) under O$_2$ (1 atm), 110°C, 24 h
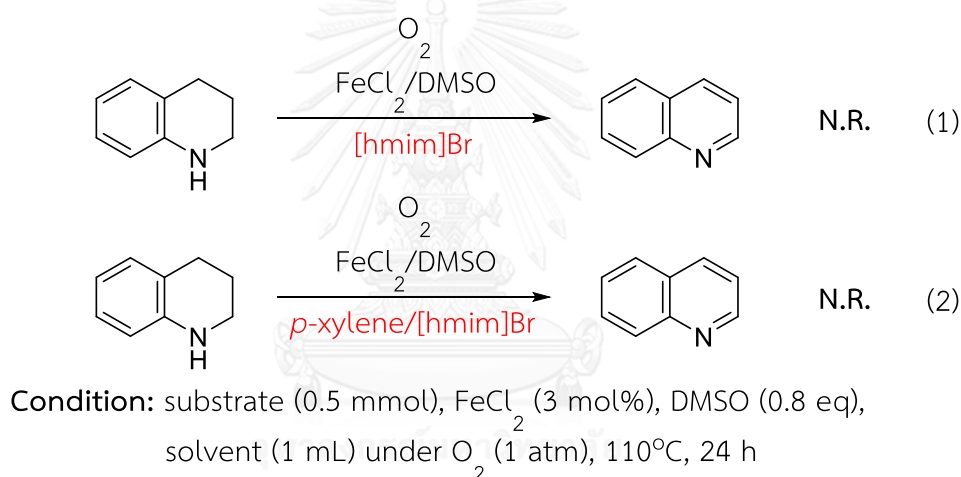
Figure 4.4 The oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline in IL

In reaction (1) from Figure 4.4, [hmim]Br was used resulting in the full recovery of the substrate. It may be because the substrate could not dissolve well in IL, the reaction thus provided no reaction. When a small amount of *p*-xylene was added to the reaction to improve the solubility of the substrate (2), the substrate remained intact in the reaction. In conclusion, the developed procedure was not suitable to be applied in the chosen IL without any optimization.

(c) The oxidative dehydrogenation of cyclic hydrocarbons
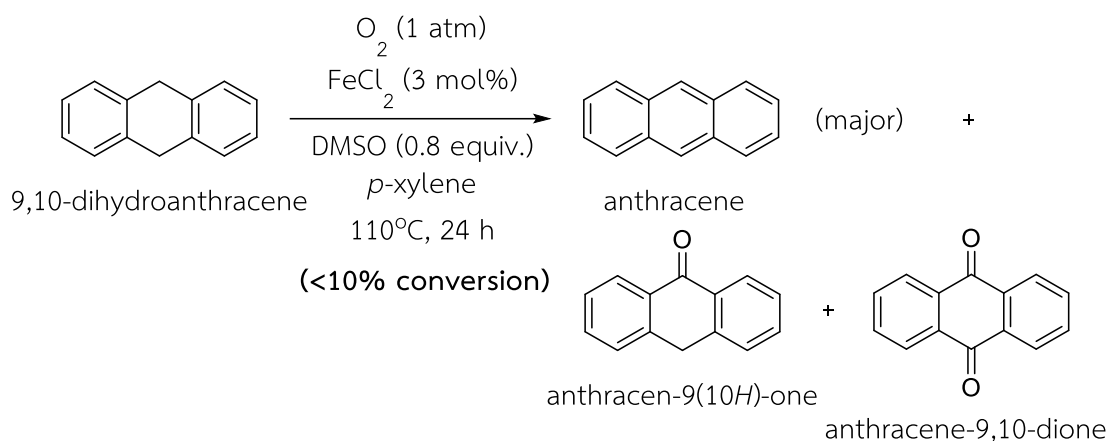
The FeCl$_2$/DMSO system was also applied to the dehydrogenation of cyclic hydrocarbons. 9,10-Dihydroanthracene was treated with both optimum condition and typical method as the oxidative dehydrogenation of *N*-heterocycles. After 24 h, the reaction was stopped and all possible compounds obtained from the mixture were investigated roughly by NMR. Three possible products were anthracene as the major product, anthracen-9(10H)-one, and anthracene-9,10-dione. According to the results, even though the target compound (anthracene) was obtained as the major product, the unwanted compounds were also detected. Moreover, the product was found in small amounts compared to the substrate recovery (less than 10% conversion). Therefore, additional work is needed to further improve the reactions.

CHAPTER V

CONCLUSION

This research aims to develop the new methodology utilizing metal salt/IL for transformation of organic compounds *via* oxidation process. The chosen IL was employed in combination with simple transition-metal salts to create new recyclable catalytic systems.

5.1 Oxidation of Alcohols

A new catalytic system containing $FeCl_3$/[hmim]Br in the presence of TBHP can smoothly furnish the expected carbonyl compounds in good yields from oxidation of a variety of alcohol substrates. Primary and secondary benzylic alcohols are the most reactive compounds towards this catalytic system. No effect was observed from the substituents of alcohol substrate. $FeCl_3$/[hmim]Br can be recovered and reused for next cycles at least nine times with little change in of the product yield compared to the previous cycle.
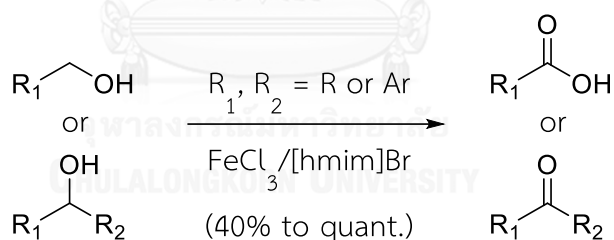
5.2 Aromatization of Cyclic Dienes

Aromatic compounds could be easily prepared in good yields from a number of cyclic dienes hydrocarbons and *N*-heterocycles by using the developed catalytic system ($CuCl_2$/[hmim]Br) and TBHP with short reaction time. In both substrate types, due to the nature of some substrates or products such as indoline and naphthalene that can be simply transformed under oxidation process, these expected products were not obtained in high yields. The yield could be improved by deactivating those substrates.

5.3 Oxidative Dehydrogenation of Heterocyclic Amines

O_2 was chosen as an oxidizing agent instead of TBHP. Iron-catalyzed reactions for oxidative dehydrogenation of *N*-heterocycles in ILs have rarely been studied. This work thus investigated the new catalytic system in conventional organic solvents.

The oxidative dehydrogenation of *N*-heterocycles catalyzed by $FeCl_2$/DMSO could furnish the desired products in high yields. Moreover, the target products could be easily obtained in high purity from the mixtures by simple column chromatography purification without any work-up required. Furthermore, the investigation on the influences of the substituents indicated that the substitution at the 2 position on 1,2,3,4-tetrahydroquinoline displayed the most effects towards this developed protocol.

The mechanisic study could evidently explain that the reaction proceeded *via* radical intermediates.

Isolated yield: 52-82%
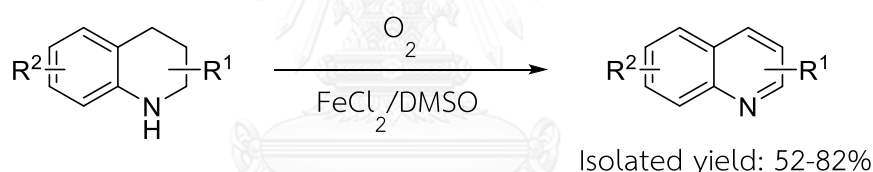
5.4 Proposal of Future Work

From the technical point of views, the developed condition should be able to prepare some bioactive compounds by the transformation of simple organic molecules such as alcohols, alkenes, amines, *etc*.

For alcohol substrates, the controlled selectivity of the oxidation under $FeCl_3$/[hmim]Br for the conversion of polyhydroxy compounds is one of the crucial points that need to be evaluated. The adjustment on the solubility of this catalytic system should be thoroughly investigated.

Metal salt/IL should be further applied to other organic substrates in the presence of different reagents so that various functional groups can be created under other reactions besides the oxidation.

REFERENCES

[1]   Hendrickson, J.B. A Logical Characterization of Organic Chemistry. Journal of Chemical Education 55 (1978).

[2]   Larock, R.C. Comprehensive Organic Transformations: A Guide to Functional Group Preparations. 2nd ed. New York: Wiley-VCH, 1999.

[3]   Gharnati, L., Doring, M., and Arnold, U. Catalytic Oxidation with Hydrogen Peroxide in Ionic Liquids. Current Organic Synthesis 6 (2009): 342-361.

[4]   Muzart, J. Ionic Liquids as Solvents for Catalyzed Oxidations of Organic Compounds. Advanced Synthesis & Catalysis 348 (2006): 275-295.

[5]   Sun, H., Harms, K., and Sundermeyer, J. Aerobic Oxidation of 2,3,6-Trimethylphenol to Trimethyl-1,4-benzoquinone with Copper(II) Chloride as Catalyst in Ionic Liquid and Structure of the Active Species. Journal of the American Chemical Society 126 (2004): 9550-9551.

[6]   Chauhan, S.M.S., Kumara, A., and Srinivasa, K.A. Oxidation of Thiols with Molecular Oxygen Catalyzed by Cobalt(II) Phthalocyanines in Ionic Liquid. Chemical Communications (2003): 2348-2349.

[7]   Cimpeanu, V., Parvulescu, V.I., Amoros, P., Beltran, D., Thompson, J.M., and Hardacre, C. Heterogeneous Oxidation of Pyrimidine and Alkyl Thioethers in Ionic Liquids over Mesoporous Ti or Ti/Ge Catalysts. Chemistry - A European Journal 10 (2004): 4640-4646.

[8]   Howarth, J. Oxidation of Aromatic Aldehydes in the Ionic Liquid [Bmim]PF_6. Tetrahedron Letters 41 (2000): 6627-6629.

[9]   Bernini, R., Coratti, A., Fabrizib, G., and Goggiamani, A. CH_3ReO_3/H_2O_2 in Room Temperature Ionic Liquids: An Homogeneous Recyclable Catalytic System for the Baeyer–Villiger Reaction. Tetrahedron Letters 44 (2003): 8991–8994.

[10]   Jain, N., Kumar, A., and Chauhan, S.M.S. Metalloporphyrin and Heteropoly Acid Catalyzed Oxidation of C=NOH Bonds in an Ionic Liquid: Biomimetic Models of Nitric Oxide Synthase. Tetrahedron Letters 46 (2005): 2599–2602.

[11] Wang, J.-R., Liu, L., Wang, Y.-F., Zhang, Y., Deng, W., and Guo, Q.-X. Aerobic Oxidation with *N*-Hydroxyphthalimide Catalysts in Ionic Liquid. <u>Tetrahedron Letters</u> 46 (2005): 4647–4651.

[12] Song, C.E. and Roh, E.J. Practical Method to Recycle a Chiral (salen)Mn Epoxidation Catalyst by Using an Ionic Liquid. <u>Chemical Communications</u> (2000): 837-838.

[13] Yao, Q. OsO_4 in Ionic Liquid [Bmim]PF_6: A Recyclable and Reusable Catalyst System for Olefin Dihydroxylation. Remarkable Effect of DMAP. <u>Organic Letters</u> 4(13) (2002): 2197-2199.

[14] Namboodiri, V.V., Varma, R.S., Sahle-Demessie, E., and Pillai, U.R. Selective Oxidation of Styrene to Acetophenone in the Presence of Ionic Liquids. <u>Green Chemistry</u> 4 (2002): 170-173.

[15] Li, Z. and Xia, C.-G. Oxidation of Hydrocarbons with Iodobenzene Diacetate Catalyzed by Manganese(III) Porphyrins in A Room Temperature Ionic Liquid. <u>Journal of Molecular Catalysis A: Chemical</u> 214 (2004): 95–101.

[16] Peng, J., Shi, F., Gu, Y., and Deng, Y. Highly Selective and Green Aqueous–Ionic Liquid Biphasic Hydroxylation of Benzene to Phenol with Hydrogen Peroxide. <u>Green Chemistry</u> 5 (2003): 224-226.

[17] Kaufmann, D.E., Nouroozian, M., and Henze, H. Molten Salts as an Efficient Medium for Palladium Catalyzed C-C Coupling Reactions. <u>Synlett</u> 11 (1996): 1091-1092.

[18] Mathews, C.J., Smith, P.J., and Welton, T. Palladium Catalysed Suzuki Cross-Coupling Reactions in Ambient Temperature Ionic Liquids. <u>Chemical Communications</u> 14 (2000): 1249-1250.

[19] Bellefon, C.d., Pollet, E., and Grenouillet, P. Molten Salts (Ionic Liquids/ to Improve the Activity, Selectivity and Stability of the Palladium Catalysed Trost–Tsuji C–C Coupling in Biphasic Media. <u>Journal of Molecular Catalysis A: Chemical</u> 145 (1999): 121-126.

[20] Fukuyama, T., Shinmen, M., Nishitani, S., Sato, M., and Ryu, I. A Copper-Free Sonogashira Coupling Reaction in Ionic Liquids and Its Application to a

Microflow System for Efficient Catalyst Recycling. <u>Organic Letters</u> 4(10) (2002): 1691-1694.

[21]   Zim, D., Souza, R.F.d., Dupont, J., and Monteiro, A.L. Regioselective Synthesis of 2-Arylpropionic Esters by Palladium-Catalyzed Hydroesterification of Styrene Derivatives in Molten Salt Media. <u>Tetrahedron Letters</u> 39 (1998): 7071-7074.

[22]   Klingshirn, M.A., Broker, G.A., Holbrey, J.D., Shaughnessy, K.H., and Rogers, R.D. Polar, Non-Coordinating Ionic Liquids as Solvents for the Alternating Copolymerization of Styrene and CO Catalyzed by Cationic Palladium Catalysts. <u>Chemical Communications</u> 13 (2002): 1394-1395.

[23]   Chauvin, Y., Mussmann, L., and Olivier, H. A Novel Class of Versatile Solvents for Two-Phase Catalysis: Hydrogenation, Isomerization, and Hydroformylation of Alkenes Catalyzed by Rhodium Complexes in Liquid 1,3-Dialkylimidazolium Salts. <u>Angewandte Chemie</u> 107 (1995): 2941.

[24]   Howarth, J., James, P., and Ryan, R. Sodium Borohydride Reduction of Aldehydes and Ketones in the Recyclable Ionic Liquid [Bmim]Pf$_6$. <u>Synthetic Communications</u> 31(19) (2001): 2935–2938.

[25]   Holbrey, J.D. and Seddon, K.R. Ionic Liquids. <u>Clean Products and Processes 1</u> (1999): 223-236.

[26]   Nara, S.J., Harjani, J.R., and Salunkhe, M.M. Friedel-Crafts Sulfonylation in 1-Butyl-3-methylimidazolium Chloroaluminate Ionic Liquids. <u>Journal of Organic Chemistry</u> 66 (2001): 8616-8620.

[27]   Peng, J. and Deng, Y. Catalytic Beckmann Rearrangement of Ketoximes in Ionic Liquids. <u>Tetrahedron Letters</u> 42 (2001): 403-405.

[28]   Deng, Y., Shi, F., Beng, J., and Qiao, K. Ionic Liquid as a Green Catalytic Reaction Medium for Esterifications. <u>Journal of Molecular Catalysis A: Chemical</u> 165 (2001): 33-36.

[29]   Rebeiro, G.L. and Khadilkar, B.M. Chloroaluminate Ionic Liquid for Fischer Indole Synthesis. <u>Synthesis</u> 3 (2001): 370-372.

[30]   Ley, S.V. and Madin, A. <u>in Comprehensive Organic Synthesis</u>. Oxford: Pergamon, 1991.

[31]   McMurry, J. <u>Organic Chemistry</u>. Californai: Brooks/Cole Punishing Company, 1996.

[32]   Ley, S.V., Norman, J., Griffith, W.P., and Marsden, S.P. Tetrapropylammonium Perruthanate, $Pr_4N^+RuO_4^-$ TPAP: A Catalytic Oxidant for Organic Synthesis. <u>Synthesis</u> (1994): 639-666.

[33]   Smith, A.B., Condon, S.M., McCauley, J.A., LeazerJr., J.L., Leahy, J.W., and MaleczkaJr., R.E. Total Synthesis of Rapamycin and Demethoxyrapamycin. <u>Journal of the American Chemical Society</u> 117(19) (1995): 5407-5408.

