แอโรแมไทเซชันของคอนจูเกตและสคิปไดอีนที่เร่งปฏิกิริยาด้วยคอปเปอร์

นายนิติ งามสมประเสริฐ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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COPPER CATALYZED AROMATIZATION OF CONJUGATED AND SKIPPED DIENES

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Chemistry
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Thesis Title	COPPER CATALYZED AROMATIZATION OF CONJUGATED AND SKIPPED DIENES
By	Mr. Niti Ngamsomprasert
Field of Study	Chemistry
Thesis Advisor	Assistant Professor Warinthorn Chavasiri, Ph.D.

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นิติ งามสมประเสริฐ : แอโรแมไทเซชันของคอนจูเกตและสคิปไดอีนที่เร่งปฏิกิริยาด้วยคอปเปอร์. (COPPER CATALYZED AROMATIZATION OF CONJUGATED AND SKIPPED DIENES.) อ.ที่ปรึกษาวิทยานิพนธ์หลัก : ผศ. ดร. วรินทร ชวศิริ, 64 หน้า.

งานวิจัยนี้มุ่งศึกษาหาระบบตัวเร่งปฏิกิริยาใหม่สำหรับแอโรแมไทเซชันของสคิปและคอนจูเกตไดอีนที่มีประสิทธิภาพ ระบบนี้ประกอบด้วยเกลือคอปเปอร์ (II) คลอไรด์เป็นตัวเร่งปฏิกิริยาร่วมกับเทอร์เชียรีบิวทิลไฮโดรเปอร์ออกไซด์เป็นตัวออกซิไดซ์ ตัวแปรหลายชนิดที่ส่งผลต่อประสิทธิภาพของปฏิกิริยา เช่น ชนิดของลิแกนด์, ตัวทำละลาย, อุณหภูมิและเวลาที่ใช้ในการทำปฏิกิริยา สคิปไดอีน เช่น แกมมาเทอร์ไพนีนและ 9,10-ไดไฮโดรแอนทราซีนสามารถเกิดปฏิกิริยาแอโรแมไทเซชันได้ดีและให้ผลิตภัณฑ์ในปริมาณสูงที่อุณหภูมิห้องภายในเวลา 5 นาที ในทางตรงกันข้าม คอนจูเกตไดอีน เช่น แอลฟาเทอร์ไพนีน 9,10-ไดไฮโดรฟีแนนทรีนและ 1,2-ไดไฮโดรแนฟทาลีน ต้องใช้ภาวะที่รุนแรงกว่าและเวลาในการทำปฏิกิริยาที่นานกว่า ยิ่งไปกว่านั้น $CuCl_2$-TBHP ยังให้ผลผลิตปานกลางของผลิตภัณฑ์ของสารเฮเทอโรไซคลิก เช่น อินโดลีน ระบบตัวเร่งปฏิกิริยานี้ยังประยุกต์ได้สำหรับแอโรแมไทเซชันของซิงจิเบอรีนเปลี่ยนเป็นสารที่สอดคล้องกัน คือ เคอร์คิวมีน ซึ่งมีฤทธิ์ทางชีวภาพหลายประเภท

ภาควิชา……เคมี……ลายมือชื่อนิสิต…….

สาขาวิชา……เคมี……ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก……..

ปีการศึกษา……2554….

5272375823 : MAJOR CHEMISTRY
KEYWORDS: AROMATIZATION / COPPER CATALYST / CONJUGATED AND SKIPPED DIENES.

NITI NGAMSOMPRASERT : COPPER CATALYZED AROMATIZATION OF CONJUGATED AND SKIPPED DIENES. ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 64 pp.

This research aims to develop a new and efficient catalytic system for aromatization of conjugated and skipped dienes. A system consisting of $CuCl_2$ as a catalyst coupled with *tert*-butylhydroperoxide as an oxidant. Various parameters including type of ligands, solvent, temperature and reaction time display significant effects on the efficiency of the reaction. Skipped dienes such as γ-terpinene and 9,10-dihydroanthracene could be aromatized in high yields at room temperature in 5 minutes. On the other hand, conjugated dienes such as α-terpinene, 9,10-dihydrophenanthrene and 1,2-dihydronaphthalene needed more severe conditions or longer reaction time to produce high yield of their corresponding aromatized products. In addition, $CuCl_2$-TBHP also gave moderate yield of aromatized product of heterocyclic such as indoline. Further application of this catalytic system could be utilize for aromatization of zingiberene to its corrresponding product, curcumene which possessed many bioactivities.

Department:.....Chemistry..... Student's Signature: .....
Field of Study: .....Chemistry..... Advisor's Signature: .....
Academic Year: .....2011.....

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LIST OF ABBREVIATIONS

OAc	=	acetate group
Ac	=	acetyl group
b.p.	=	boiling point
br	=	broad (NMR)
C	=	carbon
^{13}C-NMR	=	carbon-13 nuclear magnetic resonance
cm	=	centimeter (s)
COSY	=	correlation spectroscopy
J	=	coupling constant
ºC	=	degree Celsius
C_6D_6	=	deuterated benzene
$CDCl_3$	=	deuterated chloroform
DMSO-d_6	=	deuterated dimethylsulfoxide
DCM	=	dichloromethane
d	=	doublet (NMR)
dd	=	doublet of doublet (NMR)
ESI-MS	=	electrospray ionization mass spectroscopy
OEt	=	ethoxy group
Et	=	ethyl group
GC	=	gas chromatography
g	=	gram (s)
Hz	=	hertz (NMR)
HMBC	=	heteronuclear multiple bond correlation
HSQC	=	heteronuclear single quantum coherence
h	=	hour
H	=	hydrogen
kg	=	kilogram (s)
in vitro	=	literally in glass
MHz	=	megahertz (NMR)
m.p.	=	melting point

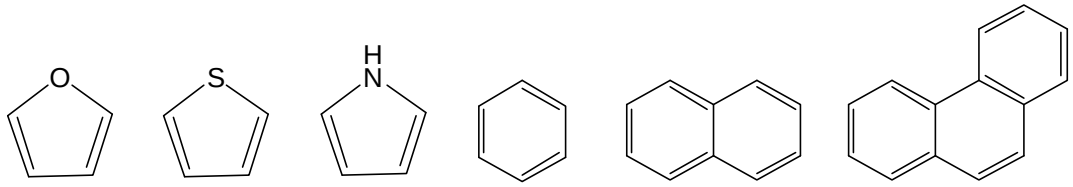
M	=	meter (s)
OMe	=	methoxy group
Me	=	methyl group
μg	=	microgram (s)
μL	=	microliter (s)
μM	=	micromolar
mg	=	milligram (s)
mL	=	milliliter (s)
mM	=	millimolar
min	=	minute (s)
M	=	molarity
m	=	multiplet (NMR)
nm	=	nanometer (s)
N	=	normality
o-	=	ortho substitution
p-	=	para substitution
ppm	=	part per million
p	=	pentet (NMR)
%	=	percentage
^{1}H-NMR	=	proton-1 nuclear magnetic resonance
q-TOF	=	quadrupole time-of-flight tandem
R_f	=	retarding factor in chromatography
RT	=	room temperature
s	=	singlet (NMR)
t	=	triplet (NMR)
δ	=	unit of chemical shift
vs	=	versus
v	=	volume
H_2O	=	water
w	=	weight

CHAPTER I

INTRODUCTION

1.1 Introduction to aromatic compounds

Aromatic compounds are defined as chemicals possessing aromatic property, ring conjugated double bonds system with cyclic electron delocalization. This makes aromatic compounds more stable than normal conjugated systems resulting them readily to store without self-ring opening or losing their aromaticities. Aromatic compounds are not only consisted of fundamental elements: carbon and hydrogen, but can also have heteroatom(s) such as oxygen, nitrogen or sulfur. The latter is classified as heterocyclic compounds. Some examples are listed below.



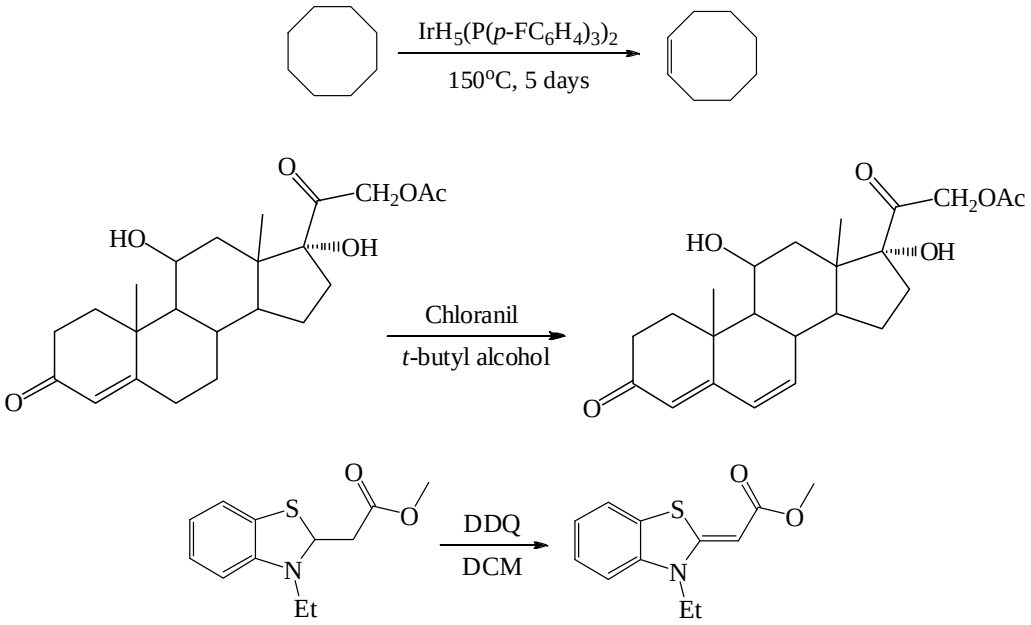
furan thiophene pyrrole benzene naphthalene phenanthrene

The most common aromatic hydrocarbon is benzene which usually found as a core or a part of many natural substances [1] such as flavonoids [2], xanthones [3], coumarins [4], anthraquinones [5] and terpenoids [6]. These bioactive compounds are usually extracted in a little amount and not related to the consumer's demand in medicine, pharmaceutical sciences and manufactures. Thus, the supply can be served by using organic synthesis with dehydrogenation or aromatization as a necessary step [7], to remove hydrogen molecule(s) from the substrate in order to achieve target bioactive compounds. However, the total synthesis has ordinarily many steps [8], so high productivities in each step are essentially needed to furnish high total yield of the target product.

1.1.1 Introduction to dehydrogenation

The dehydrogenation is an important reaction commonly utilized in organic synthesis. From previous researches, many reagents or catalysts were developed in a

dehydrogenation step such as iridium complex [9], quinone compounds such as chloranil [10] and 2,3-dichloro-5,6-dicyanoquinone (DDQ) [11].



Iridium complexes generally spent long reaction time and mostly reacted under high temperature, which are not suitable conditions in certain cases. Quinone compounds such as chloranil and DDQ, on the other hand, were not appropriate for large scale reactions since it is mandatory to employ at least stoichiometric amount for dehydrogenation; moreover, some substrates containing labile sites could be multi-dehydrogenated when quinone compounds were used [11].

1.1.2 Introduction to aromatization

Aromatization is a subclass of dehydrogenation that takes hydrogen molecule(s) away from substrate and also makes the final product become aromatics, a potent driving force. From previous research [12], various reagents and catalysts for aromatization of polycyclic hydroaromatic compounds have been introduced as accumulated in Table 1.1.

Table 1.1 Catalytic aromatization of polycyclic hydrocarbons [12]

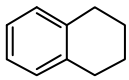
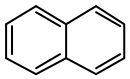
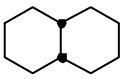
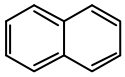
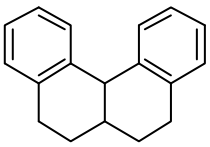
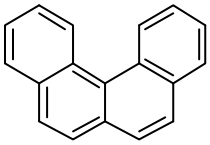
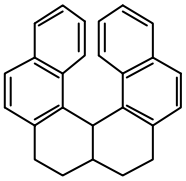
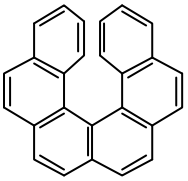
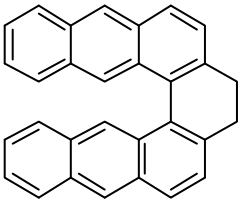
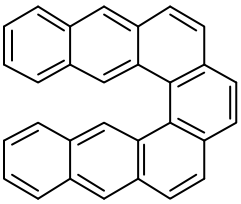
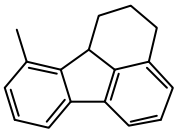
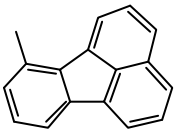
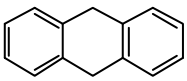
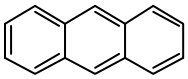
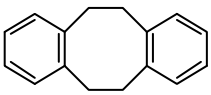
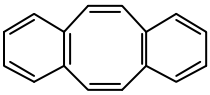
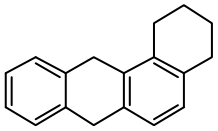
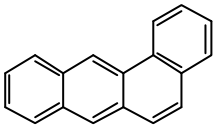
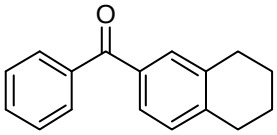
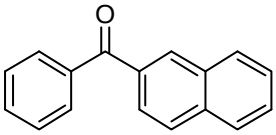
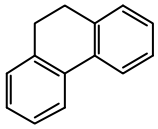
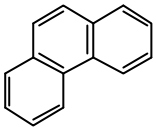
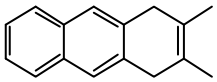
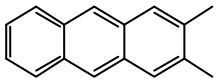
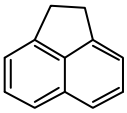
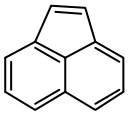
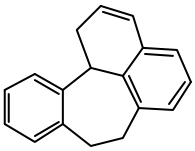
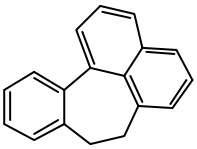
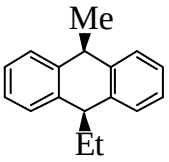
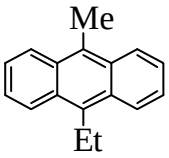
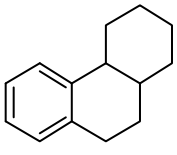
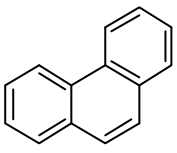
Substrate	Product	Catalyst	Condition	%Yield
		Pd/C	Reflux, 22 h	97
		Pt/C	300°C	95
		Pt	310-320°C, 15 min	61
		Rh,Al	300°C	64
		Pd	*p*-Cumene, reflux, 4 h	80
		$Pd/BaSO_4$	200-290°C	81
		$RhCl(PPh_3)_3$	225°C, 15 h	97
		$RhCl(PPh_3)_3$	225°C, 15 h	1

Table 1.1 (continued)

Substrate	Product	Catalyst	Condition	%Yield
		$IrCl(CO)(Ph_3)_2$	225°C, 12 h	92
		S	270°C	58
		Se	260°C, 1 h	46
		*p*-Chloranil	xylene	~100
		*o*-Chloranil	benzene, 20 h	60
		DDQ	benzene	65
		TTFA	20 h	85
		NBS	HOAc, KOAc 4 h	21

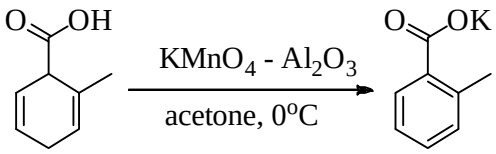
With reference to Table 1.1, various catalysts and reagents such as single metals, metal complexes, quinone compounds and oxidizing agents have been employed in aromatization of polycyclic hydrocarbons. Single metals or metal

complexes, at the beginning, mostly reacted under high temperature and spent long reaction time that are not suitable to apply to other substrates which readily to decompose and also gave other minor products. Quinone compounds such as *o*- and *p*-chloranil and DDQ needed more than stoichiometric ratio and spent long reaction time, on the other side.

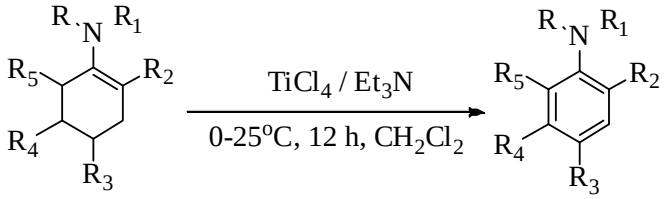
According to previous reports, some problems still remained such as high temperature, long reaction time and large amount of reagents. Therefore, many studies are devoted to the development of new aromatization methodologies to reduce those mentioned disadvantages. Hence, the suitable methodologies under mild conditions with good productivities are accordingly still called for organic chemists.

1.2 Literature reviews on aromatization

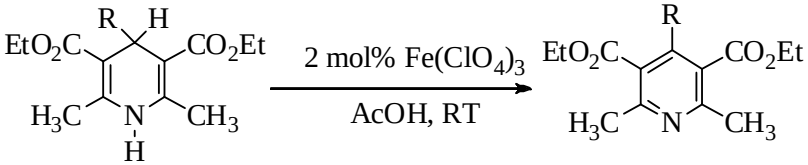
In 1999, Mcbride and co-workers [13] synthesized benzene derivatives from substituted 1,3- or 1,4-cyclohexadienes using $KMnO_4$ supported on alumina as a catalyst in aromatization step with the yield of expected products of 70-95%.



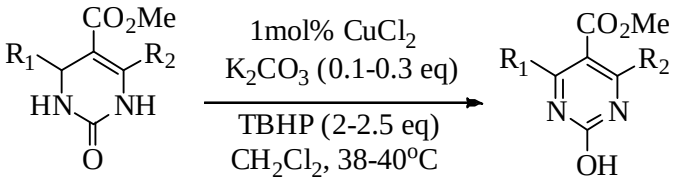
In 2002, Srinivas and Periasamy [14] studied the aromatization of enamines using $TiCl_4$ as a catalyst coupled with Et_3N in CH_2Cl_2.



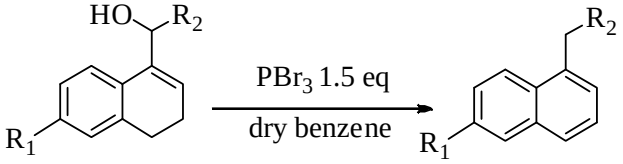
In 2005, Heravi and co-workers [15] reported the aromatization of Hantzsch 1,4-dihydropyridines using $Fe(ClO_4)_3$ in acetic acid as a catalytic system. As a result, the expected corresponding products were isolated in 78-97%.



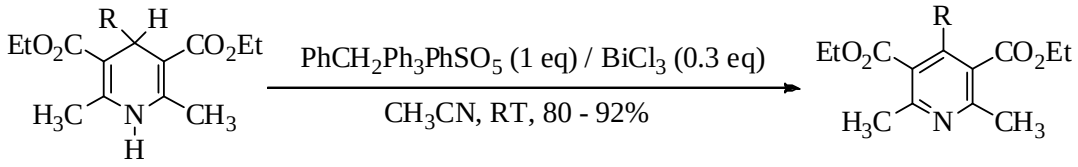
In the same year, Yamamoto and co-workers [16] addressed a mild procedure for oxidative aromatization of dipyrimidone to dihydropyrimidine. From solvent and catalyst screening, CuCl and $CuCl_2$ were found as excellent catalysts when combined with *tert*-butylhydroperoxide (TBHP) in CH_2Cl_2.



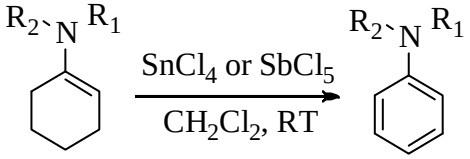
In the same year, Shagufta and co-workers [17] used PBr_3 as an aromatizing agent in benzene for synthesizing substituted 1-arylmethylnaphthalene from 1-tetralone derivatives, but with not practical yields.



