ปฏิกิริยาคอปเปอร์ฟรีโซโนกาชิราคัปปลิงที่ใช้แพลเลเดียมรองรับบนอนุภาคเปลือกหอยเพื่อเป็นตัวเร่งปฏิกิริยาวิวิธพันธุ์ที่ใช้ซ้ำได้

นายตฤณ แซ่ตั้น

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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COPPER-FREE SONOGASHIRA COUPLING REACTIONS USING PALLADIUM SUPPORTED ON SHELL PARTICLES AS REUSABLE HETEROGENEOUS CATALYST

Mr. Trin Saetan

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Chemistry
Department of Chemistry
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Thesis Title	COPPER-FREE SONOGASHIRA COUPLING REACTIONS USING PALLADIUM SUPPORTED ON SHELL PARTICLES AS REUSABLE HETEROGENEOUS CATALYST
By	Mr. Trin Saetan
Field of Study	Chemistry
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ตฤณ แซ่ตั้น : ปฏิกิริยาคอปเปอร์ฟรีโซโนกาชิราคัปปลิงที่ใช้แพลเลเดียมรองรับบนอนุภาคเปลือกหอยเพื่อเป็นตัวเร่งปฏิกิริยาวิวิธพันธุ์ที่ใช้ซ้ำได้ (COPPER-FREE SONOGASHIRA COUPLING REACTIONS USING PALLADIUM SUPPORTED ON SHELL PARTICLES AS REUSABLE HETEROGENEOUS CATALYST) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร. สัมฤทธิ์ วัชรสินธุ์, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ศ. ดร.มงคล สุขวัฒนาสินิทธิ์, 84 หน้า.

เราได้ค้นพบตัวเร่งปฏิกิริยาแพลเลเดียมชนิดใหม่ที่ถูกตรึงบนแผ่นแคลเซียมคาร์บอเนตชนิดเดี่ยว (Pd/ICCP) ที่ได้รับจากเปลือกหอยแมลงภู่ (*Perna viridis*) เพื่อใช้สำหรับปฏิกิริยาคอปเปอร์ฟรีโซโนกาชิราคัปปลิง แผ่นแคลเซียมคาร์บอเนตชนิดเดี่ยวนี้ (ICCP) ได้เตรียมขึ้นมาจากการใช้ไฮโดรเจนเปอร์ออกไซด์ควบคู่กับการสั่นด้วยเสียงอัลตร้าโซนิค การแช่แผ่นแคลเซียมคาร์บอเนตชนิดเดี่ยวด้วยสารละลายแพลเลเดียม (0) สามารถเตรียมแพลเลเดียมนาโนพาร์ติเคิลตรึงอยู่บนแผ่นแคลเซียมคาร์บอเนตชนิดเดี่ยว เราได้พิสูจน์ทราบอสัญฐานของตัวเร่งปฏิกิริยา Pd/ICCP อย่างครบถ้วนโดยเทคนิค SEM, TEM, EDX, XRD, ICP-OES, TGA และ IR ซึ่งแสดงให้เห็นว่าแผ่นซับพอร์ท ICCP นี้มีลักษณะเป็นระเบียบขนาด 3 ไมโครเมตร และแพลเลเดียมนาโนพาร์ติเคิลกระจายทั่วบนแผ่นของ ICCP ยิ่งไปกว่านั้นเราพบว่ามีปริมาณแพลเลเดียม 6.1% โดยน้ำหนักของตัวเร่งปฏิกิริยาซึ่งถูกระบุโดยเทคนิค ICP-OES และเราสามารถระบุปริมาณโปรตีนเท่ากับ 1.8% โดยใช้เทคนิค TGA สำหรับสมรรถภาพในการเร่งปฏิกิริยาของ Pd/ICCP นั้น เราได้ใช้ตัวเร่งปฏิกิริยานี้เพื่อการศึกษาหาสถาวะที่เหมาะสม โดยพบว่าการใช้ 1 โมลเปอร์เซ็นของ Pd/ICCP กับโพแทสเซียมคาร์บอเนตในตัวทำละลายเอทานอลสามารถเร่งปฏิกิริยาโซโนกาชิราคัปปลิงที่ไม่ใช้โลหะทองแดง ระหว่างเอริลไอโอไดด์ต่างๆ และเทอร์มินอลแอลคายน์ต่างๆ ที่อุณหภูมิ 77 องศาเซลเซียส โดยปราศจากลิแกนด์ภายนอก โดยสามารถเตรียมไดเอริลเอทายน์ได้ในปริมาณถึง 57-98 ร้อยละผลได้ เมื่อประเมินความสามารถในการเร่งปฏิกิริยาเคมี และใช้ซ้ำของ Pd/ICCP กับตัวเร่งปฏิกิริยาแพลเลเดียมบนอนุภาคเปลือกหอยธรรมดาและแพลเลเดียมบนแคลเซียมคาร์บอเนต (Pd/SP and Pd/$CaCO_3$) พบว่า Pd/ICCP แสดงความสามารถในการเร่งปฏิกิริยาเคมีใกล้เคียงกับ Pd/$CaCO_3$ แต่สูงกว่า Pd/SP มาก นอกจากนี้ Pd/ICCP แสดงความสามารถในการใช้ซ้ำดีกว่าตัวเร่งปฏิกิริยา Pd/SP และ Pd/$CaCO_3$ ความสามารถในการเร่งปฏิกิริยาเคมีและใช้ซ้ำที่ยอดเยี่ยมที่เกิดขึ้นน่าจะมาจากความเป็นระเบียบและการจับกันของแพลเลเดียมศูนย์กับโปรตีนบนพื้นผิวของตัวซับพอร์ท ICCP

ภาควิชา เคมี	ลายมือชื่อนิสิต .....
สาขาวิชา เคมี	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
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TRIN SAETAN: COPPER-FREE SONOGASHIRA COUPLING REACTIONS USING PALLADIUM SUPPORTED ON SHELL PARTICLES AS REUSABLE HETEROGENEOUS CATALYST. ADVISOR: ASST. PROF. SUMRIT WACHARASINDHU, Ph.D., CO-ADVISOR: PROF. MONGKOL SUKWATTANASINITT, Ph.D., 84 pp.

A novel palladium catalyst supported on individual calcium carbonate plates (Pd/ICCP) has been prepared from Asian green mussel (*Perna viridis*) shell for the copper-free Sonogashira coupling reaction. Treatment of virgin shell under sonication with hydrogen peroxide results in the formation of ICCP. Impregnation of ICCP with Pd(0) generates the a Pd nanoparticle embedded on ICCP. Morphology of the prepared Pd/ICCP catalyst has been fully characterized by SEM, TEM, EDX, XRD, ICP-OES, TGA and IR showing that the ICCP supported catalyst are uniform with 3 micron size and Pd nanoparticle is uniformly dispersed onto the surface of ICCP at 6.1% (wt./wt.). For catalytic performance, the optimized study reveals that the use of 1 mol% of Pd/ICCP in the present of potassium carbonate in ethanol can catalyze the copper-free Sonogashira coupling reaction between a variety of aryl iodides and terminal alkynes at 77 ^{0}C without using external ligand to provide the corresponding diarylethynes in 57-98 %yields. The catalytic activity and recyclability of the prepared Pd/ICCP along with the shell particle and calcium carbonate supported palladium (Pd/SP and Pd/$CaCO_3$) catalysts have been evaluated. Pd/ICCP demonstrates comparable catalytic activity with Pd/$CaCO_3$ but higher than Pd/SP. Importantly, Pd/ICCP exhibits better reusability than both Pd/SP and Pd/$CaCO_3$. The remarkable Pd/SP activity and stability has been attributed to the well uniform and the chelation of Pd (0) with the surface protein of the supported ICCP.

Department:	Chemistry	Student's Signature .....
Field of Study:	Chemistry	Advisor's Signature .....
Academic Year:	2015	Co-Advisor's Signature .....

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Ar	aromatic
^{13}C NMR	carbon-13 nuclear magnetic resonance
$CDCl_3$	deuterated chloroform
d	doublet (NMR)
dd	doublet of doublet (NMR)
DIPA	Diisopropylamine
EtOH	ethanol
equiv	equivalent (s)
FT-IR	fourier transform infrared spectroscopy
g	gram (s)
^{1}H NMR	proton nuclear magnetic resonance
Hz	Hertz
h	hour (s)
IR	*infrared*
ICCP	*individual calcium carbonate plate*
J	coupling constant
mg	milligram (s)
mL	milliliter (s)
mmol	millimole (s)
m/z	mass per charge
m	multiplet (NMR)
M.W.	molecular weight
M	molar

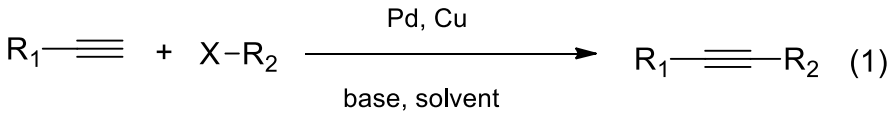
MHz	megahertz
Pd	palladium
s	singlet (NMR)
SP	shell particle
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
δ	chemical shift
°C	degree Celsius
% yield	percentage yield

CHAPTER I
INTRODUCTION

1.1 Introduction

Palladium-catalyzed reactions are a useful tool to synthesize organic compound, especially carbon-carbon bond formation. One of the powerful palladium-catalyzed reactions is Sonogashira coupling reaction. It is a cross coupling reaction between aryl halide and terminal alkyne in the presence of palladium catalyst (Scheme 1.1) [1]. It has been widely used for synthesizing many drugs, natural products and polymers [2]. In general, the reaction is catalyzed by homogeneous palladium catalyst which has high reactivity and specificity [3-6]. However, such catalyst is hardly be reused, so it causes a loss of precious metal catalyst and also increasing toxic metal waste [7]. To overcome this problem, there are many researchers trying to develop heterogeneous catalyst which can be reused for Sonogashira coupling reaction. Several of solid matrices have been employed to support palladium metal catalysts for Sonogashira reaction such as Pd on modified silica [8], Pd on zeolite [9] and Pd on carbon [10]. However, for the first two catalysts, it needs multi-step for preparation and requires toxic amine as base or solvent. In contrast, the Pd/C is cheap and easy to prepare but it suffers from pyrophoric behavior. Recently, calcium carbonate which is safe and has high abundant in nature was used to prepare palladium catalyst for Heck [11] and Stille coupling reaction [12]. More recently, Zeng and co-workers reported shell particles derived from natural abundant calcium carbonate for palladium supported catalyst in Heck [13] and homo coupling reactions [14]. Recently, Lertvachirapaiboon and co-workers reported the method to prepared calcium carbonate plate from Asian Green mussel shell [15]. It demonstrated highly stable structure composed of thin calcium carbonate plates which are suitable to use as support of catalyst. To the best of our knowledge, such calcium carbonate has not been applied as catalyst support in any reaction. In this research, we thus aim to develop palladium supported on individual

calcium carbonate derived from natural shell for Sonogashira coupling reaction (Scheme 1).

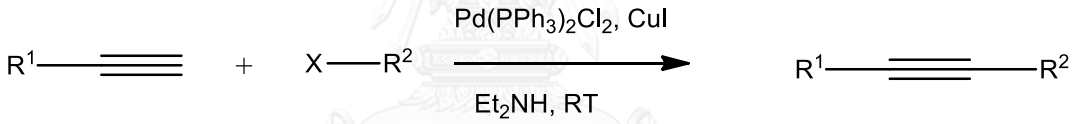


R1 = H, Aryl, alkyl
R2 = Aryl, Hetaryl, Vinyl

Scheme 1.1 General Sonogashira coupling reaction.

1.2 Introduction to Sonogashira coupling reaction

In 1975, Sonogashira and his coworker reported coupling reaction between aryl or vinyl halide with terminal alkyne at room temperature in the presence of $Pd(PPh)_3Cl_2$ and cuprous iodide, using diethylamine as base and solvent (Scheme 1.2) [1].



R^1 = H, Aryl, alkyl
R^2 = Aryl, Hetaryl, Vinyl
X = I, Br

Scheme 1.2 Sonogashira coupling reaction.

The exact mechanism of the Sonogashira coupling reaction is still not clearly understood, it is believed to occur through two independent catalytic cycles as illustrate in Figure 1.1 [2]. First, palladium-cycle (cycle A) start with the catalytically active species Pd^0L_2, which reacts with aryl halide in an oxidative addition step to form $[Pd(II)R^1L_2X]$ and this step are considered to be the rate-limiting step of the reaction. The intermediate reacts with copper acetylide from copper cycle (Cycle B) to produce $[Pd(II)L_2R^1(CCR^2)]$ in transmetallation step. Next, the the $[Pd(II)L_2R^1(CCR^2)]$ undergoes trans/cis isomerization and reductive elimination to produce the final product with regeneration of the active species catalyst. Second, copper-cycle (Cycle B) start with copper halide reacts with terminal alkyne to produce p-alkyne copper

complex. This complex would make alkyne terminal proton more acidic for deprotonation of base to form copper acetylide. The copper acetylide continues to react with the [Pd(II)R^1L_2X], with regeneration of the copper halide.

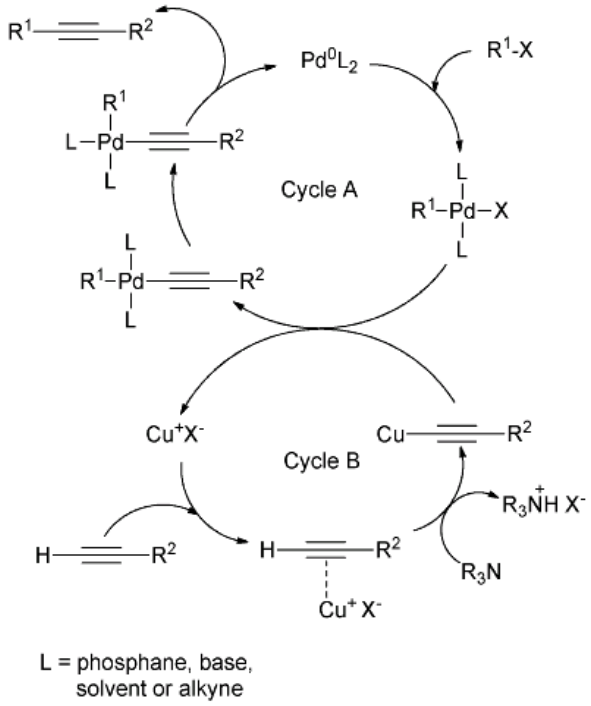
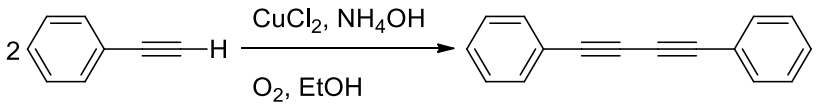


Figure 1.1 Sonogashira catalytic cycle.

However, although copper co-catalyst increase reactivity of the reaction but it can lead to homo coupling product from Glaser type oxidative dimerization reaction (Scheme 1.3) that cause decreased efficiency of the reaction and wasted terminal alkynes [15].