[34]   Ireland, R.E. and Liu, L. An Improved Procedure for the Preparation of the Dess-Martin Periodinane. <u>Journal of Organic Chemistry</u> 58 (1993): 2899.

[35]   Allan, K.M., Kobayashi, K., and Rawal, V.H. A Unified Route to the Welwitindolinone Alkaloids: Total Syntheses of (−)-*N*-Methylwelwitindolinone C Isothiocyanate, (−)-*N*-Methylwelwitindolinone C Isonitrile, and (−)-3-Hydroxy-*N*-methylwelwitindolinone C Isothiocyanate. <u>Journal of the American Chemical Society</u> 134 (2012): 1392-1395.

[36]   Bonhote, P., Dias, A.-P., Papageorgiou, N., Kalyanasundaram, K., and Gratzel, M. Hydrophobic, Highly Conductive Ambient-Temperature Molten Salts. <u>Inorganic Chemistry</u> 35 (1996): 1168-1178.

[37]   Ansari, I.A. and Gree, R. TEMPO-Catalyzed Aerobic Oxidation of Alcohols to Aldehydes and Ketones in Ionic Liquid [bmim][PF_6]. <u>Organic Letters</u> 4(9) (2002): 1507-1509.

[38]   Bianchini, G., Crucianelli, M., Angelis, F.D., Nerib, V., and Saladino, R. Highly Efficient C–H Insertion Reactions of Hydrogen Peroxide Catalyzed by Homogeneous and Heterogeneous Methyltrioxorhenium Systems in Ionic Liquids. <u>Tetrahedron Letters</u> 46 (2005): 2427-2432.

[39]   Jiang, N. and Ragauskas, A.J. TEMPO-Catalyzed Oxidation of Benzylic Alcohols to Aldehydes with the H_2O_2/HBr/Ionic Liquid [bmim]PF_6 System. <u>Tetrahedron Letters</u> 46 (2005): 3323-3326.

[40]   Lei, M., Hu, R.-J., and Wang, Y.-G. Mild and Selective Oxidation of Alcohols to Aldehydes and Ketones Using $NaIO_4$/TEMPO/NaBr System under Acidic Conditions. <u>Tetrahedron</u> 62 (2006): 8928-8932.

[41] Jiang, N. and Ragauskas, A.J. Vanadium-Catalyzed Selective Aerobic Alcohol Oxidation in Ionic Liquid [bmim]PF$_6$. Tetrahedron Letters 48 (2007): 273-276.

[42] Kumar, A., Jain, N., and Chauhan, S.M.S. Biomimetic Oxidation of Veratryl Alcohol with H$_2$O$_2$ Catalyzed by Iron(III) Porphyrins and Horseradish Peroxidase in Ionic Liquid. Synlett 3 (2007): 411-414.

[43] Fan, X., Qu, Y., Wang, Y., Zhang, X., and Wang, J. Ru(III)-Catalyzed Oxidation of Homopropargyl Alcohols in Ionic Liquid: An Efficient and Green Route to 1,2-Allenic Ketones. Tetrahedron Letters 51 (2010): 2123-2126.

[44] Liu, L., et al. Supported Ionic-Liquid Layer on Polystyrene–TEMPO Resin: A Highly Efficient Catalyst for Selective Oxidation of Activated Alcohols with Molecular Oxygen. Monatshefte fuer Chemie 144 (2013): 251-254.

[45] Yadav, J.S., Reddy, B.V.S., Basak, A.K., and Narsaiah, A.V. Recyclable 2nd Generation Ionic Liquids as Green Solvents for the Oxidation of Alcohols with Hypervalent Iodine Reagents. Tetrahedron 60 (2004): 2131-2135.

[46] Li, J.W., Sun, W., Xu, L.W., Xia, C.G., and Wang, H.W. Room Temperature Ionic Liquid. A Powerful Additive Of Mn(Salen)-Catalyzed Oxidation of sec-Alcohols. Chinese Chemical Lettes 15(12) (2004): 1437-1440.

[47] Chhikara, B.S., Tehlan, S., Kumar, A., and Ambedkar, B.R. 1-Methyl-3-butylimidazolium Decatungstate in Ionic Liquid: An Efficient Catalyst for the Oxidation of Alcohols. Synlett 1 (2005): 63-66.

[48] Chhikara, B.S., Chandra, R., and Tandon, V. Oxidation of Alcohols with Hydrogen Peroxide Catalyzed by a New Imidazolium Ion Based Phosphotungstate Complex in Ionic Liquid. Journal of Catalysis 230 (2005): 436-439.

[49] Jain, S.L., Sharma, V.B., and Sain, B. Methyltrioxorhenium and Sodium Bromide-Catalyzed Oxidation Of Alcohols to Carbonyl Compounds with H$_2$O$_2$ Using 1-Butyl-3-methyl-imidazolium Tetrafluoroborate Ionic Liquid as a Novel Recyclable Green Solvent. Bulletin of the Chemical Society of Japan 79(10) (2006): 1601-1603.

[50] Liu, C., Han, J., and Wang, J. A Simple, Efficient and Recyclable Copper(II) Acetylacetonate Catalytic System for Oxidation of sec-Alcohols in Ionic Liquid. <u>Synlett</u> 4 (2007): 643-645.

[51] Lee, S.B. and Lee, J.C. Oxidation of Benzylic Alcohols with Iodine and Lithium Carbonate in Ionic Liquid. <u>Bulletin of the Korean Chemical Society</u> 30(12) (2009): 3107-3108.

[52] Lee, J.C., Kim, J., Lee, S.B., Chang, S.-U., and Jeong, Y.J. Efficient Oxidation of Benzylic Alcohols with Trichloroisocyanuric Acid and Ionic Liquid in Water. <u>Synthetic Communications</u> 41 (2011): 1947-1951.

[53] Liu, Z., Chen, Z.-C., and Zheng, Q.-G. Mild Oxidation of Alcohols with *O*-Iodoxybenzoic Acid (IBX) in Ionic Liquid 1-Butyl-3-methyl-imidazolium Chloride and Water. <u>Organic Letters</u> 5(18) (2003): 3321-3323.

[54] Chhikara, B.S., Chandra, R., and Tandon, V. IBX in an Ionic Liquid: Eco-Friendly Oxidation of 17α-Methylandrostan-3β,17β-diol, an Intermediate in the Synthesis of Anabolic Oxandrolone. <u>Tetrahedron Letters</u> 45 (2004): 7585-7588.

[55] Yadav, L.D.S., Awasthi, C., and Rai, A. Ionic liquid-Promoted One-Pot Oxidative Michael Addition of TMSCN to Baylis–Hillman Adducts. <u>Tetrahedron Letters</u> 49 (2008): 6360-6363.

[56] Shaabani, A., Farhangi, E., and Rahmati, A. Ionic Liquid Promoted Selective Oxidation of Organic Compounds with $NaBrO_3$. <u>Monatshefte fuer Chemie</u> 139 (2008): 905-908.

[57] Sharma, U.K., Sharma, N., Kumar, R., Kumar, R., and Sinha, A.K. Biocatalytic Promiscuity of Lipase in Chemoselective Oxidation of Aryl Alcohols/Acetates: A Unique Synergism of CAL-B and [hmim]Br for the Metal-Free H_2O_2 Activation. <u>Organic Letters</u> 11(21) (2009): 4846-4848.

[58] Ramakrishna, D. and Bhat, B.R. Cobalt Complexes in [EMIM]Cl – A Catalyst for Oxidation of Alcohols to Carbonyls. <u>Inorganic Chemistry Communications</u> 13 (2010): 195-198.

[59] Sharma, N., Sharma, U.K., Salwan, R., Kasana, R.C., and Sinha, A.K. A Synergic Blend of Newly Isolated Pseudomonas mandelii KJLPB5 and [hmim]Br for

Chemoselective 2° Aryl Alcohol Oxidation in H_2O_2: Synthesis of Aryl Ketone or Aldehydes *via* Sequential Dehydration-Oxidative C=C Cleavage. <u>Catalysis Letters</u> 141 (2011): 616-622.

[60]   Kumar, R., Sharma, N., Sharma, N., Sharma, A., and Sinha, A.K. Metal-Free Activation of H_2O_2 by Synergic Effect of Ionic Liquid and Microwave: Chemoselective Oxidation of Benzylic Alcohols to Carbonyls and Unexpected Formation of Anthraquinone in Aqueous Condition. <u>Molecular Diversity</u> 15 (2011): 687-695.

[61]   Marinescu, L., Mølbach, M., Rousseau, C., and Bols, M. Supramolecular Oxidation of Anilines Using Hydrogen Peroxide as Stoichiometric Oxidant. <u>Journal of the American Chemical Society</u> 127 (2005): 17578-17579.

[62]   Betz, D., Altmann, P., Cokoja, M., Herrmann, W.A., and Kühn, F.E. Recent Advances in Oxidation Catalysis Using Ionic Liquids as Solvents. <u>Coordination Chemistry Reviews</u> 255 (2011): 1518-1540.

[63]   Armarego, W.L.F. and Chai, C.L.L. <u>Purification of Laboratory Chemicals</u>. 6th ed., 2009.

[64]   Dieskau, A.P., Begouin, J.-M., and Plietker, B. $Bu_4N[Fe(CO)_3(NO)]$-Catalyzed Hydrosilylation of Aldehydes and Ketones. <u>European Journal of Organic Chemistry</u> (2011): 5291-5296.

[65]   Cao, L., Ding, J., Gao, M., Wang, Z., Li, J., and Wu, A. A Novel and Direct Transformation of Methyl Ketones or Carbinols to Primary Amides by Employing Aqueous Ammonia. <u>Organic Letters</u> 11(17) (2009): 3810-3813.

[66]   Ford, L., Atefi, F., Singer, R.D., and Scammells, P.J. Grignard Reactions in Pyridinium and Phosphonium Ionic Liquids. <u>European Journal of Organic Chemistry</u> (2011): 942-950.

[67]   Maytum, H.C., Francos, J., Whatrup, D.J., and Williams, J.M.J. 1,4-Butanediol as a Reducing Agent in Transfer Hydrogenation Reactions. <u>Chemistry - An Asian Journal</u> 5(3) (2010): 538-542.

[68]   Kuriyama, M., Shimazawa, R., and Shirai, R. Efficient 1,2-Addition of Aryl- and Alkenylboronic Acids to Aldehydes Catalyzed by the Palladium/Thioether-

Imidazolinium Chloride System. <u>Journal of Organic Chemistry</u> 73 (2008): 1597-1600.

[69]   Brandt, A., Hallett, J.P., Leak, D.J., Murphy, R.J., and Welton, T. The Effect of the Ionic Liquid Anion in the Pretreatment of Pine Wood Chips. <u>Green Chemistry</u> 12 (2010): 672-679.

[70]   Baltazar, Q.Q., Chandawalla, J., Sawyer, K., and Anderson, J.L. Interfacial and Micellar Properties of Imidazolium-Based Monocationic and Dicationic Ionic Liquids. <u>Colloids and Surfaces A: Physicochemical and Engineering Aspects</u> 302 (2007): 150-156.

[71]   Wasserscheid, P. and Welton, T. <u>Ionic Liquids in Synthesis</u>. Wiley-VCH, 2009.

[72]   Barton, D.H.R., Bévière, S.D., Chabot, B.M., Chavasiri, W., and Taylor, D.K. Studies on the Oxidation of Alcohols Employing *t*-Butyl Hydroperoxide (TBHP) and Fe(III) Catalysts. <u>Tetrahedron Letters</u> 35(27) (1994): 4681-4684.

[73]   Barton, D.H.R., Boivin, J., Ozbalik, N., and Schwartzentruber, K.M. On the Mechanism of the Gif System for the Oxidation of Saturated Hydrocarbons. <u>Tetrahedron Letters</u> 26(4) (1985): 447-450.

[74]   Barton, D.H.R., Doller, D., and Geletii, Y.V. On the Mechanism of Carbon-Hydrogen Activation in Gif-type Reactions. Kinetic Isotopic Effects in Fyridine Solution. <u>Tetrahedron Letters</u> 32(31) (1991): 3811-3814.

[75]   Ulbricht, C., Becer, R., Winter, A., and Schubert, U.S. Copolymers by Radical Polymerization Containing Phosphorescent Iridium(Iii) Complexes. <u>Polymer Preprints (American Chemical Society, Division of Polymer Chemistry)</u> 48(2) (2007): 593-594.

[76]   Solomons, T.W.G. and Fryhle, C.B. <u>Organic Chemistry</u>. 10th ed. USA: John Wiley & Sons, INC., 2011.

[77]   Qin, S., Xing, K., Jiang, J.-H., Xu, L.-H., and Li, W.-J. Biodiversity, Bioactive Natural Products and Biotechnological Potential of Plant-Associated Endophytic Actinobacteria. <u>Applied Microbiology and Biotechnology</u> 89 (2011): 457–473.

[78]   Koehn, F.E. and Carter, G.T. The Evolving Role of Natural Products in Drug Discovery. <u>Nature Reviews</u> 4 (2005): 207-220.

[79] Kuranaga, T., et al. Total Synthesis of (-)-Brevisin: A Concise Synthesis of a New Marine Polycyclic Ether. Organic Letters 13(4) (2011): 696-699.

[80] Burk, M.J. and Crabtree, R.H. Selective Catalytic Dehydrogenation of Alkanes to Alkenes. Journal of the American Chemical Society 109 (1987): 8025-8032.

[81] Agnello, E.J. and Laubach, G.D. The Dehydrogenation of Corticosteroids with Chloranil. Journal of the American Chemical Society 82(16) (1960): 4293-4299.

[82] Weckhuysen, B.M. and Schoonheydt, R.A. Alkane Dehydrogenation over Supported Chromium Oxide Catalysts. Catalysis Today 51 (1999): 223-232.

[83] Fu, P.P. and Harvey, R.G. Dehydrogenation of Polycyclic Hydroaromatic Compounds. Chemical Reviews 78(4) (1978): 317-361.

[84] Neumann, R. Aromatization of Hydrocarbons by Oxidative Dehydrogenation Catalyzed by the Mixed Addenda Heteropoly Acid $H_5PMo_{10}V_2O_{40}$. Journal of Organic Chemistry 54 (1989): 4607-4610.

[85] McBride, C.M., Chrisman, W., Harris, C.E., and Singaram, B. Efficient Synthesis of Substituted Benzenes from 1,3-Dienes or 1,4-Cyclohexadienes with $KMnO_4$ under Mild Conditions. Tetrahedron Letters 40 (1999): 45-48.

[86] Kamata, K., Kasai, J., Yamaguchi, K., and Mizuno, N. Efficient Heterogeneous Oxidation of Alkylarenes with Molecular Oxygen. Organic Letters 6(20) (2004): 3577-3580.

[87] Breton, T., Liaigre, D., and Belgsir, E.M. Allylic Oxidation: Easy Synthesis of Alkenones from Activated Alkenes with TEMPO. Tetrahedron Letters 46 (2005): 2487-2490.

[88] Iteya, K., Ichihara, J., Sasaki, Y., and Itoh, S. Vanadomolybdophosphoric Acid/Fluorapatite Solid-Phase System for Aerobic Oxidative Dehydrogenation. Catalysis Today 111 (2006): 349-353.

[89] Buranaprasertsuk, P., Tangsakol, Y., and Chavasiri, W. Epoxidation of Alkenes Catalyzed by Cobalt(II) Calix[4]pyrrole. Catalysis Communications 8 (2007): 310-314.

[90] Bercaw, J.E., Hazari, N., and Labinger, J.A. Oxidative Aromatization of Olefins with Dioxygen Catalyzed by Palladium Trifluoroacetate. Journal of Organic Chemistry 73 (2008): 8654-8657.

[91]   Bueno, A.C., Brandão, B.B.N.S., and Gusevskaya, E.V. Aromatization of Para-Menthenic Terpenes by Aerobic Oxidative Dehydrogenation Catalyzed by *p*-Benzoquinone. Applied Catalysis A: General 351 (2008): 226-230.

[92]   Zhang, W., et al. Organocatalytic Oxidative Dehydrogenation of Dihydroarenes by Dioxygen Using 2,3-Dichloro-5,6-dicyano-benzoquinone (DDQ) and $NaNO_2$. Molecules 13 (2008): 3236-3245.

[93]   Ngamsomprasert, N. Copper Catalyzed Aromatization of Conjugated and Skipped Dienes. M.Sc., Department of Chemistry Chulalongkorn University, 2011.