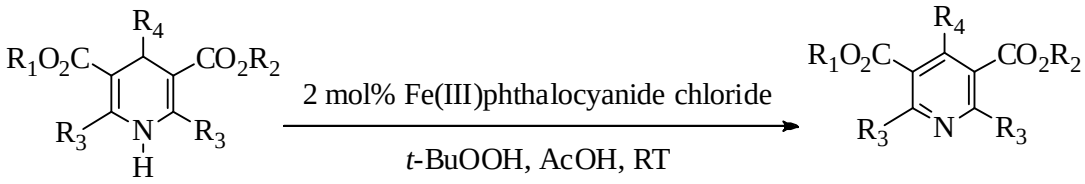
In 2007, Adibi and Hajipour [18] synthesized Hantzsch 1,4-dihydropyridine using benzyltripheylphosphonium peroxymonosulfate as an oxidizing agent coupled with $BiCl_3$ as a catalyst in the aromatization step.



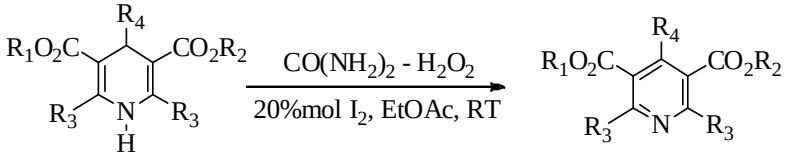
In the same year, Bigdeli and co-workers [19] reported that the use of $SnCl_4$ as a catalyst in CH_2Cl_2 was better than that of $SbCl_5$ for aromatizing enamines. The mechanism of $SnCl_4$ has additionally been proposed.



In 2008, Litvic and co-workers [20] examined the aromatization of Hantzsch 1,4-dihydropyridines by exploring various oxidizing agents, metal complexes, amount of oxidizing agent and metal complex using Fe(III) phthalocyanide chloride associated with TBHP in acetic acid. As a result, the final product was achieved approximately to the stoichiometric amount.



In the same year, Litvic and co-workers [21] reported the aromatization of Hantzsch 1,4-dyhidropyridine derivatives using numerous oxidants, solvents and substituents, and found that urea-H_2O_2 coupled with I_2 in EtOAc was the best system.

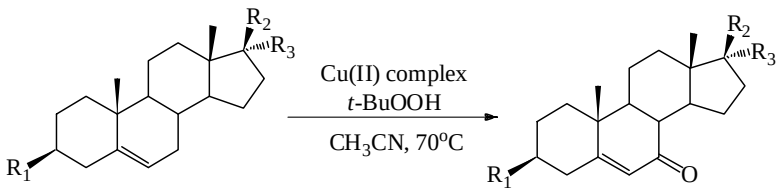


Regarding to previous works, a lot of systems have been developed for aromatization; however, there are still many disadvantages. Some must be handled at low temperature due to their high reactivities which may cause side reactions or easily to decompose. Some catalysts or oxidizing agents developed had low solubilities in common organic solvents.

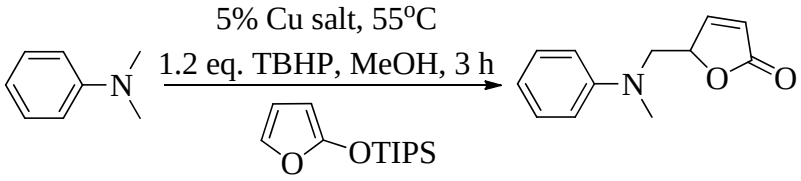
A $CuCl_2$ associated with TBHP system revealed a great profile when using in aromatization of dipyrimidone to dihydropyrimidine [16]; moreover, this procedure could be carried out at RT which is suitable to prevent side reactions and the decomposition of substrate or product.

1.3 Literature reviews on Cu-salt coupled with TBHP

In 2009, Li and co-workers [22] reported a procedure of the oxidation of steroids using Cu(II) complex with TBHP in 70-99% yield.

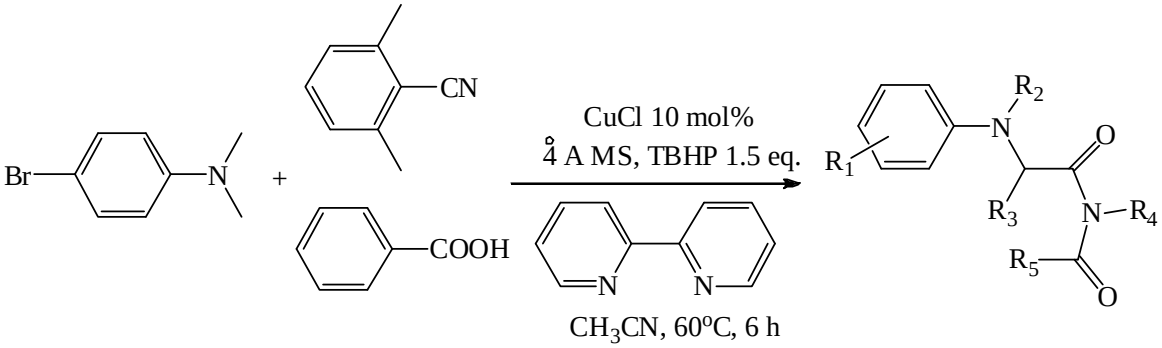


In the same year, Shen and co-workers [23] used Cu salt/TBHP under mild and efficient conditions in oxidative coupling process of tertiary amines and siloxyfurans to synthesize γ-aminoalkyl butenolides. As a result, copper halide salts such as CuCl, $CuCl_2$, CuBr and $CuBr_2$ are suitable for this reaction that produce 50-80% yield.



In 2010, Rayati and co-workers [24] reported that Cu(II) complexes such as Cu{salnptn(3-OMe)$_2$} and Cu{hnaphtnptn} combined with TBHP in CH_3CN could convert cyclooctene and styrene to their related products, 60% cyclooctene oxide and 96% benzaldehyde, respectively

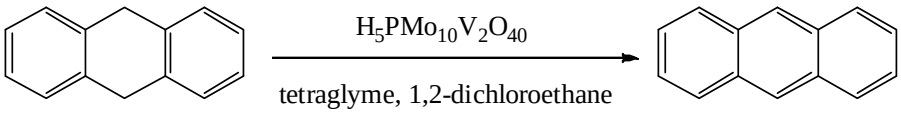
In the same year, Ye and co-workers [25] exhibited the synthetic pathway to synthesize α-amino imides from tertiary amines using CuCl as a catalyst coupled with TBHP to achieve 78% yield.



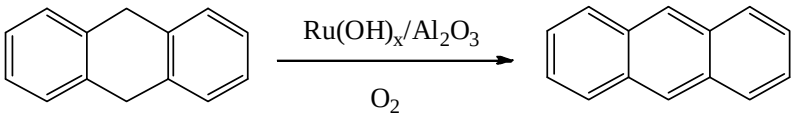
According to previous researches, Cu-salts or complexes coupled with TBHP mostly used in oxidation step, there was only one publication that used Cu-salt/TBHP in aromatization [16]. Hence, the exploration of this inexpensive, safe and easy to deal with protocol is interesting for applying to skipped and conjugated dienes.

1.4 Literature reviews on aromatization of skipped and conjugated dienes

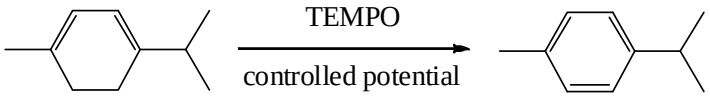
In 1989, Neumann and Lissel [26] used $H_5PMo_{10}V_2O_{40}$ as a catalyst in aromatization of 9,10-dihydroanthacene to anthracene in 89% isolated yield.



In 2004, Kamata and co-workers [27] explored the efficient methodology of the oxidation of akylarines to their corresponding products in 93% yield.

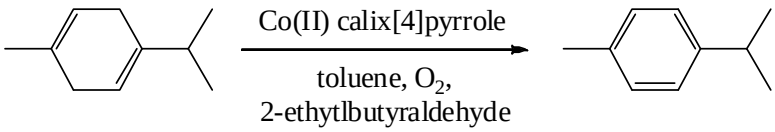


In 2005, Breton and co-workers [28] synthesized alkenone compounds from activated alkenes at allylic position with excellent yields by generating the oxidizing agent from TEMPO in an electrochemical cell to give 63% isolated yield.

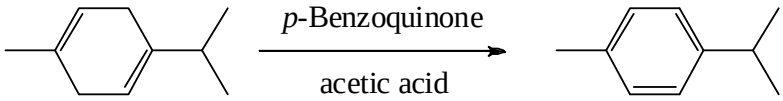


In 2006, Iteya and co-workers [29] developed a solid-phase-oxidation system using vanadomolybdophosphoric acid as a catalyst with molecular oxygen as a new green methodology to convert α-terpinene to 70-80% of *p*-cymene.

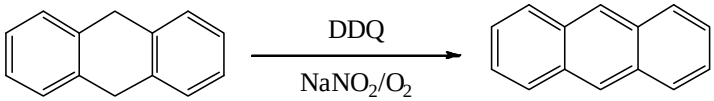
In 2007, Buranaprasertsuk and co-workers [30] developed an epoxidation protocol using cobalt(II) calix[4]pyrrole complexes as a catalyst. In addition, the aromatization of some dienes to their related products was addressed in 43% yield.



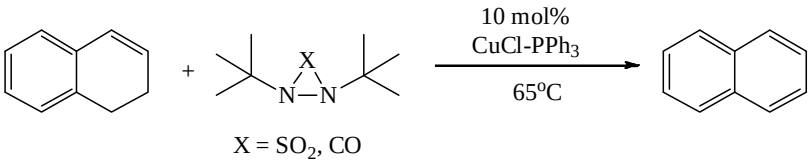
In 2008, Bueno and co-workers [31] studied the aromatization of terpenes using *p*-benzoquinone as a catalyst in various solvents to produce *p*-cymene in 90-100% yield.



In the same year, Zhang and co-workers [32] exploited various benzoquinones and anthraquinones combined with $NaNO_2$ in the aromatization of dihydroarenes. As a result, DDQ showed a superb efficient oxidizing agent to give 99% of anthracene.



In 2010, Ramirez and co-workers [33] used CuCl associated with *N,N*-di-*tert*-butylthiadiaziridine 1,1-dioxide or *N,N*-di-*tert*-butyldiaziridinone as a catalyst in the dehydrogenation step to produce naphthalene in 62% yield.



1.5 Goal of this research

This research aims to explore a new and efficient protocol to aromatize skipped and conjugated dienes using Cu-salt/TBHP system which has not been reported. To search for optimal conditions for the production of related aromatic compounds under mild condition and to prove the mechanism of this catalytic system will also be other aims of this research.

CHAPTER II

EXPERIMENTAL

2.1 Instruments and equipments

Thin layer chromatography (TLC) was performed 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 Kiesekgel 60, GF_{254}). Column chromatography was carried out using silica gel (Merck Kieselgel 60, 70-230 mesh).

The ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ with TMS as an internal reference on a Varian nuclear magnetic resonance spectrometer, model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ^{1}H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons. 2D-NMR spectra such as COSY, HMBC and HSQC were used to confirm the structures of new compounds isolated from reactions.

Gas chromatography was performed on Varian CP-3800 instrument using CP-sil8 column, FID as a detector and N_2 as a carrier gas.

High Resolution Mass Spectrometry used ESI as a source type, calibrated by using Sodium formate, set nebulizer at 1.0 Bar, set dry heater at 150^{o}C and dry gas at 6.0 l/min. The spectra was collected positive ions at 100 – 1000 m/z.

2.2 Chemicals

All solvents used in this research were purified, except for those of reagent grades, and dried prior to use by standard methodology [34]. The substrates and

reagents for synthesizing the products employed in this work were purchased from Fluka, Aldrich and TCI chemical companies and were used without further purification.

2.3 Typical procedure for aromatization of skipped dienes

In a pear-shaped consisting of a solution of copper salt (0.05 mmol) in CH_3CN (1 mL) was added skipped diene (1 mmol) and 70% TBHP in water (1.5 mmol). The mixture was stirred at RT for 15 min and the reaction was quenched by adding water (0.5 mL) and brine (0.2 mL). The organic phase was removed, dried and analyzed by GC with the addition of cyclohexanone (0.25M in EtOAc) as an internal standard.

2.4 Optimal conditions for aromatization of skipped dienes

Optimal conditions for aromatization of skipped dienes were performed using γ-terpinene as a starting material.

2.4.1 Solvent screening

Following the typical procedure for aromatization of skipped dienes, various solvents (1 mL) selected from diverse polarities including *n*-hexane, CH_3CN, CH_2Cl_2, EtOAc and MeOH were experimented to compare their effects on the reaction efficiency.

2.4.2 Catalyst screening

This observation was carried out following the typical procedure for aromatization of skipped dienes using Cu(I) or Cu(II) salts including CuCl, CuCN, $Cu(OAc)_2$, $CuCl_2$, and $CuSO_4$ to compare their potentials on the reaction capability.

2.4.3 Defining catalyst ratio

This experiment was performed following the typical procedure for aromatization of skipped dienes using $CuCl_2$ 0.01, 0.025, 0.05 and 0.1 mmol as a catalyst to define the catalyst ratio.

2.5 Typical procedure for aromatization of conjugated dienes

A similar protocol to the aromatization of skipped dienes (topic 2.3) was carried out. The mixture was stirred at 60^{o}C for 30 min. The work-up and analysis procedures were performed as those previously mentioned.

2.6 Optimal conditions for aromatization of conjugated dienes

Optimal conditions for aromatization of conjugated dienes were performed using α-terpinene as a starting material.

2.6.1 Effect of reaction time

This experiment was carried out using the typical procedure for aromatization of conjugated dienes, but the reaction times examined were 15, 30 and 60 min.

2.6.2 Effect of temperature

This study was performed following the typical procedure for aromatization of conjugated dienes. Two reaction temperatures were explored, at RT (27^{o}C) and 60^{o}C.

2.7 Study on reaction mechanisms

The mechanism of Cu-salt/TBHP system was believed to take place *via* radical mechanism. To proof this assumption, a radical scavenger was added to trap radicals in the reaction. This experiment was performed following the general procedure for aromatization of skipped diene with optimal parameters for 2 min with the addition of 1 mmol of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO).

2.8 Aromatization of other substrates

Other substrates including 9,10-dihydroanthracene, 9,10-dihydrophenanthrene, 1,2-dihydronaphthalene and acenaphthene were used as substrates to prove the efficiency of this developed aromatization system. The aromatizations of these substances were carried out using the general procedure under the optimal conditions as stated.

2.8.1 Aromatization of 9,10-dihydroanthracene

According to the typical procedure of skipped dienes, anthracene was produced as a corresponding aromatized product of 9,10-dihydroanthracene.

2.8.2 Aromatization of 9,10-dihydrophenanthrene

Following by the typical procedure of conjugated dienes, the reaction was analyzed by GC; moreover, an unknown compound was separated by column chromatograph with CH_2Cl_2:*n*-hexane (1:1) as a mobile phase.

2.8.3 Aromatization of 1,2-dihydronaphthalene

The aromatization of 1,2-dihydronaphthalene was followed a typical procedure of conjugated dienes. The product was analyzed by GC; in addition, an unassigned compound in GC chromatogram was isolated by column chromatograph using CH_2Cl_2:*n*-hexane (1:1) as a mobile phase and elucidated its structure based on spectroscopic evidence.

2.8.4 The reaction with acenaphthene

The reaction was carried out following a typical procedure of conjugated dienes. After the reaction was completed, pale yellow solid was filtered and identified by ^{1}H and ^{13}C-NMR. Filtrate was isolated by column chromatography with CH_2Cl_2:*n*-hexane (2:3) as a mobile phase. All products were identified by spectroscopic techniques.

2.9 Aromatization of indoline

2.9.1 Protection of indoline with benzyl group [35]

Indoline (20 mL, 180 mmol) and 30 mL of 5M NaOH were added in a round bottom flask containing a solution of benzyl chloride (24 mL, 200 mmol) in THF (100 mL). Water was added to the reaction to stop the reaction after stirred at RT for 24 h and extracted with 100 mL of Et_2O for 4 times. The organic layers were separated

and dried over anhydrous $MgSO_4$, filtered, and evaporated. The brown crude product was purified by silica gel column using CH_2Cl_2:*n*-hexane (3:7) as a mobile phase.

1-Benzylindoline: light-yellow oil (78%). ^{1}H NMR ($CDCl_3$) δ 3.04 ppm (*t*, 2H, $CH_2C\underline{H}_2$, *J* = 8.4 Hz), δ 3.36 ppm (*t*, 2H, $C\underline{H}_2CH_2$, *J* = 8.4 Hz), δ 4.32 ppm (*s*, 2H, $NC\underline{H}_2Ph$), δ 6.59 ppm (*d*, 1H, *J* = 8.0 Hz), δ 6.75 ppm (*t*, 1H, *J* = 7.6 Hz), δ 7.16 ppm (*m*, 2H) and δ 7.39 ppm (*m*, 5H).

2.9.2 Aromatization of 1-benzylindoline

The aromatization of 1-benzylindoline was carried out following the general procedure with the optimal conditions for aromatization of conjugated dienes. The product was isolated by silica gel column using CH_2Cl_2:*n*-hexane (2:3) as a mobile phase.

1-Benzylindole: light-yellow oil (48%). ^{1}H NMR ($CDCl_3$) δ 5.37 ppm (*s*, 2H), δ 6.66 ppm (*d*, 1H, *J* = 3.2 Hz), δ 7.17-7.38 ppm (*m*, 9H) and δ 7.77 ppm (*d*, 1H, *J* = 7.6 Hz).

2.9.3 Deprotection of benzyl group [36]

A mixture of 1-benzylindole (311 mg, 1.5 mmol), 10% Pd-C (160 mg, 0.15 mmol) in MeOH (20 mL) and CH_2Cl_2 (10 mL) was stirred in a round bottom flask under H_2 at RT and atmospheric pressure. After 48 h, catalyst was filtered out and filtrate was evaporated and purified by column chromatograph using CH_2Cl_2:*n*-hexane (2:3) as a mobile phase.

2.10 Aromatization of zingiberene

2.10.1 Isolation of zingiberene from ginger oil [37]

Ginger oil (Thai-China Flavours and Fragrances Industry Co.,Ltd.) was distilled by Kugelrohr equipment at 0.1 mmHg and collected a fraction of 60-100^{o}C. A distillate was dissolved in 20 mL of dry THF and stirred at RT, while adding a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD, 0.88 g, 5 mmol) in THF (10

mL) dropwise. The mixture was concentrated and purified by flash chromatograph using 15% acetone in *n*-hexane as an eluent. The product was refluxed in 10 mL of 2.1 KOH in 95% EtOH under atmospheric N_2. After 3 h, the mixture was diluted with water and extracted with *n*-hexane. The extract was washed with brine, dried over anhydrous Na_2SO_4, and purified by silica gel short column and eluted with *n*-hexane. The solution was concentrated and then redistilled by Kugelrohr.

2.10.2 Aromatization of zingiberene

The aromatization of zingiberene was carried out following a typical procedure with the optimal condition for conjugated dienes. The product, α-curcumene, was isolated by column chromatograph and identified by spectroscopic techniques.

CHAPTER III

RESULTS AND DISCUSSION

According to previous literatures, there were many common disadvantages of catalysts used in aromatization of skipped and conjugated dienes such as requirement of stoichiometric ratio, long reaction time and high temperature. This research aims to find out a more suitable catalytic system for aromatization of skipped and conjugated dienes. In addition, there was no report of Cu-salt coupled with *tert*-butylhydroperoxide (TBHP) as catalyst in a particular type of aromatization.

3.1 Optimal conditions for aromatization of skipped dienes

Many factors affected on the efficiency of aromatization of skipped dienes such as solvent, type and amount of catalyst, reaction time and temperature. The investigation of each factor was carried out using γ-terpinene as a chemical model. The reaction was stopped by adding brine, extracted with CH_3CN, and analyzed by GC with the addition of cyclohexanone as an internal standard. The mixed standards of *p*-cymene, γ-terpinene and cyclohexanone were analyzed by GC to check their retention times as shown in Figure 3.1.