Scheme 1.3 Glaser type oxidative dimerization reaction.

Recently, many researchers are working to develop the copper-free Sonogashira reactions version. The absent of copper should prohibit the formation of dimerization reaction. The exact mechanism of the copper-free Sonogashira coupling reaction is still also under debate. The catalytic cycle starts with the catalytically active species Pd^0L_2, which reacts with aryl halide in an oxidative addition step to

form [Pd(II)R^1L_2X] (Figure 1.2). The next step is a reversible pi-coordination of the alkyne which provide an alkyne–Pd(II) complex after that the base deprotonate acetylenic proton to produce [Pd(II)$L_2R^1(CCR^2)$]. Next, the the [Pd(II)$L_2R^1(CCR^2)$] undergoes trans/cis isomerization and reductive elimination to produce the coupling product with regeneration of the active species catalyst [2].

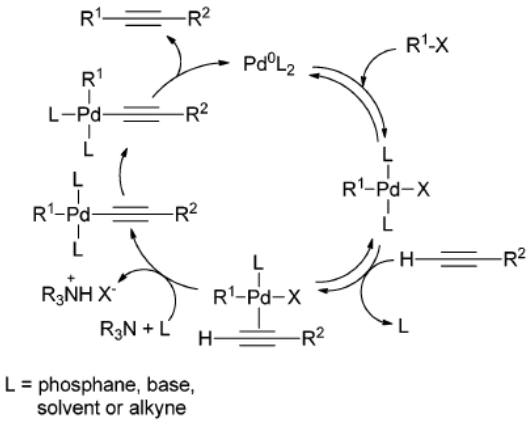
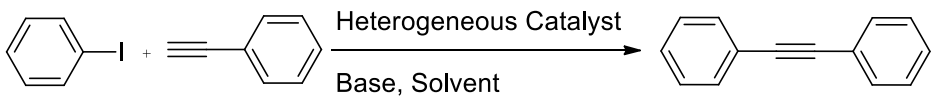


Figure 1.2 Copper-free Sonogashira catalytic cycle.

1.3 Introduction to heterogeneous catalyst in Sonogashira

In general, the Sonogashira reaction is catalyzed by homogeneous catalyst which has high reactivity and specificity. However, homogeneous catalysis has some drawbacks, in particular, the deficiency of reuse of the catalyst or at least the problem of recycling of the catalyst. Therefore, it causes losing precious metal catalyst and also increasing toxic metal waste. In order to address these problems, environmentally benign heterogeneous catalyst is a promising option. Several of solid matrices have been employed to support palladium metal catalysts for Sonogashira reaction such as Pd on carbon [10], Pd on zeolite [9] and Pd on modified silica [8] as shown in Scheme 1.4.



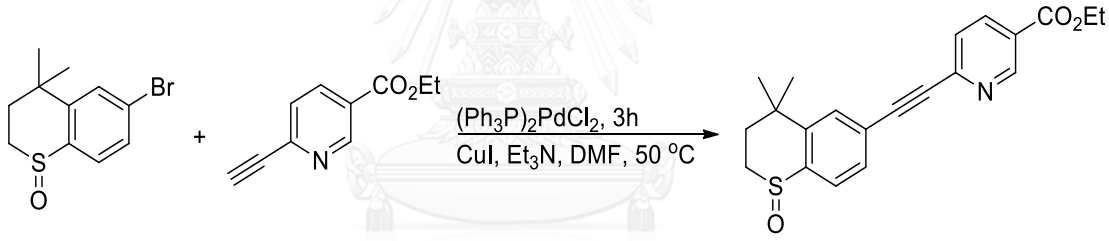
Heterogeneous Catalyst = Pd/C or NaY or SiO_2/TEG/Pd

Scheme 1.4 Sonogashira coupling reaction catalyzed by heterogeneous catalyst.

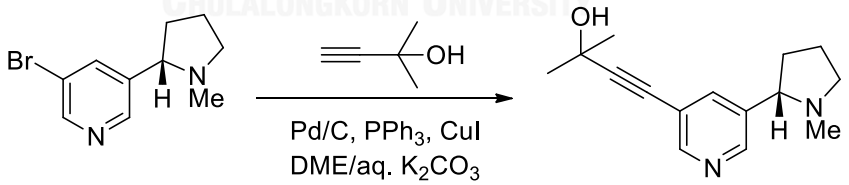
1.4 Literature reviews

1.4.1 Sonogashira coupling reaction

Sonogashira coupling reaction is palladium catalysed C-C bond formation. It is capable to couple a terminal alkyne with an aryl or vinyl halide (or triflate). The reaction name results from the discovery in 1975 by Sonogashira, Tohda, and Hagihara. The reaction can be conducted easily at room temperature using a palladium source such as $Pd(PPh_3)_2Cl_2$ as catalyst, combined with a co-catalytic amount of CuI with base and solvent [1]. According to the usefulness of Sonogashira reaction, it has been used in variety areas including pharmaceuticals, natural products, and organic materials [2]. For example, it was used in the synthesis of tazarotene [16], which is a treatment for psoriasis and acne and in the preparation of Altinicline [17], which is a potential treatment for Parkinson's disease as shown in Scheme 1.5 and Scheme 1.6.



Scheme 1.5 Sonogashira reaction for synthesizing tazarotene derivative.

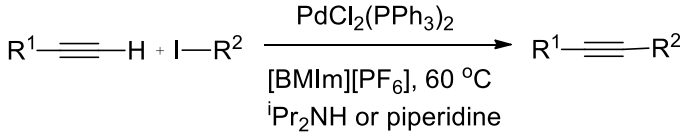


Scheme 1.6 Sonogashira reaction for synthesizing altinicline derivative.

1.4.2 Copper-free Sonogashira coupling reaction

In 2002, Ionic liquid ([BMIm][PF6]) have been successfully employed in copper-free Sonogashira cross-coupling reactions with $PdCl_2(PPh_3)_2$ and iPr_2NH or piperidine as bases (Scheme 1.7) [3]. Using Ionic liquid as solvent can fluent separation and recycling of the catalyst. This method has been extended to aryl

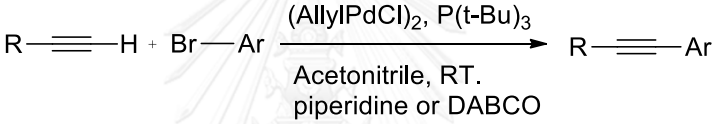
iodides which have varied functional groups with terminal aryl and alkyl that afforded the corresponding products in good yields.



R^1 = Alkyl, Aryl
R^2 = Aryl

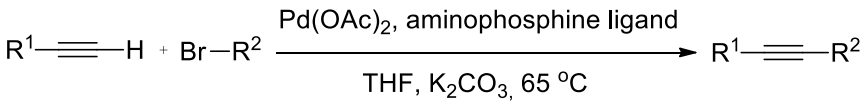
Scheme 1.7 Copper-free Sonogashira coupling reaction in Ionic Liquids.

In 2003, Soheili and co-workers [4] reported cross-coupling reaction of aryl bromide with terminal alkyne in acetonitrile at room temperature in the presence of $(AllylPdCl)_2$ and $P(t\text{-}Bu)_3$, using piperidine or DABCO as base, afforded the corresponding products in good yields (Scheme 1.8).



Scheme 1.8 Copper-free Sonogashira coupling of aryl bromides with terminal alkyne at room temperature.

In 2004, aminophosphines have been successfully employed in copper-free Sonogashira cross-coupling reactions with $Pd(OAc)_2$, K_2CO_3, and THF as solvent (Scheme 1.9) [5]. The influence of the bases, ligands, and solvents in the Sonogashira Reaction were investigated. The authors reported that the coupling reaction between aryl bromide with terminal aryl and alkyl alkynes under the same cross-coupling conditions affords coupling products in 72-96 %yields.

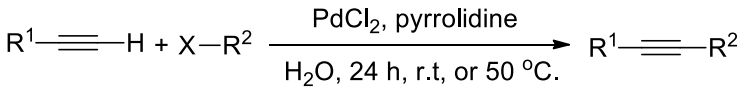


R^1 = Alkyl, Aryl
R^2 = Aryl

Scheme 1.9 Copper-free Sonogashira reaction employing aminophosphines as ligand

In 2005, Liang and co-workers [6] developed copper-free Sonogashira cross-coupling reaction of aryl bromide with terminal alkyne in water at room temperature

or 50 °C under aerobic condition in the presence of $PdCl_2$, using pyrrolidine as base, afforded the corresponding products in good yields (Scheme 1.10).



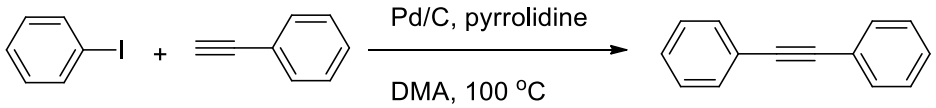
R^1 = Alkyl, Aryl
R^2 = Aryl
X = I

Scheme 1.10 Copper-free Sonogashira coupling reaction with $PdCl_2$ in water under aerobic conditions.

1.4.3 Sonogashira reaction using heterogeneous catalyst

To overcome homogeneous palladium catalyst drawbacks as mentioned in previous section. There are many heterogeneous catalysts that have been developed for Sonogashira reaction.

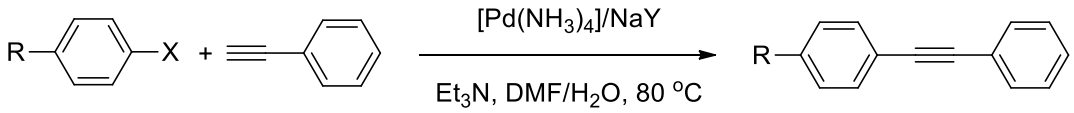
In 2002, Heidenreich and co-workers [10] demonstrated a palladium on activated carbon catalyst. It is highly active, selective and convenient heterogeneous catalyst for Sonogashira reactions. The Pd/C catalyst was used with dimethylacetamide as solvent and pyrrolidine as base to catalyze reaction between iodobenzene and phenylacetylene (Scheme 1.11). The coupled products were obtained in moderate to good yields in hours. The catalyst could be separated and recovered.



Scheme 1.11 Pd/C-catalyzed Sonogashira coupling of iodobenzene with phenylacetylene.

In 2004, a heterogeneous [Pd(NH3)4]–NaY catalyst was reported by Djakovitch and Rollet [9]. It was applied to the copper-free Sonogashira cross-coupling of aryl halides and terminal alkynes. The heterogeneous Pd-catalyst is reactive, stable and recyclable. Aryl iodides and activated aryl bromides were transformed to the

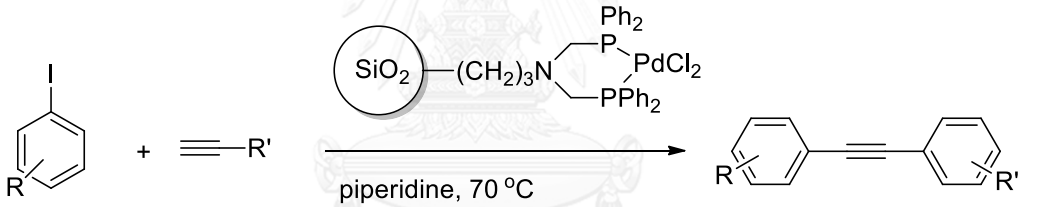
corresponding product with 1%mol of catalyst and triethylamine as base and mixture of DMF and water at 80 ^{o}C in 3 hours (Scheme 1.12).



X = I, Br
R = OMe, Me, F, NO_2

Scheme 1.12 $[Pd(NH_3)_4]^{2+}$/NaY-catalyzed copper-free Sonogashira reactions.

In 2005, Tyrrell and co-workers [8] reported palladium catalyst on silica. It was prepared by functionalizing 3-aminopropyl-modified silica gel with phosphine ligands. Then, it was transformed into a stable immobilized palladium complex. The catalyst was applied in copper-free Sonogashira coupling reaction between terminal alkynes and a number of aryl iodides with piperidine as base and solvent (Scheme 1.13). The cross coupling products were obtained in 85-92 %yield.



R = H, Me, OMe, Et
R' = Ph, Bu, PhMe

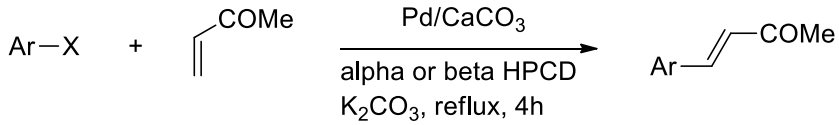
12 examples, 85 - 92 %Yield

Scheme 1.13 Modified silica supported palladium catalyzed copper-free Sonogashira coupling.

1.4.4 Calcium carbonate as support for palladium cross coupling reaction catalyst

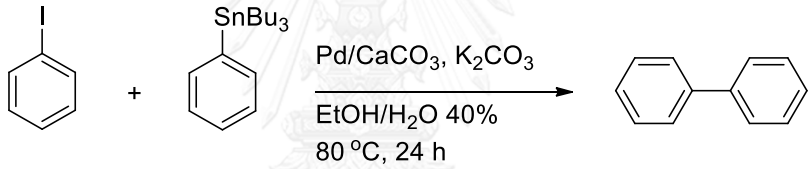
The use of calcium carbonate has many advantages. For example, it is a common substance found in nature, cheap, stable and non-pyrophoric. Hence, calcium carbonate can consider as an alternative support as heterogeneous catalyst. In the Pd catalyzed cross coupling reaction, it was used as support for Heck and Stille reactions.

In 2007, Senra and co-workers [11] reported phosphine-free Heck reactions between aryl halide and methyl acrylate in water by using hydroxyl propylated cyclodextrins as supramolecular hosts (Scheme 1.14). The catalyst can be reused up to three times.



Scheme 1.14 Heck coupling reaction of aryl halide and methyl acrylate.

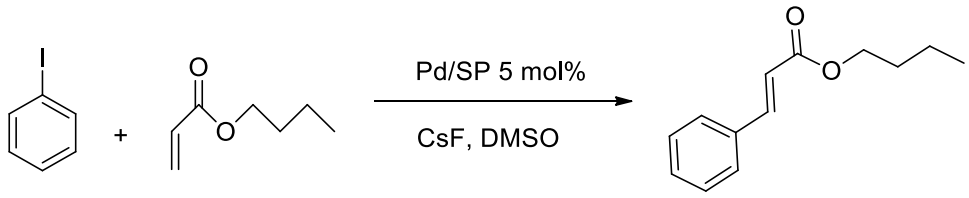
In the same year, Coelho and co-workers [12] demonstrated the using of $Pd/CaCO_3$ as catalyst reservoir in ligand-free Stille cross coupling reaction. The reactions of halobenzenes and tributylphenyltin were conducted in mixture of ethanol and water as shown in Scheme 1.15. This catalyst can be reused up to three times without losing its activity.



Scheme 1.15 Stille cross coupling reaction between iodobenzene and tributylphenyltin.