[94]   Asikainen, M., Jauhiainen, O., Aaltonen, O., and Harlin, A. Continuous Catalyst-Free Aromatization of γ-Terpinene Using Air as an Oxidant. Green Chemistry 15 (2013): 3230-3235.

[95]   Ronzani, F., et al. Visible-Light Photosensitized Oxidation of α-Terpinene Using Novel Silica-Supported Sensitizers: Photooxygenation vs. Photodehydrogenation. Journal of Catalysis 303 (2013): 164-174.

[96]   Balogh-Hergovich, É. and Speier, G. Kinetics and Mechanism of the Dehydrogenation of Indolines to Indoles with Dioxygen Catalyzed by Chloro(Pyridine)Copper(I) in Dichloromethane Solution. Journal of Molecular Catalysis 39 (1986): 309-316.

[97]   Srinivas, G. and Periasamy, M. Aromatization of Enamines Using the $TiCl_4/Et_3N$ Reagent System. Tetrahedron Letters 43 (2002): 2785–2788.

[98]   Hara, T., Mori, K., Mizugaki, T., Ebitani, K., and Kaneda, K. Highly Efficient Dehydrogenation of Indolines to Indoles Using Hydroxyapatite-Bound Pd Catalyst. Tetrahedron Letters 44 (2003): 6207-6210.

[99]   Chandra, T., Zou, S., and Brown, K.L. Low Temperature Dehydrogenation of α-Indoline Nucleosides. Tetrahedron Letters 45 (2004): 7783–7786.

[100]   Heravi, M.M., Behbahani, F.K., Oskooie, H.A., and Shoar, R.H. Catalytic Aromatization of Hantzsch 1,4-Dihydropyridines by Ferric Perchlorate in Acetic Acid. Tetrahedron Letters 46 (2005): 2775–2777.

[101] Yamamoto, K., Chen, Y.G., and Buono, F.G. Oxidative Dehydrogenation of Dihydropyrimidinones and Dihydropyrimidines. <u>Organic Letters</u> 7(21) (2005): 4673-4676.

[102] Filipan-Litvić, M., Litvić, M., and Vinković, V. A Highly Efficient Biomimetic Aromatization of Hantzsch-1,4-Dihydropyridines with *t*-Butylhydroperoxide, Catalysed by Iron(III) Phthalocyanine Chloride. <u>Bioorganic & Medicinal Chemistry</u> 16 (2008): 9276–9282.

[103] Ramirez, T.A., Zhao, B., and Shi, Y. An Effective C–C Double Bond Formation *via* Cu(I)-Catalyzed Dehydrogenation. <u>Tetrahedron Letters</u> 51 (2010): 1822–1825.

[104] Huang, B., Tian, H., Lin, S., Xie, M., Yu, X., and Xu, Q. Cu(I)/Tempo-Catalyzed Aerobic Oxidative Synthesis of Imines Directly from Primary and Secondary Amines under Ambient and Neat Conditions. <u>Tetrahedron Letters</u> 54 (2013): 2861-2864.

[105] Damodara, D., Arundhathi, R., and Likhara, P.R. Copper Nanoparticles from Copper Aluminum Hydrotalcite: An Efficient Catalyst for Acceptor- and Oxidant-Free Dehydrogenation of Amines and Alcohols. <u>Advanced Synthesis & Catalysis</u> 356 (2014): 189-198.

[106] Peng, F., McLaughlin, M., Liu, Y., Mangion, I., Tschaen, D.M., and Xu, Y. A Mild Cu(I)-Catalyzed Oxidative Aromatization of Indolines to Indoles. <u>Journal of Organic Chemistry</u> 81 (2016): 10009–10015.

[107] Maier, A.F.G., et al. Frustrated Lewis Pair Catalyzed Dehydrogenative Oxidation of Indolines and Other Heterocycles. <u>Angewandte Chemie International Edition</u> 55 (2016): 12219 –12223.

[108] Shen, Y., et al. Highly Efficient Cu-Catalyzed Oxidative Coupling of Tertiary Amines and Siloxyfurans. <u>Tetrahedron</u> 65 (2009): 158-163.

[109] Li, Y., Wu, X., Lee, T.B., Isbell, E.K., Parish, E.J., and Gorden, A.E.V. An Effective Method for Allylic Oxidation of Δ^5-Steroids Using *tert*-Butyl Hydroperoxide. <u>Journal of Organic Chemistry</u> 75 (2010): 1807–1810.

[110] Ye, X., Xie, C., Pan, Y., Han, L., and Xie, T. Copper-Catalyzed Synthesis of α-Amino Imides from Tertiary Amines: Ugi-Type Three-Component Assemblies Involving Direct Functionalization of sp^3 C-Hs Adjacent to Nitrogen Atoms. Organic Letters 12(19) (2010): 4240-4243.

[111] Rayati, S., Zakavi, S., Koliaei, M., Wojtczak, A., and Kozakiewicz, A. Electron-Rich Salen-Type Schiff Base Complexes of Cu(II) as Catalysts for Oxidation of Cyclooctene and Styrene with *tert*-Butylhydroperoxide: A Comparison with Electron-Deficient Ones. Inorganic Chemistry Communications 13 (2010): 203–207.

[112] Huang, X.-F., Zhu, Z.-Q., and Huang, Z.-Z. Copper-Catalyzed Dehydrogenative Cross-Coupling Reaction between Unactivated Ethers and Simple Ketones Mediated by Pyrrolidine. Tetrahedron 69 (2013): 8579-8582.

[113] Deb, M.L., Pegu, C.D., Borpatra, P.J., and Baruah, P.K. Copper Catalyzed Oxidative Deamination of Betti Bases: An Efficient Approach for Benzoylation/Formylation of Naphthols and Phenols. RSC Advances 6 (2016): 40552–40559.

[114] Hossain, M.M. and Shyu, S.-G. Biphasic Copper-Catalyzed C-H Bond Activation of Arylalkanes to Ketones with *tert*-Butyl Hydroperoxide in water at Room Temperature. Tetrahedron 72 (2016): 4252-4257.

[115] Choi, M.K.W. and Toy, P.H. Soluble Polystyrene-Based Sulfoxide Reagents for Swern Oxidation Reactions. Tetrahedron 59 (2003): 7171-7176.

[116] Chantarasriwong, O., Jiangchareon, B., Putra, C.K., Suwankrua, W., and Chavasiri, W. NBS and Br$_3$CCOCBr$_3$ as Highly Efficient Catalysts for the Chemoselective *N-tert*-Butyloxycarbonylation of Amines. Tetrahedron Letters 57 (2016): 4807-4811.

[117] Jiao, L.-Y. and Oestreich, M. Oxidative Palladium(II)-Catalyzed C-7 Alkenylation of Indolines. Organic Letters 15(20) (2013): 5374-5377.

[118] Barbe, G. and Charette, A.B. Total Synthesis of (+)-Lepadin B: Stereoselective Synthesis of Nonracemic Polysubstituted Hydroquinolines Using an RC-ROM

Process. <u>Journal of the American Chemical Society</u> 130(42) (2008): 13873–13875.

[119] Li, W.-J., Zhao, F.-F., and Ding, M.-W. Unexpected Synthesis of *N*-Acyl Indolines *via* a Consecutive Cyclization of Iminophosphorane. <u>Synlett</u> 2 (2011): 265-267.

[120] Ameriks, M., Arienti, K., Axe, F., and Breitenbucher, J. <u>Substituted Benzimidazoles and Imidazo-[4,5]-pyridines</u>. 2004.

[121] Gioiello, A., Rosatelli, E., Teofrasti, M., Filipponi, P., and Pellicciari, R. Building a Sulfonamide Library by Eco-Friendly Flow Synthesis. <u>ACS Combinatorial Science</u> 15 (2013): 235-239.

[122] Choy, P.Y., Lau, C.P., and Kwong, F.Y. Palladium-Catalyzed Direct and Regioselective C-H Bond Functionalization/Oxidative Acetoxylation of Indoles. <u>Journal of Organic Chemistry</u> 76 (2011): 80-84.

[123] Fraile, J.M., Jeune, K.L., Mayoral, J.A., Ravasio, N., and Zaccheria, F. CuO/SiO$_2$ as a Simple, Effective and Recoverable Catalyst for Alkylation of Indole Derivatives with Diazo Compounds. <u>Organic & Biomolecular Chemistry</u> 11 (2013): 4327-4332.

[124] Katritzky, A.R., Khelashvili, L., Mohapatra, P.P., and Steel, P.J. Efficient *N*-Aroylation of Substituted Indoles with *N*-Aroylbenzotriazoles. <u>Synthesis</u> 23 (2007): 3673-3677.

[125] Kurisaki, T., Naniwa, T., Yamamoto, H., Imagawa, H., and Nishizawa, M. Mercuric Triflate-Catalyzed Cycloisomerization of 2-Ethynylaniline Derivatives Leading Indoles. <u>Tetrahedron Letters</u> 48 (2007): 1871-1874.

[126] Vereecken, L. and Peeters, J. H-Atom Abstraction by OH-Radicals from (Biogenic) (Poly)Alkenes: C-H Bond Strengths and Abstraction Rates. <u>Chemical Physics Letters</u> 333 (2001): 162-168.

[127] Meshram, H.M., Reddy, G.S., Reddy, M.M., Eeshwaraiah, B., and Yadav, J.S. Microwave Thermolysis: Part III - A Rapid and Convenient Coupling of 2-Naphthols in Solvent-Free Condition <u>Indian Journal of Chemistry</u> 42B (2003): 2615-2617.

[128] Zhai, L.-H., Guo, L.-H., Luo, Y.-H., Ling, Y., and Sun, B.-W. Effective Laboratory-Scale Preparation of Axitinib by Two CuI-Catalyzed Coupling Reactions. Organic Process Research & Development 19 (2015): 849-857.

[129] Karkhelikar, M.V., Rao, V.V., Shinde, S.S., and Likhar, P.R. A New Synthetic Approach to Pyrrolo[3,2-*b*]indoles *via* Regioselective Formation of Pyrrole and Intramolecular C-N Coupling. Tetrahedron Letters 57 (22016): 4803-4806.

[130] Taylor, W.I. and Battersby, A.R. Oxidative Coupling Of Phenols. New York: Marcel Dekker, 1967.

[131] Tanaka, H., Sakata, I., and Senju, R. Oxidative Coupling Reaction of Phenols with Dichromate. Bulletin of the Chemical Society of Japan 43 (1970): 212-215.

[132] Brussee, J., Groenendijk, J.L.G., Koppele, J.M.t., and Jansen, A.C.A. On the Mechanism of the Formation of S(-)-(1,1'-Binaphthalene)-2,2'-diol *via* Copper(II)amine Complexes. Tetrahedron 41(16) (1985): 3313-3319.

[133] Pietikäinen, P. and Adlercreutz, P. Influence of the Reaction Medium on the Product Distribution of Peroxidase-Catalysed Oxidation of *p*-Cresol. Applied Microbiology and Biotechnology 33 (1990): 455-458.

[134] Hovorka, M., Günterová, J., and Závada, J. Highly Selective Oxidative Cross-Coupling of Substituted 2-Naphthols : A Convenient Approach to Unsymmetrical 1,1'-Binaphthalene-2,2'-diols. Tetrahedron Letters 31(3) (1990): 413-416.

[135] Noji, M., Nakajima, M., and Koga, K. A New Catalytic System for Aerobic Oxidative Coupling of 2-Naphthol Derivatives by the Use of CuCl-Amine Complex: A Practical Synthesis of Binaphthol Derivatives. Tetrahedron Letters 35(43) (1994): 7983-7984.

[136] Asakura, K., Honda, E., and Osanai, S. Selective Oxidative Coupling of *p*-Cresol Producing an *ortho-ortho* Direct-linked Dimer. Chemistry Letters (1995): 583-584.

[137] Hu, Q.-S., Vitharana, D., and Pu, L. An Efficient and Practical Direct Resolution of Racemic 1,1'-Bi-2-naphthol to Both of Its Pure Enantiomers. Tetrahedron: Asymmetry 6(9) (1995): 2123-2126.

[138]   Love, B.E. and Bills, R.A. Facile Synthesis of Binol in the Absence of Solvent. Synthetic Communications 32(13) (2002): 2067-2073.

[139]   Yadav, J.S., Reddy, B.V.S., Gayathri, K.U., and Prasad, A.R. [Bmim]PF$_6$/RuCl$_3$·xH$_2$O: A Novel and Recyclable Catalytic System for the Oxidative Coupling of β-Naphthols. New Journal of Chemistry 27 (2003): 1684-1686.

[140]   Egami, H. and Katsuki, T. Iron-Catalyzed Asymmetric Aerobic Oxidation: Oxidative Coupling of 2-Naphthols. Journal of the American Chemical Society 131(17) (2009): 6082-6083.

[141]   Furniss, B.S., Tatchell, A.R., Hannaford, A.J., and Smith, P.W.G. Vogel's Textbook of Practical Organic Chemistry. 5th ed. New York: Pearson, 1996.

[142]   Barhate, N.B. and Chen, C.-T. Catalytic Asymmetric Oxidative Couplings of 2-Naphthols by Tridentate N-Ketopinidene-Based Vanadyl Dicarboxylates. Organic Letters 4(15) (2002): 2529-2532.

[143]   Armengol, E., Corma, A., García, H., and Primo, J. A Highly Selective Synthesis of 1,1'-Bi-2-naphthol by Oxidative Coupling of Naphthol on Mesoporous Fe,Cu/MCM-41 Aluminosilicates. European Journal of Organic Chemistry (1999): 1915-1920.

[144]   Mangas-Sánchez, J., Busto, E., Gotor-Fernández, V., and Gotor, V. Straightforward Synthesis of Enantiopure 2,3-Dihydrobenzofurans by a Sequential Stereoselective Biotransformation and Chemical Intramolecular Cyclization. Organic Letters 12(15) (2010): 3498-3501.

[145]   Zhou, W., Taboonpong, P., Aboo, A.H., Zhang, L., Jiang, J., and Xiao, J. A Convenient Procedure for the Oxidative Dehydrogenation of N-Heterocycles Catalyzed by FeCl$_2$/DMSO. Synlett 27 (2016): A-D.

[146]   Gilchrist, T.L. Heterocyclic Chemistry. 3rd ed. England: Addison Wesley: Essex, 1997.

[147]   Yamaguchi, K. and Mizuno, N. Efficient Heterogeneous Aerobic Oxidation of Amines by a Supported Ruthenium Catalyst. Angewandte Chemie International Edition 42 (2003): 1479-1483.

[148] Choi, H. and Doyle, M.P. Oxidation of Secondary Amines Catalyzed by Dirhodium Caprolactamate. Chemical Communications (7) (2007): 745-747.

[149] Li, F., Chen, J., Zhang, Q., and Wang, Y. Hydrous Ruthenium Oxide Supported on CO_3O_4 as Efficient Catalyst for Aerobic Oxidation of Amines. Green Chemistry 10 (2008): 553–562.

[150] Yamaguchi, R., Ikeda, C., Takahashi, Y., and Fujita, K.-i. Homogeneous Catalytic System for Reversible Dehydrogenation-Hydrogenation Reactions of Nitrogen Heterocycles with Reversible Interconversion of Catalytic Species. Journal of the American Chemical Society 131 (2009): 8410–8412.

[151] Mikami, Y., Ebata, K., Mitsudome, T., Mizugaki, T., Jitsukawa, K., and Kaneda, K. Reversible Dehydrogenation-Hydrogenation of Tetrahydroquinoline-Quinoline Using a Supported Copper Nanoparticle Catalyst. Heterocycles 82(2) (2011): 1371-1377.

[152] Muthaiah, S. and Hong, S.H. Acceptorless and Base-Free Dehydrogenation of Alcohols and Amines Using Ruthenium-Hydride Complexes. Advanced Synthesis & Catalysis 354 (2012): 3045 – 3053.

[153] Wu, J., Talwar, D., Johnston, S., Yan, M., and Xiao, J. Acceptorless Dehydrogenation of Nitrogen Heterocycles with a Versatile Iridium Catalyst. Angewandte Chemie International Edition 52 (2013): 6983 –6987.

[154] Zhang, E., Tian, H., Xu, S., Yu, X., and Xu, Q. Iron-Catalyzed Direct Synthesis of Imines from Amines or Alcohols and Amines via Aerobic Oxidative Reactions under Air. Organic Letters 15(11) (2013): 2704-2707.