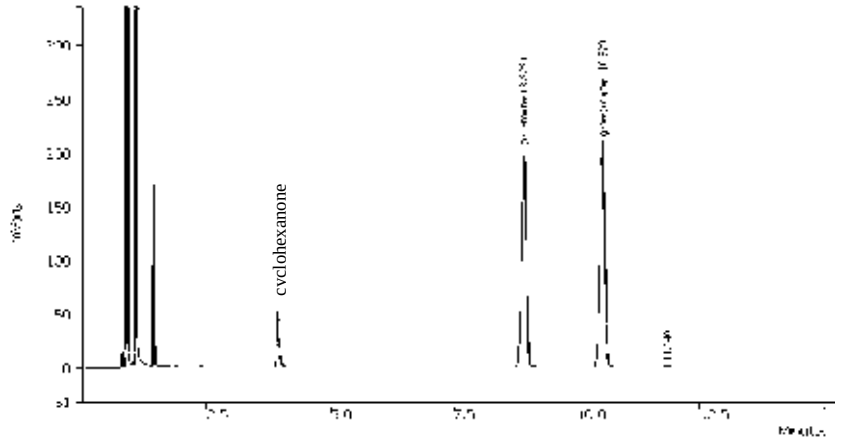
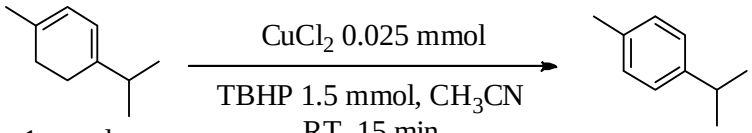


Figure 3.1 GC chromatogram of mixed standards (*p*-cymene, γ-terpinene and cyclohexanone)

3.1.1 Solvent screening

Solvent is one of important factors which affected on the reaction efficiency. Non-polar substances cannot be soluble in polar solvents due to low solubility and polar substances were also not soluble in non-polar solvents, which means solubility must be considered to make reaction homogeneous. Various solvents including EtOAc, CH_3OH, CH_2Cl_2, *n*-hexane and CH_3CN were screened to find out the most appropriate one that makes the system homogeneous and the reaction could proceed smoothly. The outcomes from solvent screening are shown in Table 3.1.

Table 3.1 The effect of solvent on aromatization efficiency of γ-terpinene.



Entry	Solvent	%Conversion	%Yield[a]
1	EtOAc	92	90
2	CH_3OH	83	82
3	CH_2Cl_2	40	37
4	*n*-hexane	20	17
5	CH_3CN	>99	99

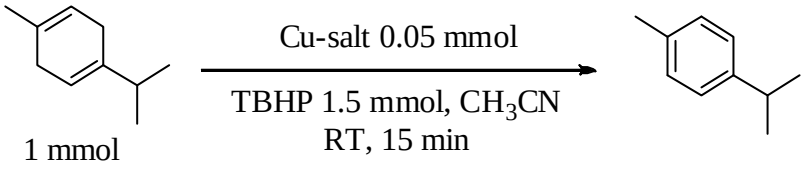
[a] GC yield.

The preliminary screening of solvent for aromatization of γ-terpinene to *p*-cymene is shown in Table 3.1. The better solubility of catalyst and starting material in the reaction media resulted in better reaction efficiency. For example, non-polar solvent such as *n*-hexane (entry 4) did not give high productivity due to low solubility of $CuCl_2$. On the other hand, complete solubility of both catalyst and substrate could be observed when polar solvents such as EtOAc, CH_3OH and CH_3CN were used. Those reactions provided a good yield of the desired product, particularly in CH_3CN, the highest yield of the desired product was produced.

3.1.2 Catalyst screening

The appropriate catalyst was explored by screening several copper salts, both Cu(I) and Cu(II), in CH_3CN. The results are presented in Table 3.2.

Table 3.2 The effect of copper salts on aromatization efficiency of γ-terpinene.



Entry	Catalyst	%Conversion	%Yield[a]
1	$CuCl_2$	>99	99
2	CuCl	98	95
3	$CuSO_4$	91	86
4	CuCN	82	63
5	$Cu(OAc)_2$	93	90

[a] GC yield.

According to Table 3.2, the use of either Cu(I) or Cu(II) did not give significant difference in terms of the reaction efficiency (entries 1 and 2). Copper salts consisted of chlorine atom(s), especially $CuCl_2$, were superb possibly because of their high solubility in CH_3CN. In addition, chloride is a good leaving group to

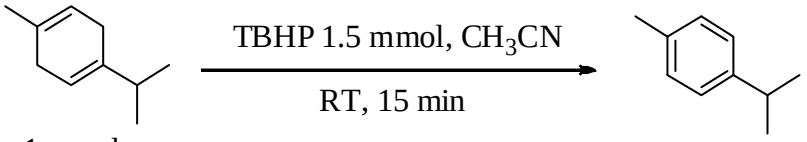
generate Cu(I) when associated with TBHP. On the contrary, CuCN did not act as a good catalyst and its solubility in CH_3CN was low.

Considering to copper salts, various ligands: chloride, sulfate, cyanide and acetate were used to compare their effect on reaction efficiency. Sulfate, cyanide and acetate anions are strong field ligands and also have back bonding effect which has strong bond between ligand and metal [38]. Among ligand studied, a cyanide ligand is the strongest ligand while sulfate and acetate are weaker, respectively. This is the reason why Cu-Cl bond was easily to dissociate and gave excellent yield of product.

3.1.3 The effect of the amount of $CuCl_2$ catalyst

The amount of catalyst added to the reaction affects on the reaction productivity. For example, lack of catalyst made the reaction incomplete or excess amount of catalyst could cause over reaction; however, when catalyst and substrate concentration were diluted by adding solvent, reaction could be retarded. The ratio of catalyst to substrate was varied from 1% to 5% mol to observe the outcome of the reaction. The results are exhibited in Table 3.3.

Table 3.3 The effect of the ratio of catalyst to substrate on aromatization efficiency of γ-terpinene.



1 mmol

Entry	Amount of $CuCl_2$ (mmol)	%Conversion	%Yield[a]
1	0.010	100	quant
2	0.025	>99	quant
3	0.050	>99	quant
4	0	5	5
5[b]	0.025	>99	quant

[a] GC yield, [b] reaction time = 5 min

Based on the data presented in Table 3.3, decreasing the amount of copper catalyst from 0.050 to 0.010 mmol, the reaction still gave excellent yield and conversion. However, to reduce the amount of catalyst lower than 0.025 mmol, it was difficult to weigh the catalyst and would cause the error. Therefore, 0.025 mmol was the appropriate amount to employ in this reaction.

Referring to entry 4 of Table 3.3, aromatization of γ-terpinene without addition of $CuCl_2$ gave little amount of *p*-cymene. Further experiment was also carried out in the absence of TBHP, only 7% of *p*-cymene was observed. That means that both $CuCl_2$ and TBHP were essential for this reaction. In addition, the reaction was completed even the reaction time was reduced to 5 min. These conditions were selected to be the best condition for aromatization of skipped dienes.

In summary, the aromatization of γ-terpinene could be accomplishedly performed using these optimal factors including solvent, catalyst and catalyst ratio as outlining in Figure 3.2.

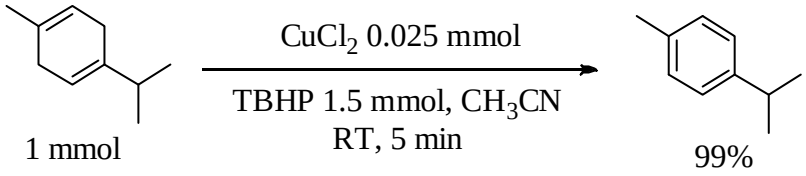


Figure 3.2 Aromatization of γ-terpinene with $CuCl_2$-TBHP catalytic system

For a practical point of view, the reaction could be performed under optimized conditions for 15 min, stopped by adding brine and water. *p*-Cymene (97%) was isolated from the reaction by extraction with CH_3CN and concentrated. Its identity was confirmed by ^{1}H-NMR (Figure 3.3).

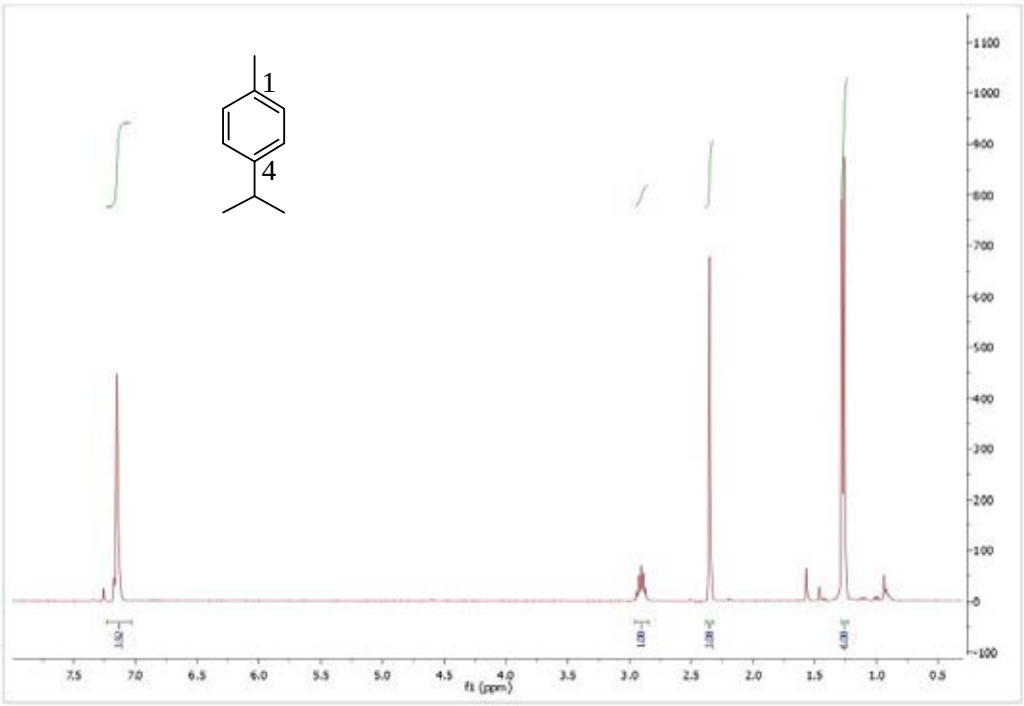


Figure 3.3 The ^{1}H-NMR spectrum of isolated *p*-cymene

Referring to Figure 3.3, a singlet peak at δ 7.13 ppm could be assigned for a signal of aromatic protons (4H). A septet peak at δ 2.85 ppm (J = 6.8 Hz) is a signal of –C<u>H</u>- next to aromatic ring. In addition, a singlet peak at δ 2.30 ppm is a signal of –C<u>H</u>$_3$ at carbon No.1. A doublet peak at δ 1.25 ppm (J = 7.2 Hz) is a signal of two groups of –C<u>H</u>$_3$ of isopropyl group.

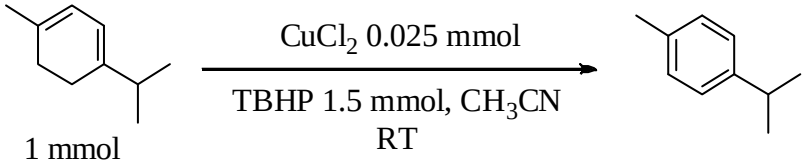
3.2 Optimal conditions for aromatization of conjugated dienes

Conjugated dienes can also be aromatized under suitable condition to provide the corresponding aromatized products. This section deals with the optimization of parameters that may have effects on the aromatization of conjugated dienes such as temperature and reaction time. α-Terpinene was selected as a chemical probe.

3.2.1 Effect of reaction time

To find out the most effective reaction time, the reactions were carried out for 15, 30 and 60 min. The results are shown in Table 3.4.

Table 3.4 The effect of reaction time on aromatization efficiency of α-terpinene.



Entry	Reaction time (min)	%Conversion	%Yield[a]
1	15	30	24
2	30	34	26
3	60	32	26

[a] GC yield.

In accordance with Table 3.4, increasing reaction time more than 15 min did not give more *p*-cymene significantly. Thus, α-terpinene was completely aromatized within 15 min with low yield at RT.

3.2.2 Effect of temperature

To improve the productivity of the aromatization of α-terpinene, temperature was another parameter to be explored. The reaction was carried out at 60°C for 15 min to compare the yield of the desired product, *p*-cymene with that performed at RT. The results are shown in Table 3.5.

Table 3.5 The effect of temperature on aromatization efficiency of α-terpinene.

Entry	Temperature	%Conversion	%Yield[a]
1	RT	30	24
2	60°C	97	93

[a] GC yield

According to Table 3.5, holding the reaction at 60°C extremely increased the yield of the target product significantly while γ-terpinene could totally transform at RT. This implied that α-terpinene required more activation energy than γ-terpinene to convert to *p*-cymene.

Compared to skipped dienes, conjugated dienes could aromatize under more severe conditions than skipped dienes. This was perhaps due to the fact that the C-H bond between the diene of skipped diene has weaker bond energy than the C-H bond next to the diene of conjugated diene. According to the previous report involving in C-H bond strength and H-abstraction rate by OH-radical [39], the computational calculation showed the bond strength of C-H bonds of 1,3-cyclohexadiene and 1,4-cyclohexadiene are 71.01 and 70.92 kcal/mol, respectively. As a result, 1,3-cyclohexadiene possessed more bond energy than 1,4-cyclohexadiene. That means that 1,3-cyclohexadiene required more energy to break C-H bond than the other. These information could be well applied to α-terpinene and γ-terpinene which had conjugated and skipped double bonds, and could be used to explain the formation of carbon radicals of γ- and α-terpinenes (Figure 3.4).

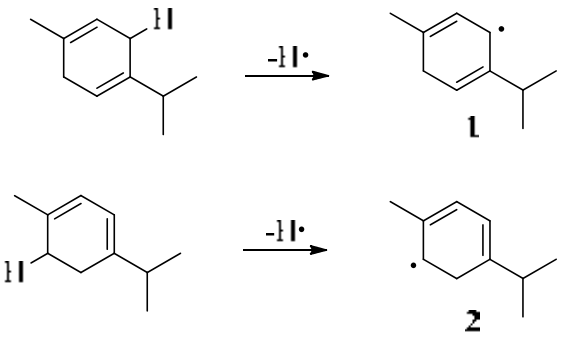


Figure 3.4 The generation of γ- and α-terpinyl radicals from C-H homolytic cleavage

Radical **1** could be stabilized by two sp^2 orbitals of diene. This made radical **1** have more stabilization energy than **2** which was stabilized by only one sp^2 orbital of diene. This was a main reason why conjugated dienes usually need more energy than skipped dienes while losing of hydrogen radical occurred.

To confirm that the C-H bond of γ-terpinene was broken easily than α-terpinene, both γ-terpinene and α-terpinene (1 mmol per each) were employed as starting materials in the same reaction. The reaction was preceded for a certain time and %recovery of each starting material was determined by GC. The results are presented in Table 3.6.

Table 3.6 Reactivity comparison of γ- and α-terpinenes

Substrate	Recovered[a] (mmol)[a]	Used(mmol)[b]	%Yield of *p*-cymene[a]
γ-terpinene	0.11	0.89	111
α-terpinene	0.78	0.22	

RT 15 min, TBHP 1.5 mmol.

Each reactant was used for 1 mmol.

[a] GC analysis

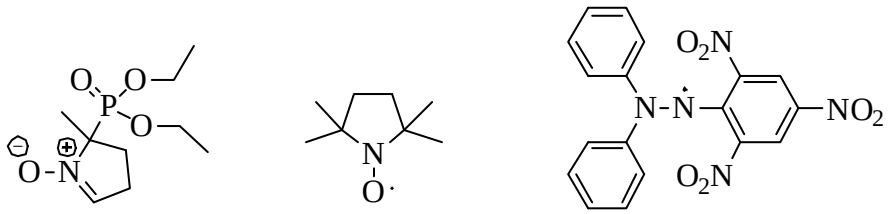
[b] Calculation from added amount – detected amount

Referring to Table 3.6, γ-terpinene was greatly consumed more than α-terpinene to produce *p*-cymene. This reaction was held at RT which the energy should not be enough for C-H bond cleavage of α-terpinene. Therefore, large amount of *p*-cymene was produced from γ-terpinene which more reactive about 4 times than α-terpinene at RT.

To prove that $CuCl_2$-TBHP catalytic system occurred either *via* homolytic cleavage of C-H bond to produce carbon radical or heterolytic cleavage to produce carbocation or carbanion, a series of experiments are conducted.

3.3 Investigation of $CuCl_2$-TBHP mechanism

The mechanistic pathway for the activation of TBHP by metal was proposed to take place *via* homolytic cleavage of TBHP with metal such as Fe [40] and Cu [41]. The common method to prove whether the reaction was proceeded *via* radical pathway is to observe the outcome of the reaction upon adding radical scavenger such as 2-diethylphosphono-2-methyl-3,4-dihydro-*2H*-pyrrole-1-oxide (DEPMPO) [42], 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) [43-44] or 2,2-diphenyl-1-picryl-hydrazyl (DPPH) [45] (Figure 3.5).

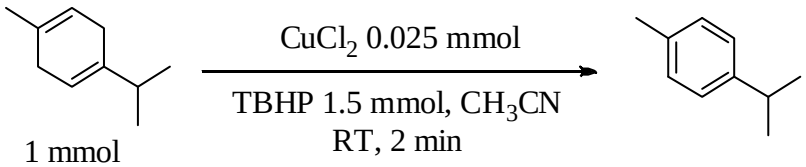


DEPMPO TEMPO DPPH

Figure 3.5 Examples of radical scavenger

In this study, TEMPO was used as a radical scavenger to trap radicals in the reaction. Its effect on the reaction was observed and compared with that without adding TEMPO as presented in Table 3.7.

Table 3.7 The aromatization of γ-terpinene catalyzed by $CuCl_2$ and TBHP in the presence and absence of TEMPO



1 mmol

Entry	Additive	%Conversion	%Yield[a]
1	none	91	85
2	TEMPO (1 mmol)	36	35

[a] GC yield

The GC chromatograms of the reactions with and without TEMPO are exhibited in Figures 3.6-3.7.

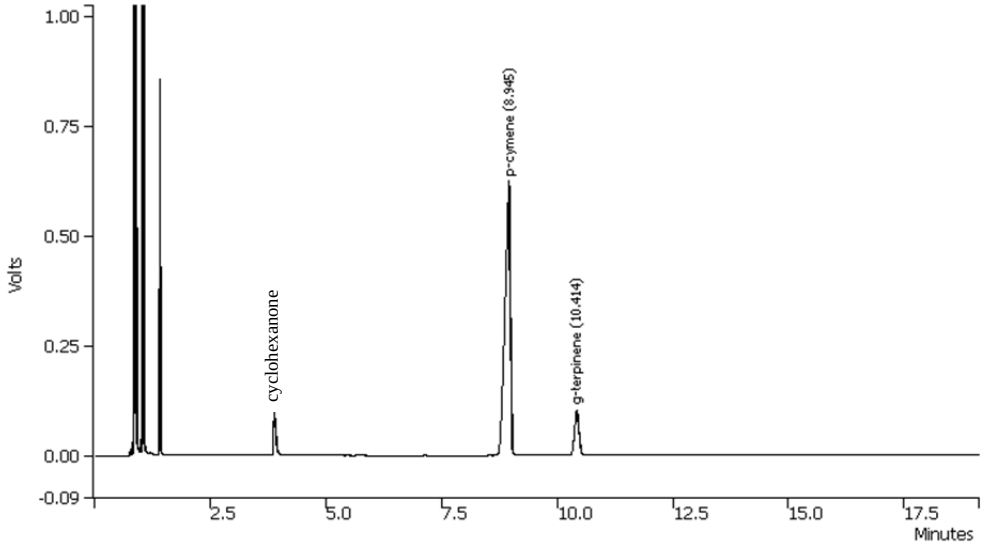


Figure 3.6 Aromatization of γ-terpinene without the addition of TEMPO

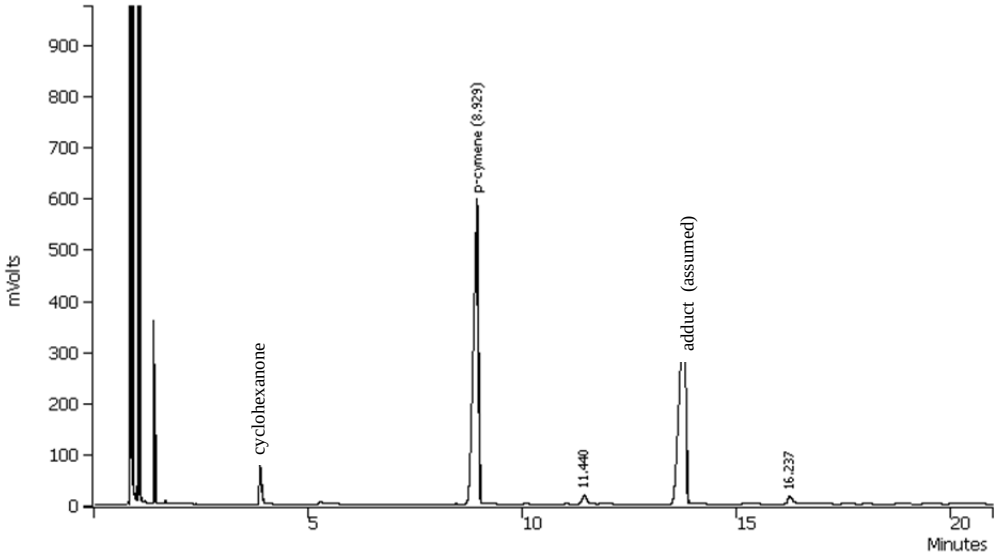


Figure 3.7 Aromatization of γ-terpinene with the addition of TEMPO

Referring to Table 3.7, the reaction without radical scavenger (entry 1) gave significantly higher amount of target product than that with TEMPO. This implied that aromatization with $CuCl_2$-TBHP should occur *via* radical mechanism, TEMPO

radical trapped *tert*-butoxyl radical and *tert*-butylperoxy radical as postulated in Figure 3.8.