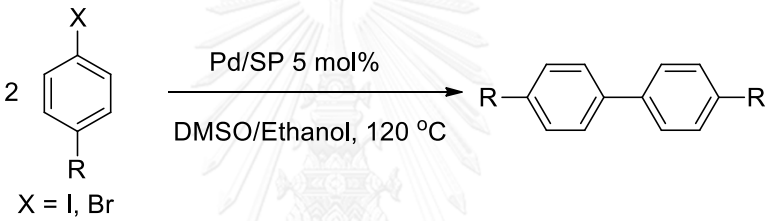
According to the mentioned researches, palladium supported on calcium carbonate catalyst can be used in the cross coupling reaction effectively. Therefore, researchers are trying to develop new heterogeneous catalyst by using shell particles which has calcium carbonate as main component for support of catalyst. Thus, the using of shell particles as catalyst support not only gains advantages of calcium carbonate but also utilizes shells which are generated from food industry.

In 2010, Shen and co-workers [13] prepared novel palladium heterogeneous catalyst from shell particles. The palladium supported shell particles (Pd/SP) was used in Heck coupling reaction between aryl iodides and olefins as shown in Scheme 1.16. The catalyst showed high activities and stability for the Heck reaction with good to excellent yields and being reused three times.



Scheme 1.16 Heck reaction between aryl iodide and butyl acrylate.

In 2011, Zeng and co-workers [14] reported using of the palladium supported shell particles (Pd/SP) in reductive homocoupling reactions of aromatic halides as shown in Scheme 1.17. The researcher compared catalytic activity and reusability of Pd/SP with Pd/C and Pd/$CaCO_3$. The Pd/SP showed higher properties than two other catalysts. It might due to the chelation of palladium metal and protein on shell particles.



Scheme 1.17 Reductive homocoupling reaction of aromatic halides.

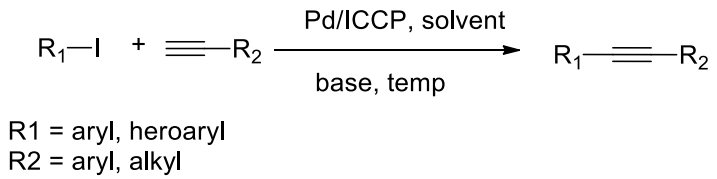
In 2015, Lertvachirapaiboon and co-workers [18] reported the preparation of individual calcium carbonate(ICCP) from vergin Asian Green mussel shell via chemical treatment (Figure 1.3). The unique in this work is that the morphology of the calcium carbonate is uniform resulting from disintegration of stacked nacreous layer into individual calcium carbonate plates (ICCP).

Figure 1.3 Disintegration of stacked calcium carbonate plate into individual calcium carbonate plates

According to the literature reviews above, calcium carbonate and shell particles were used as support of catalysts for various palladium catalyzed coupling reactions. However, there has been no report that palladium on calcium carbonate as palladium support for Sonogashira cross coupling reaction. Also if the source of calcium carbonate came from natural abundance shell, it will be not only increase reactivity due to its high surface area, but having the protein on its surface might gain the reusability of catalyst.

1.5 Objective of this research

In this this research, we will use individual calcium carbonate (ICCP) derived from natural shell particle based on Lertvachirapaiboon works [18] as a support of catalyst in copper-free Sonogashira cross coupling reaction of aryl iodides and terminal alkyne as shown in Scheme 1.18. The effect of solvents, bases and temperature will be investigated for optimization condition. Moreover, functional group compatibility of on the aryl iodides and terminal alkynes will be graded. Also reusability and palladium leeching of the Pd/ICCP also will be studied.



Scheme 1.18 Pd/ICCP catalyzed Sonogashira coupling reaction.

CHAPTER II

EXPERIMENTAL

All starting materials were obtained from commercial suppliers, and were used without further purification. All solvents were bubbled with nitrogen gas before using in the reaction. Analytical thin-layer chromatography (TLC) was performed on Kieselgel F_{254} pre-coated plastic TLC plates from EM science. Visualization was performed with a 254 nm ultraviolet lamp. Gel column chromatography was carried out with silica gel (60, 230-400 mesh) from ICN Silitech. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian or Bruker 400 MHz for ^{1}H and Bruker 100 MHz for ^{13}C in $CDCl_3$ solution. Chemical shifts of ^{1}H and ^{13}C NMR were referenced to $CDCl_3$ (δ 7.26 for ^{1}H, δ 77.00 for ^{13}C). Coupling constants (J) were reported in Hertz (Hz). Splitting patterns were designated as s (singlet), d (doublet), t (triple), q (quartet), bs (broad singlet), m (multiplet). The morphological structure of ICCP and SP was observed using a scanning electron microscope (SEM, JEOL JSM-6510A) operating at 20 kV under a high vacuum mode with a secondary electron image (SEI) detector. TEM image of Pd/ICCP was recorded by Transmission Electron Microscope (JEM-2100). The elemental composition analysis of the material was investigated using a built-in energy dispersive X-ray spectrometer (EDS). The XRD patterns were recorded by an X-ray diffractometer (DMAX 2200 Rigaku) under Cu Kα radiation. All ATR FT-IR spectra were recorded using a germanium micro-IRE with Nicolet 6700 FT-IR spectrometer equipped with a mercury–cadmium–telluride (MCT) detector) at 4 cm^{-1} resolution and 128 co-addition scans. The organic and calcium carbonate contents in the treated shells and catalysts were quantitatively determined by thermal gravimetric analysis (PerkinElmer, Pyris 1). Palladium content of catalysts was determined by Thermo Scientific, iCAP 6500 ICP-OES.

2.1 Preparation of tetrachloropalladic acid (H_2PdCl_4) solution.

A mixture of palladium metal (1g) in aqua regia (a mixture of concentrated nitric acid and hydrochloric acid with a ratio of 3:1 v/v, 5 mL) was stirred at 100 °C until the solid palladium was completely dissolved. Then the solution was kept heating until almost dry and pouring into a 100 mL volumetric flask. Water was added to adjust concentration of H_2PdCl_4 to 0.094 M.

2.2 Preparation of the individual calcium carbonate plates (ICCP) and shell particles (SP)

2.2.1 Preparation of the individual calcium carbonate plates (ICCP)

Asian green mussel (Perna viridis) shells were first rinsed with water and then dried under an ambient air. The dried shells were baked at 200 °C for 2 h. The thermal-treated shells were submerged in 30 % (w/w) hydrogen peroxide solution under ultrasonic sonication for 24 h. The treated-shells were filtered with 200 mesh filter size and washed with water (3x100 mL). The solid (ICCP) were further dried under air and kept in a desiccator.

2.1.2 Preparation of the shell particles (SP)

Asian green mussel (Perna viridis) shells were first rinsed with water and then dried under an ambient air. The dried shells were grinded. The grinded-shells were filtered with 200 mesh filter size and used as support of catalyst.

2.3 Preparation of the individual calcium carbonate plates supported palladium (Pd/ICCP) and shell particles supported palladium catalysts (Pd/SP)

2.3.1 Preparation of the individual calcium carbonate plates supported palladium catalyst (Pd/ICCP).

A 0.094 M H_2PdCl_4 25 mL was rapidly added into 5 gram of individual calcium carbonate plates in 100 mL water. The mixture was stirred until color changed from yellow to colorless. The resulting powders were washed with water until the color of supernatant turned colorless. The solid was treated with sodium borohydride (0.11 g.) in water (100mL) and stirred for 1 h. Then, the catalyst was washed with water and dried at 120 ^{o}C for 2 hour.

2.3.2 Preparation of the shell particles supported palladium catalysts (Pd/SP)

A 0.094 M H_2PdCl_4 25 mL was rapidly added into 5 gram shell particles in 100 mL water. The mixture was stirred until color changed from yellow to colorless. The resulting powders were washed with water until the color of supernatant turned colorless. The solid was treated with sodium borohydride (0.11 g.) in water (100mL) and stirred for 1 h. Then, the catalyst was washed with water and dried at 120 ^{o}C for 2 hour.

2.4 Determination of Palladium content by ICP-OES analysis.

2.4.1 General procedure for preparation of sample.

An oven-dried sealed tube equipped with a magnetic stirring bar was charged with palladium catalyst (30 mg) and aqua regia (5 mL). Then, the mixture was stirred at 100 $^{\circ}$C for 24 hour. After cooling to room temperature, the mixture was poured 100 mL volumetric flask. Finally, water was added to adjust concentration to 15 ppm.

2.4.2 Calibration curve method.

Palladium standard for ICP (1000 mg/L) was used to prepare calibration curve between 5-25 ppm as shown in Figure 2.1

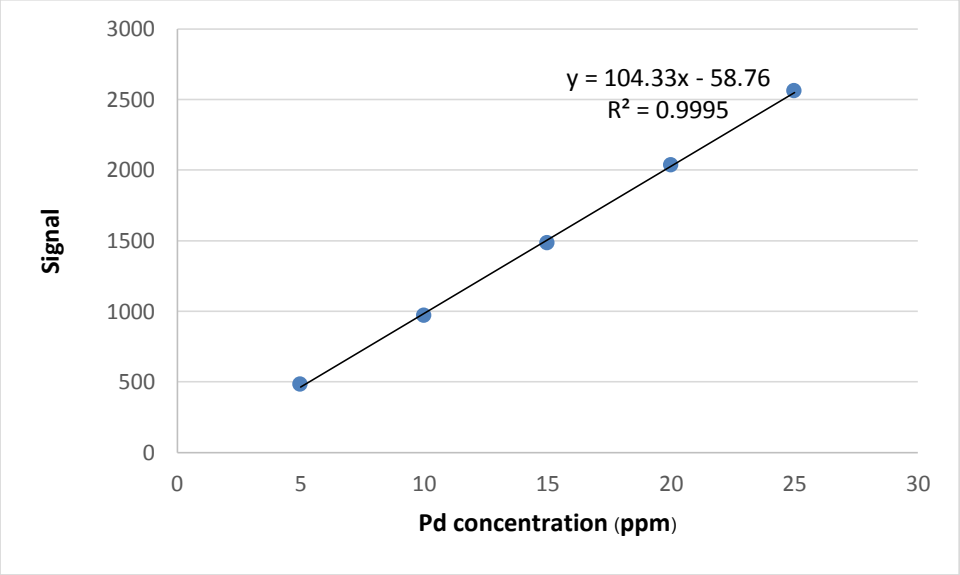


Figure 2.1 Calibration curve of Palladium standard.

2.5 Determination amount of 4-iodotoluene and 1-methyl-4-(phenylethynyl)benzene for calculation percent conversion and percent yield by gas chromatography technique (GC)

2.5.1 General procedure for preparation of sample.

After finished reaction, reaction mixture was filtered with filter paper into 25 mL volumetric flask. Finally, ethanol was added to adjust concentration.

2.5.2 Internal standard method.

Internal standard method was used for determination amount of 4-iodotoluene as starting material and 1-methyl-4-(phenylethynyl)benzene as product in the reaction. For 4-iodotoluene amount, we used response factor which was obtained from slope of calibration curve for 4-iodotoluene with biphenyl as internal standard as shown in Figure 2.2 to determine amount of 4-iodotoluene from Equation 2.1

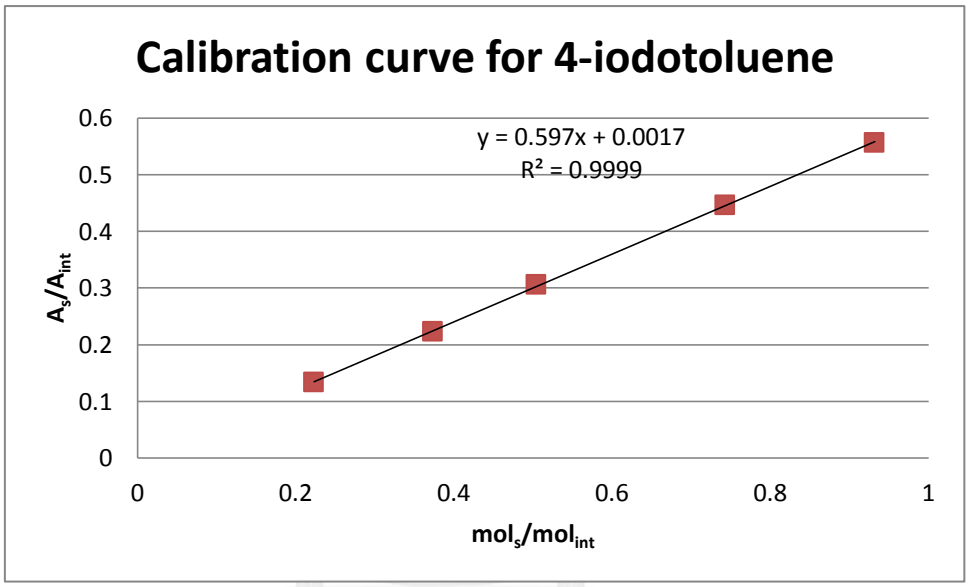


Figure 2.2 Calibration curve for 4-iodotoluene.

$$RF = \frac{A_s/A_{int}}{mol_s/mol_{int}}$$

Equation 2.1 Equation for determining amount of 4-iodotoluene.

For 1-methyl-4-(phenylethynyl)benzene amount, we used response factor which was obtained from slope of calibration curve for 1-methyl-4-(phenylethynyl)benzene with biphenyl as internal standard as shown in Figure 2.3 to determine amount of 1-methyl-4-(phenylethynyl)benzene from Equation 2.2

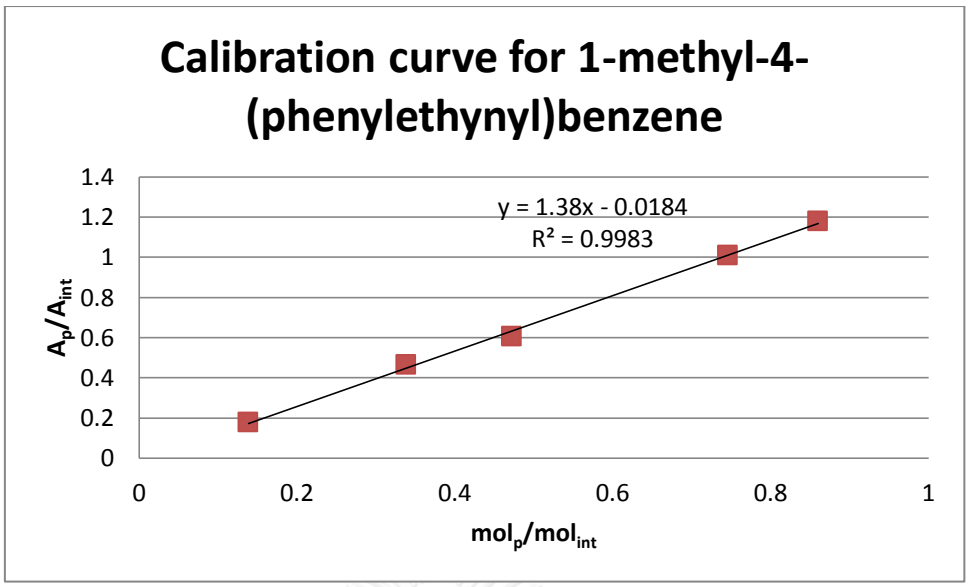


Figure 2.3 Calibration curve for 1-methyl-4-(phenylethynyl)benzene.

$$RF = \frac{A_p/A_{int}}{mol_p/mol_{int}}$$

Equation 2.2 Equation for determining amount of 1-methyl-4-(phenylethynyl)benzene.