[155] Yao, W., Zhang, Y., Jia, X., and Huang, Z. Selective Catalytic Transfer Dehydrogenation of Alkanes and Heterocycles by an Iridium Pincer Complex. Angewandte Chemie International Edition 53 (2014): 1390 –1394.

[156] Chakraborty, S., Brennessel, W.W., and Jones, W.D. A Molecular Iron Catalyst for the Acceptorless Dehydrogenation and Hydrogenation of N-Heterocycles. Journal of the American Chemical Society 136 (2014): 8564–8567.

[157] Wendlandt, A.E. and Stahl, S.S. Modular *o*-Quinone Catalyst System for Dehydrogenation of Tetrahydroquinolines under Ambient Conditions. <u>Journal of the American Chemical Society</u> 136 (2014): 11910–11913.

[158] Jawale, D.V., et al. Cooperative Dehydrogenation of *N*-Heterocycles Using a Carbon Nanotube–Rhodium Nanohybrid. <u>Chemistry - A European Journal</u> 21 (2015): 7039 – 7042.

[159] Cui, X., et al. Synthesis and Characterization of Iron–Nitrogen-Doped Graphene/Core–Shell Catalysts: Efficient Oxidative Dehydrogenation of *N*-Heterocycles. <u>Journal of the American Chemical Society</u> 137 (2015): 10652–10658.

[160] Iosub, A.V. and Stahl, S.S. Catalytic Aerobic Dehydrogenation of Nitrogen Heterocycles Using Heterogeneous Cobalt Oxide Supported on Nitrogen-Doped Carbon. <u>Organic Letters</u> 17 (2015): 4404–4407.

[161] Xu, R., Chakraborty, S., Yuan, H., and Jones, W.D. Acceptorless, Reversible Dehydrogenation and Hydrogenation of *N*-Heterocycles with a Cobalt Pincer Catalyst. <u>ACS Catalysis</u> 5 (2015): 6350–6354.

[162] Punniyamurthy, T., Velusamy, S., and Iqbal, J. Recent Advances in Transition Metal Catalyzed Oxidation of Organic Substrates with Molecular Oxygen. <u>Chemical Reviews</u> 105 (2005): 2329-2363.

[163] Nose, A. and Kudo, T. Reduction of Heterocyclic Compounds. II. Reduction of Heterocyclic Compounds with Sodium-Borohydride-Transition Metal Salt Systems. <u>Chemical and Pharmaceutical Bulletin</u> 32(6) (1984): 2421-2425.

[164] Kumar, R.A., Maheswari, C.U., Ghantasala, S., Jyothi, C., and Reddy, K.R. Synthesis of 3*H*-Quinazolin-4-ones and 4*H*-3,1-Benzoxazin-4-ones *via* Benzylic Oxidation and Oxidative Dehydrogenation using Potassium Iodide-*tert*-Butyl Hydroperoxide. <u>Advanced Synthesis & Catalysis</u> 353 (2011): 401 – 410.

[165] Reichardt, C. <u>Solvents and Solvent Effects in Organic Chemistry</u>. 3rd ed. Weinheim: Wiley-VCH, 2003.

[166] MacGregor, W.S. The Chemical and Physical Properties of DMSO. <u>Annals of the New York Academy of Sciences</u> 141 (1967): 3-12.

[167] Kamieńska-Trela, K., Kania, L., Bechcicka, M., and Kaczmarek, Ł. ^{13}C NMR Studies on the Structure of 5*H*- and 6*H*-Indolo-[2,3-B]quinolines and the Related Compounds. Journal of Molecular Structure 661-662 (2003): 209-218.

[168] Xing, R.-G., et al. Selective Reduction of Nitroarenes by a Hantzsch 1,4-Dihydropyridine: A Facile and Efficient Approach to Substituted Quinolines. Synthesis (13) (2011): 2066-2072.

[169] Luo, W., et al. A Novel Friedlander-Type Synthesis of 3-Aryl quinolines from 3-oxo-2,3-Diarylpropionaldehydes. Tetrahedron 67 (2011): 7090-7095.

[170] Abraham, R.J. and Reid, M. ^{1}H Chemical Shifts in NMR. Part 18.1. Ring Currents and π-Electron Effects in Hetero-Aromatics. Journal of the Chemical Society, Perkin Transactions 2 (2002): 1081-1091.

[171] De, K., Legros, J., Crousse, B., and Bonnet-Delpon, D. Solvent-Promoted and -Controlled Aza-Michael Reaction with Aromatic Amines. Journal of Organic Chemistry 74 (2009): 6260-6265.

[172] Konishi, S., Kawamorita, S., Iwai, T., Steel, P.G., Marder, T.B., and Sawamura, M. Site-Selective C-H Borylation of Quinolines at the C8 Position Catalyzed by a Silica-Supported Phosphane–Iridium System. Chemistry – An Asian Journal 9(2) (2014): 434-438.

[173] Sridharan, V., Avendaño, C., and Menéndez, J.C. CAN-Catalyzed Three-Component Reaction between Anilines and Alkyl Vinyl Ethers: Stereoselective Synthesis of 2-Methyl-1,2,3,4-tetrahydroquinolines and Studies on Their Aromatization. Tetrahedron 63 (2007): 673–681.

[174] Choi, H.Y., Srisook, E., Jang, K.S., and Chi, D.Y. Electrophilic Aromatic Addition Reaction: Electrophilic Attack at an Aromatic H Substituent Position. Journal of Organic Chemistry 70 (2005): 1222-1226.

[175] Pan, J., Wang, X., Zhang, Y., and Buchwald, S.L. An Improved Palladium-Catalyzed Conversion of Aryl and Vinyl Triflates to Bromides and Chlorides. Organic Letters 13(18) (2011): 4974-4976.

[176] Ramesh, C., Kavala, V., Kuo, C.-W., and Yao, C.-F. Iron/Acetic Acid-Mediated Carbon Degradation: A Facile Route for the Synthesis of Quinoline Derivatives. <u>Tetrahedron Letters</u> 51 (2010): 5234-5237.

[177] Yi, C.S. and Yun, S.Y. Ruthenium-Catalyzed Intermolecular Coupling Reactions of Arylamines with Ethylene and 1,3-Dienes: Mechanistic Insight on Hydroamination vs *ortho*-C-H Bond Activation. <u>Organic Letters</u> 7(11) (2005): 2181-2183.

[178] Schmidt, E.Y., Senotrusova, E.Y., Ushakov, I.A., Mikhaleva, A.b.I., and Trofimov, B.A. The Peculiar Reaction of 2-Arylazo-1-vinylpyrroles with Trifluoroacetic Acid: A Novel Synthesis of 2-Methylquinolines. <u>Tetrahedron</u> 65 (2009): 4855-4858.

[179] Gómez, C.M.M., Kouznetsov, V.V., Sortino, M.A., Álvarez, S.L., and Zacchino, S.A. In Vitro Antifungal Activity of Polyfunctionalized 2-(Hetero)Arylquinolines Prepared through Imino Diels–Alder Reactions. <u>Bioorganic & Medicinal Chemistry</u> 16 (2008): 7908–7920.

[180] Venuti, M.C. 2,3-Dihydroxy-1,4-dioxane: A Stable Synthetic Equivalent of Anhydrous Glyoxal. <u>Synthesis</u> 1 (1982): 61-63.

[181] Siu, J., Baxendale, I.R., and Ley, S.V. Microwave Assisted Leimgruber–Batcho Reaction for the Preparation of Indoles, Azaindoles and Pyrroylquinolines. <u>Organic & Biomolecular Chemistry</u> 2 (2004): 160-167.

[182] Ahmad, S. and Ali, M. An Efficient Solid Acid Promoted Synthesis of Quinoxaline Derivatives at Room Temperature. <u>Chinese Journal of Chemistry</u> 25 (2007): 818-821.

[183] Talwar, D., Gonzalez-de-Castro, A., Li, H.Y., and Xiao, J. Regioselective Acceptorless Dehydrogenative Coupling of *N*-Heterocycles toward Functionalized Quinolines, Phenanthrolines, and Indoles. <u>Angewandte Chemie International Edition</u> 54 (2015): 5223 –5227.