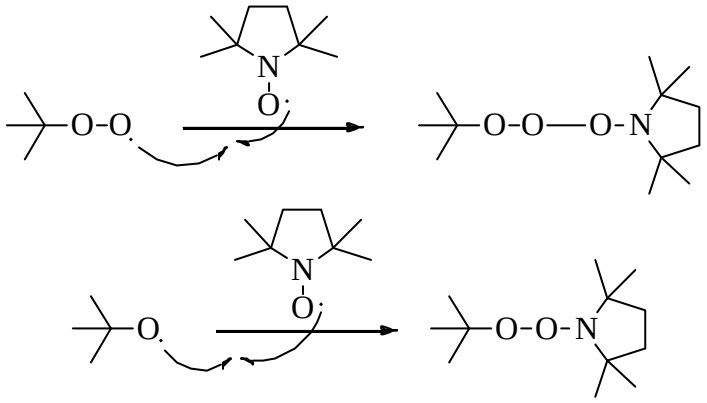


Figure 3.8 Trapping of generated radicals from reaction with TEMPO

From Figure 3.8, TEMPO not only trapped *tert*-butoxyl radicals, but also terpinene radicals resulting in the reduced productivity of *p*-cymene about 50%.

To confirm that TBHP could dissociate at O-O bond to generate ^{t}BuO• , *tert*-butanol must be detected by GC. The GC chromatogram (Figure 3.9) displayed manifestly the presence of *tert*-butanol.

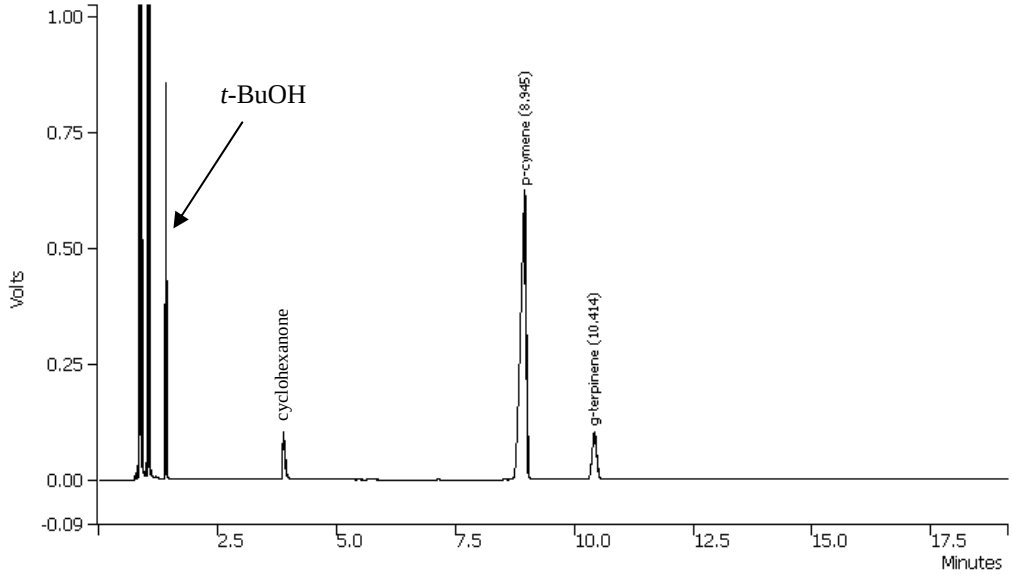
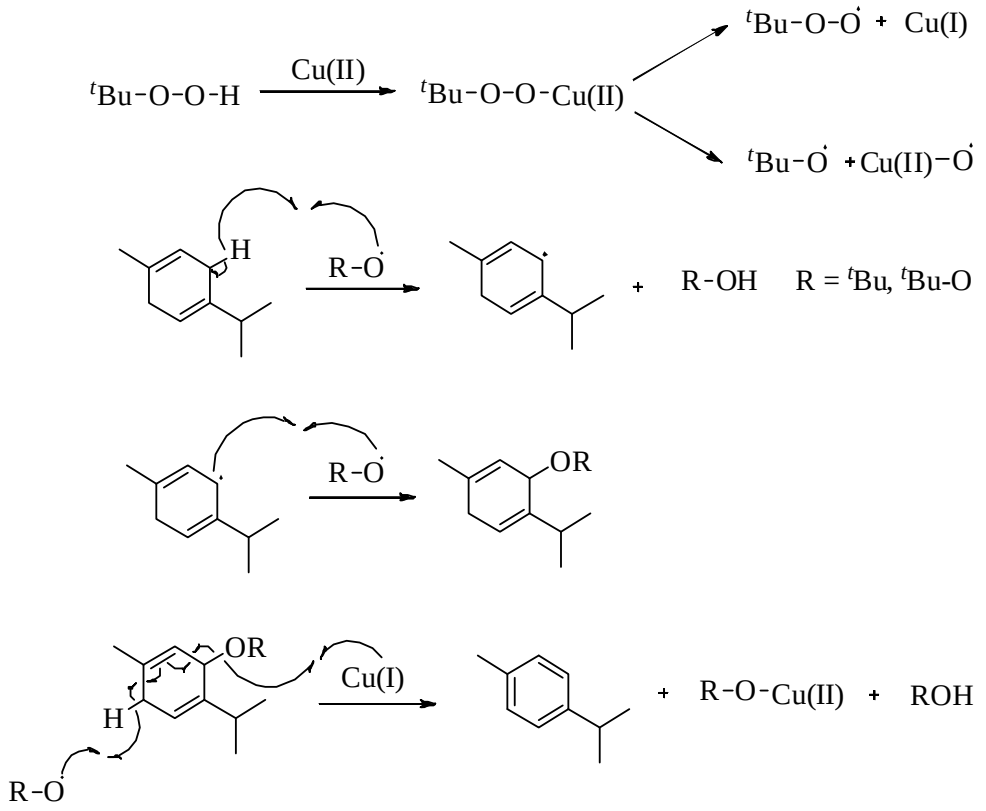


Figure 3.9 Chromatogram of *tert*-butanol from reaction mixture

According to the previous observation and literatures about Cu-TBHP system [22-25], the proposed mechanism for aromatization of γ-terpinene is shown in Scheme 3.1.



Scheme 3.1 The proposed mechanism for aromatization of γ-terpinene by Cu-TBHP catalytic system

The initial step was copper-catalyzed decomposition of TBHP to generate two possible radicals, *i.e.* ^{t}BuO• and ^{t}BuOO• that could further abstract H-atom of γ-terpinene to form terpinene radical. The second step was associated with *tert*-butoxyl radicals to produce terpinyl peroxide which easily aromatized by leaving of peroxide radical, abstracted by Cu(I).

3.4 Aromatization of 9,10-dihydroanthracene and 9,10-dihydrophenanthrene

Following by the Hückel's rule, aromatic compounds consisted of π-electrons equal to 4n+2 and also have aromatic property. This effect of delocalized electrons in cyclic ring molecules makes aromatic compounds more stable than normal alkenes

[46-47]. Aromaticity is thus an important driving force to drive the aromatization of skipped and conjugated dienes.

9,10-Dihydroanthracene is one of skipped dienes which separated two aromatic rings by two sp^3-carbons. The aromatization of this compound was performed using the typical procedure for skipped dienes as shown in Figure 3.10.

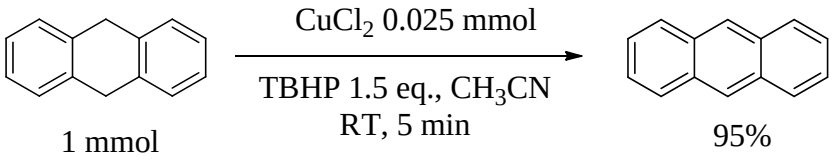


Figure 3.10 Aromatization of 9,10-dihydroanthracene

In the same way of the aromatization of γ-terpinene, 9,10-dihydroanthracene could also aromatize under mild conditions with short reaction time. This could be explained by the C-H bond strength between double bonds in skipped diene which was weaker than that closed to diene in conjugated diene (Figure 3.4).

After the reaction was quenched by adding water and brine, anthracene was solidified as white crystal with high purity without contaminants. The ^{1}H-NMR spectrum of isolated anthracene is shown below (Figure 3.11).

Figure 3.11 The ^{1}H-NMR spectrum of anthracene

A proton signal at δ 8.43 ppm was a signal of H_A (*s*, 2H), while the signals at δ 8.01 ppm was a signal of H_B (*dd*, 4H, *J* = 6.4, 3.2 Hz) and at δ 7.47 ppm (*dd*, 4H, *J* = 6.4, 3.2 Hz) should belong to H_C.

For the other case, the aromatization of 9,10-dihydrophenanthrene was carried out using the general procedure of conjugated dienes. Two main spots could be visualized from the crude reaction mixture on TLC. The purification was performed by means of silica gel column affording phenanthrene, the main spot corresponding aromatized product in moderate yield (65% yield). The ^{1}H-NMR spectrum of isolated phenanthrene was depicted in Figure 3.12. In addition, compound **A** (the minor spot), was isolated as colorless oil in 12% yield. This compound was further characterized by NMR (Figures 3.13-3.17) and high resolution mass spectrometry (HRMS).

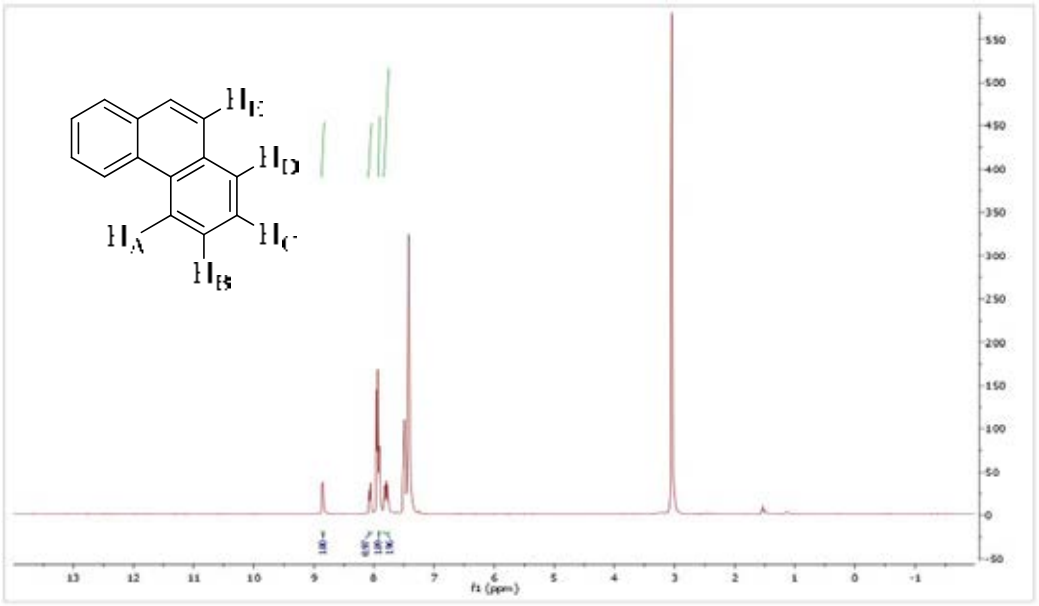


Figure 3.12 The ^{1}H-NMR spectrum of isolated phenanthrene

Phenanthrene is a symmetric compound. From ^{1}H-NMR spectrum in Figure 3.12, there are 5 groups of protons, H_A-H_D, which response to the magnetic field in the different frequency. A proton signal at δ 8.85 ppm is a signal of H_A (*d*, 2H, *J* = 8.0 Hz). A proton signal at δ 8.06 ppm is a signal of H_D (*d*, 2H, *J* = 7.6 Hz). A proton H_E revealed the signal at δ 7.89 ppm (*s*, 2H). H_B and H_C showed their signals at the same chemical shift, δ 7.80 ppm (*ddd*, 2H, *J* = 8.0, 8.0, 2.0 Hz).