2.6 Optimization studies on the Sonogashira coupling reaction.

2.6.1 Optimization of the reaction conditions

Table 3.2 Effect of base**:** An oven-dried sealed tube equipped with a magnetic stirring bar was charged with the base (1.0 mmol) and Pd/ICCP (1 mol%). Then, 4-iodotoluene **(1a)** (0.5 mmol), ethynylbenzene **(2a)** (0.6 mmol), and solvent (6 mL) were added and the reaction mixture was stirred at 77 $^{\circ}$C under nitrogen for 4 hour. After cooling to room temperature, the reaction mixture was filtered and solvent was evaporated. The residue was purified by silica chromatography, eluting with hexane to give the 1-methyl-4-(phenylethynyl)benzene (**3b)** as white solid in in corresponding yield.

Table 3.3 Effect of solvent**:** oven-dried sealed tube equipped with a magnetic stirring bar was charged with K_2CO_3 (1.0 mmol) and Pd/ICCP (1 mol%). Then, 4-iodotoluene **(1a)** (0.5 mmol), ethynylbenzene **(2a)** (0.6 mmol), and solvent (6 mL) were added and the reaction mixture was stirred at 77 $^{\circ}$C under nitrogen for 4 hour. After cooling to room temperature, the reaction mixture was filtered and solvent was evaporated. The residue was purified by silica chromatography, eluting with hexane to give the 1-methyl-4-(phenylethynyl)benzene (**3b)** as white solid in in corresponding yield.

Based on the above study, we selected ethanol as solvent and K_2CO_3 as a base and performed the reaction from 50°C to 77°C in order to find the optimal temperature. The results in Table 3.4 demonstrated that lowering the temperature resulted in the lower yield even though the reaction was carried over 24 hour. Therefore, we selected 77°C as optimal temperature of the reaction

Table 3.4 Effect of temperature**:** An oven-dried sealed tube equipped with a magnetic stirring bar was charged with K_2CO_3 (1.0 mmol) and Pd/ICCP (1 mol%). Then, 4-iodotoluene **(1a)** (0.5 mmol), ethynylbenzene **(2a)** (0.6 mmol), and ethanol (6 mL) were added and the reaction mixture was stirred at corresponding temperature under nitrogen for 4 hour. After cooling to room temperature, the reaction mixture was filtered and solvent was evaporated. The residue was purified by silica

chromatography, eluting with hexane to give the 1-methyl-4-(phenylethynyl)benzene (**3b)** as white solid in corresponding yield.

2.6.2 General procedure for screening aryl iodide via Sonogashira coupling reaction using Pd/ICCP as catalyst.

An oven-dried sealed tube equipped with a magnetic stirring bar was charged with K_2CO_3 (1.0 mmol) and 6.1% Pd/ICCP (1 mol%). Then, aryl iodide (0.50 mmol), terminal alkyne (0.60 mmol), and ethanol (6 mL) were added and the reaction mixture was stirred at 77 $^{\circ}C$ under nitrogen for 4 hour. After cooling to room temperature, the reaction mixture was filtered and solvent was evaporated. The residue was purified by silica chromatography, eluting with hexane to give the desired compound.

1,2-diphenylethyne [19] (3a): synthesized according to general procedure from 4-iodobenzene (102 mg, 0.50 mmol), ethynylbenzene (2a) (61 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3a (78.4 mg, 0.44 mmol, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, J = 6.6, 1.8 Hz, 4H), 7.51 – 7.32 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 131.67, 128.40, 128.30, 123.37, 89.47; GC-MS: m/z: 178.1.

1-methyl-4-(phenylethynyl)benzene [19] (3b): Synthesized according to procedure A using 4-iodotoluene (109 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3b (80.7 mg, 0.42 mmol, 84%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.43 – 7.31 (m, 3H), 7.20 (d, *J* = 7.8 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.39, 131.57, 131.53, 129.13, 128.33, 128.08, 123.54, 120.26, 89.60, 88.76, 21.50; GC-MS: m/z: 192.0.

1-methyl-3-(phenylethynyl)benzene [19] (3c): Synthesized according to procedure A using 3-iodotoluene (109 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3c (88.4 mg, 0.42 mmol, 92%) as a colorless oil. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.64 – 7.53 (m, 2H), 7.40 (dd, *J* = 11.3, 5.2 Hz, 5H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.46, 132.65, 132.06, 129.61, 129.15, 128.78, 128.69, 128.61, 123.88, 123.57, 90.05, 89.51, 21.66; GC-MS: m/z: 191.9.

1-methyl-2-(phenylethynyl)benzene [19] (3d): Synthesized according to procedure A using 2-iodotoluene (109 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3d (86.5 mg, 0.45 mmol, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.53 (m, 2H), 7.40 (dd, *J* = 11.3, 5.2 Hz, 5H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.46, 132.65, 132.06, 129.61, 129.15, 128.78, 128.69, 128.61, 123.88, 123.57, 90.05, 89.51, 21.66; GC-MS: m/z: 191.9.

2-iodo-1,3-dimethylbenzene [20] (3e): Synthesized according to procedure A using 2-iodo-1,3-dimethylbenzene (116 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3e (56.7 mg, 0.28 mmol, 55%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.57 (m, 2H), 7.47 – 7.33 (m, 3H), 7.18 (dt, *J* = 19.5, 6.9 Hz, 3H), 2.60 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.38, 131.52, 128.48, 128.20, 127.90, 126.83, 124.01, 123.13, 98.00, 87.30, 21.22; GC-MS: m/z: 205.9.

1-methoxy-4-(phenylethynyl)benzene [19] (3f): Synthesized according to procedure A using 1-iodo-4-methoxybenzene (117 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3f (91.6 mg, 0.44 mmol, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 2H), 7.59 – 7.53 (m, 2H), 7.42 – 7.34 (m, 3H), 2.61 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.22, 136.24, 131.76, 131.70, 128.82, 128.46, 128.27, 128.20, 122.70, 92.75, 88.66, 26.55; GC-MS: m/z: 207.9

4-(phenylethynyl)aniline [21] (3g): Synthesized according to procedure A using 4-iodoaniline (110 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol),

Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3g (82.1 mg, 0.43 mmol, 85%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 2H), 7.30 – 7.19 (m, 5H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.72 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.79, 133.09, 131.49, 128.39, 127.78, 114.89, 114.75, 112.79, 90.26, 87.47; GC-MS: m/z: 218.9.

1-azido-4-(phenylethynyl)benzene [22] (3h): Synthesized according to procedure A using 1-azido-4-iodobenzene (122 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3o (71.2 mg, 0.32 mmol, 65%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (q, *J* = 8.3 Hz, 4H), 7.60 – 7.53 (m, 2H), 7.47 – 7.34 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.08, 132.04, 131.80, 129.14, 128.52, 128.26, 122.26, 118.50, 111.51, 93.81, 87.75.

1-nitro-4-(phenylethynyl)benzene [23] (3i): Synthesized according to procedure A using 1-iodo-4-nitrobenzene (125 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3j (101.6 mg, 0.44 mmol, 91%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.56 (dd, *J* = 5.9, 2.6 Hz, 2H), 7.46 – 7.32 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.11, 132.37, 131.96, 130.37, 129.40, 128.66, 123.74, 122.23, 94.83, 87.68; GC-MS: m/z: 222.9.

1-(4-(phenylethynyl)phenyl)ethanone [19] (3j): Synthesized according to procedure A using 1-(4-iodophenyl)ethanone (123 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3k (112.2 mg, 0.51 mmol, 102%(quantitative yield)) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 2H), 7.59 – 7.53 (m, 2H), 7.42 – 7.34 (m, 3H), 2.61 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.22, 136.24, 131.76, 131.70, 128.82, 128.46, 128.27, 128.20, 122.70, 92.75, 88.66, 26.55; GC-MS: m/z: 219.9.

4-(phenylethynyl)benzaldehyde [24] (3k): Synthesized according to procedure A using 4-iodobenzaldehyde (116 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3l (65.9 mg, 0.32 mmol, 64%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.56 (dd, *J* = 6.3, 2.8 Hz, 2H), 7.43 – 7.32 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.50, 135.57, 132.24, 131.93, 129.70, 129.10, 128.61, 122.65, 93.59, 88.66.; GC-MS: m/z: 205.9.

1-(phenylethynyl)-4-(trifluoromethyl)benzene [19] (3l): Synthesized according to procedure A using 1-iodo-4-(trifluoromethyl)benzene (136 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3m (91.1 mg, 0.37 mmol, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H), 7.59 (dd, *J* = 6.3, 2.9 Hz, 2H), 7.45 – 7.36 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.96, 131.91, 128.98, 128.60, 125.48, 125.44, 125.41, 125.37, 122.75, 91.93, 88.12; GC-MS: m/z: 245.9.

4-(phenylethynyl)benzonitrile [25] (3m): Synthesized according to procedure A using 4-iodobenzonitrile (114 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3n (72.2 mg, 0.35 mmol, 71%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (q, *J* = 8.3 Hz, 4H), 7.60 – 7.53 (m, 2H), 7.47 – 7.34 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.08, 132.04, 131.80, 129.14, 128.52, 128.26, 122.26, 118.50, 111.51, 93.81, 87.75; GC-MS: m/z: 202.9.

1-chloro-4-(phenylethynyl)benzene [26] (3n): Synthesized according to procedure A using 1-chloro-4-iodobenzene (119 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3h (94.6 mg, 0.44 mmol, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.43 –

7.32 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.39, 132.93, 131.73, 128.81, 128.59, 128.51, 123.10, 121.95, 90.49, 88.40; GC-MS: m/z: 211.8.

1-bromo-4-(phenylethynyl)benzene [27] (3o): Synthesized according to procedure A using 1-bromo-4-iodobenzene (141 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3i (115.7 mg, 0.44 mmol, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.45 (m, 4H), 7.43 – 7.31 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.17, 131.76, 131.74, 128.65, 128.54, 123.08, 122.62, 122.42, 90.66, 88.45; GC-MS: m/z: 255.8.

ethyl 4-(phenylethynyl)benzoate [28] (3p): Synthesized according to procedure A using methyl 4-iodobenzoate (131 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3v (100.1 mg, 0.40 mmol, 80%) as a white solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.65 – 7.46 (m, 4H), 7.45 – 7.30 (m, 3H), 4.39 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.21, 131.88, 131.60, 130.02, 129.62, 128.87, 128.57, 128.04, 122.91, 92.41, 88.84, 61.26, 14.45; GC-MS: m/z: 249.9

methyl 4-(phenylethynyl)benzoate [29] (3q): Synthesized according to procedure A using methyl 4-iodobenzoate (131 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , triethylamine (101 mg, 1.0 mmol) in MeCN (6 mL) for 4 h to afford 3v (96.8 mg, 0.41 mmol, 86%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.58 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.40 (dd, *J* = 9.1, 5.8 Hz, 3H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.97, 132.17, 131.94, 129.95, 129.19, 128.87, 128.46, 123.17, 92.81, 89.08, 52.62.; GC-MS: m/z: 235.9.

1-(phenylethynyl)naphthalene [19] (3r): Synthesized according to procedure A using 1-iodonaphthalene (127 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3p (93.6 mg, 0.41 mmol, 82%) as a white solid. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.3 Hz, 1H), 7.88 (dt, *J* = 21.1, 11.4 Hz, 3H), 7.80 – 7.65 (m, 3H), 7.60 (dd, *J* = 14.3, 7.2 Hz, 1H), 7.56 – 7.37 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.75, 133.69, 132.12, 130.82, 129.21, 128.88, 128.82, 128.76, 127.22, 126.87, 126.68, 125.72, 123.89, 121.38, 94.81, 88.03; GC-MS: m/z: 228.0.

4-(phenylethynyl)-1,1'-biphenyl [30] (3s): Synthesized according to procedure A using 4-iodo-1,1'-biphenyl (140 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3q (101.7 mg, 0.40 mmol, 80%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dt, *J* = 8.1, 5.9 Hz, 8H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.46 – 7.35 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.43, 140.82, 132.49, 132.08, 129.31, 128.82, 128.72, 128.08, 127.47, 123.78, 122.66, 90.55, 89.79; GC-MS: m/z: 253.9.

3-(phenylethynyl)pyridine [29] (3t): Synthesized according to procedure A using 3-iodopyridine (103 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3r (179.2 mg, 0.43 mmol, 86%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 1.4 Hz, 1H), 8.55 (dd, J = 4.9, 1.6 Hz, 1H), 7.82 (dt, J = 7.9, 1.9 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.42 – 7.33 (m, 3H), 7.29 (ddd, J = 7.8, 4.9, 0.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.25, 148.52, 138.70, 131.85, 128.98, 128.60, 123.22, 122.66, 120.73, 92.91, 86.00; GC-MS: m/z: 178.9.

2.6.3 General procedure for screening terminal alkyne via Sonogashira coupling reaction using Pd/ICCP as catalyst.

General procedure for screening terminal alkyne via Sonogashira coupling reaction using Pd/ICCP as catalyst: An oven-dried sealed tube equipped with a magnetic stirring bar was charged with K_2CO_3 (1.0 mmol) and Pd/ICCP (1 mol%). Then, 4-iodobenzene (0.5 mmol), terminal alkyne (0.6 mmol), and ethanol (6 mL) were added and the reaction mixture were stirred at 77 $^{\circ}C$ under nitrogen for 4 hour. After cooling to room temperature, the reaction mixture was filtered and solvent was evaporated. The residue was purified by silica chromatography, eluting with hexane to give the desired compound.

1-fluoro-4-(phenylethynyl)benzene [31] (3u): Synthesized according to procedure A using 4-iodobenzene (102 mg, 0.50 mmol), 1-ethynyl-4-fluorobenzene (72 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3s (81.4 mg, 0.42 mmol, 83%) as a white solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.52 (dt, J = 9.1, 5.2 Hz, 4H), 7.35 (dd, J = 9.2, 4.8 Hz, 3H), 7.04 (t, J = 8.6 Hz, 2H). 13C NMR (101 MHz, $CDCl_3$) δ 163.89, 161.41, 133.65, 133.57, 131.70, 128.50, 128.46, 123.27, 119.56, 119.53, 115.87, 115.65, 89.20, 88.45; GC-MS: m/z: 195.9.