APPENDIX
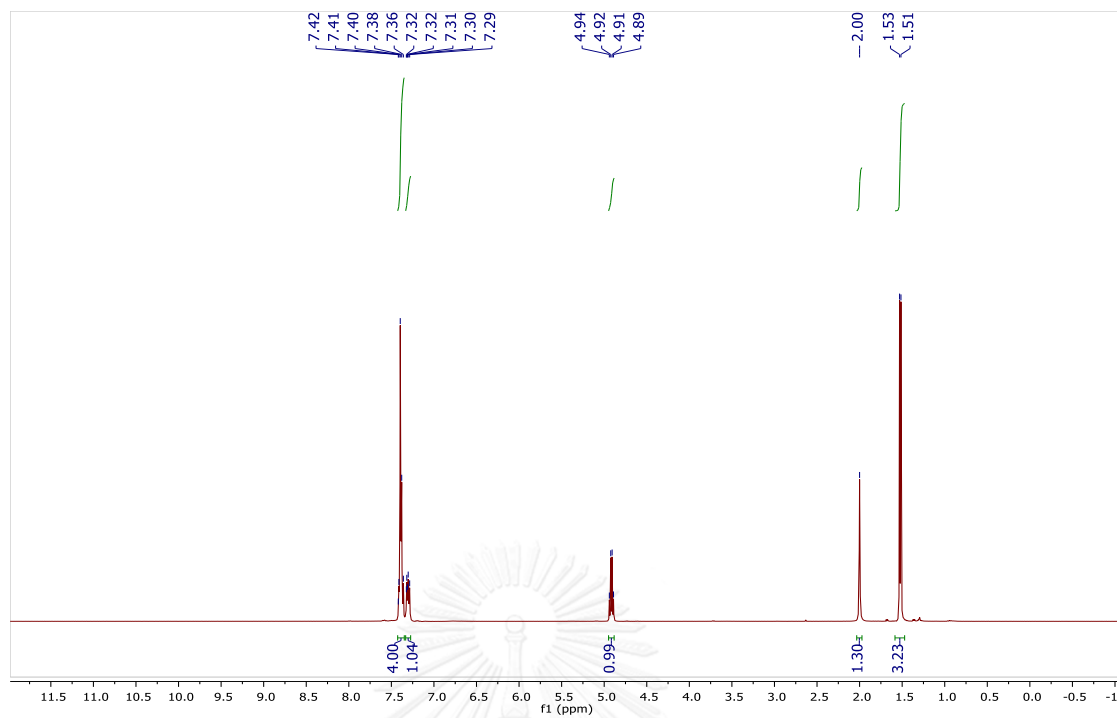
Figure A-1 The ^{1}H NMR spectra of 1-phenylethanol
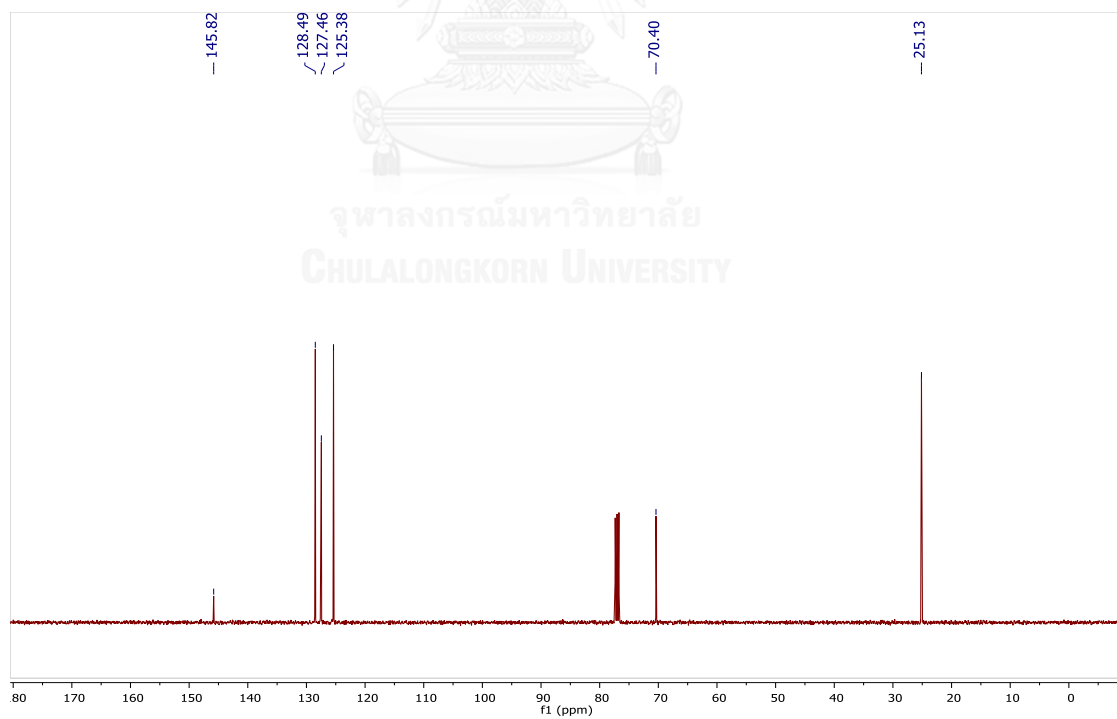
Figure A-2 The ^{13}C NMR spectra of 1-phenylethanol
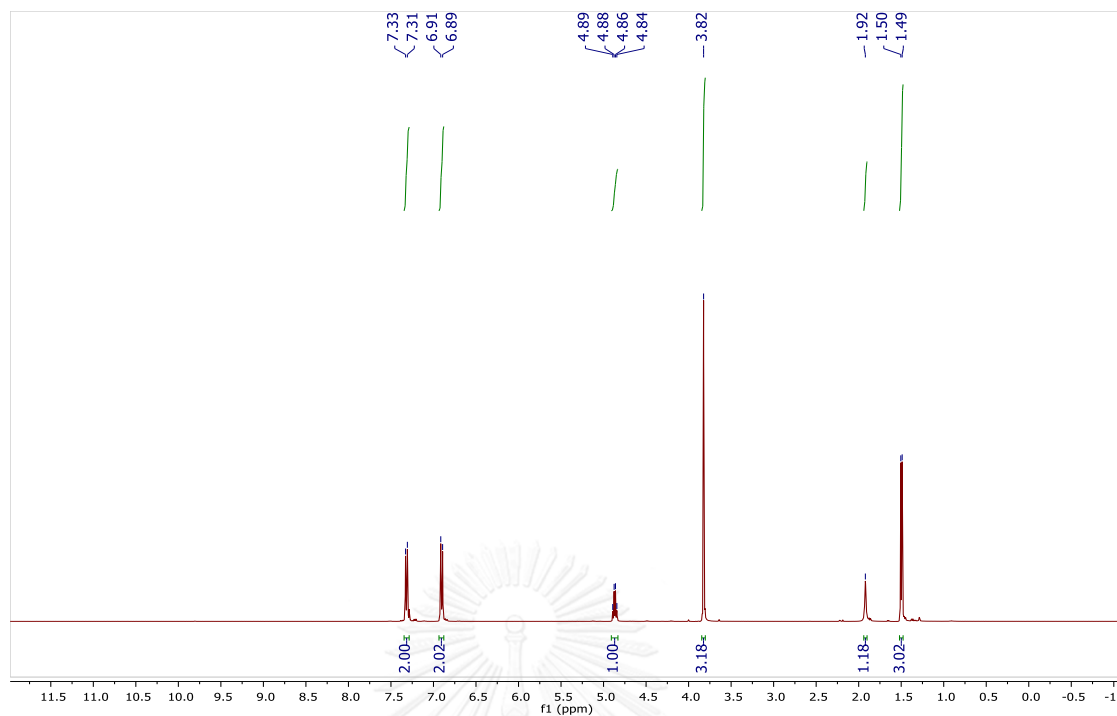
Figure A-3 The ^{1}H NMR spectra of 1-(4-Methoxyphenyl)ethanol
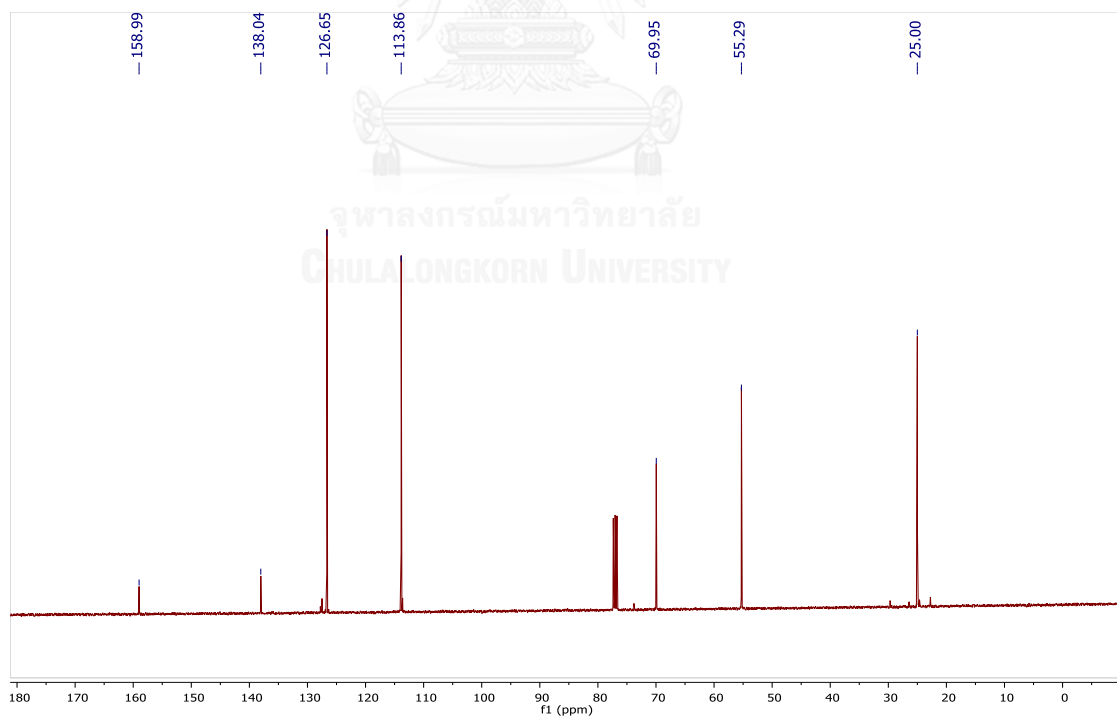
Figure A-4 The ^{13}C NMR spectra of 1-(4-Methoxyphenyl)ethanol
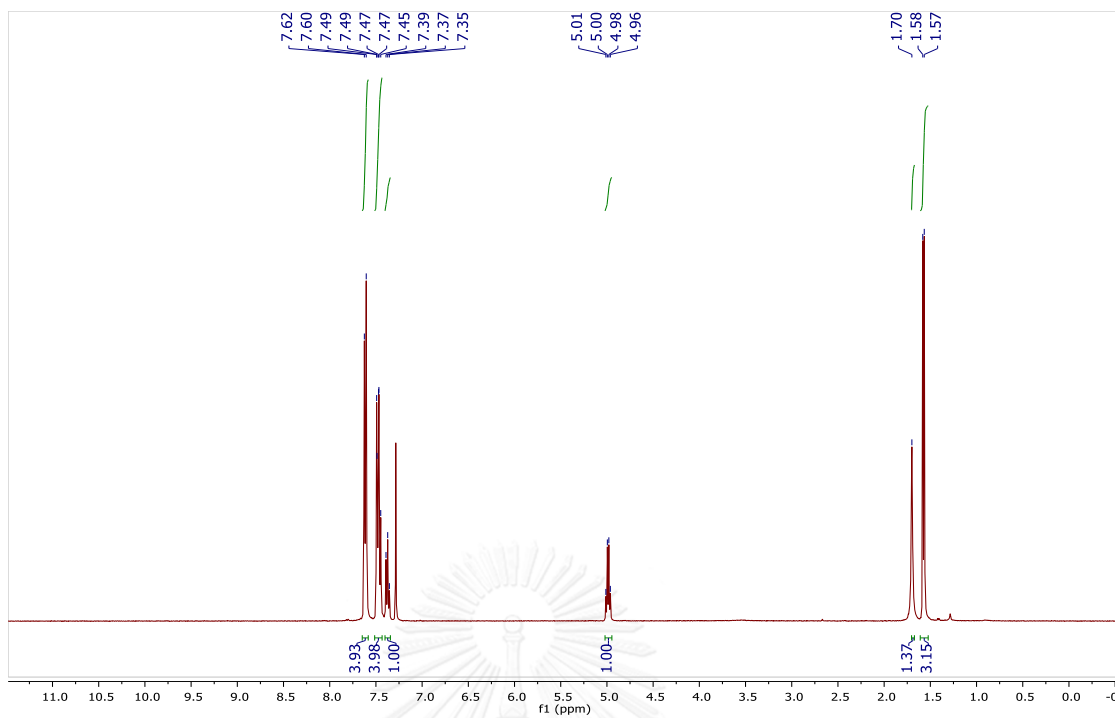
Figure A-5 The ^{1}H NMR spectra of 1-([1,1'-Biphenyl]-4-yl)ethanol
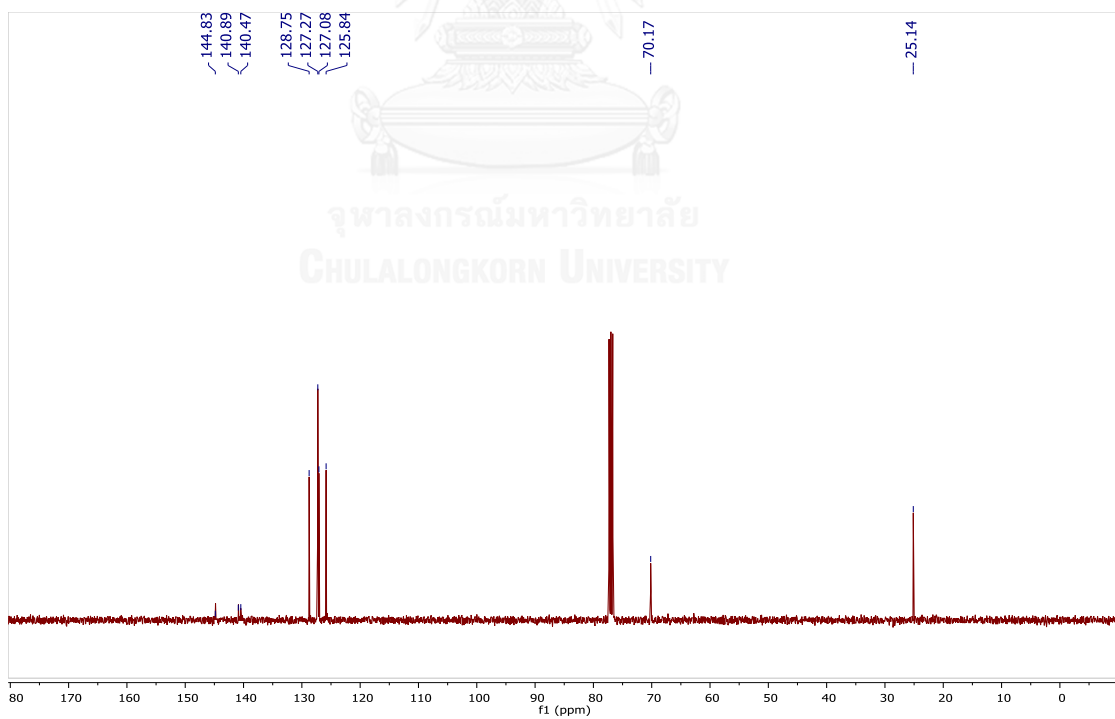
Figure A-6 The ^{13}C NMR spectra of 1-([1,1'-Biphenyl]-4-yl)ethanol
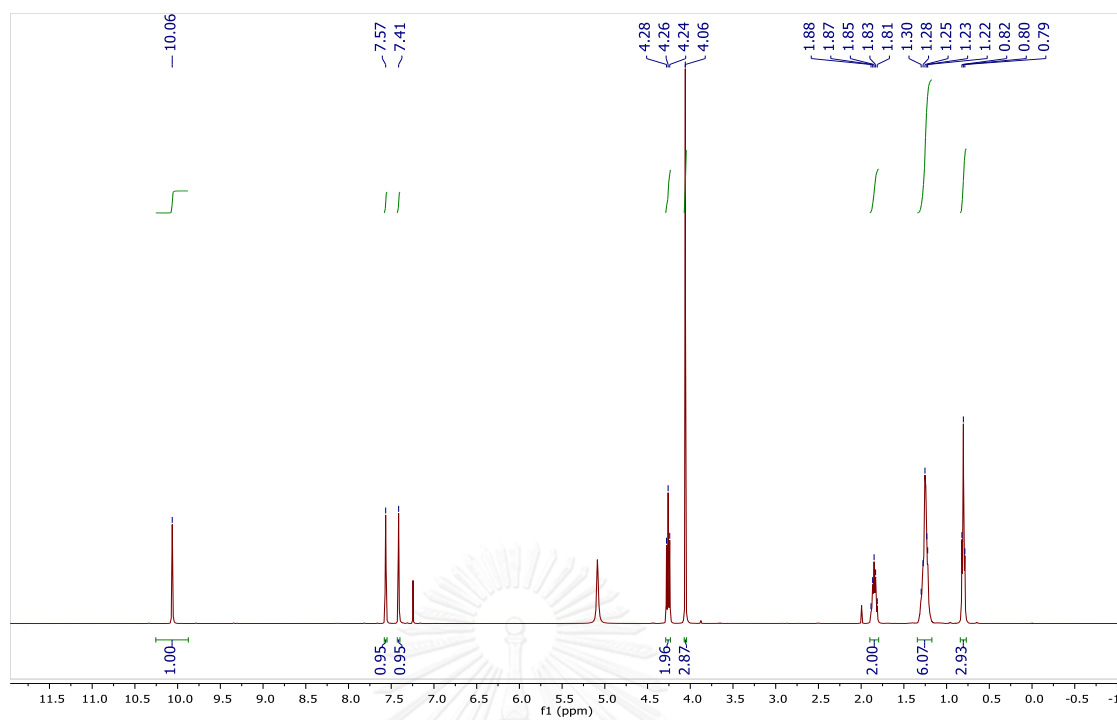
Figure A-7 The ^{1}H NMR spectra of [hmim]Br
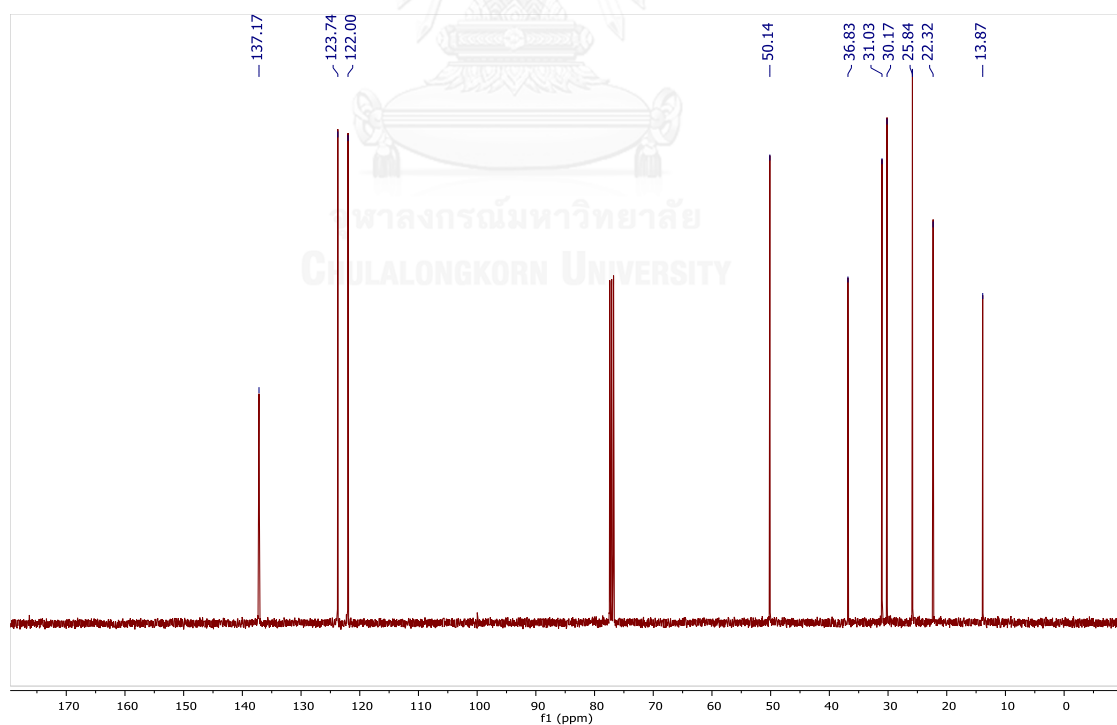