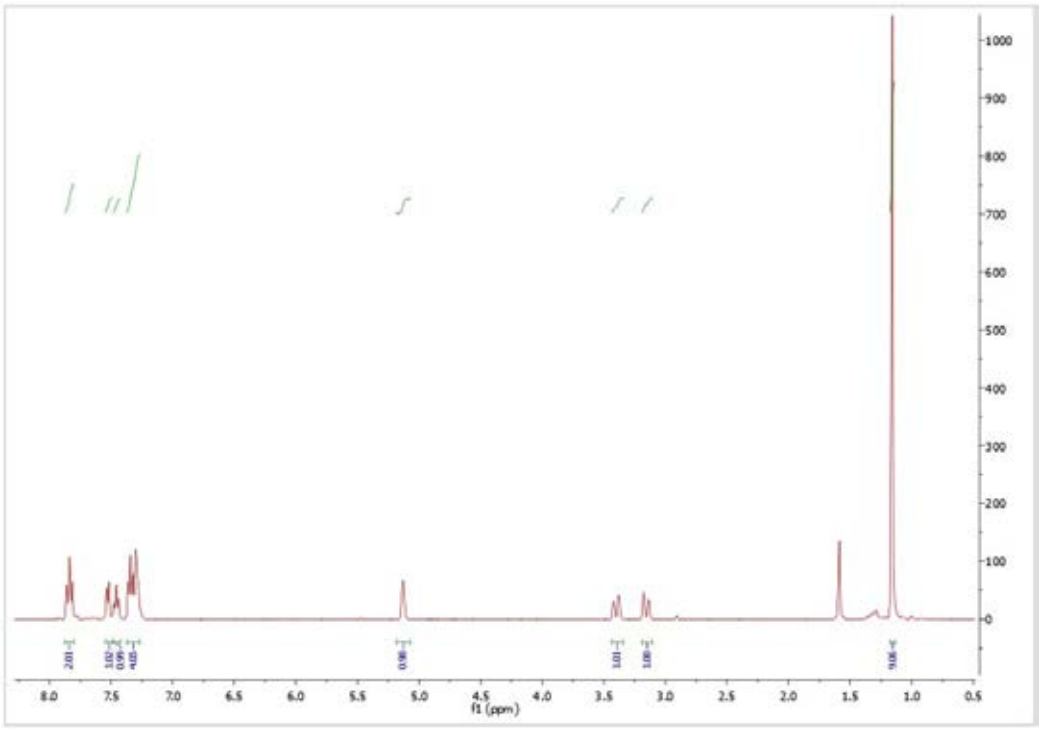


Figure 3.13 The ^{1}H-NMR spectrum of compound **A**

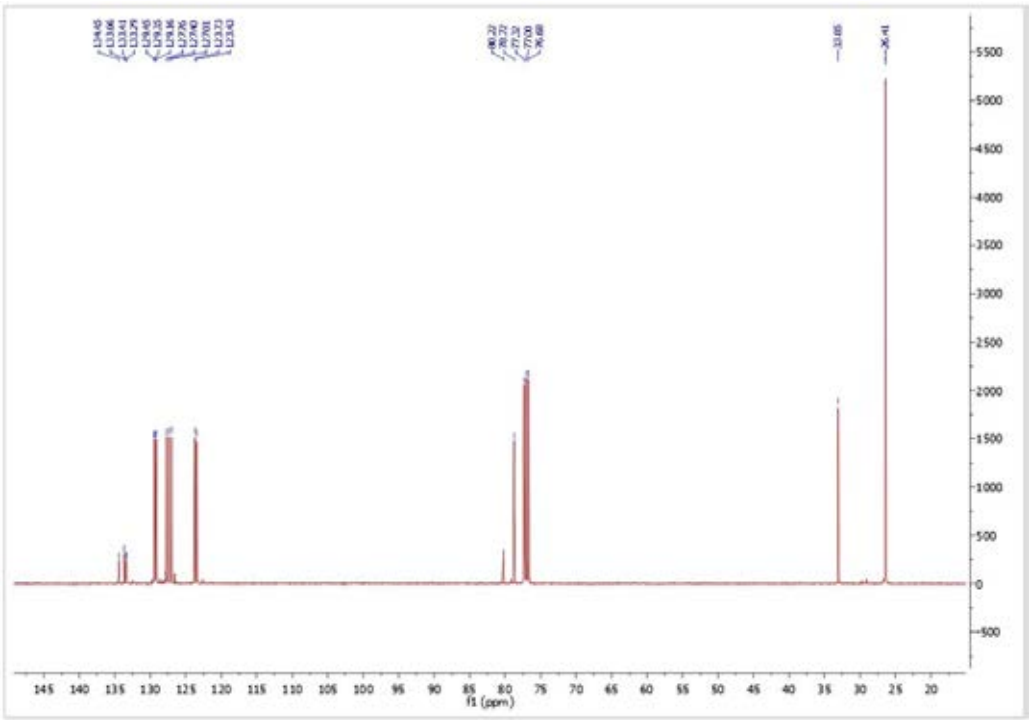


Figure 3.14 The ^{13}C-NMR spectrum of compound **A**

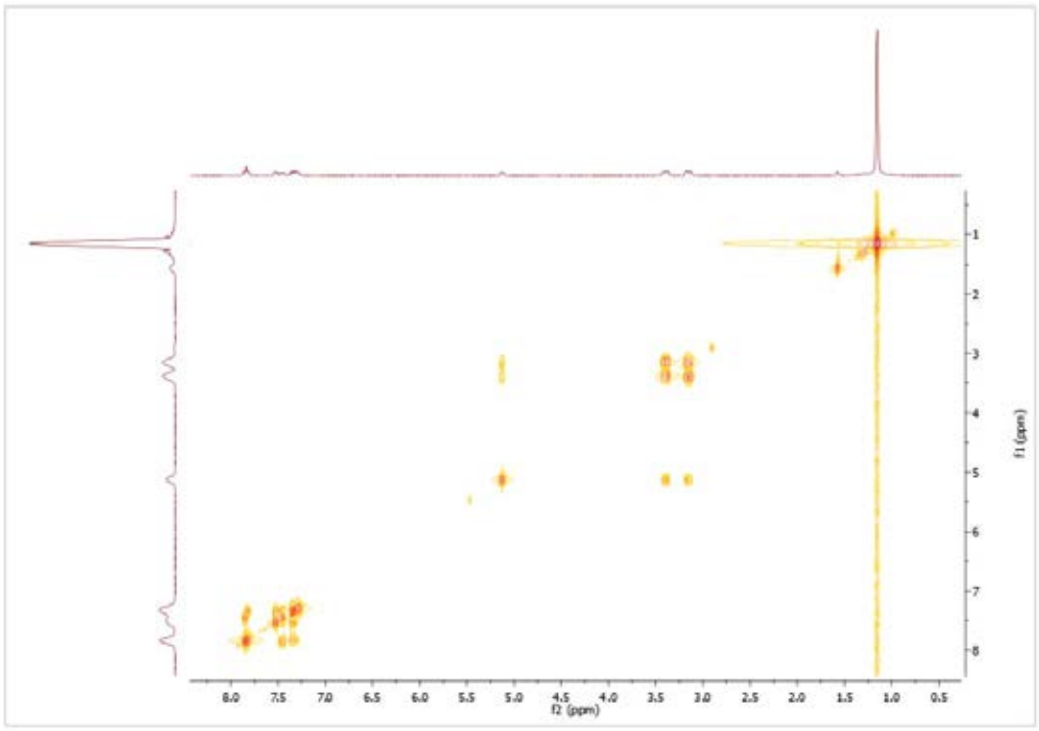


Figure 3.15 The COSY spectrum of compound **A**

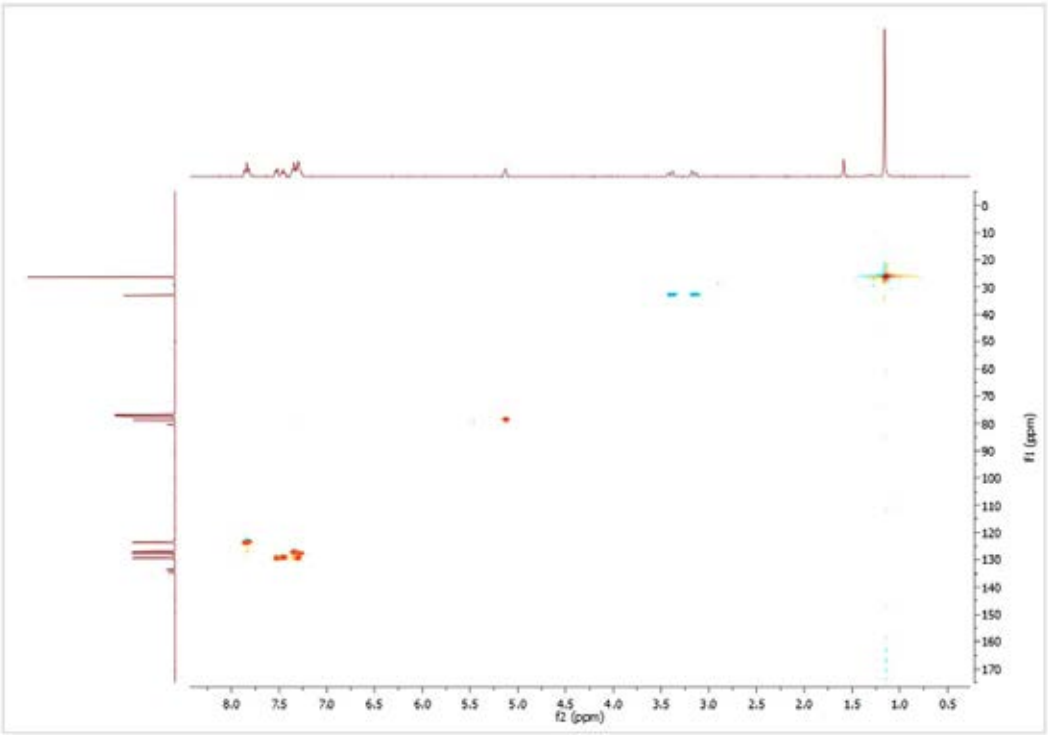


Figure 3.16 The HSQC spectrum of compound **A**

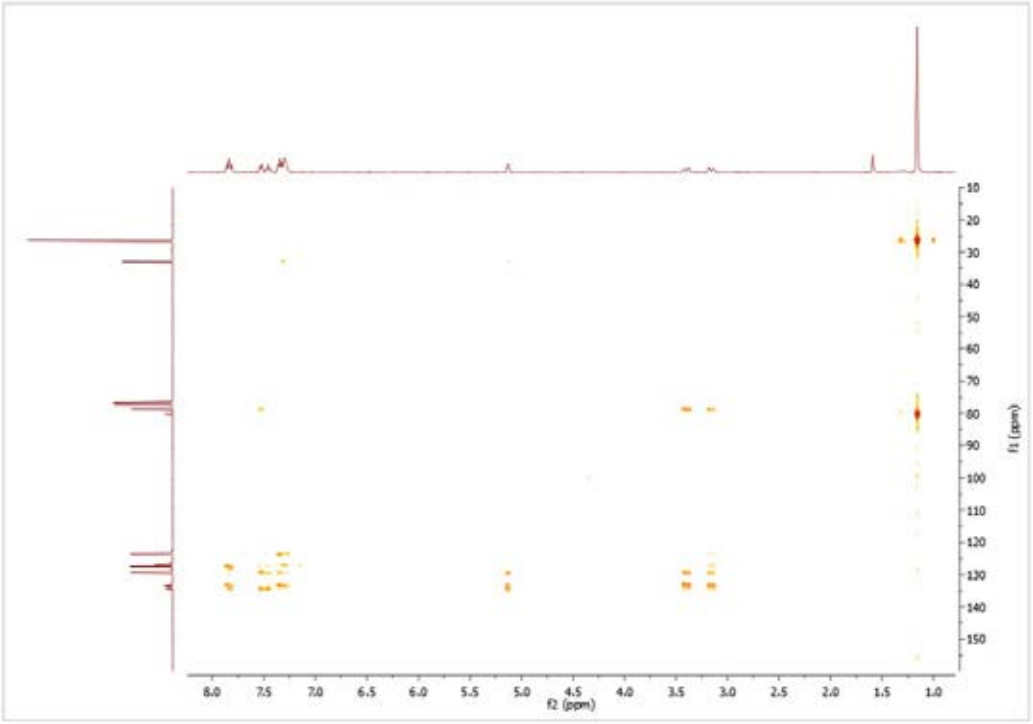


Figure 3.17 The HMBC spectrum of compound **A**

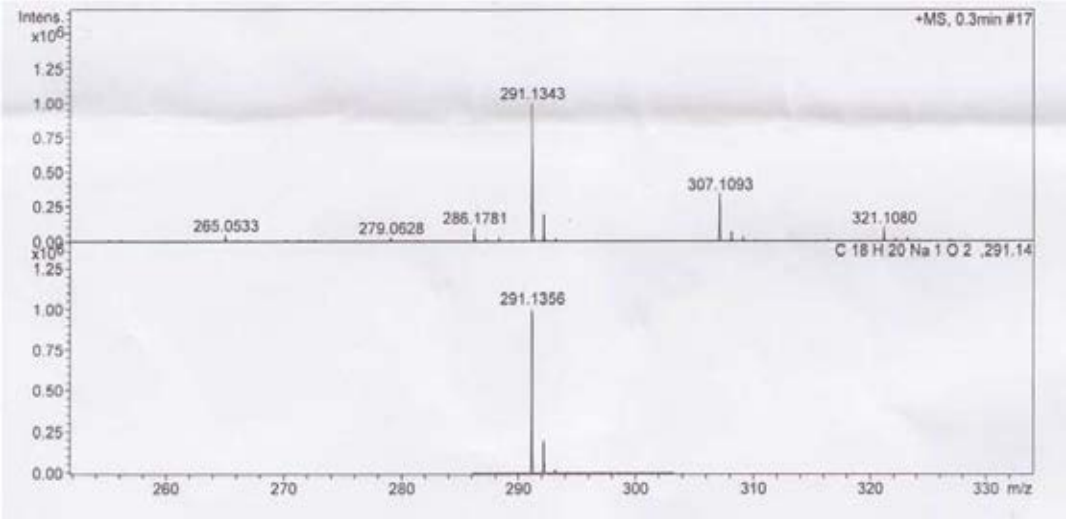


Figure 3.18 The HRMS of compound **A**

According to the HRMS of compound **A** (Figure 3.18), the molecular formula of $C_{18}H_{20}O_2Na$ was proposed for molecular weight of 291.14 g/mol. Compound **A** should have the formula $C_{18}H_{20}O_2$ with molecular weight 268.12 g/mol. Its structure

was further confirmed by NMR spectrum as shown in Figures 3.13-3.17. The proposed structure of compound **A** is shown in Figure 3.19.

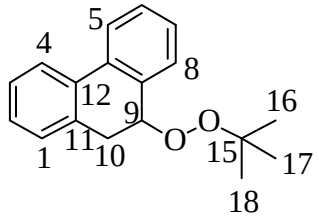


Figure 3.19 Proposed structure of compound **A**

The NMR data of compound **A** is summarized in Table 3.8. The HMBC and COSY correlation of compound **A** were displayed in Figure 3.20. To our best knowledge, according to previous literature, compound **A** was discovered to be a new compound.

Table 3.8 The NMR data of compound **A**

Position	Compound A			
	δ_C	δ_H	HMBC	COSY
1	129.4	7.29 (1H, *d*, 6.8 Hz)	C-10,C-12	H-2
2	127.4	7.34 (1H, *t*, 7.2 Hz)	C-1,C-11	H-1,H-3
3	127.8	7.29 (1H, *t* , 6.8 Hz)	C-4	H-2,H-4
4	123.4	7.83 (1H, *d*, 9.6 Hz)	C-3	H-3
5	123.7	7.85 (1H, *d*, 8.4 Hz)	C-14	H-6
6	129.2	7.46 (1H, *t*, 7.4 Hz)	C-8,C-13	H-5,H-7
7	127.0	7.34 (1H, *t*, 7.6 Hz)	C-5,C-14	H-6,H-8
8	129.5	7.51 (1H, *d*, 7.2 Hz)	C-6,C-9,C-13	H-7
9	78.7	5.13 (1H, *br*)	C-8,C-10,C-13	H-10
10	33.1	3.40 (1H, *dd*, 16.0,4.8 Hz) 3.16 (1H, *dd*, 16.2,4.8 Hz)	C-1,C-9,C-14 C-1,C-9,C-14	H-9
11	133.4	-	C-2,C-4,C-9,C-10	-
12	133.7	-	C-1,C-3,C-5,C-10	-
13	134.5	-	C-6,C-8,C-9	-
14	133.3	-	C-5,C-6,C-7,C-10	-
15	80.2	-	-	-
16	26.4	1.16 (3H, *s*)	C-17,C-18	-
17	26.4	1.16 (3H, *s*)	C-16,C-18	-
18	26.4	1.16 (3H, *s*)	C-16,C-17	-

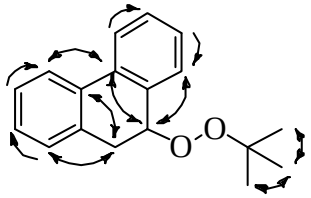
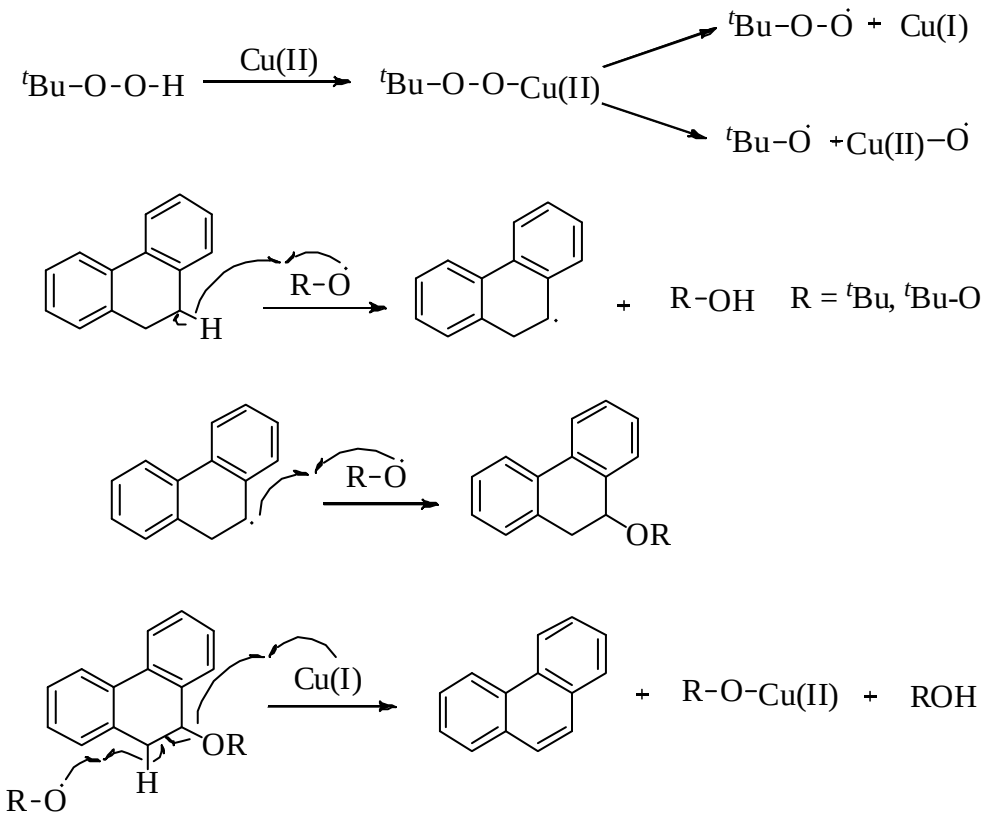


Figure 3.20 HMBC (↔) and COSY (→) correlation of compound **A**

The isolation and well characterization of compound **A**, an adduct derived from phenanthrene radical and *tert*-butoxyl radical, was in fact a good evidence to endorse the aforementioned proposed Cu-TBHP mechanism. The aromatization of conjugated diene using Cu-TBHP catalytic system and 9,10-dihydrophenanthrene as a starting material is shown in Scheme 3.2.

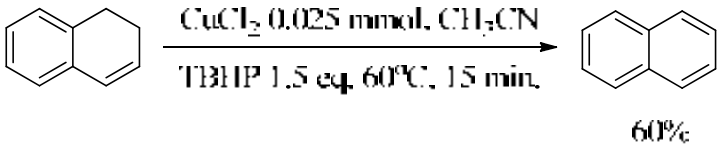


Scheme 3.2 The aromatization of phenanthrene using Cu(II)-TBHP system

3.5 Aromatization of 1,2-dihydronaphthalene

1,2-Dihydronaphthalene is a conjugated diene which can aromatize under Cu/TBHP catalytic system like phenanthrene. The production of a related aromatized product should be an important driving force.

Following the general procedure of conjugated dienes, naphthalene was produced in the moderate yield as outlining in the following equation.



From TLC screening, there were three spots appeared *i.e.* starting material (1,2-dihydronaphthalene), product (naphthalene) and an unknown compound (compound **B**). The isolation of naphthalene was achieved by silica gel column with 1:1 of CH_2Cl_2:*n*-hexane as a mobile phase. The unknown compound was subsequently isolated and identified its structure by spectroscopic techniques and mass spectrum. The lower amount of the target product was probably due to the sublimation of naphthalene at high temperature during experiment. The isolated naphthalene was confirmed by ^{1}H-NMR (Figure 3.21).

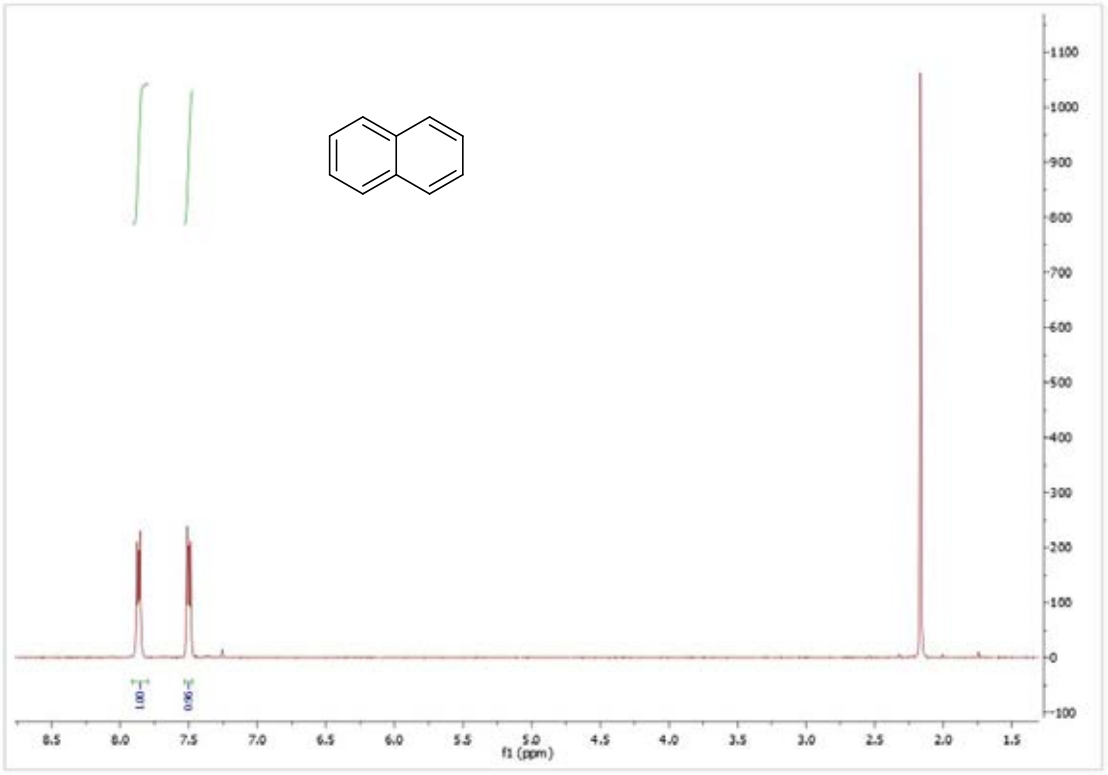


Figure 3.21 The ^{1}H-NMR spectrum of isolated naphthalene

Referring to Figure 3.21, there are only two proton signals, a peak at δ 7.86 ppm (*dd*, 4H, *J* = 6.0, 3.2 Hz) and a peak at δ 7.50 ppm (*dd*, 4H, *J* = 6.4, 3.2 Hz). The ^{1}H-NMR spectrum was confirmed by comparing to the spectroscopic database.