1-methoxy-4-(phenylethynyl)benzene [19] (3v): Synthesized according to procedure A using 1-iodo-4-methoxybenzene (117 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3f (91.6 mg, 0.44 mmol, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.45 (m, 4H), 7.42 – 7.29 (m, 3H), 6.90 (dd, *J* = 8.8, 2.2 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.74, 133.16, 131.55, 128.41, 128.03, 123.73, 115.50, 114.24, 114.12, 89.53, 88.20, 55.36; GC-MS: m/z: 207.9.

oct-1-yn-1-ylbenzene [32] (3w): Synthesized according to procedure A using 4-iodobenzene (102 mg, 0.50 mmol), oct-1-yne (66 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol) , potassium carbonate (138 mg, 1.0 mmol) in EtOH (6 mL) for 4 h to afford 3u (73.6 mg, 0.40 mmol, 79%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.35 – 7.25 (m, 3H), 2.44 (t, *J* = 7.1 Hz, 2H), 1.67 – 1.62 (m, 2H), 1.55 – 1.32 (m, 10H), 0.94 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.99, 128.60, 127.86, 90.91, 81.04, 31.83, 29.21, 29.06, 23.01, 19.87, 14.48; GC-MS: m/z: 186.0.

2.7 Reusability test of Palladium catalysts

Table 3.9 Comparing reusability of palladium catalysts: An oven-dried sealed tube equipped with a magnetic stirring bar was charged with K_2CO_3 (138 mg, 1.0 mmol) and Pd/ICCP (9 mg, 0.005 mmol). Then, 4-iodotoluene (109 mg, 0.50 mmol), ethynylbenzene (51 mg, 0.60 mmol), and ethanol (6 mL) were added and the reaction mixture were stirred at 100 $^{\circ}$C under nitrogen for 4 hour. After cooling to room temperature, the reaction mixture was filtered into 25 mL volumetric flask and ethanol was added to adjust concentration. Percent conversion was determined by gas chromatography technique. The heterogeneous palladium catalyst was separated from the reaction mixture by centrifugation. The reused palladium catalyst was washed with ethanol, followed by removal of the solvent under a reduced pressure before the next reaction.

2.8 Determination of Palladium content in reaction mixture by ICP-OES analysis

Table 3.10 Palladium content in reaction mixture**:** The reaction was carried followed procedure 2.6.2 and then the reaction mixture was filtered into 250 mL round bottom flask and solvent was evaporated. Then, the round bottom flask was charged with aqua regia (5 mL). After that, the mixture was stirred at 100 $^{\circ}$C for 24 hour. After cooling to room temperature, the mixture was poured 100 mL volumetric flask. Finally, water was added to adjust concentration. The Pd content was determinated followed the procedure in section 2.4.2

CHAPTER III
RESULTS AND DISCUSSION

3.1 Preparation of individual calcium carbonate plates supported palladium (Pd/ICCP) and shell particles supported palladium (Pd/SP) catalysts

In this works, the calcium carbonate supports were received from naturally abundant Asian green mussel [33]. In general, the sea shell is composed of calcium carbonate layer bounded with proteins. As mentioned above, we hypothesized that the protein in shell particle will be suitable for stabilizing the palladium metal nano particle resulting in the high reusability as heterogeneous catalyst support. However, the previous reports on the use of shell particles as supports for heterogeneous catalysts used simple grinding that resulted in large and non-uniform particles which could reduce the catalytic activity and recycling ability of the catalyst. Luckily, Lertvachirapaiboon and co-workers recently reported the preparation of pseudo-hexagonal aragonite calcium carbonate particles with highly uniform structure form the Asian green mussel [18]. Calcium carbonate supports prepared by this method are proposed as "individual calcium carbonate plates" (ICCP). The catalytic activity of Pd catalyst supported by ICCP will be tested and compared with simple shell particles (SP). To prepare ICCP, the virgin shell was treated with hydrogen peroxide under the sonication for overnight. This process can degrade and dissolve the organic binder between aragonite plates in shell particle resulting in the formation of ICCP (Figure 1 right). On the other hands, SP were received from grinding and filtering of virgin shell through 200 mesh filter as depicted in Figure 1 (left)[14]. Palladium deposition onto ICCP and SP were achieved by impregnation-reduction of tetrachloropalladic acid (H_2PdCl_4) in aqueous solution providing Pd/ICCP and Pd/SP catalyst as black powders (Figure 3.1).

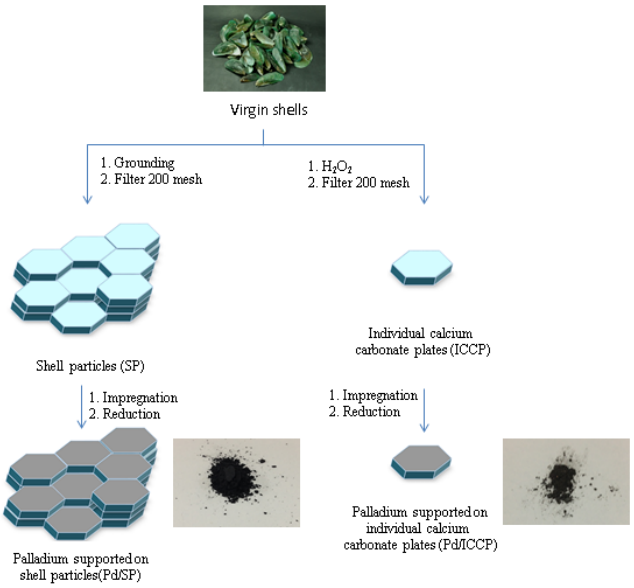


Figure 3.1 Preparation of individual calcium carbonate plates and shell particles supported palladium (Pd/ICCP and Pd/SP) catalysts.

3.2 characterizations of Pd/ICCP and Pd/SP

Then prepared Pd/ICCP and Pd/SP catalysts were fully characterized by SEM, TEM, EDX, XRD, FTIR and ICP-OES as described in details in the following sections

3.2.1. Morphological characterization of Pd/ICCP and Pd/SP

The scanning electron microscopy (SEM) reveals the morphology of Pd deposited on individual calcium carbonate plates (Pd/ICCP) as single polygonal particles with 3 micrometer size (Figure 2a). On the other hands, the catalyst received from fresh grinded shell particles (Pd/SP) gave lager particle size (9 micrometer) with aggregate structure (Figure 2b). X-ray spectroscopy (EDX) analysis revealed that palladium is well dispersed onto surface of both ICCP and SP. (Figure 2c and 2d)

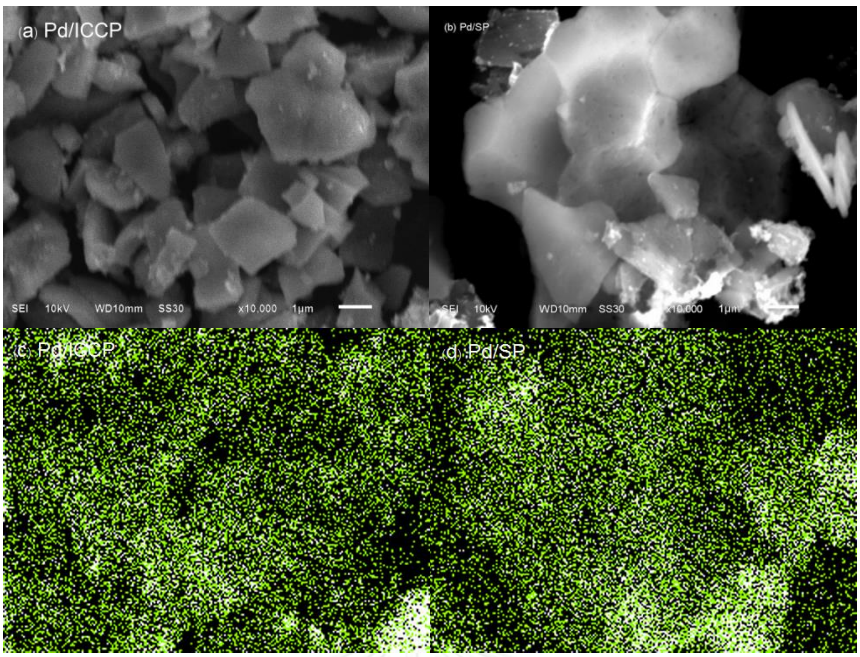


Figure 3.2 SEM images (2a and 2b) and EDX images (2c and 2d) of individual calcium carbonate plates and shell particles supported palladium (Pd/ICCP and Pd/SP) catalysts.

In zoomed view, both palladium of prepared Pd/ICCP and Pd/SP catalysts also disperses uniformly on individual calcium carbonate plates and shell particles as shown in Figure 3.3. In addition, SEM image of commercially available Pd/$CaCO_3$ shows porcupine like structure of calcium carbonate particles with 3-10 micrometer size as depicted in Figure 3.4. Moreover, thickness of ICCP and SP was investigated by SEM technique. The results showed that the ICCP thickness was around 300-400 nanometer. However, SP composed of 2-4 ICCP plates, so the thickness of SP was around 800-1600 nanometer (Figure 3.6).

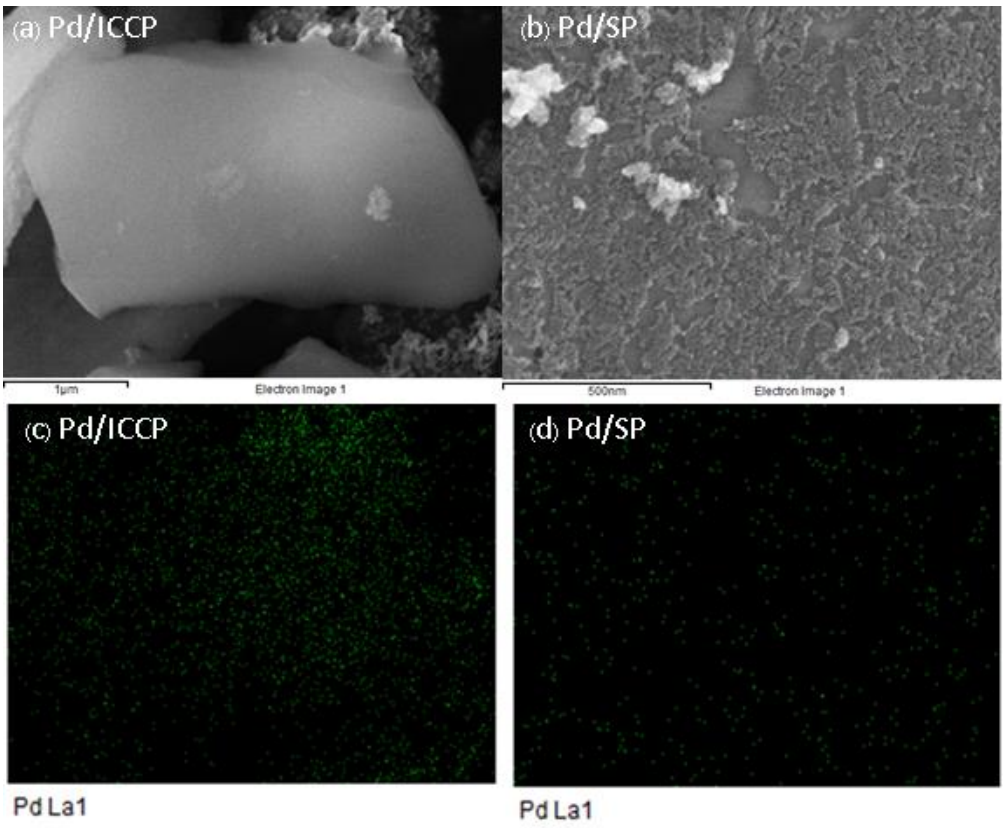


Figure 3.3 Zoomed view of SEM images (3a and 3b) and EDX images (3c and 3d) of individual calcium carbonate plates and shell particles supported palladium (Pd/ICCP and Pd/SP) catalysts.

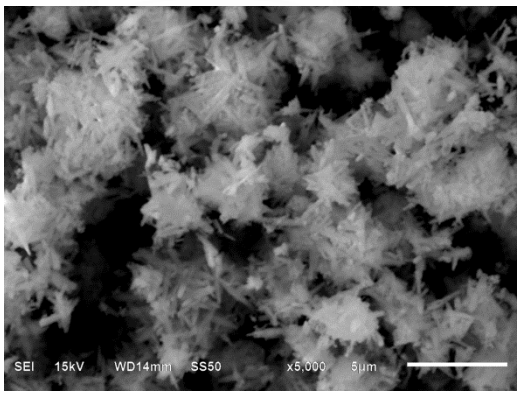


Figure 3.4 SEM image of calcium carbonate supported palladium ($Pd/CaCO_3$) catalyst.

Transmission electron microscopy (TEM) analysis of Pd/ICCP (Figure 3.5) shows round black particles of Pd with the size ca. 5 nm suggesting the formation of palladium nanoparticles on the surface of ICCP.

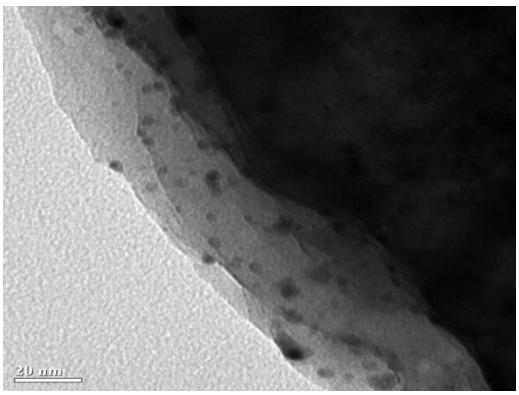


Figure 3.5 TEM images of individual calcium carbonate plates supported palladium (Pd/ICCP) catalyst.

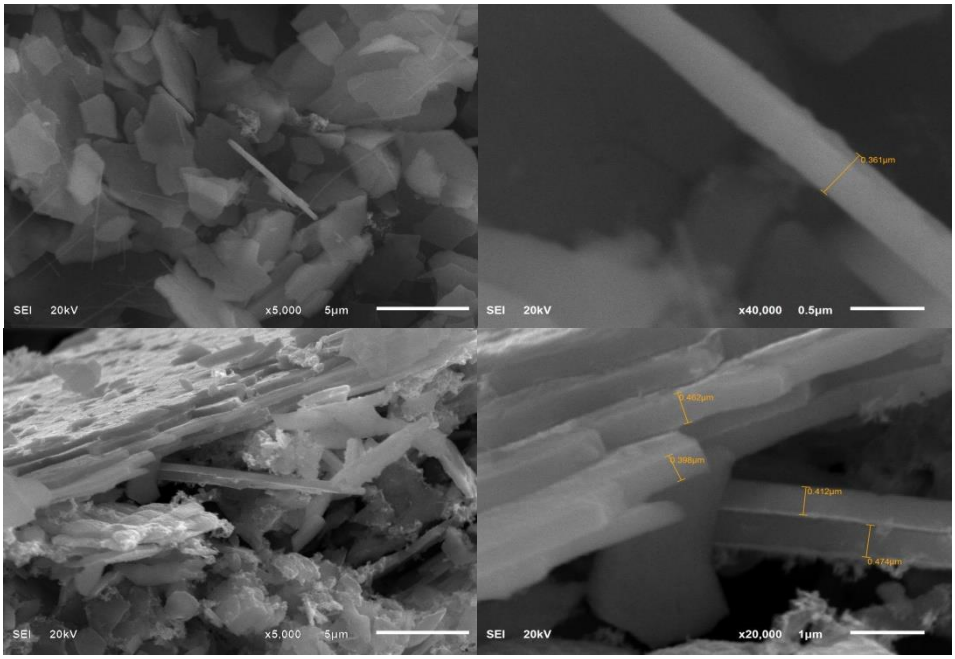


Figure 3.6 SEM images of individual calcium carbonate plates supported palladium and shell particle for thickness investigation.