Figure A-8 The ^{13}C NMR spectra of [hmim]Br
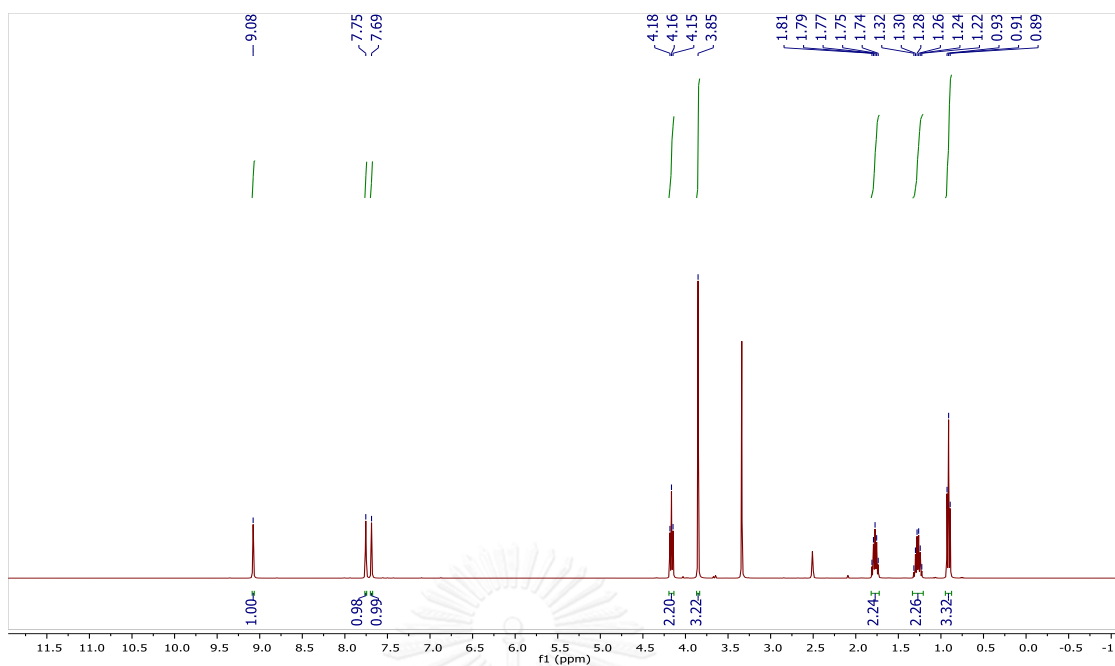
Figure A-9 The ^{1}H NMR spectra of [bmim]BF$_4$
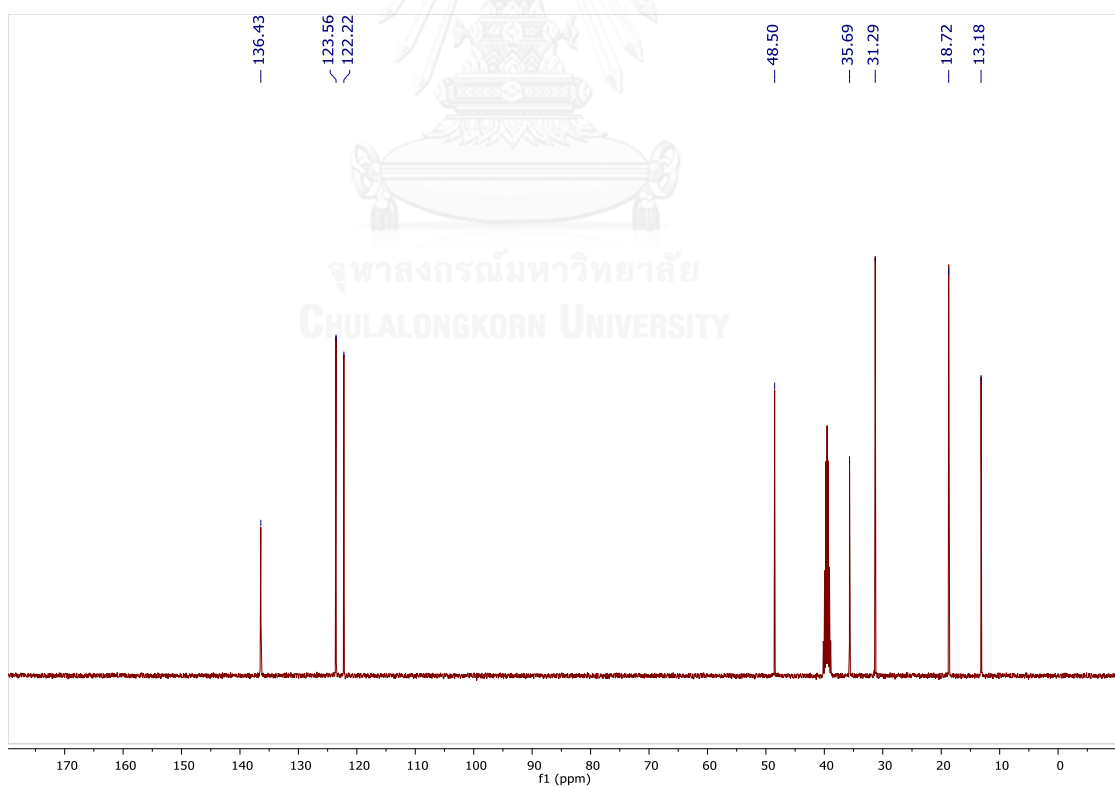
Figure A-10 The ^{13}C NMR spectra of [bmim]BF$_4$
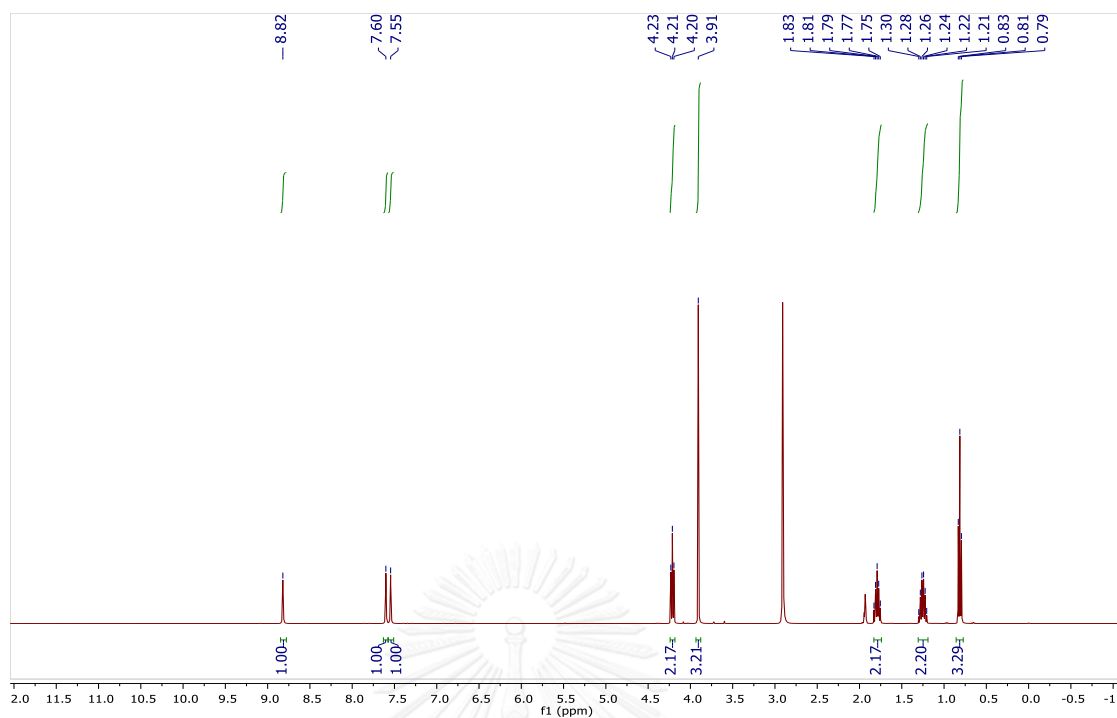
Figure A-11 The ^{1}H NMR spectra of [bmim]PF$_6$
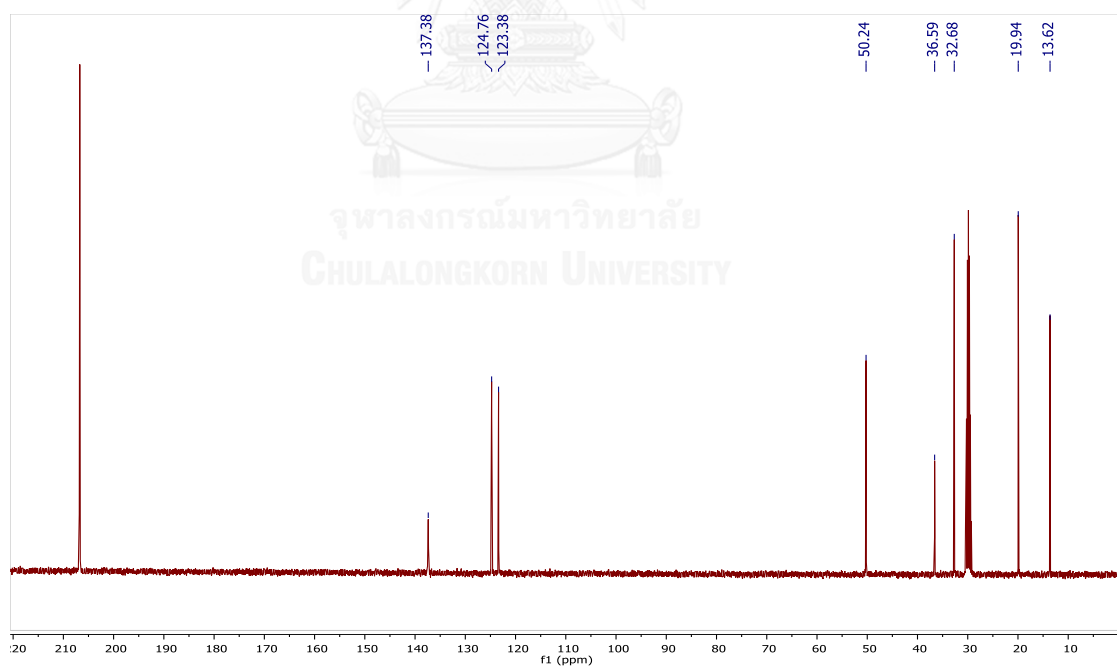
Figure A-12 The ^{13}C NMR spectra of [bmim]PF$_6$
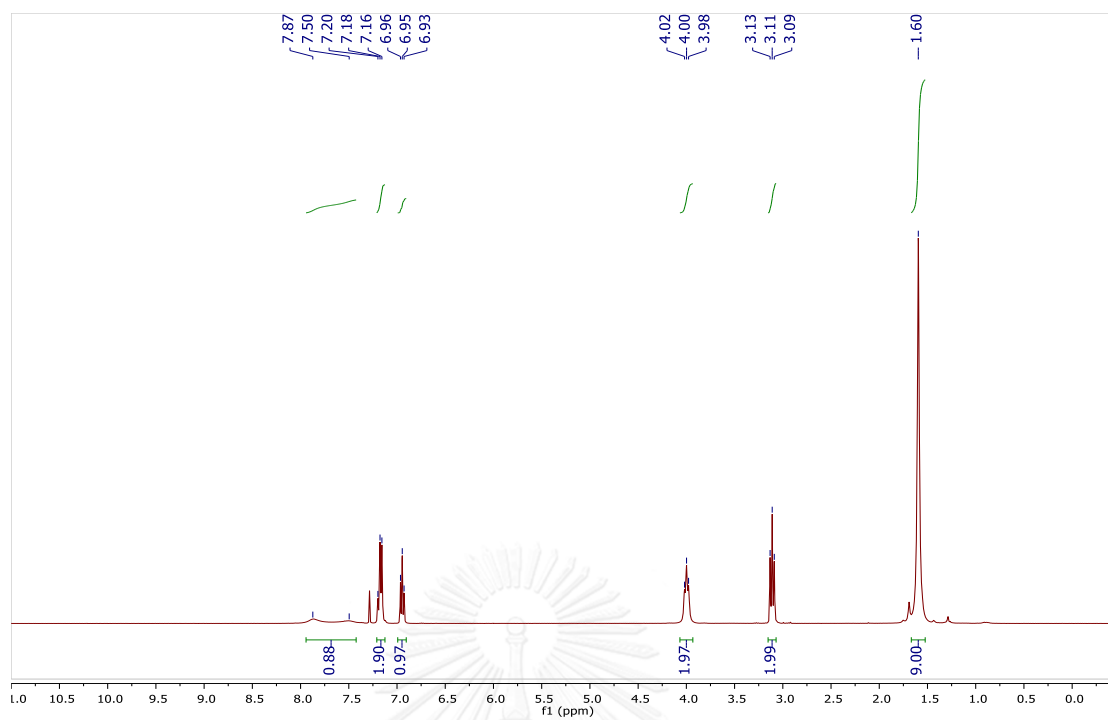
Figure A-13 The ^{1}H NMR spectra of *N*-Boc-indoline
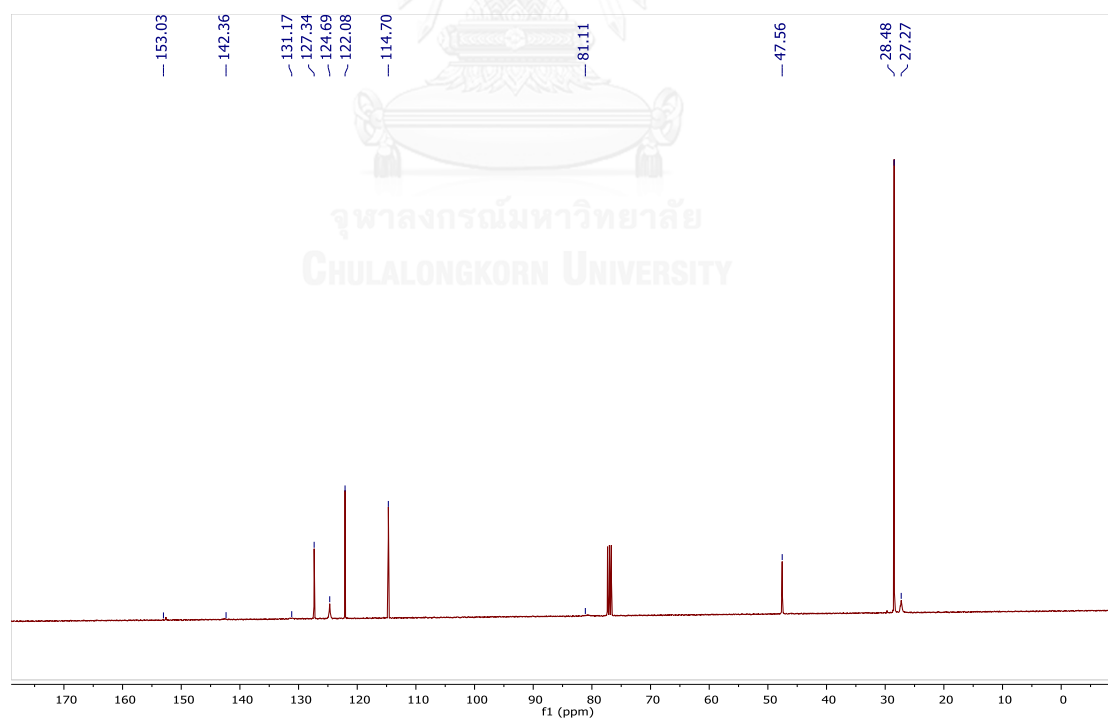
Figure A-14 The ^{13}C NMR spectra of *N*-Boc-indoline
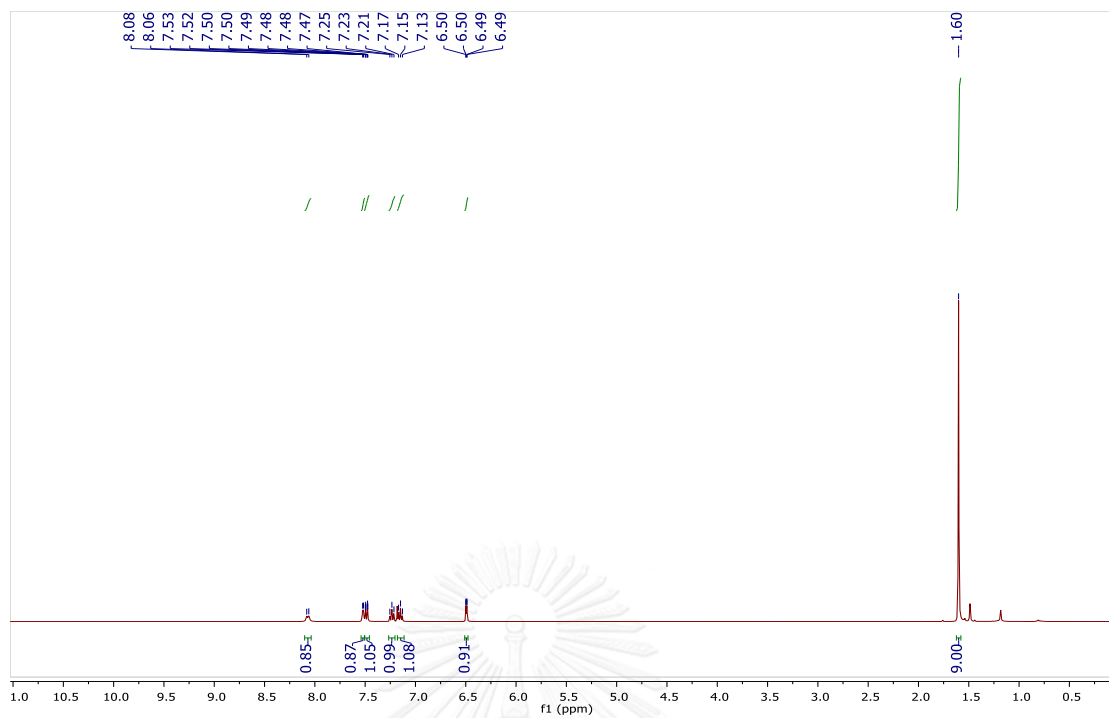
Figure A-15 The ^{1}H NMR spectra of *N*-Boc-indole
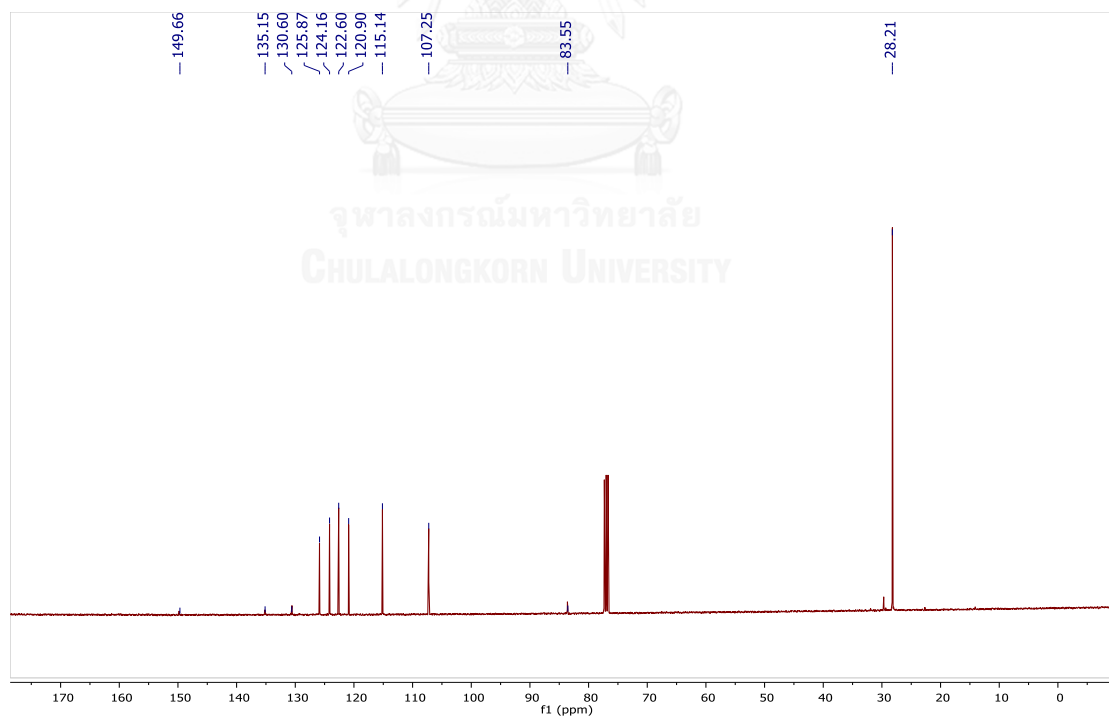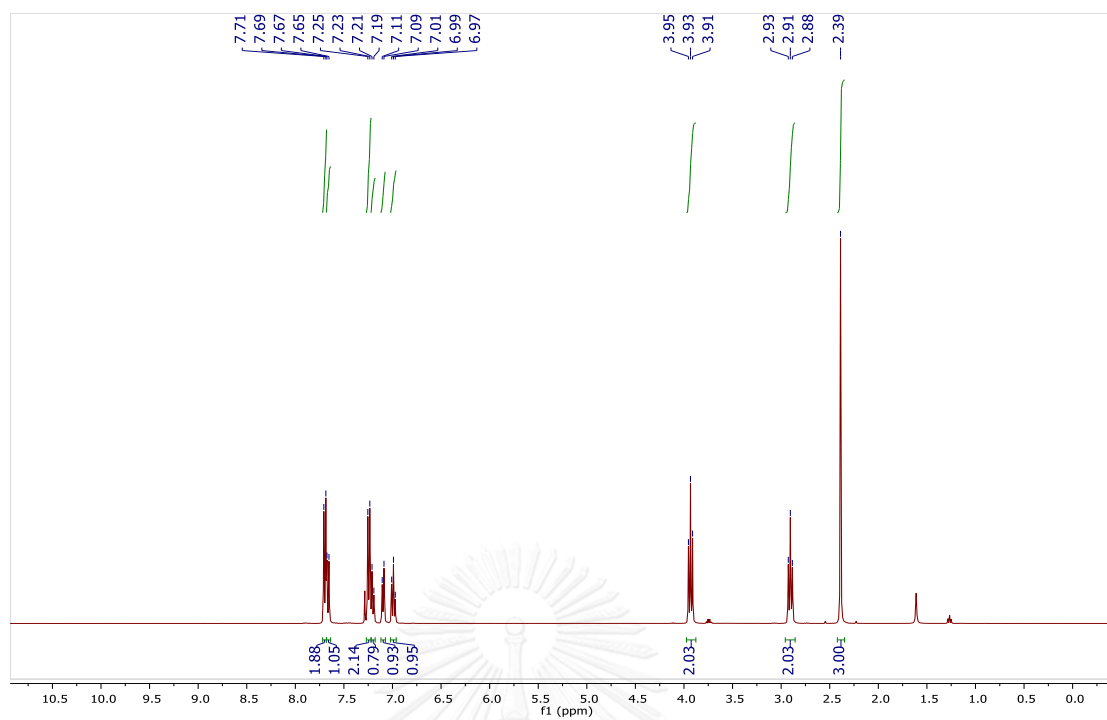