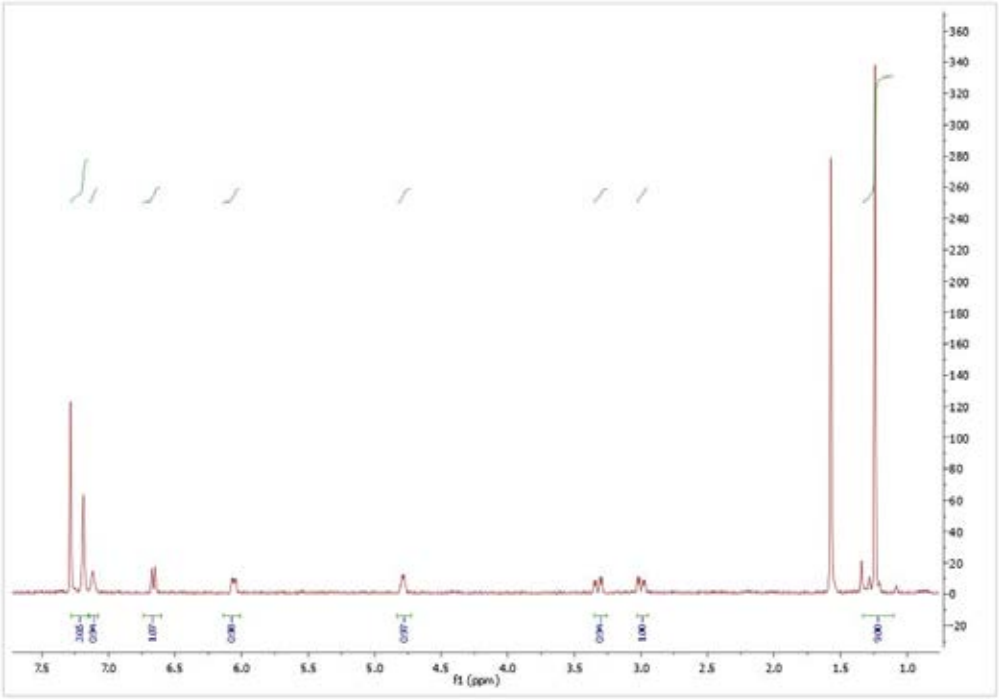


Figure 3.22 The ^{1}H-NMR spectrum of compound **B**

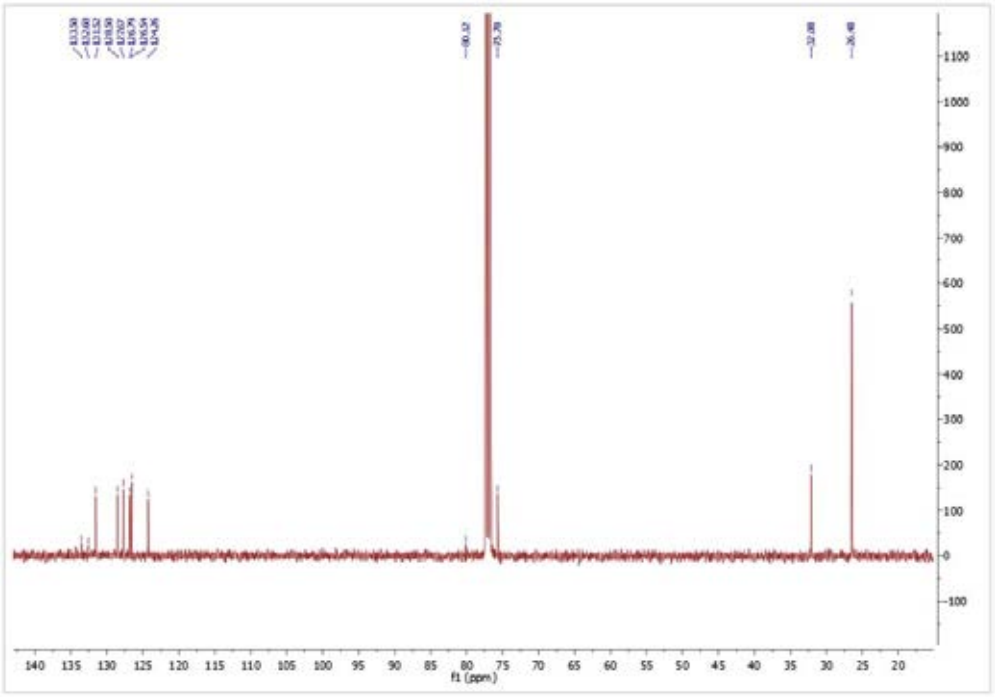


Figure 3.23 The ^{13}C-NMR spectrum of compound **B**

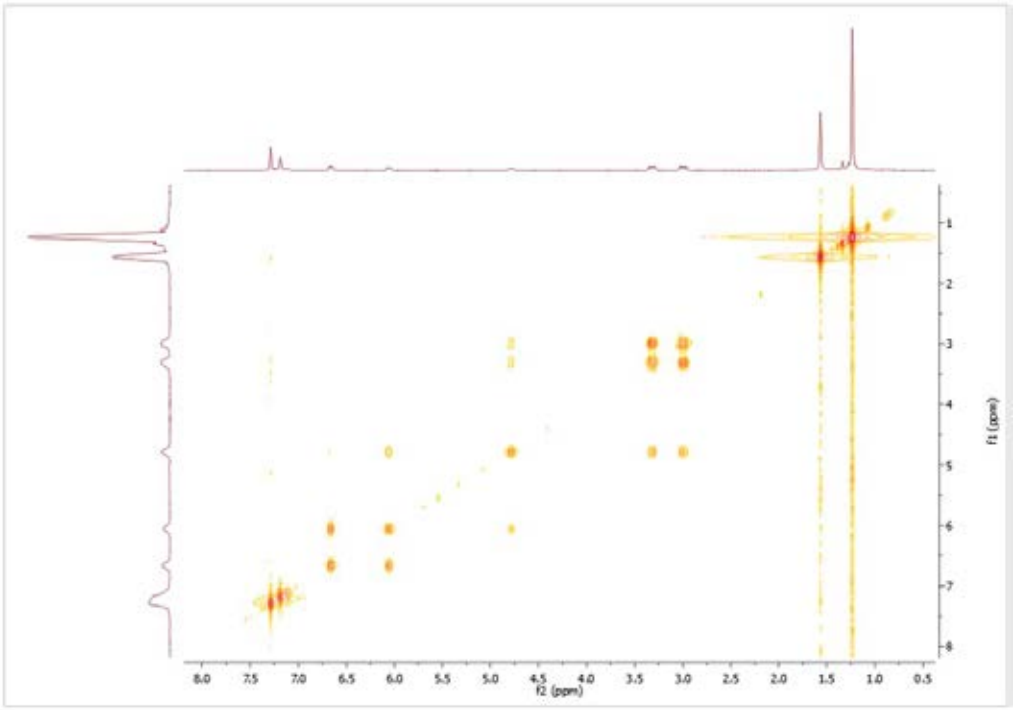


Figure 3.24 The COSY spectrum of compound **B**

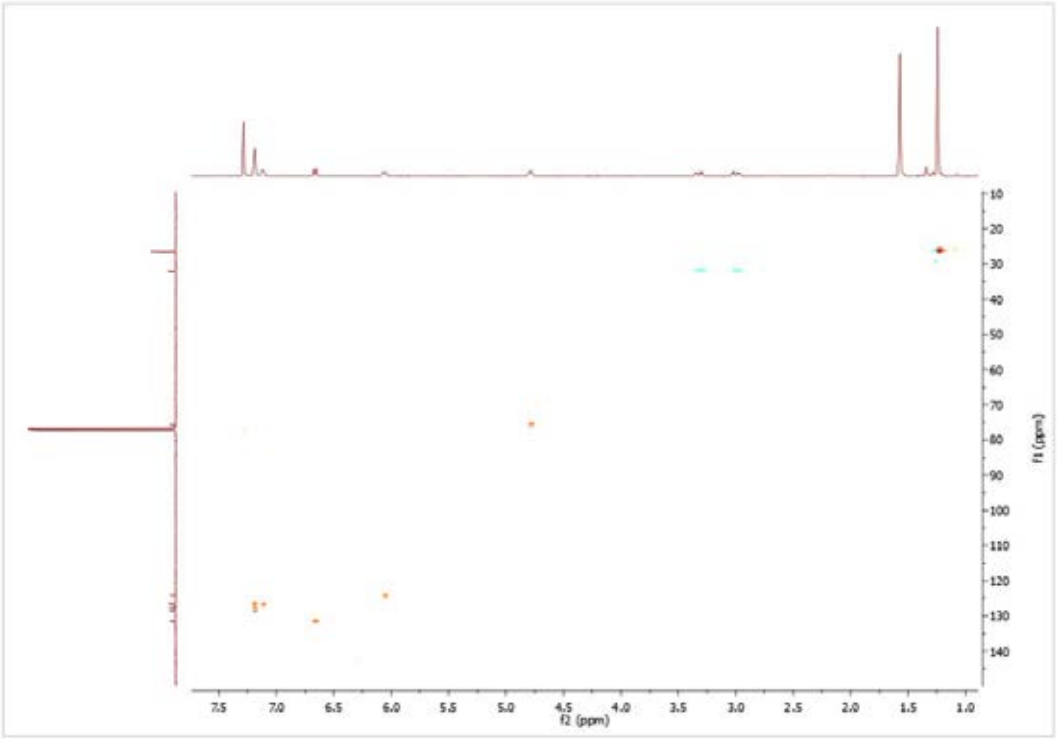


Figure 3.25 The HMBC spectrum of compound **B**

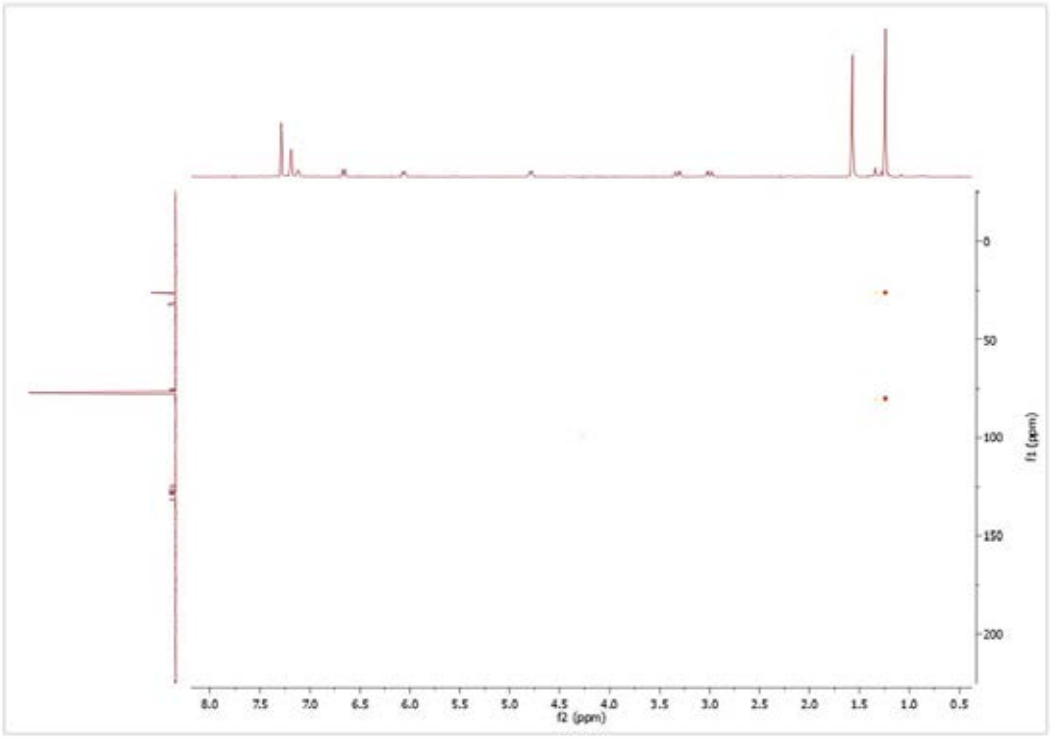


Figure 3.26 The HSQC spectrum of compound **B**

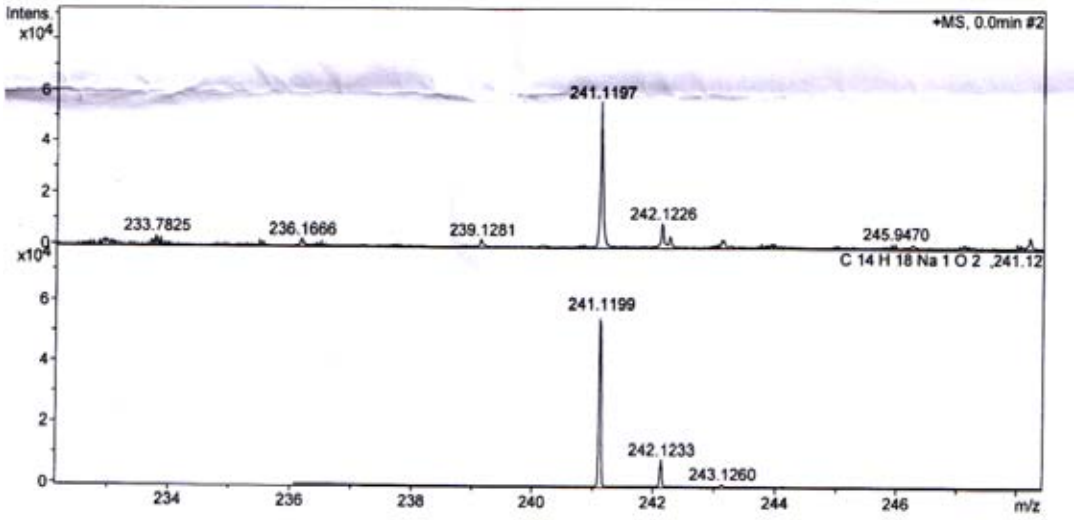
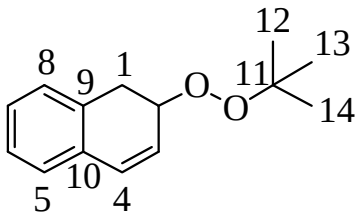


Figure 3.27 The mass spectrum of compound **B**

Referring to the mass spectrum of compound **B** in Figure 3.27, $C_{14}H_{18}O_2Na$ with molecular weight 241.12 g/mol was detected by high resolution mass spectrometry; in addition, a proposed compound $C_{14}H_{18}O_2$ with molecular weight 218.10 g/mol was isolated by preparative chromatography and characterized by spectroscopic method, resulting in Figures 3.22-3.26. The possible structure of compound **B** is shown below. The position of *tert*-butylperoxyl group was confirmed by COSY spectrum in Figure 3.24.



Like other conjugated dienes such as 9,10-dihydrophenanthrene, high temperature condition was required. However, increasing temperature did not give high yield of naphthalene due to low sublimating point of naphthalene that made naphthalene converted to gas phase and went out from the reactor. This problem was considered by adjusting some factors such as increasing reaction time at RT, increasing ratio of TBHP and $CuCl_2$ to substrate, addition TBHP 2 times to prevent the decomposition of TBHP. As a result, these solutions did not increase the reaction productivity as well may due to low reactivity of Cu/TBHP catalytic system to 1,2-dihydronaphthalene. This point must be considered in the future work to improve the reaction efficiency by utilize more active oxidative species or metal.

Table 3.9 The NMR data of compound **B**

Position	compound B			
	δ_C	**δ_H**	**HMBC**	**COSY**
1	32.1	3.00 (1H, *dd*, 16.4,6.0 Hz) 3.32 (1H, *dd*, 16.4,5.6 Hz)	C-2,C-3,C-9	H-2
2	75.7	4.78 (1H, *br*)	C-3,C-9	H-1,H-3
3	124.3	6.06 (1H, *dd* , 9.6,4.4 Hz)	C-10	H-2,H-4
4	131.5	6.66 (1H, *d*, 9.6 Hz)	C-2,C-5,C-9	H-3
5	126.8	7.12 (1H, *d*, 2.8 Hz)	C-6	H-6
6	127.7	7.19 (1H, *m*)	C-8	H-5,H-7
7	128.5	7.19 (1H, *m*)	C-5	H-6,H-8
8	126.5	7.19 (1H, *m*)	C-6	H-7
9	133.5	-	C-2,C-4	-
10	132.6	-	C-3	-
11	80.1	-	-	-
12	26.5	1.26 (3H, *s*)	C-13,C-14	H-13,H-14
13	26.5	1.26 (3H, *s*)	C-12,C-14	H-12,H-14
14	26.5	1.26 (3H, *s*)	C-12,C-13	H-12-H-13

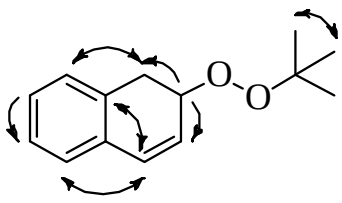


Figure 3.28 HMBC (↔) and COSY (→) correlation of compound **B**

3.6 The reaction of acenaphthene with Cu(II)-TBHP

Acenaphthene is a three-fused ring compound with two aromatic rings. Acenaphthylene, expected dehydrogenated product, has only 12 π-electrons which mean that aromaticity is not an important driving force, but the π-conjugated system of the molecule was also a good potent. The endeavor to convert acenaphthene to acenaphthylene was followed the general procedure of conjugated dienes (Figure 3.29), unfortunately acenaphthylene was not observed.

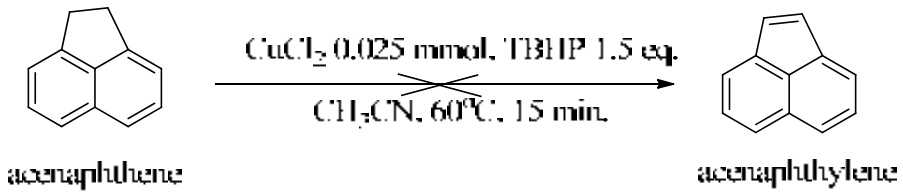


Figure 3.29 Synthetic plan to convert acenaphthene to acenaphthylene

After 10 min at 60°C, pale yellow solid (45% yield) appeared in the reaction mixture which was then filtered and identified by NMR. Supported by the ^{1}H-NMR spectrum (Figure 3.30), the pale yellow solid was in fact 1,2-acenaphthenedione.

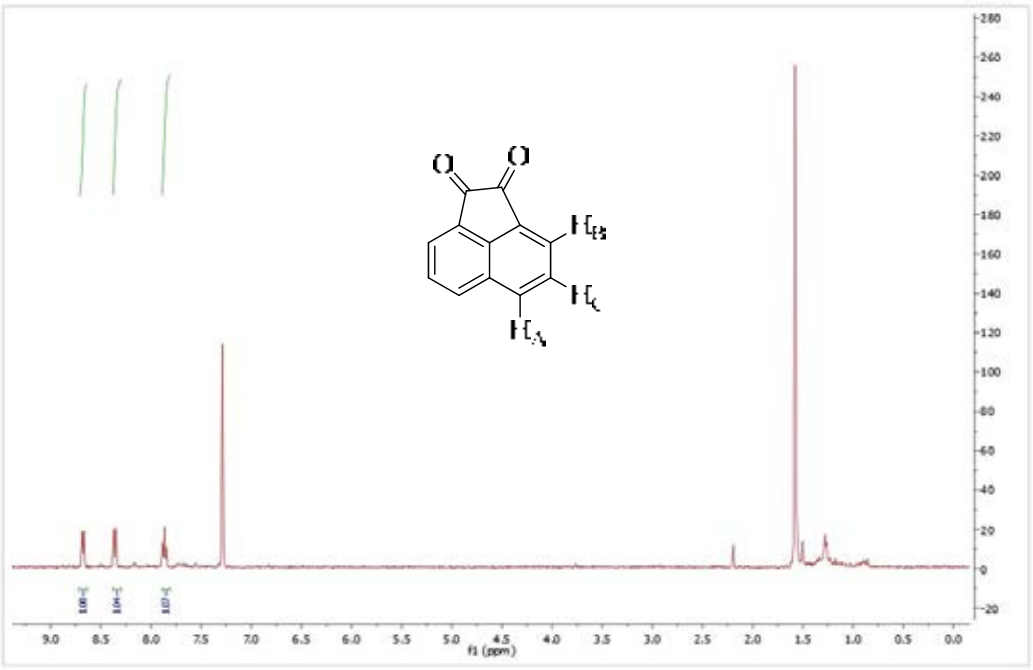


Figure 3.30 The ^{1}H-NMR spectrum of 1,2-acenaphthenedione

The peak at δ 8.67 ppm could be analyzed for a proton signal of H_A (*d*, 2H, *J* = 7.6 Hz). H_B showed its signal at δ 8.36 ppm (*d*, 2H, *J* = 8.8 Hz). A proton signal at δ 7.86 ppm was a signal of H_C (*t*, 2H, *J* = 7.6 Hz).

The filtrate was further analyzed by TLC using 2:3 of CH_2Cl_2:*n*-hexane as a mobile phase. Five spots were observed and isolated by preparative chromatography and characterized by NMR. As a result, 1,2-acenaphthenedione was found as a major product (~50% yield) together with 1-acenaphthenone (~20% yield). Their structures were confirmed by comparing ^{1}H-NMR spectra with previous literatures [48]. The ^{1}H-NMR spectrum of 1-acenaphthenone is shown in Figure 3.31.

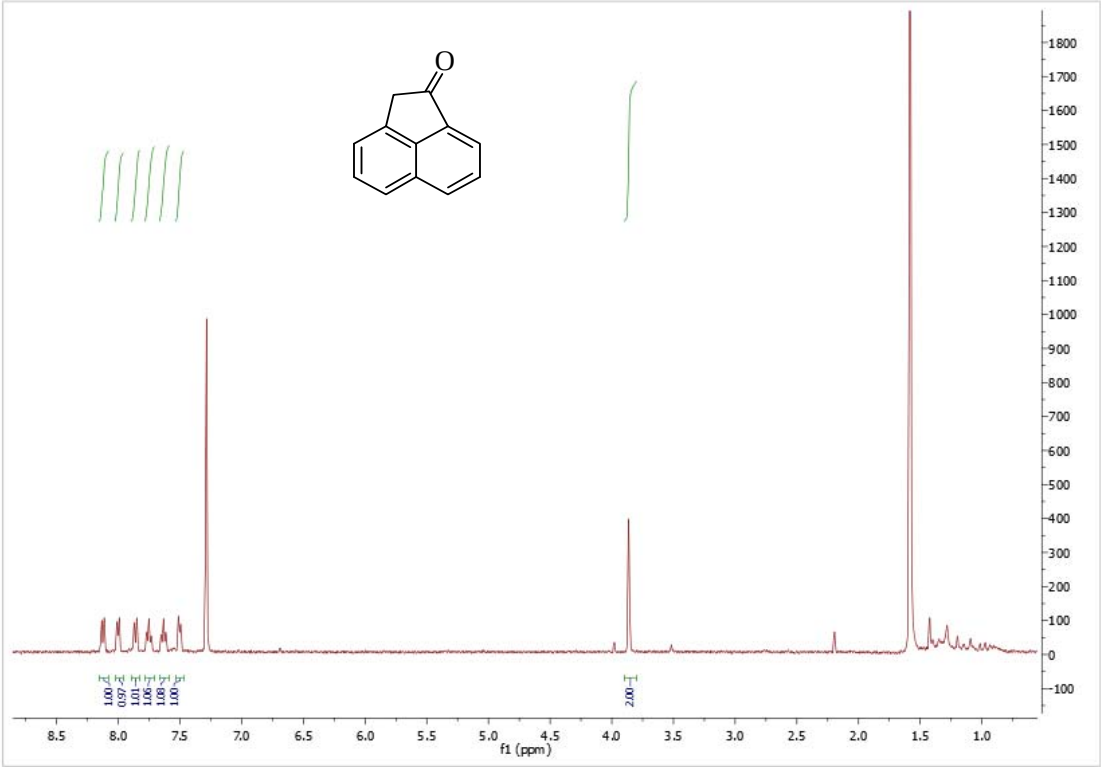


Figure 3.31 The ^{1}H-NMR spectrum of 1-acenaphthenone

Moreover, 1-*tert*-butylperoxylacenaphthene was isolated in 2% yield. Its structure was characterized by NMR spectroscopic technique. 1-*tert*-Butylperoxylacenaphthene decomposed easily, so the isolation and characterization steps needed to perform quickly. The NMR spectroscopic data (Figures 3.33-3.37) and mass spectrum (Figure 3.32) of 1-*tert*-butylperoxylacenaphthene are shown below.