3.2.2. The X-ray diffraction (XRD) Studies.

The XRD patterns of Pd/$CaCO_3$, SP, Pd/SP and Pd/ICCP were shown in Figure 3.7. It can be seen that these diffraction peaks of SP, Pd/ICCP and Pd/SP are almost identical. All sharp peaks contribute to the diffraction of the supporting-calcium carbonate. However, the XRD patterns of Pd/ICCP and Pd/SP are slightly different from Pd/$CaCO_3$, for example, there is no peak at 29 degree of Pd/ICCP and Pd/SP

which belonging to calcite form of calcium carbonate [25]. However, the characteristic peak of palladium (40.03 degree) cannot be detected in Pd/ICCP and Pd/SP. It suggested that Pd was dispersed uniformly on both ICCP and SP with the Pd crystallites at below the XRD detection limit.

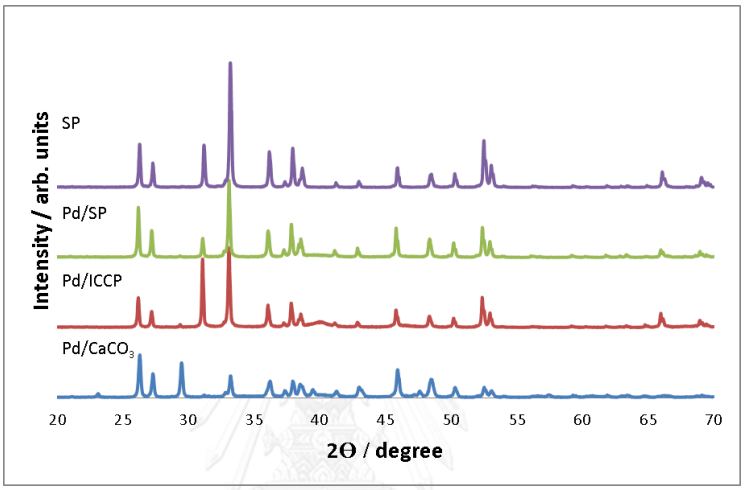


Figure 3.7 X-ray diffraction patterns of the $Pd/CaCO_3$, SP, Pd/ICCP and Pd/SP catalysts.

3.2.3. Thermogravimetric analysis.

As methoined above, the protein content in the shell particle is the key for the recycling ability of the catalyst. Therefore, the TGA analysis was performed in order to determined protein content in those catalysts. Figure 3.8 showed TGA thermogram of Pd/ICCP, Pd/SP and $Pd/CaCO_3$. For Pd/ICCP and Pd/SP, TGA thermogram displayed two major losses. The first decomposition at 200–300 $^{\circ}C$ was due to organic matrix. The TG curves provided that the organic content in the Pd/ICCP and Pd/SP were 1.8% and 3.2% respectively. Those weight losses found in both catalysts came from the protein in the shell surface. However, Pd/ICCP has protein content lower than Pd/SP due to the degradation and dissolution of organic matrix from the shell in the preparation step. Moreover, the second weight loss at 600–800 $^{\circ}C$ observed in all Pd catalysts governed by the liberation of carbon dioxide as calcium carbonate was thermally decomposed to calcium oxide [33]. Notably,

TGA thermogram of commercial $Pd/CaCO_3$ showed only single weight loss of calcium carbonate at 600–800 ^{o}C suggesting that there are no organic content in the catalyst.

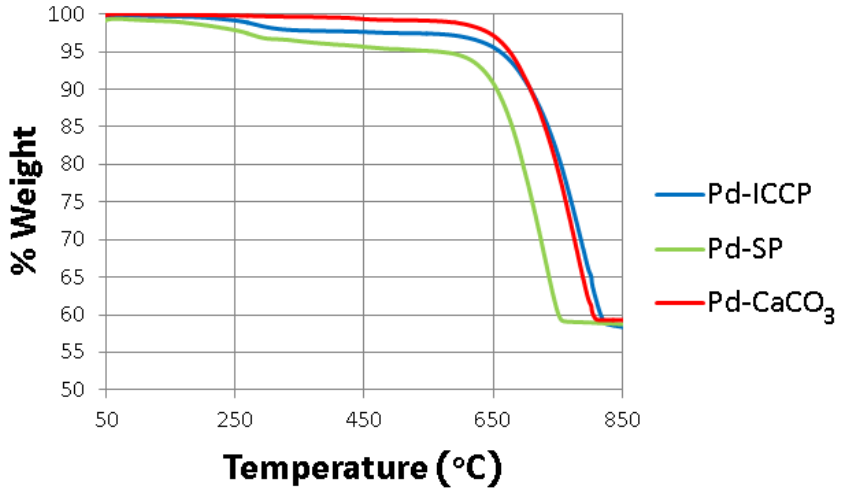


Figure 3.8 Thermal gravimetric (TG) thermogram of Pd/ICCP, Pd/SP and $Pd/CaCO_3$.

3.2.4 IR spectroscopic studies.

The palladium deposition onto the individual calcium carbonate plates resulted in slight shift of the characteristic IR absorption peaks of carbonyl group at 1440.0 cm^{-1} by 3.1 cm^{-1}(Figure 3.9). Identically, the palladium deposition onto the calcium carbonate particle resulted in slight shifts of the characteristic IR absorption peaks of carbonyl group at 1389.2 cm-1 by 1.5 cm^{-1}.The slight shifts is governed by the chelation between palladium species and calcium carbonate.

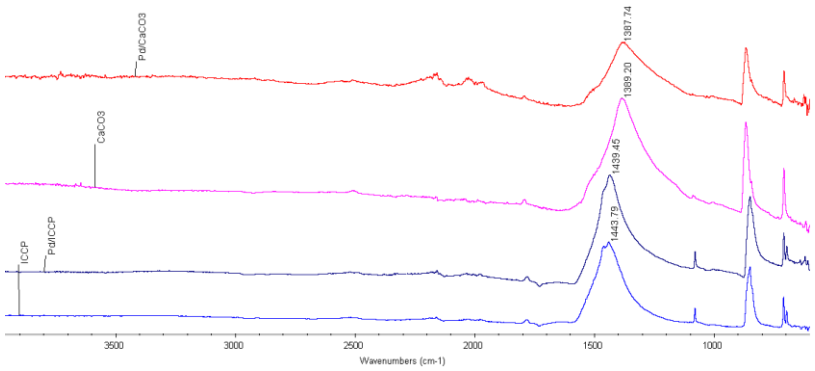


Figure 3.9 FTIR spectra of ICCP, $CaCO_3$, Pd/ICCP and $Pd/CaCO_3$ catalysts.

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3.2.5 Determination of Palladium content by ICP-OES analysis

The palladium contents of prepared catalysts were determined by inductively coupled plasma optical emission spectrometry analysis (ICP-OES) by using calibration curve as shown in appendix (Figure 2.1). Palladium content of 7.0%Pd/ICCP, 7.0%Pd/SP and 5%Pd/$CaCO_3$ were found at 6.1, 5.7, and 4.3% (wt./wt.) respectively. However, the reason why the palladium contents were slightly lower from expected palladium content in each catalyst is perhaps due to the binding ability of palladium nanoparticle onto different calcium carbonate structure. Notably, the content of copper in Pd/ICCP catalyst was not able to detect in ICP analysis, suggesting that the amount of copper in the prepared catalyst can be negligible.

Table 3.1 Determination of Palladium content in the catalysts.

Entry	Catalyst	Expected Palladium Content(% wt/wt)	Palladium Content[a](% wt/wt)
1	Pd/ICCP	7.0	6.1 ± 0.2%
2	Pd/SP	7.0	5.7 ± 0.1%
3	Pd/$CaCO_3$	5.0	4.3 ± 0.1%

[a] **Palladium weight percentage was determined from ICP-OES analysis.**

3.3 Optimization studies on the Sonogashira coupling reaction

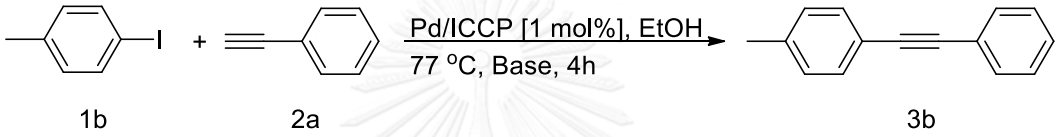
3.3.1 Optimization of the reaction conditions

With Pd/ICCP in hand, we tested the catalytic performance in copper free Sonogashira coupling reaction. 4-iodotoluene **1b** was selected as starting material for optimization studies because it has moderate electron donating power on benzene ring. The effect of solvents, bases and temperature were studied in the following section.

3.3.1.1 Screening type of bases

In this section, we used 109 mg of 4-iodotoluene, ethynylbenzene (51 mg, 0.60 mmol), Pd/ICCP (9 mg, 0.005 mmol), base and 6 mL of ethanol. All the reactions were carried out in a sealed tube and heated at 77°C for 4 h and the reaction were monitored by GC analysis. The results in Table 3.2 indicated that among six bases, potassium carbonate is proven to be the most efficient base giving coupling product (3b) in 99% yield (Table 3.2, entry 6). This result can be explained by the good solvation of potassium carbonate in EtOH.

Table 3.2 Effect of base.



1b 2a 3b

Entry	Base	Yield [%][a]
1	DIPA	2
2	TEA	4
3	Piperidine	9
4	KOAc	1
5	Cs_2CO_3	15
6	K_2CO_3	99

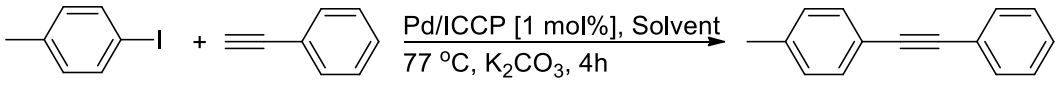
[a] GC yield.

3.3.1.2. Screening solvent

In this section, 6 solvents were screened under the above condition from previous section. The results in Table 3.3 indicated that commonly used polar aprotic solvents (THF, CH_3CN, DMSO, and DMF) as well as non-polar solvent (toluene) gave inferior results. These results are probably due to poor solvation of potassium carbonate in those solvents. In conclusion, polar protic solvent (EtOH) still

considered as the most efficient solvent giving coupling product (**3b)** in 99% yield (Table 3.3, entry 1).

Table 3.3 Effect of solvent.



1b 2a 3b

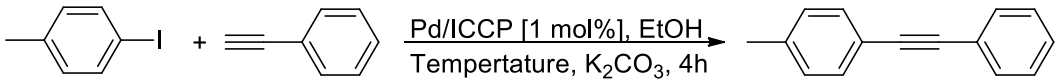
Entry	Solvent	Yield [%][a]
1	EtOH	99
2	toluene	0
3	THF	0
4	MeCN	5
5	DMSO	3
6	DMF	4

[a] GC yield.

3.1.1.3 Temperature of reaction

Based on the above study, we selected ethanol as solvent and K_2CO_3 as a base to perform the reaction at 50°C to 77°C in order to find the optimal temperature. The results in Table 3.4 demonstrated that lowering the temperature resulted in the lower yield even though the reaction was conducted for 24 hour. Therefore, we selected 77 °C as optimal temperature for the reaction.

Table 3.4 Effect of temperature.



1b 2a 3b

Entry	Temperature	Reaction time	Yield [%][a]
1	50°C	24 h	68
2	77°C	4h	99

Reaction condition: 4-iodotoluene (0.5 mmol), phenyl acetylene (0.6 mmol) catalysts (0.005 mmol), bases (1.0 mmol), in solvents (6.0 mL). [a] GC yield.

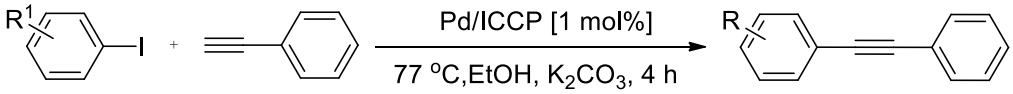
3.2.2 Substrate scope on aryl iodides

With the optimal condition in hand, we next demonstrate the generality of our method. A panel of aryl iodides (**1a-1t**) carrying various functional groups was subjected to the optimized reaction condition with ethynylbenzene 2a. In this section, aryl iodides starting materials were divided into 4 groups as shown in Tables 3.5-3.8

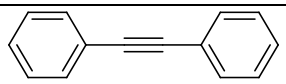
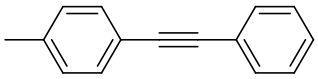
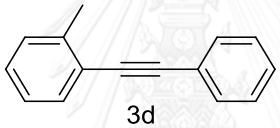
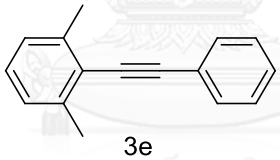
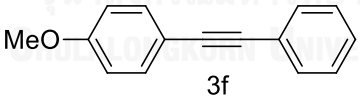
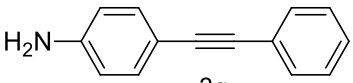
3.2.2.1 Aryl iodides carrying electron-donating groups (**1a**-**1g**)

The aryl iodides bearing electron-donating group, including 4-iodobenzene **1a,** 4-iodotoluene **1b,** 3-iodotoluene **1c,** 2**-**iodotoluene **1d,** 2-iodo-1,3-dimethylbenzene **1e**, 1-iodo-4-methoxybenzene **1f** and 4-iodoaniline **1g** were subjected to the optimized condition and the results were presented in Table 3.5. Electron donating functional groups such as methyl, methoxy and amine were well tolerated and the coupling products **3a**-**3g** were isolated in good to high yields (entry 1-7). We would like to note that these substituents are known to retard the oxidative addition step in catalytic cycle and hetero atoms can complex with palladium species resulting in the poor reaction rate [28]. These results suggest the high performance of our catalyst. Moreover, the cross-coupling of sterically hindered aryl iodides (2-iodotoluene **1d** and 2-iodo-1,3-dimethylbenzene **1e** also proceeded quite well to produce the target products **3d** and **3e** respectively in 57 and 91% yields (entry 4 and 5).

Table 3.5 Substrates scope: aryl iodide carrying electron donating group.



1a-1g 2a 3a-3g

entry	products	yield(%)[a]
1	 3a	88
2	 3b	84
3	 3c	92
4	 3d	90
5	 3e	57[b]
6	 3f	88
7	 3g	85

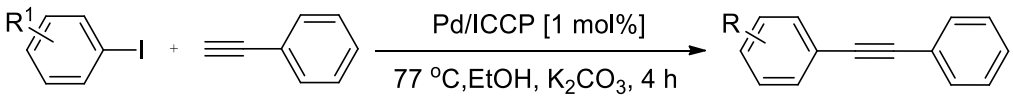
[a] Isolated yield, [b] 5% catalyst was used.