Figure A-16 The ^{13}C NMR spectra of *N*-Boc-indole
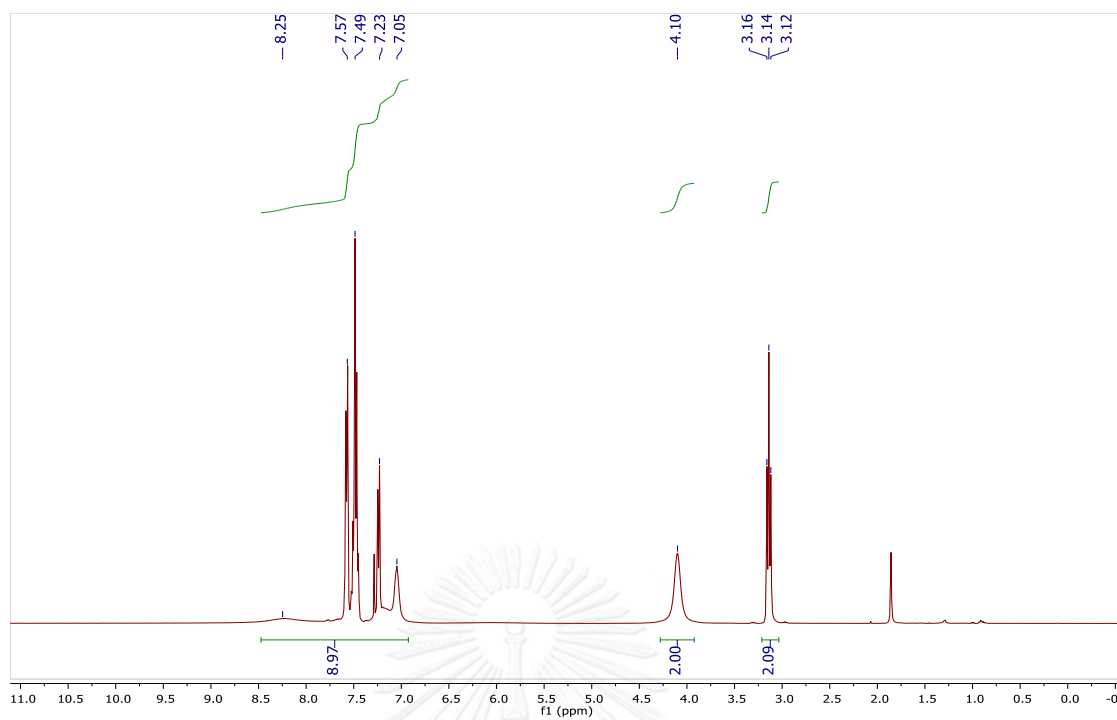
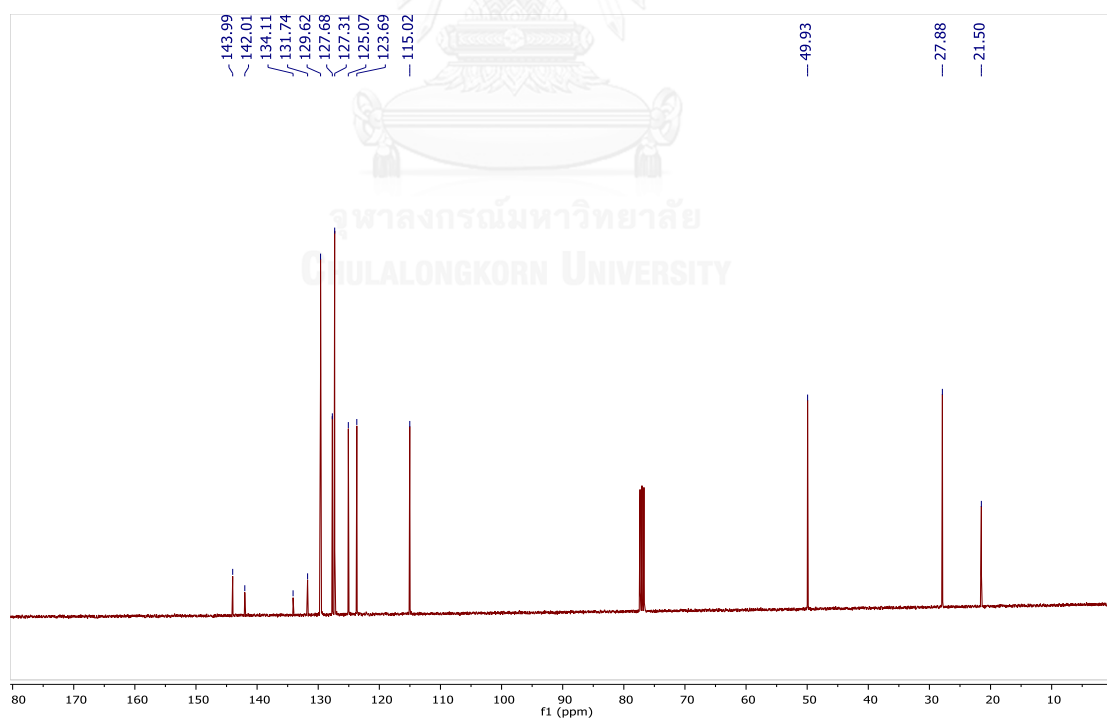**Figure A-17** The ^{1}H NMR spectra of *N*-benzoyl-indoline
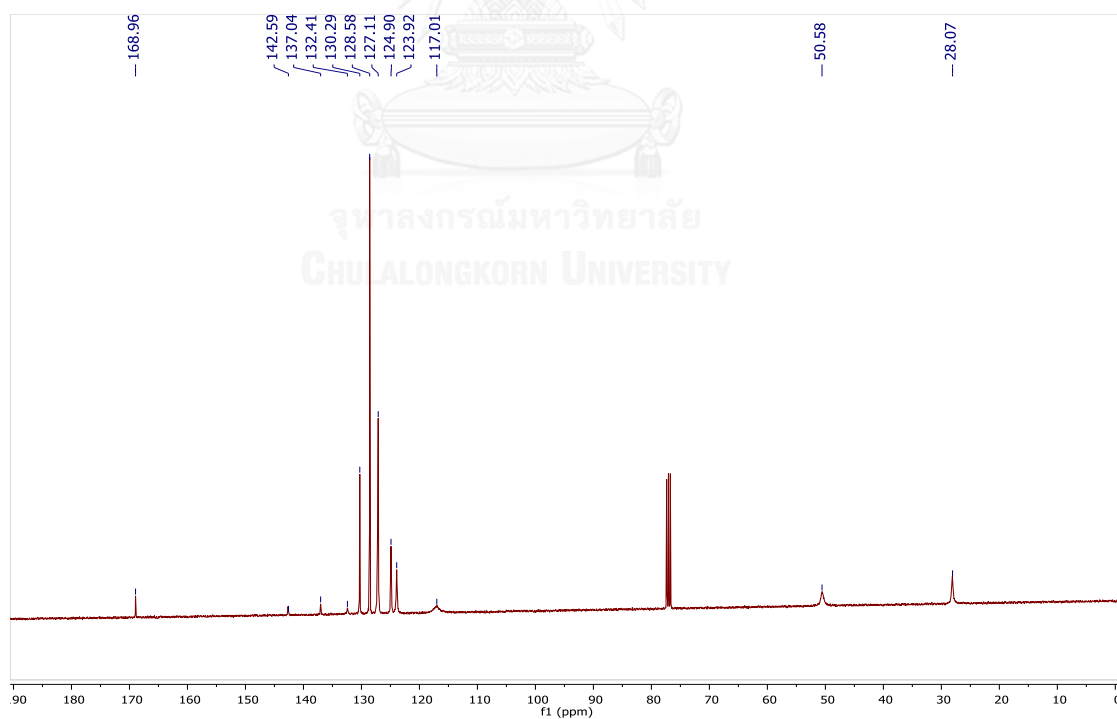
Figure A-18 The ^{13}C NMR spectra of *N*-benzoyl-indoline
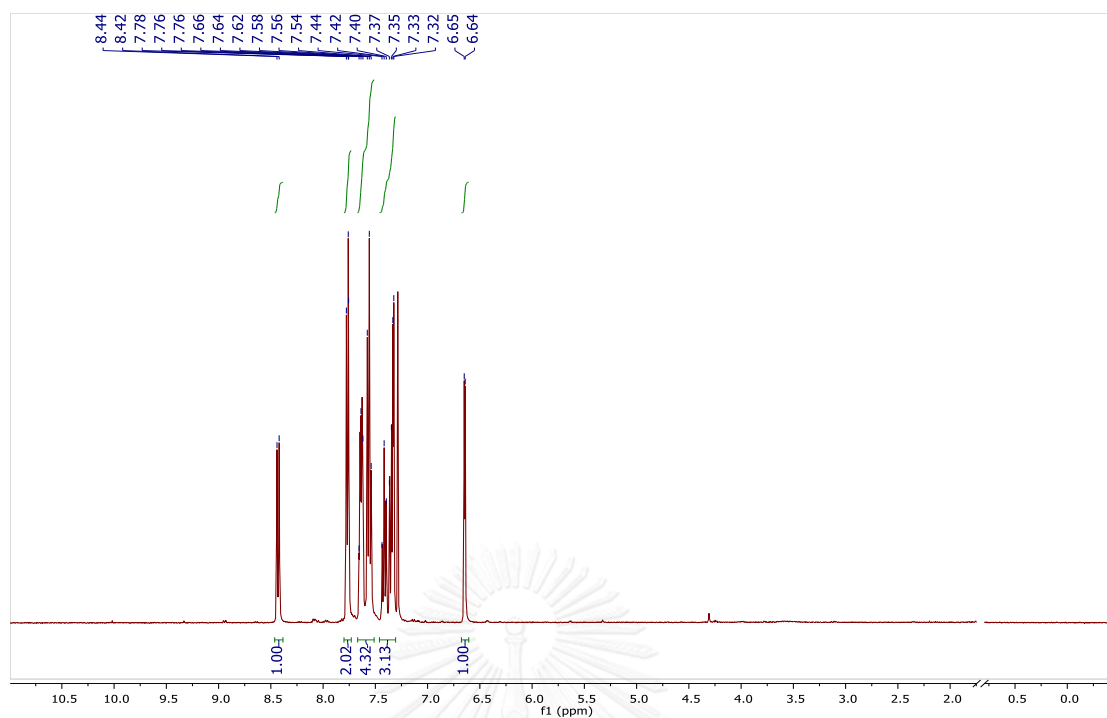
Figure A-19 The ^{1}H NMR spectra of *N*-benzoyl-indole
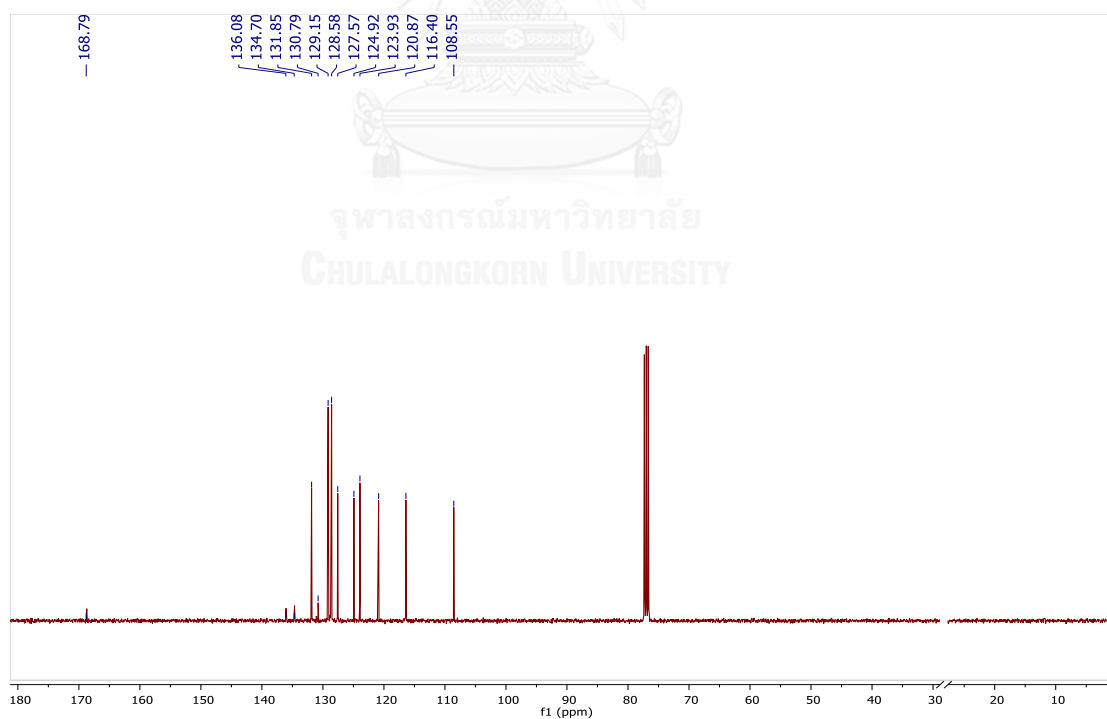
Figure A-20 The ^{13}C NMR spectra of *N*-benzoyl-indole