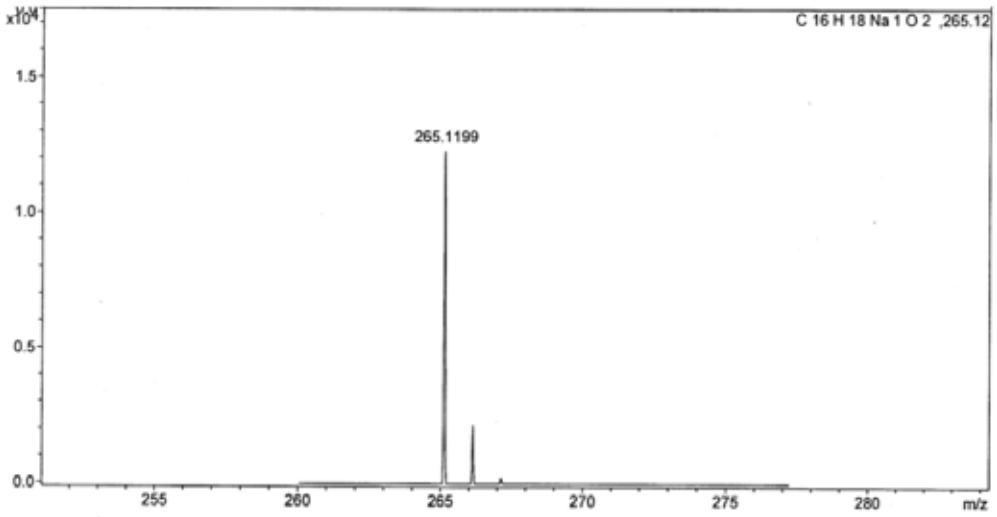


Figure 3.32 The mass spectrum of 1-*tert*-butylperoxylacenaphthene

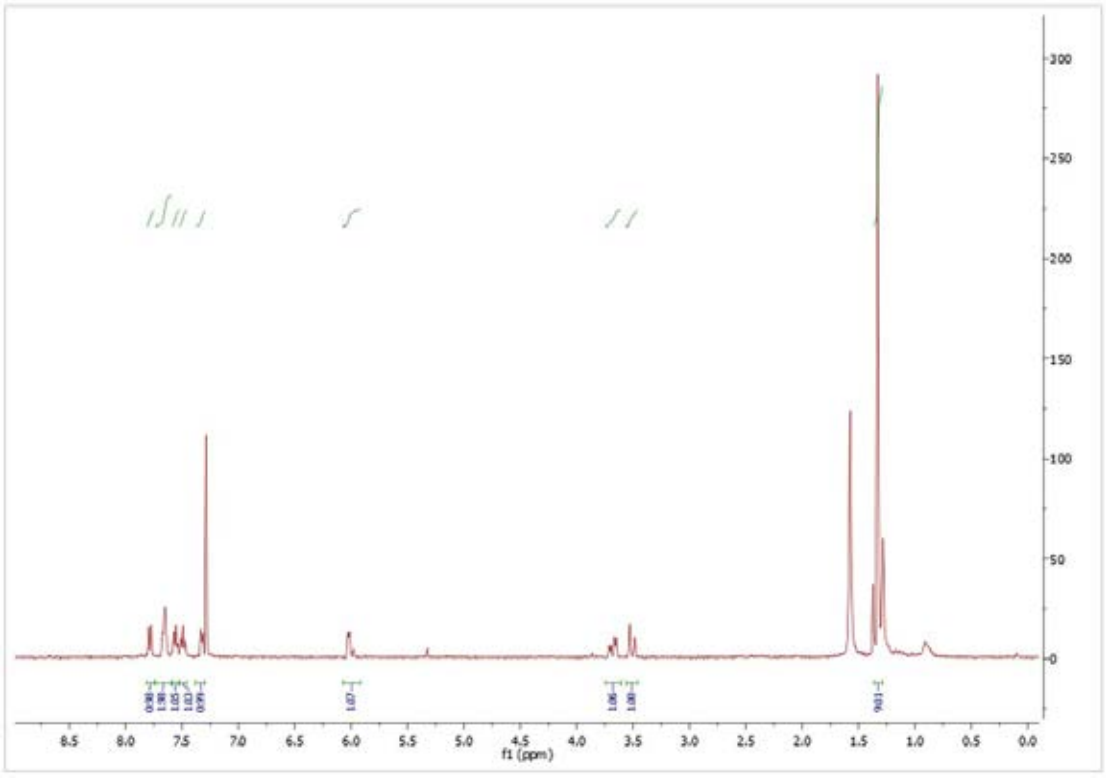


Figure 3.33 The ^{1}H-NMR spectrum of 1-*tert*-butylperoxylacenaphthene

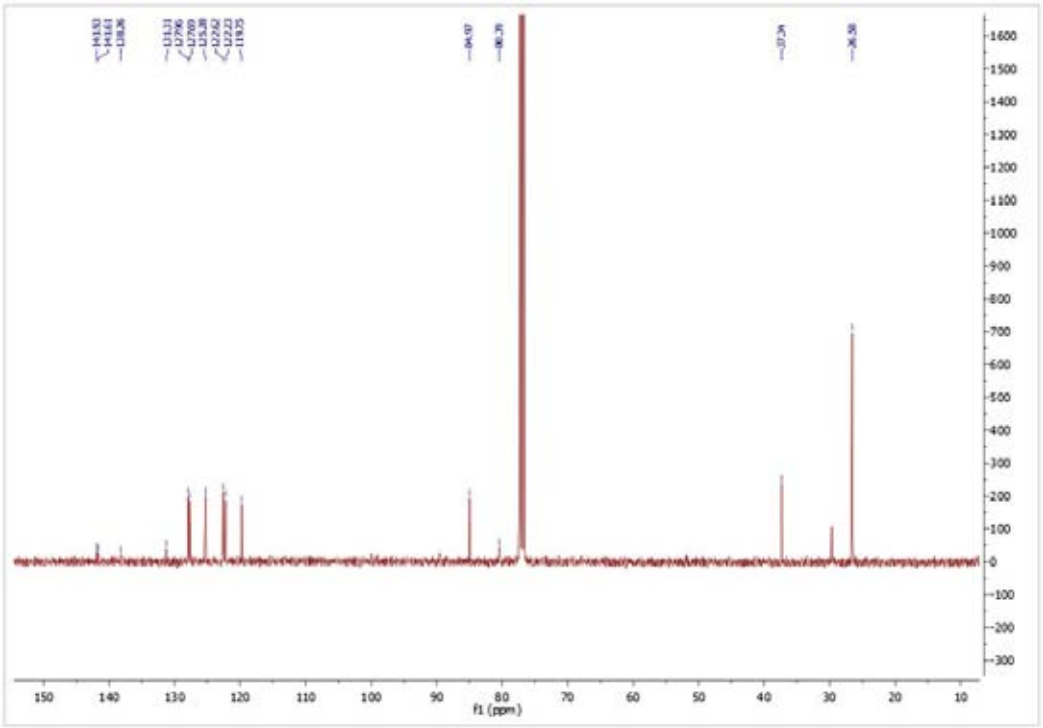


Figure 3.34 The ^{13}C-NMR spectrum of 1-*tert*-butylperoxylacenaphthene

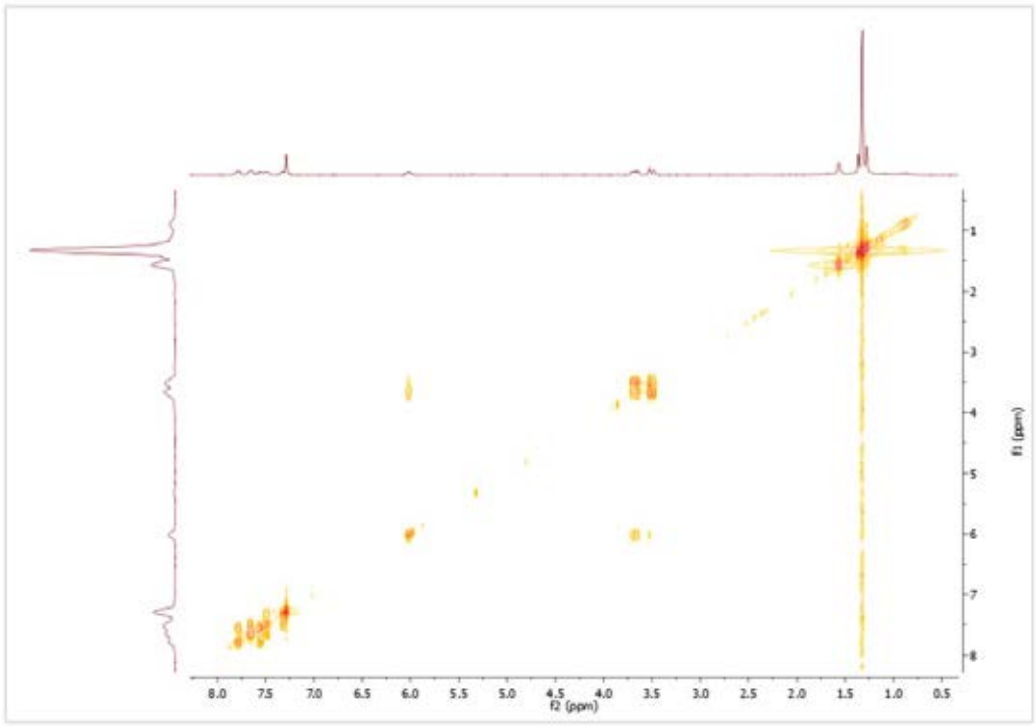


Figure 3.35 The COSY spectrum of 1-*tert*-butylperoxylacenaphthene

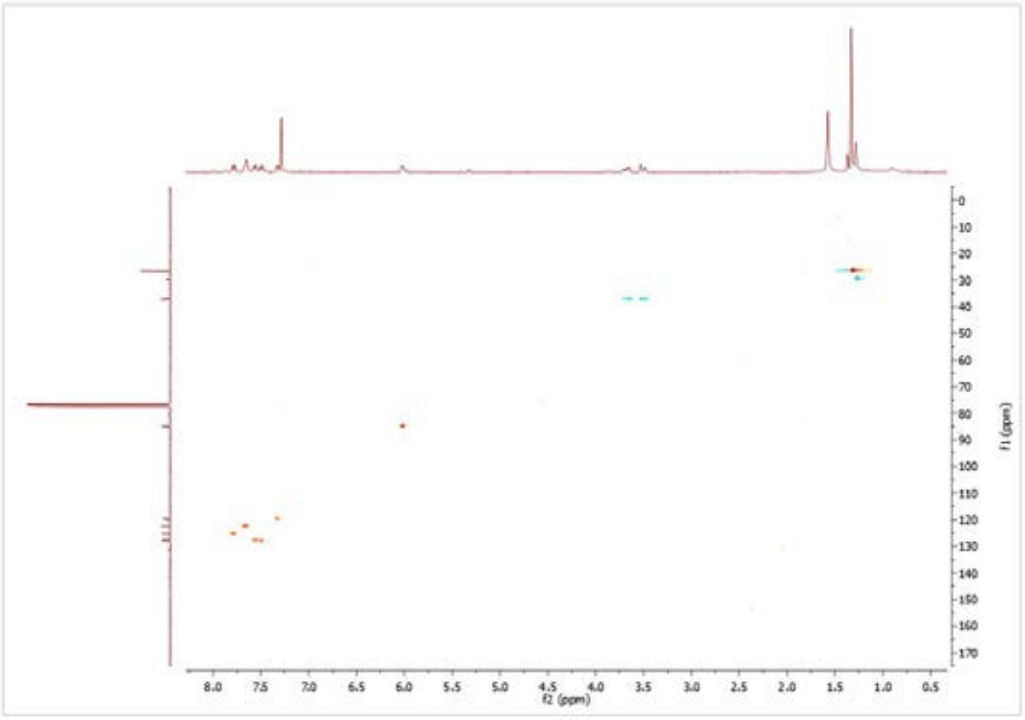


Figure 3.36 The HSQC spectrum of 1-*tert*-butylperoxylacenaphthene

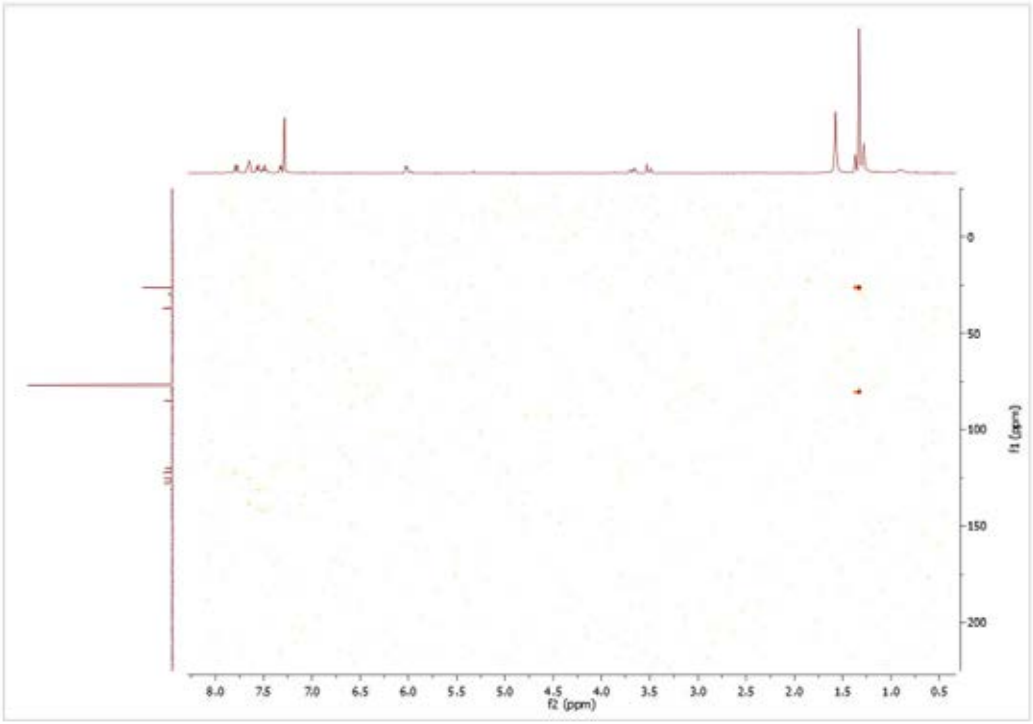


Figure 3.37 The HMBC spectrum of 1-*tert*-butylperoxylacenaphthene

From spectroscopic data, ^{1}H-NMR showed signals of asymmetric protons on aromatic ring compared to starting material, acenaphthene which had a plane of symmetry of molecule. Compared with ^{1}H-NMR of compounds **A** and **B**, there are three proton signals at δ_H 5.0, 3.4 and 3.1 ppm with similar splitting patterns. The mass spectrum was used to confirm that there were two oxygen atoms in the molecule. Three protons on -CH_2CH_2- bridged are identified by other spectroscopic data such as COSY, HSQC and HMBC.

Table 3.10 The NMR data of 1-*tert*-butylperoxylacenaphthene

Position	**1-*tert*-butylperoxylacenaphthene**			
	δ_C	**δ_H**	**HMBC**	**COSY**
1	85.0	6.01 (1H, *t*, 7.2 Hz)	C-8,C-11	H-2
2	37.3	3.51 (1H, *dd*, 16.8,0.4 Hz) 3.68 (1H, *dd*, 16.8,7.2 Hz)	C-3	H-1
3	125.3	7.78 (1H, *d* , 8.8 Hz)	C-5,C-10	H-4
4	127.7	7.56 (1H, *t*, 6.8 Hz)	C-11,C-12	H-3,H-5
5	122.2	7.65 (1H, *d*, 8.0 Hz)	C-3,C-10	H-4
6	119.8	7.32 (1H, *d*, 7.2 Hz)	C-5,C-8,C-10	H-7
7	128.0	7.49 (1H, *t*, 6.8 Hz)	C-9,C-12	H-6,H-8
8	122.6	7.65 (1H, *d*, 7.8 Hz)	C-1,C-6,C-10	H-7
9	141.9	-	C-7	-
10	138.3	-	C-3,C-5,C-6,C-8	-
11	141.6	-	C-4	-
12	131.3	-	C-4,C-7	-
13	80.4	-	-	-
14	26.6	1.31 (3H, *s*)	C-15,C-16	H-15-H-16
15	26.6	1.31 (3H, *s*)	C-14,C-16	H-14,H-16
16	26.6	1.31 (3H, *s*)	C-14,C-15	H-14,H-15

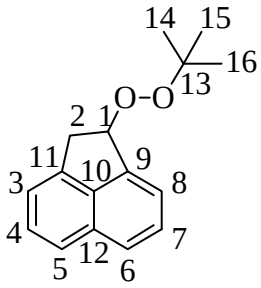


Figure 3.38 Structure of 1-*tert*-butylperoxylacenaphthene (compound **C**)

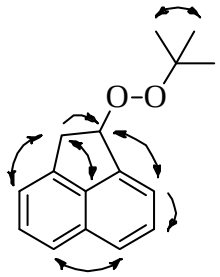


Figure 3.39 HMBC (↔) and COSY (→) correlation of compound **C**

There was another substance detected on TLC plate in trace amount which isolated by preparative chromatography and identified by NMR spectroscopy. As a result, it decomposed easily to be other molecules, appearance of many tiny proton signals on ^{1}H-NMR which interpreted to show the expected compound **D**. The ^{1}H-NMR spectrum of compound **D** is shown in Figure 3.41.

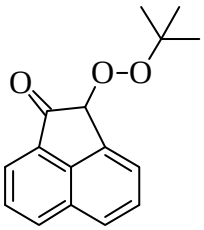


Figure 3.40 Proposed structure of compound **D**

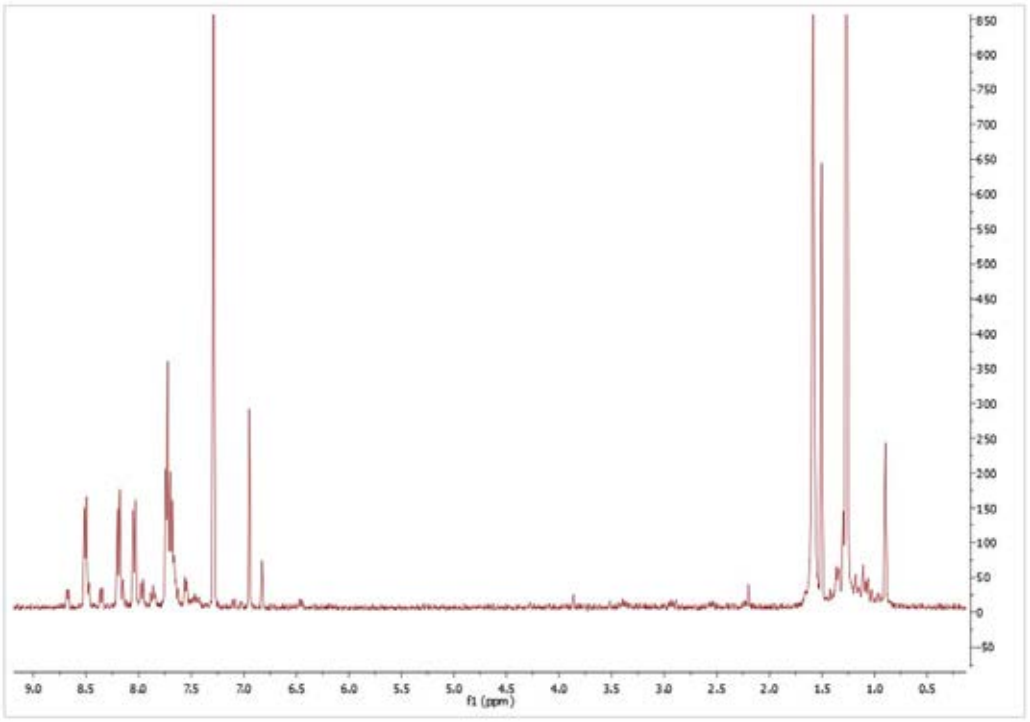


Figure 3.41 The ^{1}H-NMR spectrum of compound **D**

Cu-TBHP is therefore not suitable to convert acenaphthene to acenaphthylene or dehydrogenate to achieve their corresponding dehydrogenated substances.