3.2.2.2 Aryl iodides carrying electron-withdrawing groups (**1h**-**1o**)

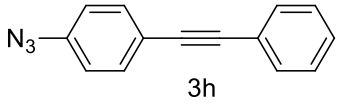
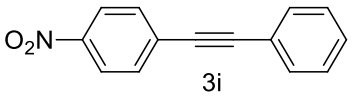
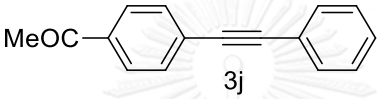
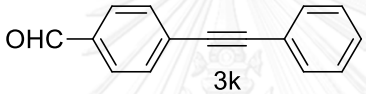
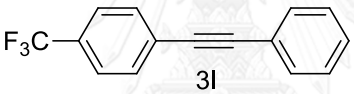
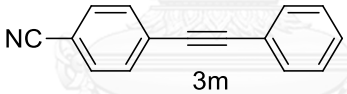
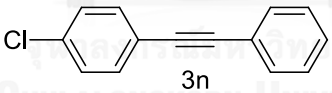
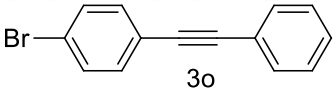
Aryl iodide bearing electron-withdrawing groups for example, azido **1h,** nitro **1i**, keto **1j**, aldehyde **1k**, trifluoromethyl **1l** nitrile **1m**, chloro **1n**, and bromo groups **1o** were successfully coupled with ethynylbenzene and the results were summarized in Table 3.6. Good to excellent yields of alkyne **3h-3o** were obtained under

optimized condition as show in Table 3.6 (entry 1-8). The other leaving group such as chloro **1n** and bromo **1o** which are capable for coupling reaction remain untouched under the optimized condition. However, aryl iodide bearing methyl ester group (**1p**) was unable to proceed via the optimized condition using ethanol as solvent. The reaction generated ethyl ester **3p** in 80 % yield resulting from the base-catalyzed transesterification of ethanol at carbonyl group of starting material (Scheme 3.1). Therefore, we switched the condition of Sonogashira coupling reaction to use acetonitrile as solvent and triethylamine as base (**Scheme 3.2**). Under this condition, the product **3q** was obtained in 82 %yield.

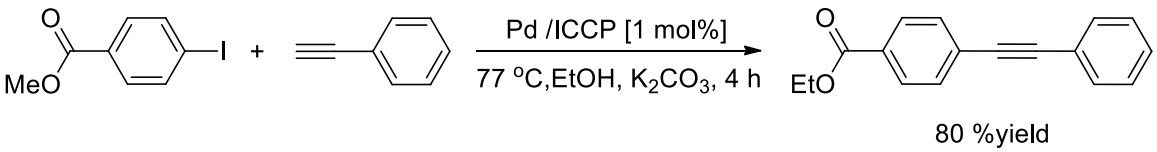
Table 3.6 Substrates scope: aryl iodide carrying electron-withdrawing group.



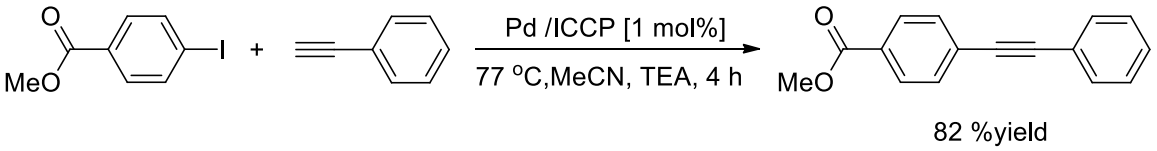
1h-1o 2a 3h-3o

entry	products	yield(%)[a]
1	 3h	82[b]
2	 3i	91
3	 3j	Quantitative yield
4	 3k	98[b]
5	 3l	77[b]
6	 3m	80[b]
7	 3n	89
8	 3o	90

[a] Isolated yield, [b] 5% catalyst was used.



Scheme 3.1 Sonogashira reaction of methyl 4-iodobenzoate.

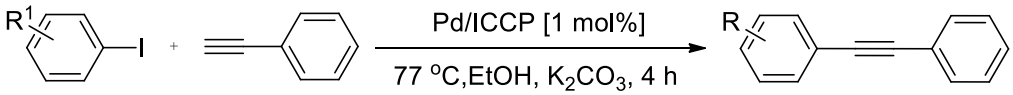


Scheme 3.2 Sonogashira reaction of methyl 4-iodobenzoate with acetonitrile and TEA

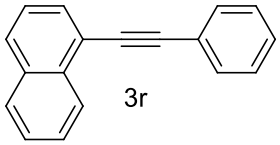
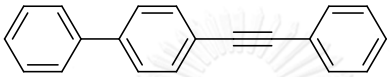
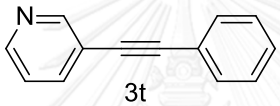
3.2.2.3 Aryl iodides carrying polyaromatic and heteroaromatic groups (1r-1t)

The aryl iodides bearing polyaromatic group, including 4-iodo-1,1'-biphenyl **1r** and 1-iodonaphthalene **1s** and heteroaromatic, 3-iodopyridine **1t** were reacted with alkyne **2a** under the optimized condition as shown in Table 3.7 All aryl iodides **1r**-**1t** reacted smoothly to yield the product 3r-3t in excellent yields (Table 3.7, entry 1-3).

Table 3.7 Substrates scope: aryl iodide carrying polyaromatic and heteroaromatic group.



1r-1t 2a 3r-3t

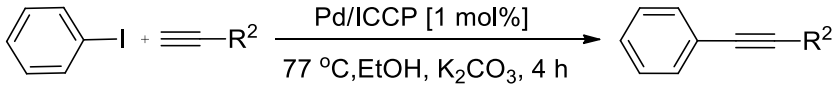
entry	products	yield(%)[a]
1	 3r	82
2	 3s	80
3	 3t	86

[a] Isolated yield

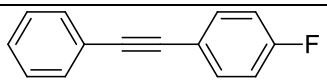
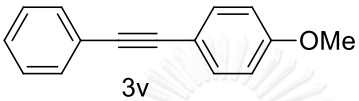
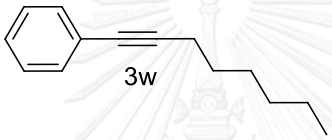
3.2.3 Substrate scope on terminal alkynes (**2b**-**2d**)

After screening functional group compatibility on the aryl iodide as coupling partner, we then turned our attention to substrate scope on the terminal alkynes. We selected 1-ethynyl-4-fluorobenzene **2b**, 1-ethynyl-4-methoxybenzene **2c** and oct-1-yne **2d** as model for terminal alkyne substrates containing electron donating, electron-withdrawing and alkyl group respectively. These three terminal alkynes (**2b**-**2d**) underwent Sonogashira coupling reaction successfully under optimized condition and the desired products **3u**-**3w** were obtained in excellent yields as shown in Table 3.8.

Table 3.8 Substrates scope: the terminal alkyne.



1a 2b-2d 3u-3w

Entry	product	yield(%)a
1	 3u	83
2	 3v	81
3	 3w	79

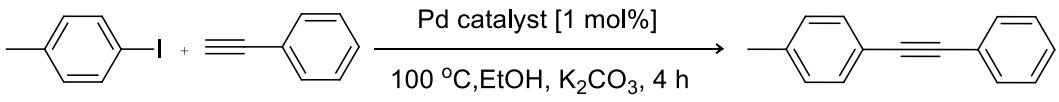
[a] Isolated yield

3.4 Reusability test and catalytic activity comparison between Pd/ICCP, Pd/SP and Pd/$CaCO_3$

For the reusability test of the catalysts, we used percent conversion of the reaction between 4-iodotoluene **1b** with ethylnylbenzene **2a** to evaluate the relative catalytic activities of the recycled Pd/ICCP, Pd/SP and Pd/$CaCO_3$ catalysts for five consecutive runs by using procedure in section 2.4 and the results were summarized in Table 3.9. In the first run, we found that the Pd/ICCP and Pd/$CaCO_3$ are more reactive than Pd/SP and no remaining starting material (entry 1). This result suggested that the chemical treatment in the preparation of ICCP is important in order to use natural shell particle as catalytic support. We hypothesized that the high surface area of ICCP is responsible for its high catalytic activity over shell particle (SP). Moreover, percent conversion of 4-iodotoluene for Pd/SP and Pd/$CaCO_3$ decreased dramatically after the first run. The poor reusability of Pd/$CaCO_3$ could be attributed to the palladium leaching due to the lacking of organic content in the surface of particle.

In contrast, the percent conversion of reused Pd/ICCP catalyst slightly decreased for three cycles. The noticeable stability of the Pd/ICCP catalyst might be attributed to the chelation of palladium species with the surface chitin and protein molecules of the pearl shell particles.

Table 3.9 Comparing reusability of palladium catalysts.



1b 2a 3b

Entry	Conversion [%] [a]		
	Pd/ICCP	Pd/SP	$Pd/CaCO_3$
1	100	72	100
2	92	26	52
3	88	15	33
4	67	26	28
5	41	20	20

Reaction condition: 4-iodotoluene (0.5 mmol), phenyl acetylene (0.6 mmol) catalysts (0.005 mmol), bases (1.0 mmol), in solvents (6.0 mL), solution at 100 °C. [a] determined from the GC measurement.

3.5 Determination of Palladium content in reaction mixture by ICP-OES analysis

Metal leaching was another concern for supported heterogeneous catalyst. In this section, palladium leaching was studied by determining palladium content of the reaction mixture after filtration using procedure in section 2.8. The palladium contents of crude from Pd/ICCP, Pd/SP and Pd/$CaCO_3$ were determined by ICP analysis giving Pd amount as followed 1.1, 1.4 and 8.6% (Table 3.10). As a result, Pd contents of Pd/ICCP and Pd/SP are lower than Pd/$CaCO_3$. This may be due to the chelation between Pd and protein in shell particles or individual calcium carbonate plates [14]. Therefore, Pd/ICCP catalyst is promising option for low level leaching metal heterogeneous catalyst with high reactivity and reusability of the catalyst.

Table 3.10 Palladium content in reaction mixture

Catalyst	Palladium leaching (wt./wt.)
Pd/ICCP	1.1 %
Pd/SP	1.4 %
Pd/$CaCO_3$	8.6 %

CHAPTER IV
CONCLUSION

In conclusion, a novel heterogeneous palladium catalyst using individual calcium carbonate plates (ICCP) from naturally abundant shell powders has been developed. The catalyst features a low-leaching, ligand-free, and copper-free Sonogashira coupling reaction with the higher activity than that of Pd/$CaCO_3$ and simple Pd on shell particle (Pd/SP). It can be reused at least three times without a noticeable decrease in the product yield and its catalytic activity. Also the leaching of Pd/ICCP is negligible. The high catalytic efficiency and reusability of the Pd/ICCP catalyst may be attributed to high surface area and the chelation of the palladium (0) species with the surface protein of the ICCP. Moreover, the low cost, wide availability and green preparation method of Pd/ICCP can be considered as economic and environmental friendly catalyst which is value for synthetic chemists for academic research and industry application.

REFERENCES

[1] Sonogashira, K., Tohda, Y., and Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes and Bromopyridines. Tetrahedron Letters 16(50) (1975): 4467-4470.

[2] Chinchilla, R. and Nájera, C. The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. Chemical Reviews 107(3) (2007): 874-922.

[3] 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. Organic Letters 4(10) (2002): 1691-1694.

[4] Soheili, A., Albaneze-Walker, J., Murry, J.A., Dormer, P.G., and Hughes, D.L. Efficient and General Protocol for the Copper-Free Sonogashira Coupling of Aryl Bromides at Room Temperature. Organic Letters 5(22) (2003): 4191-4194.

[5] Cheng, J., et al. A Copper- and Amine-Free Sonogashira Reaction Employing Aminophosphines as Ligands. The Journal of Organic Chemistry 69(16) (2004): 5428-5432.

[6] Liang, B., Dai, M., Chen, J., and Yang, Z. Copper-Free Sonogashira Coupling Reaction with $PdCl_2$ in Water under Aerobic Conditions. The Journal of Organic Chemistry 70(1) (2005): 391-393.

[7] Garrett, C.E. and Prasad, K. The Art of Meeting Palladium Specifications in Active Pharmaceutical Ingredients Produced by Pd-Catalyzed Reactions. Advanced Synthesis & Catalysis 346(8) (2004): 889-900.

[8] Tyrrell, E., Al-Saardi, A., and Millet, J. A Novel Silica-Supported Palladium Catalyst for a Copper-Free Sonogashira Coupling Reaction. Synlett (3) (2005): 487-488.

[9] Djakovitch, L. and Rollet, P. Sonogashira Cross-coupling Reactions Catalysed by Heterogeneous Copper-free Pd-zeolites. Tetrahedron Letters 45(7) (2004): 1367-1370.

[10] Heidenreich, R.G., Köhler, K., Krauter, J.G.E., and Pietsch, J. Pd/C as a Highly Active Catalyst for Heck, Suzuki and Sonogashira Reactions. Synlett 2002(07) (2002): 1118-1122.

[11] Senra, J.D., Malta, L.F.B., de Souza, A.L.F., Medeiros, M.E., Aguiar, L.C.S., and Antunes, O.A.C. Phosphine-free Heck Reactions in Aqueous Medium Using Hydroxypropylated Cyclodextrins as Supramolecular Hosts. Tetrahedron Letters 48(46) (2007): 8153-8156.

[12] Coelho, A.V., de Souza, A.L.F., de Lima, P.G., Wardell, J.L., and Antunes, O.A.C. Ligand-free Stille Cross-coupling Reaction Using Pd/$CaCO_3$ as Catalyst Reservoir. Tetrahedron Letters 48(43) (2007): 7671-7674.

[13] Shen, Y.-M., et al. Heck Reaction Catalyzed by a Recyclable Palladium Supported on Shell Powder. Applied Organometallic Chemistry 24(9) (2010): 631-635.

[14] Zeng, M., et al. An Efficient and Recyclable Heterogeneous Palladium Catalyst Utilizing Naturally Abundant Pearl Shell Waste. Green Chemistry 13(2) (2011): 350-356.

[15] Elangovan, A., Wang, Y.-H., and Ho, T.-I. Sonogashira Coupling Reaction with Diminished Homocoupling. Organic Letters 5(11) (2003): 1841-1844.

[16] Frigoli, S., Fuganti, C., Malpezzi, L., and Serra, S. A Practical and Efficient Process for the Preparation of Tazarotene. Organic Process Research & Development 9(5) (2005): 646-650.

[17] King, A.O. and Yasuda, N. Palladium-Catalyzed Cross-Coupling Reactions in the Synthesis of Pharmaceuticals. in Organometallics in Process Chemistry, pp. 205-245. Berlin, Heidelberg: Springer Berlin Heidelberg, 2004.