Figure A-21 The ^{1}H NMR spectra of *N*-tosyl-indoline

Figure A-22 The ^{13}C NMR spectra of *N*-tosyl-indoline
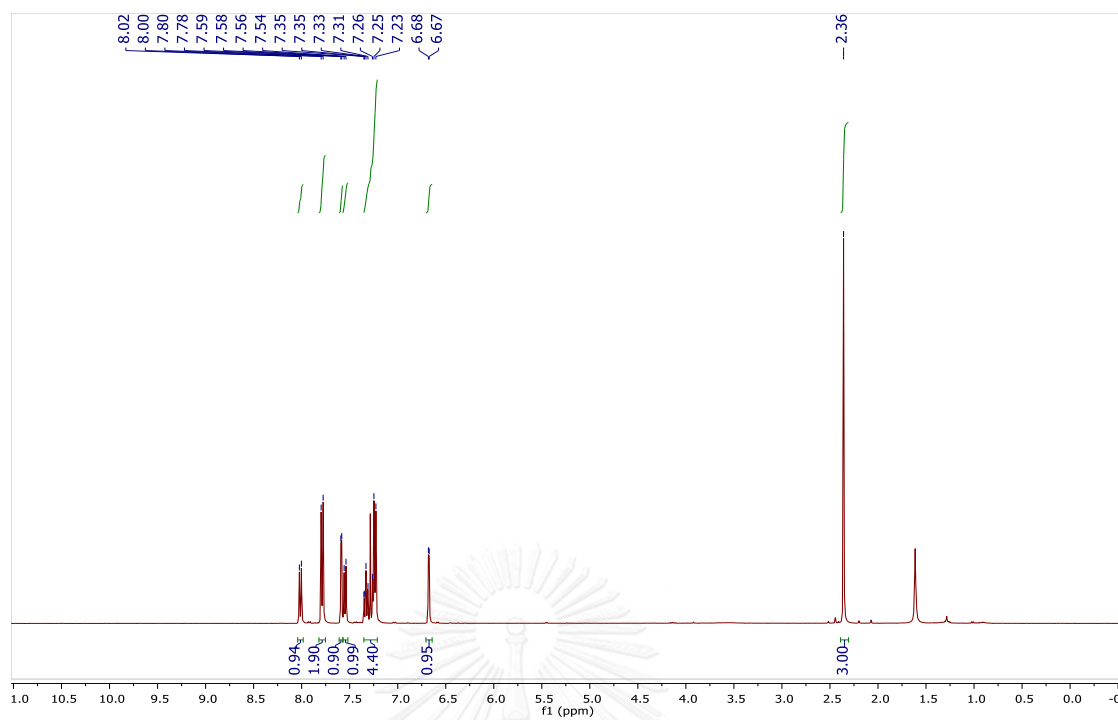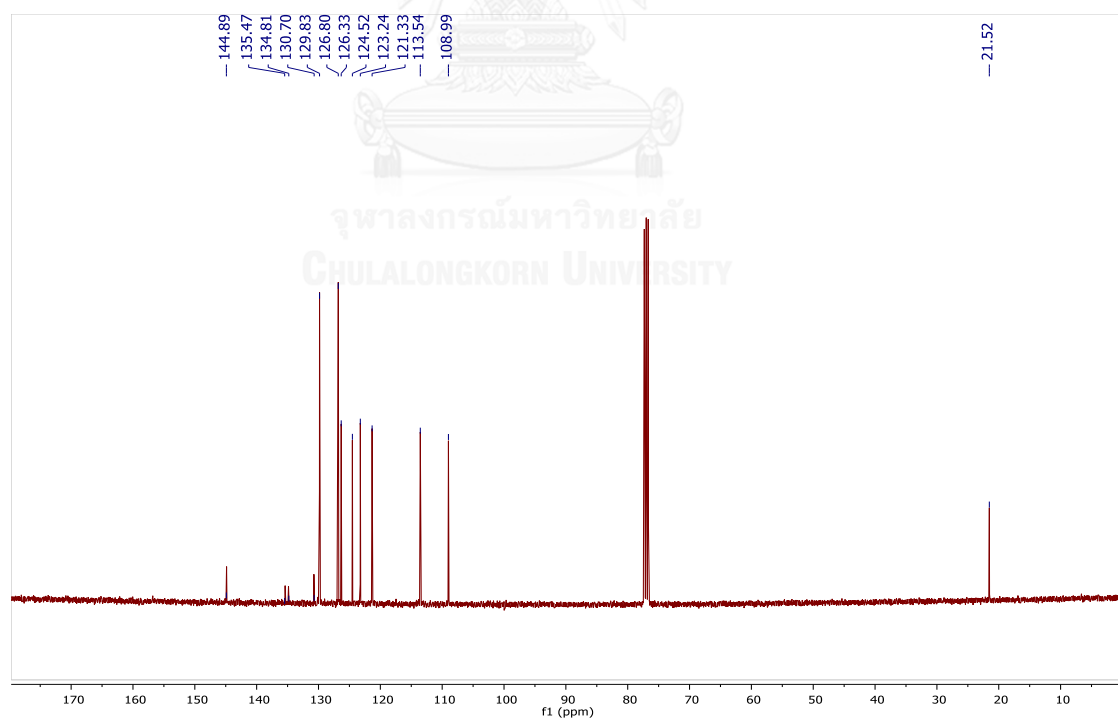
Figure A-23 The ^{1}H NMR spectra of *N*-tosyl-indole

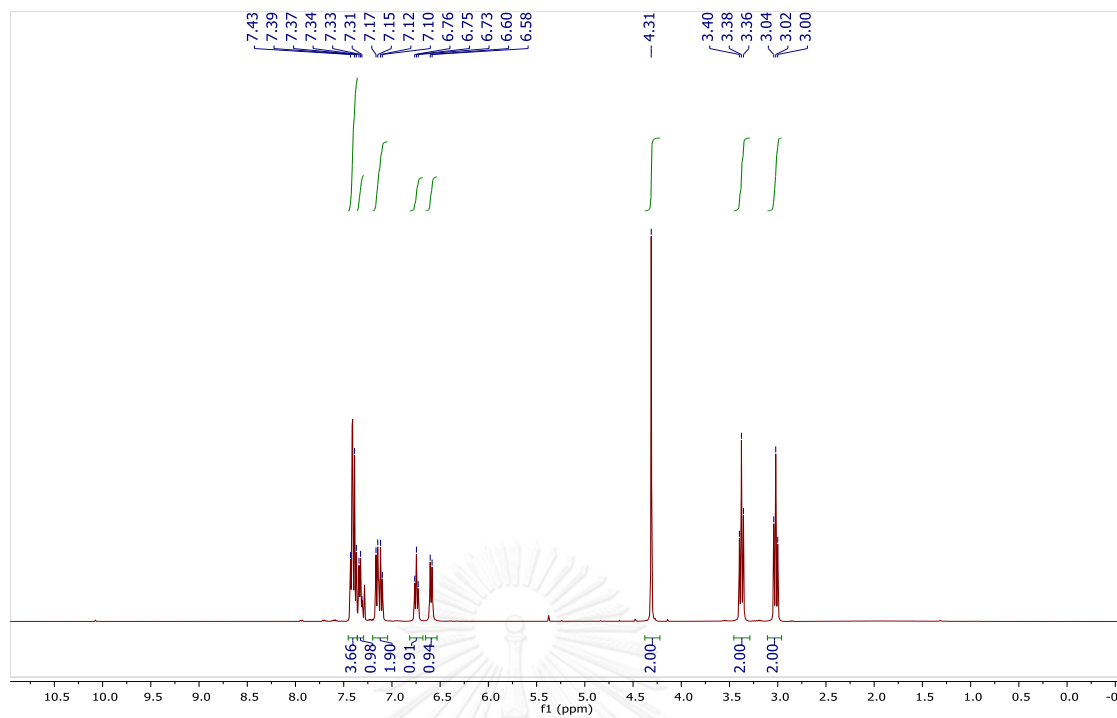**Figure A-24** The ^{13}C NMR spectra of *N*-tosyl-indole

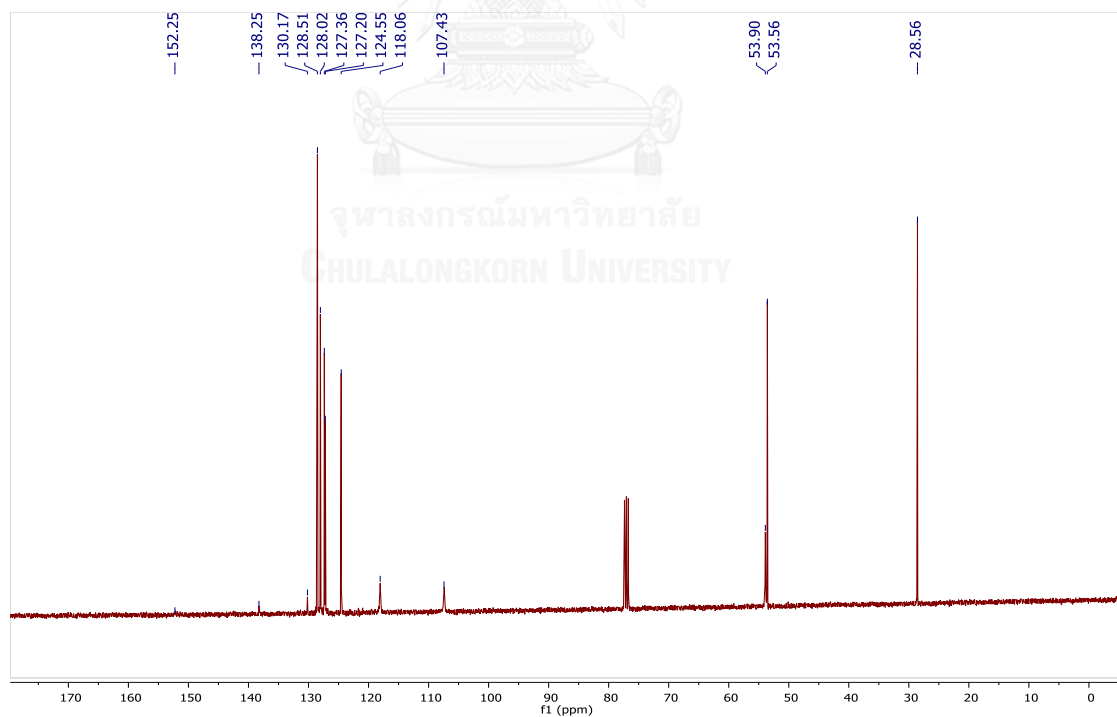**Figure A-25** The ^{1}H NMR spectra of *N*-benzyl-indoline
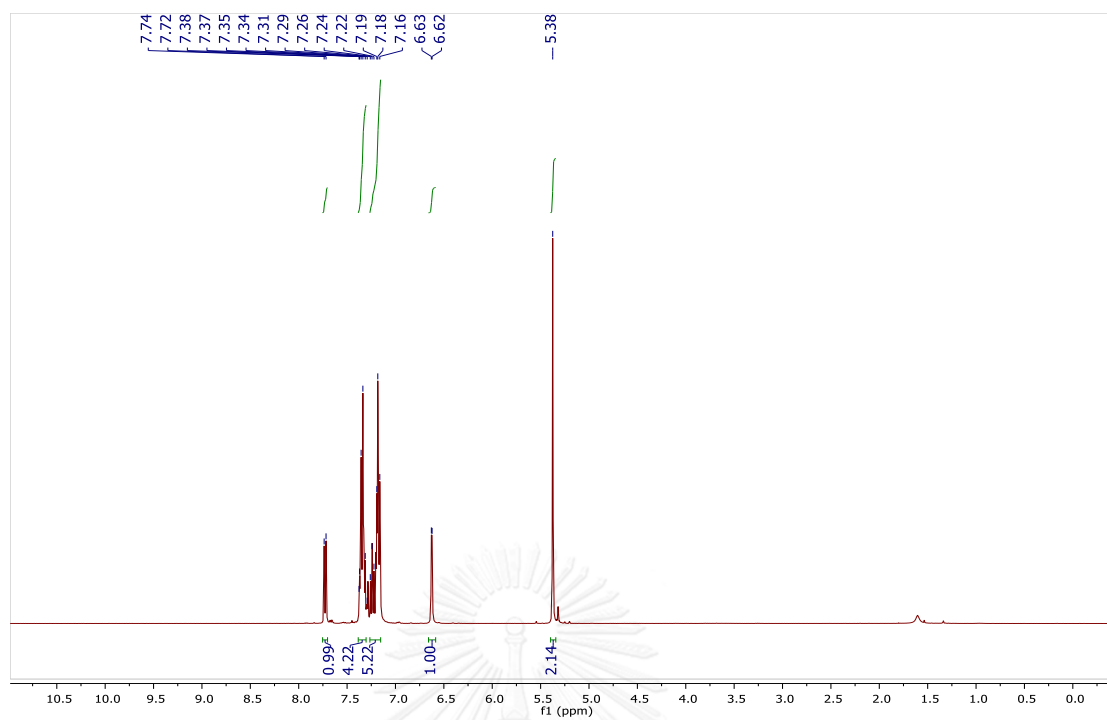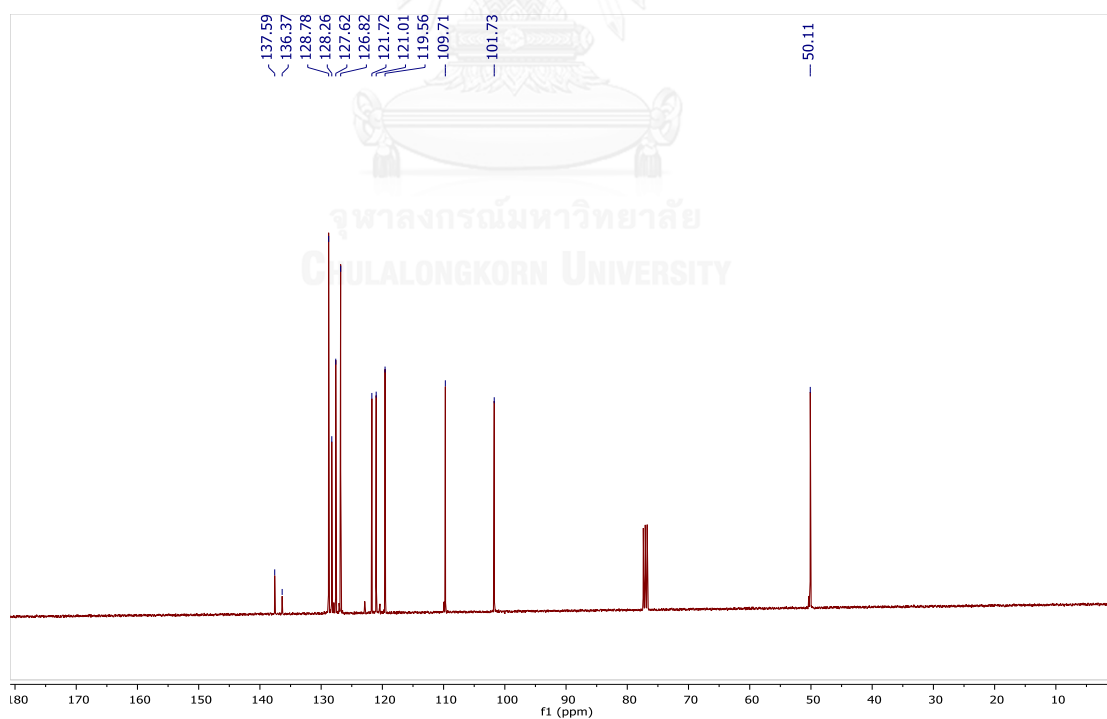

Figure A-26 The ^{13}C NMR spectra of *N*-benzyl-indoline

Figure A-27 The ^{1}H NMR spectra of *N*-benzyl-indole

Figure A-28 The ^{13}C NMR spectra of *N*-benzyl-indole

VITA

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