3.7 Aromatization of indoline

After adding $CuCl_2$ catalyst to the solution of indoline in CH_3CN, the solution was changed from a pale yellow-brown solution to a dark brown-black solution. Moreover, the addition of TBHP made the solution stickier and a lot of heat was produced. This implied that indoline was very reactive with peroxide reagent and the reaction is exothermic; therefore, indoline should be deactivated by protecting an amino group before the aromatization step.

3.7.1 Protection of indoline with benzyl group

Sodium hydroxide was used to deprotonate the proton of secondary amine to increase nucleophilicity of indoline. The reaction was stirred at RT for 48 h and 1-

benzylindoline was isolated by silica gel column yielding 80% of product. The ^{1}H-NMR spectrum is shown in Figure 3.42.

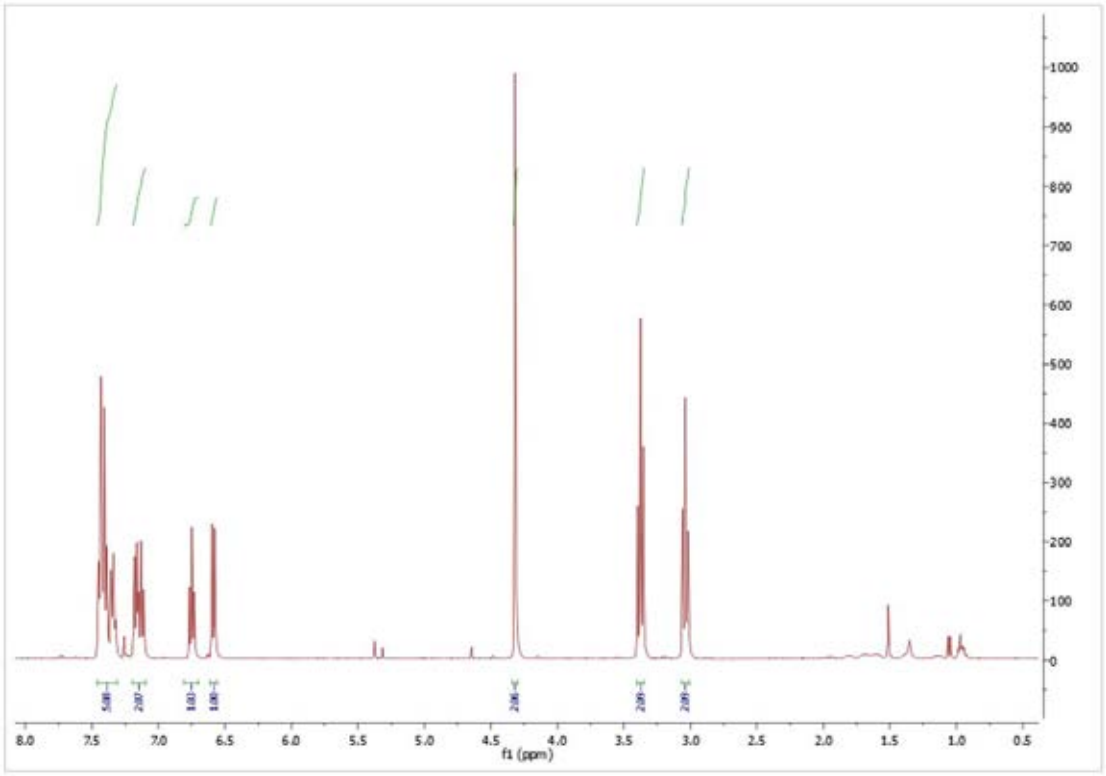


Figure 3.42 The ^{1}H-NMR spectrum of 1-benzylindoline

3.7.2 Aromatization of 1-benzylindoline

1-Benzylindoline was aromatized using $CuCl_2$-TBHP catalytic system to achieve related aromatized product, 1-benzylindole. Nonetheless, the reaction still changed to dark brown-black color and produced heat but not much as using indole as a starting material.

1-Benzylindole, was isolated in 50% yield, R_f~0.65, by column chromatograph using 3:7 of CH_2Cl_2:*n*-hexane as a mobile phase, 20-30% of product coupled with $CuCl_2$ to form complexes which stacked on the surface of silica gel.

To increase productivity of 1-benzylindole, some parameters that can affect on the reaction efficiency such as reaction time, catalyst amount and equivalent of TBHP

and handled reaction under air or N_2 gas were scrutinized. As a result, increasing the catalyst amount from 0.025 mmol to 0.05 mmol enlarged amount of Cu complex; on the other hands, adjustment of other factors did not affect on the reaction efficiency. The ^{1}H-NMR spectrum of 1-benzylindole is shown in Figure 3.43.

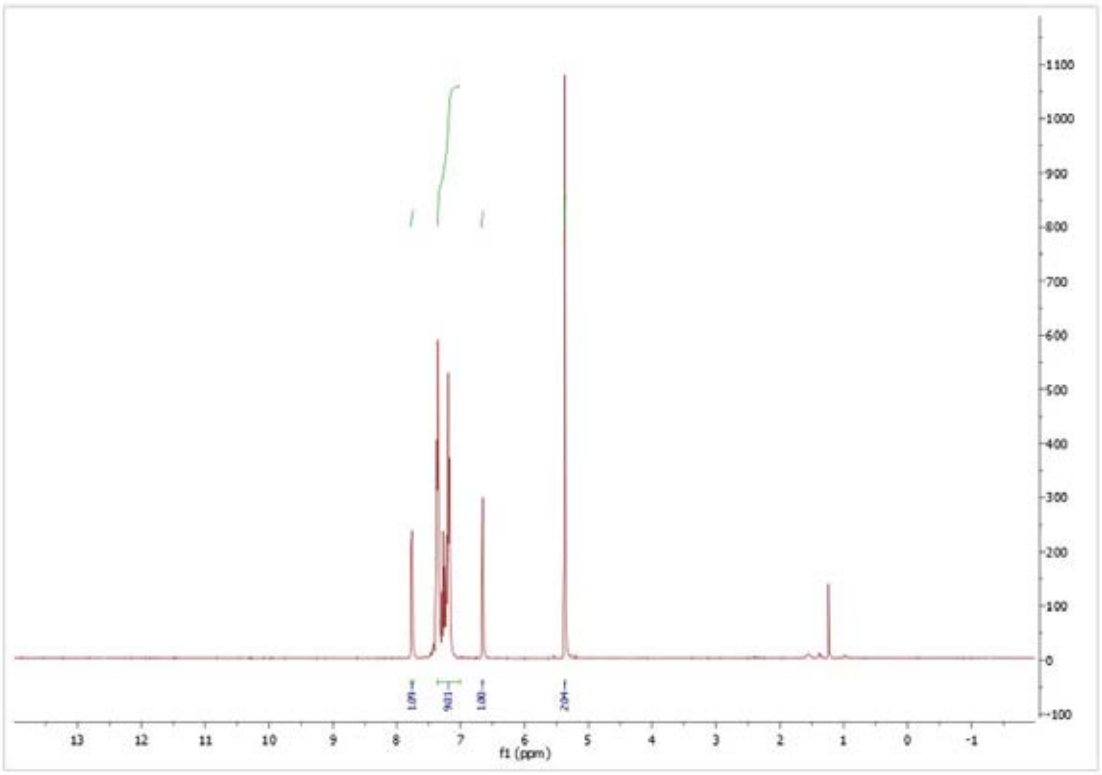


Figure 3.43 The ^{1}H-NMR spectrum of 1-benzylindole

3.7.3 Deprotection of benzyl group

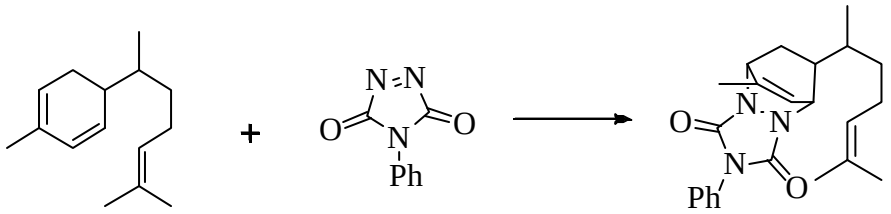
The last step to aromatize indoline to indole is a deprotection of benzyl group using Pd/C under atmospheric H_2. After stirred under H_2 for 48 h, Pd/C was filtered through celite. The filtrate was concentrated by rotary evaporator and crude of product mixture was isolated by column chromatograph using 2:3 of CH_2Cl_2:*n*-hexane as a mobile phase resulting three compounds were obtained, 10% of 1-benzylindole (starting material), 15% of indole and 16% of indoline.

Pd/C-H_2 was used as a deprotecting agent to deprotect benzyl group of 1-benzylindole; however, but Pd/C-H_2 also acted as a hydrogenating agent which added H_2 into indole to indoline. Thus, other suitable reagents for deprotecting step should be investigated.

3.8 Aromatization of zingiberene

3.8.1 Isolation of zingiberene from ginger oil

The isolation of zingiberene was carried out following the previous literature [37]. The Kugelrohr distillation of ginger oil was carried out and the distilled fraction at <100^{o}C was mainly monoterpenoid fraction. Moreover, sesquiterpenoid fraction (49.46%yield) consisted of zingiberene was distilled at oven temperature 100-200^{o}C. The obtained zingiberene was further trapped by 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to form Diels-Alder adduct (Figure 3.44).



Zingiberene PTAD Adduct

Figure 3.44 The adduct of zingiberene formation

The adduct of zingiberene was isolated by flash column chromatograph using 15%acetone in *n*-hexane as a mobile phase to achieve 43.3% yield of adduct based on sesquiterpeneoid fraction. PTAD was removed by reflux under N_2 in basic solution; furthermore, zingiberene was extracted and purified by short column, eluted with *n*-hexane, to eliminate aniline which left from PTAD in the deprotection step. The isolated zingiberene was characterized by ^{1}H-NMR and compared with the literature data [45]. The ^{1}H and ^{13}C-NMR spectra of zingiberene are shown in Figures 3.45-3.46.

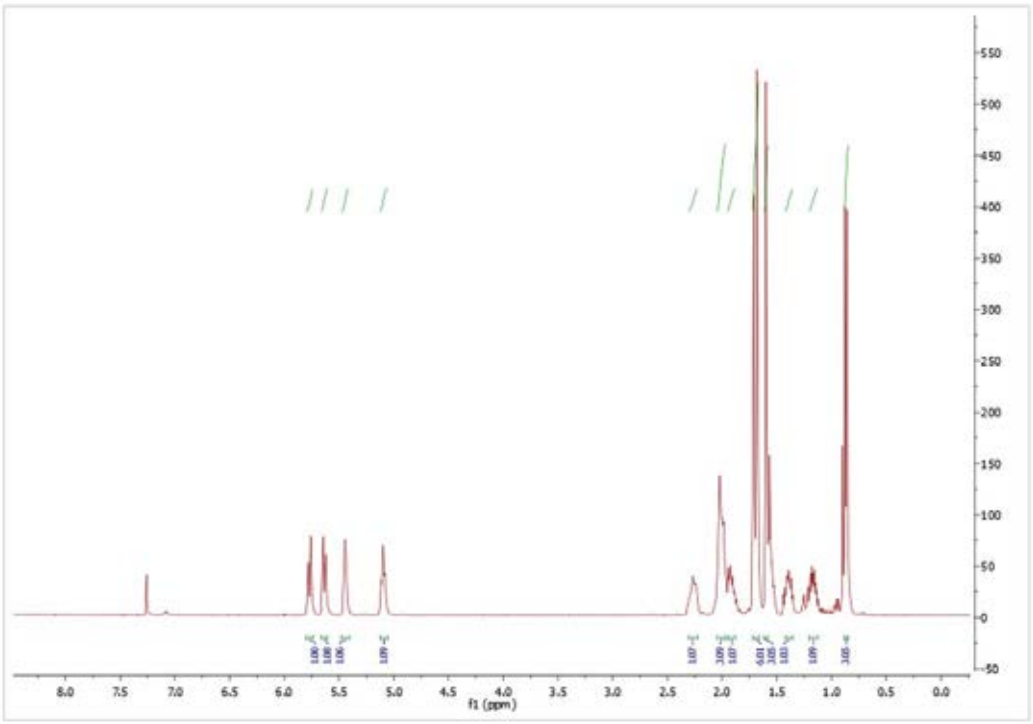


Figure 3.45 The ^{1}H-NMR spectrum of zingiberene

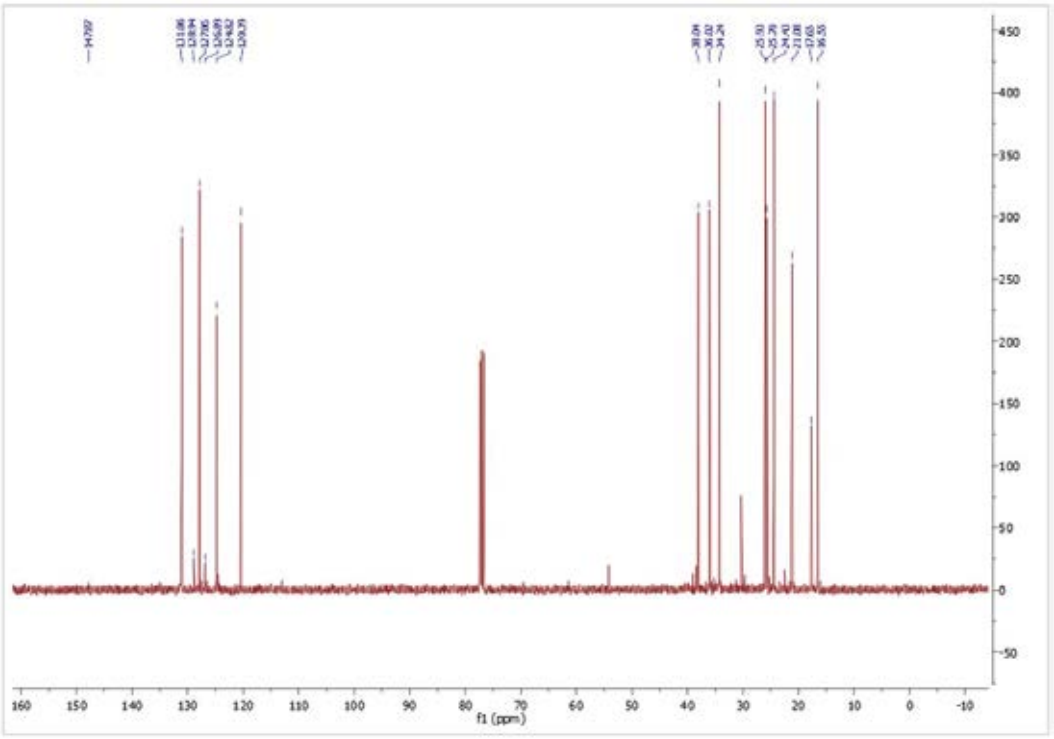


Figure 3.46 The ^{13}C-NMR spectrum of zingiberene

3.8.2 Aromatization of zingiberene

The aromatization of zingiberene was performed utilizing the typical procedure for aromatization of conjugated diene. After 30 min, the reaction was extracted with CH_3CN, concentrated and characterized by ^{1}H-NMR (Figure 3.47).

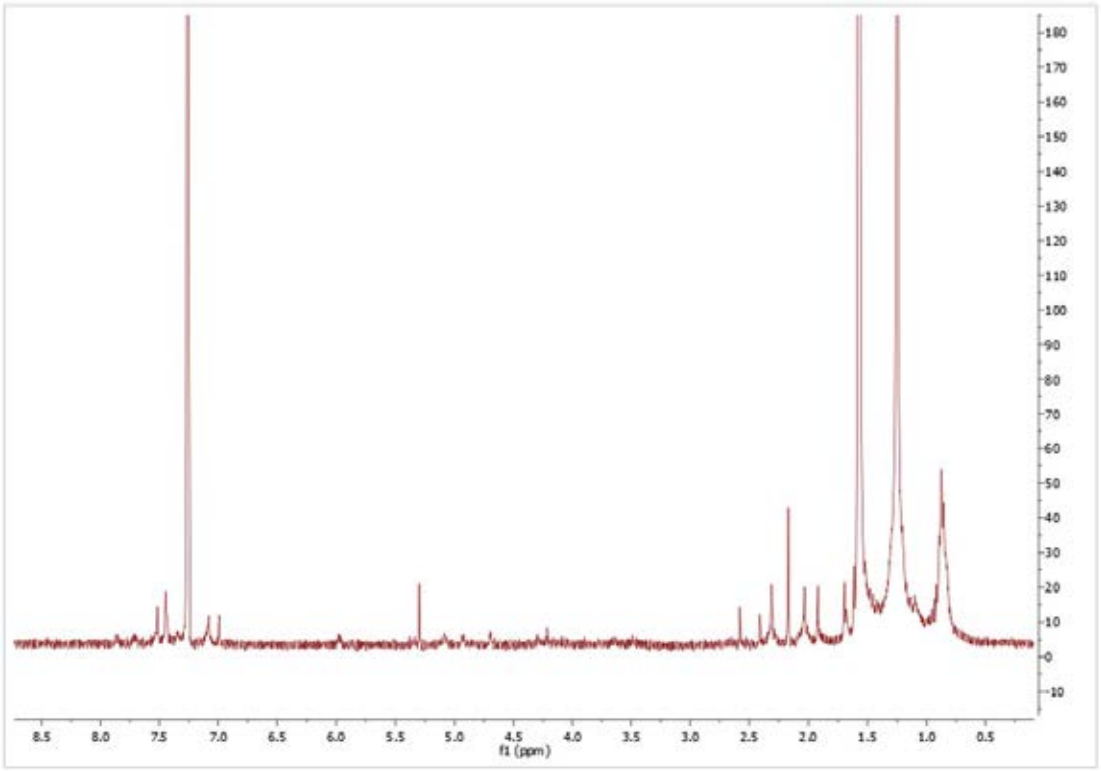


Figure 3.47 The ^{1}H-NMR of curcumene

Referring to Figure 3.47, there are four proton signals at δ 7.21-7.54 ppm (*s*, 4H). The peak at δ 5.27 ppm (*t*, 1H, *J* = 6.4 Hz) which is a signal of H on double bond. There is a peak at δ 2.58 ppm (*m*, 1H) that is assigned for -C<u>H</u>- at benzylic position. The peak at δ 2.41 ppm (*s*, 3H) is a signal of -C<u>H</u>$_3$ substituent on aromatic ring. A proton signal at δ 2.17 ppm (*d*, 3H, *J* = 3.0 Hz) is a peak of -C<u>H</u>$_3$. There is a peak at δ 2.03 ppm (*m*, 2H) which is assigned for -C<u>H</u>$_2$CH$_2$-. The peak at δ 1.92 ppm (*m*, 2H) is a signal of -C<u>H</u>$_2$CH$_2$- and the peak at δ 1.65 ppm (*s*, 6H) is a signal of protons of two symmetrical -C<u>H</u>$_3$ groups. Thus, this reaction completely converted zingiberene to its related aromatized product, curcumene (~82% yield).

CHAPTER IV

CONCLUSION

A new catalytic Cu-TBHP system using for aromatization of conjugated and skipped dienes has been developed. Many parameters were chosen to define the most suitable condition to aromatize conjugated and skipped dienes, using γ-terpinene and α-terpinene as starting materials. As a result, 0.25% mol of $CuCl_2$ in CH_3CN was selected to be a catalyst with superb profile. In addition, aromatization of skipped dienes can be completed in 5 min at RT. On the other side, conjugated dienes must be held at 60^oC for 15 min to achieve their related aromatized products due to C-H bond energy of conjugated dienes is higher than skipped dienes.

The optimized conditions of Cu-TBHP catalytic system also applied to other cyclic dienes including 9,10-dihydroanthracene, 9,10-dihydrophenanthrene, indoline, 1,2-dihydronaphthalene and zingiberene, natural compound which isolated from ginger oil. As a result, Cu-TBHP also showed great reactivity in aromatization step.

The mechanism study proved that Cu-TBHP catalytic system occurred *via* radical mechanism by adding TEMPO, a radical scavenger to trap *tert*-butoxyl and/or *tert*-butylperoxyl radicals. Three new compounds, compounds **A**, **B** and 1-*tert*-butylperoxylacenaphthene could be isolated as evidences of this investigation.

Propose for the future work

Cu-TBHP catalytic system will be developed to increase productivity of conjugated diene and to aromatize cycloalkenes to their corresponding aromatized products.

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