[18] Lertvachirapaiboon, C., Parnklang, T., Pienpinijtham, P., Wongravee, K., Thammacharoen, C., and Ekgasit, S. Selective Colors Reflection from Stratified Aragonite Calcium Carbonate Plates of Mollusk Shells. Journal of Structural Biology 191(2) (2015): 184-189.

[19] Suzuka, T., Okada, Y., Ooshiro, K., and Uozumi, Y. Copper-Free Sonogashira Coupling in Water with An Amphiphilic Resin-supported Palladium Complex. Tetrahedron 66(5) (2010): 1064-1069.

[20] Maji, M.S., Murarka, S., and Studer, A. Transition-Metal-Free Sonogashira-Type Coupling of ortho-Substituted Aryl and Alkynyl Grignard Reagents by Using 2,2,6,6-Tetramethylpiperidine-N-oxyl Radical as an Oxidant. Organic Letters 12(17) (2010): 3878-3881.

[21] Adjabeng, G., et al. Palladium Complexes of 1,3,5,7-Tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane: Synthesis, Crystal Structure and Use in the Suzuki and Sonogashira Reactions and the α-Arylation of Ketones. The Journal of Organic Chemistry 69(15) (2004): 5082-5086.

[22] Tomioka, H. and Sawai, S. Photolysis of Regioisomeric Diazides of 1,2-Diphenylacetylenes Studied by Matrix-isolation Spectroscopy and DFT Calculations. Organic & Biomolecular Chemistry 1(24) (2003): 4441-4450.

[23] Bong Park, S. and Alper, H. Recyclable Sonogashira Coupling Reactions in An Ionic liquid, Effected in the Absence of Both a Copper Salt and a Phosphine. Chemical Communications (11) (2004): 1306-1307.

[24] Salvi, L., Jeon, S.-J., Fisher, E.L., Carroll, P.J., and Walsh, P.J. Catalytic Asymmetric Generation of (Z)-Disubstituted Allylic Alcohols. Journal of the American Chemical Society 129(51) (2007): 16119-16125.

[25] Kim, H. and Lee, P.H. Palladium-Catalyzed Decarboxylative sp-sp2 Cross-Coupling Reactions of Aryl and Vinyl Halides and Triflates with α,β-Ynoic Acids using Silver Oxide. Advanced Synthesis & Catalysis 351(17) (2009): 2827-2832.

[26] Melzig, L., Metzger, A., and Knochel, P. Pd- and Ni-Catalyzed Cross-Coupling Reactions of Functionalized Organozinc Reagents with Unsaturated Thioethers. Chemistry – A European Journal 17(10) (2011): 2948-2956.

[27] Karastatiris, P., Mikroyannidis, J.A., Spiliopoulos, I.K., Kulkarni, A.P., and Jenekhe, S.A. Synthesis, Photophysics, and Electroluminescence of New

Quinoxaline-Containing Poly(p-phenylenevinylene)s. Macromolecules 37(21) (2004): 7867-7878.

[28] Urgaonkar, S. and Verkade, J.G. Ligand-, Copper-, and Amine-Free Sonogashira Reaction of Aryl Iodides and Bromides with Terminal Alkynes. The Journal of Organic Chemistry 69(17) (2004): 5752-5755.

[29] Chen, H.-J., et al. A New, Efficient, and Inexpensive Copper(II)/Salicylic acid Complex Catalyzed Sonogashira-type Cross-coupling of Haloarenes and Iodoheteroarenes with Terminal alkynes. Tetrahedron 66(39) (2010): 7755-7761.

[30] Li, P., Wang, L., and Li, H. Application of Recoverable Nanosized Palladium(0) Catalyst in Sonogashira Reaction. Tetrahedron 61(36) (2005): 8633-8640.

[31] Kakusawa, N., Yamaguchi, K., and Kurita, J. Palladium-catalyzed Cross-coupling Reaction of Ethynylstibanes with Organic Halides. Journal of Organometallic Chemistry 690(12) (2005): 2956-2966.

[32] Wang, L. and Li, P. Sonogashira Coupling Reaction with Palladium Powder, Potassium Fluoride in Aqueous Media. Synthetic Communications 33(21) (2003): 3679-3685.

[33] Lertvachirapaiboon, C., Jirapisitkul, T., Pienpinijtham, P., Wongravee, K., Thammacharoen, C., and Ekgasit, S. Air-gap-enhanced Pearlescent Effect in Periodic Stratified Bilayers of Perna Viridis Shell. Journal of Materials Science 49(18) (2014): 6282-6289.

APPENDIX

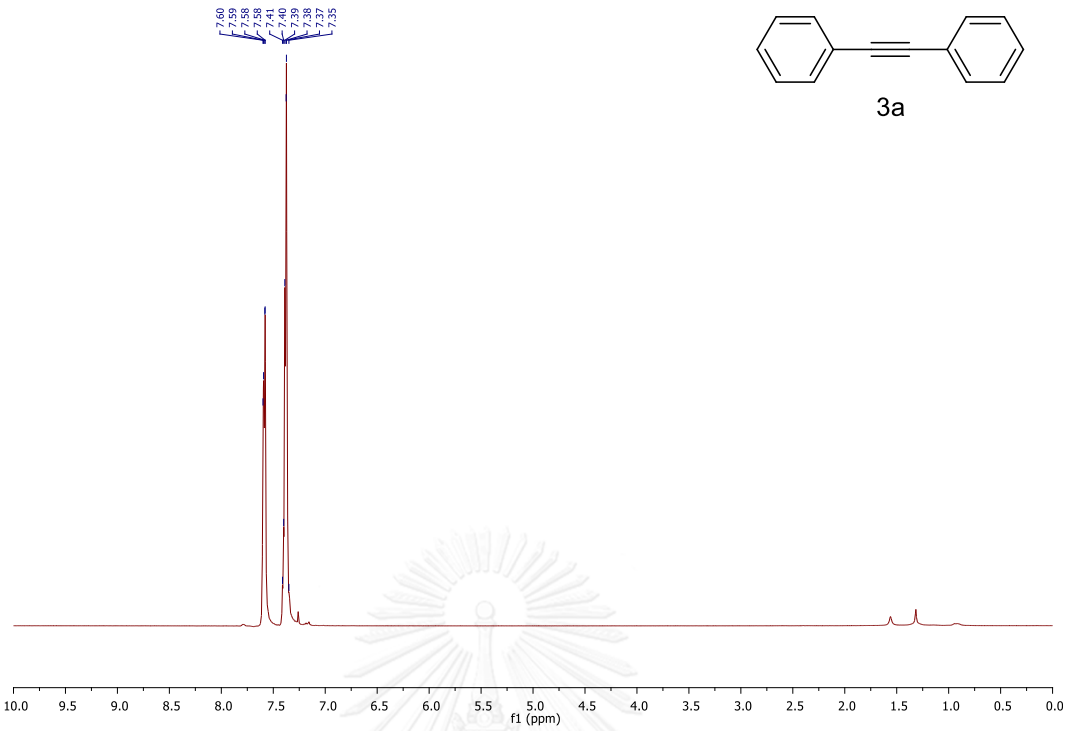


Figure A1 ^{1}H NMR spectrum of 3a ($CDCl_3$)

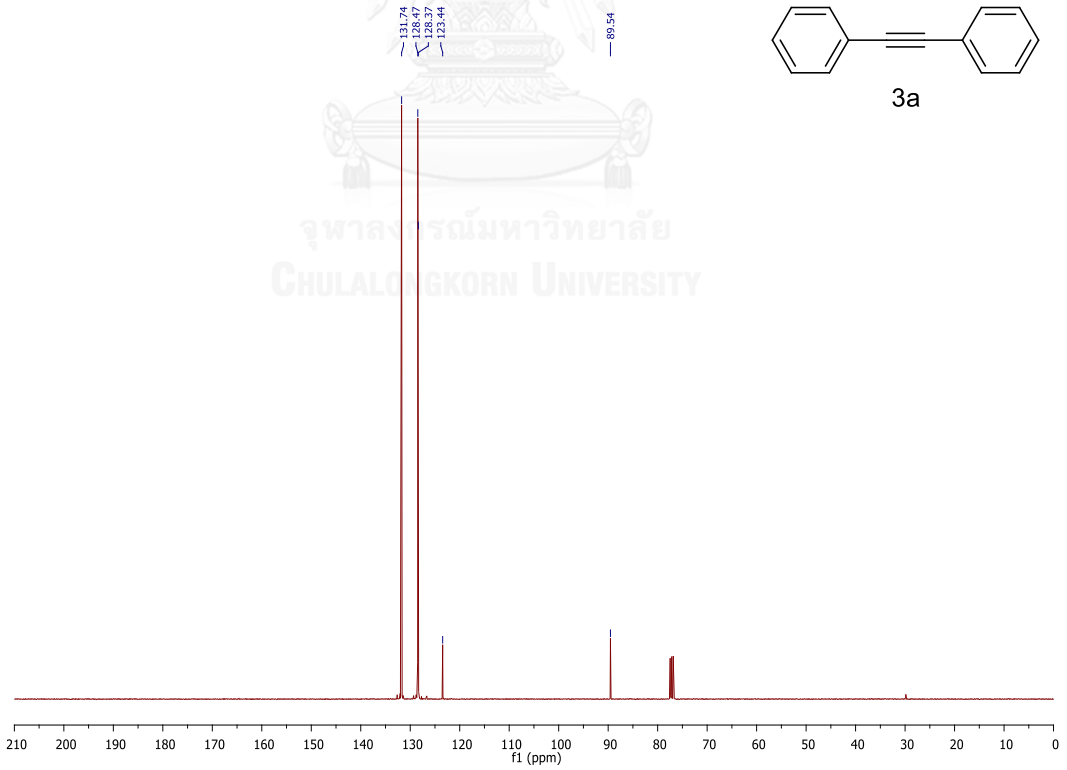


Figure A2 ^{13}C NMR spectrum of 3a ($CDCl_3$)

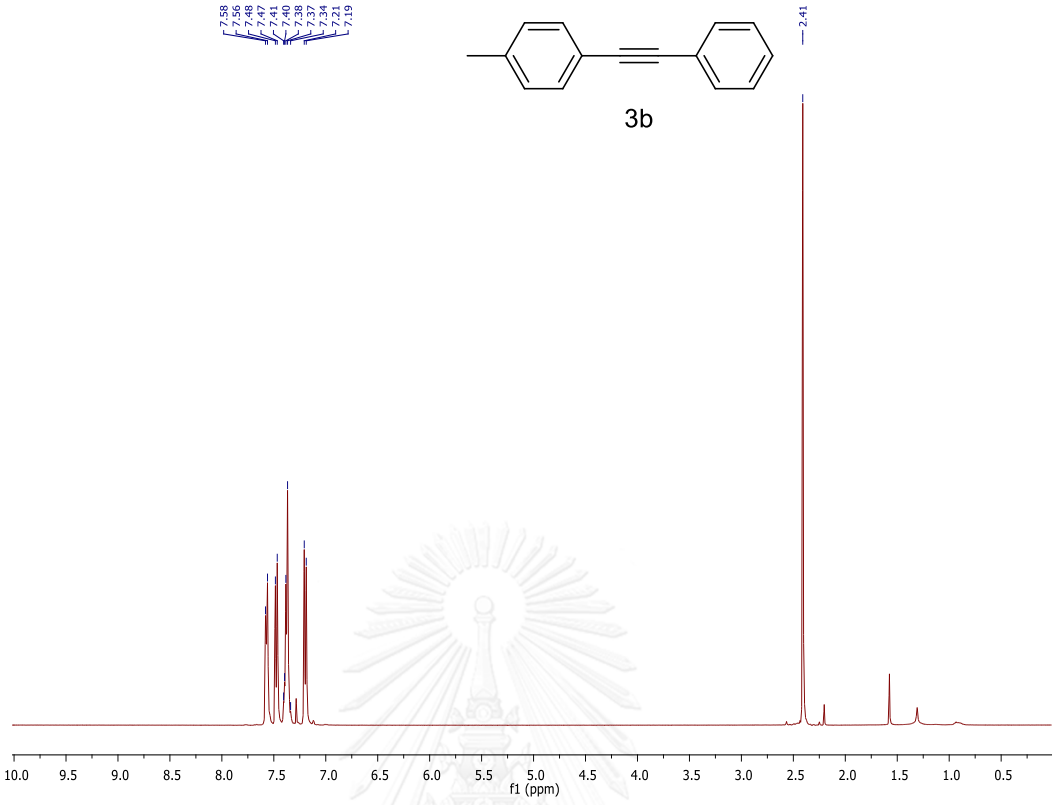


Figure A3 ^{1}H NMR spectrum of 3b ($CDCl_3$)

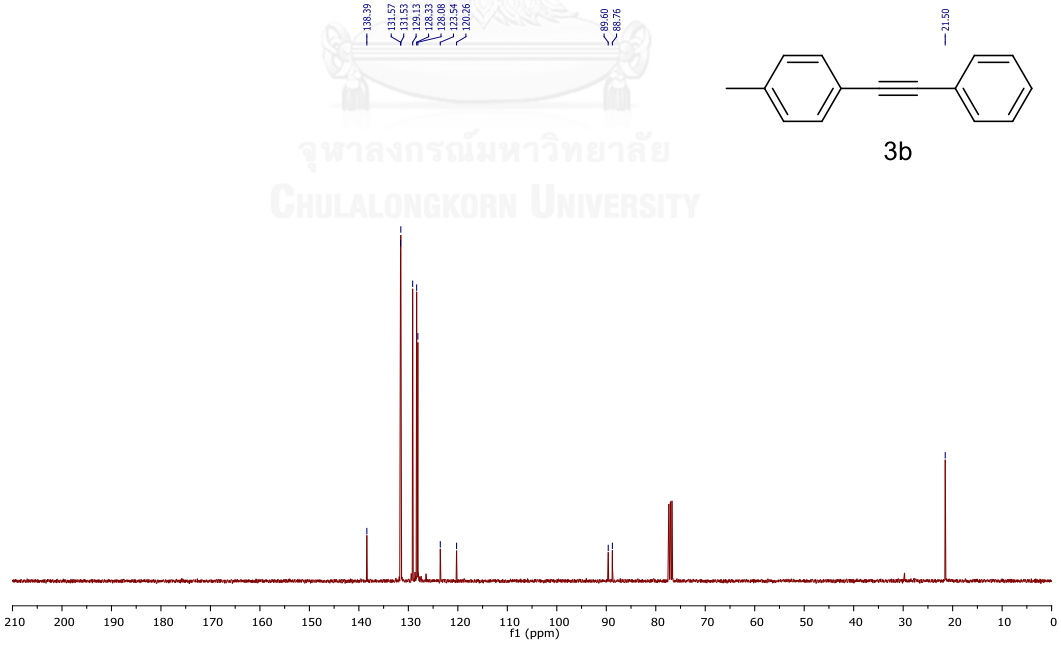


Figure A4 ^{13}C NMR spectrum of 3b ($CDCl_3$)

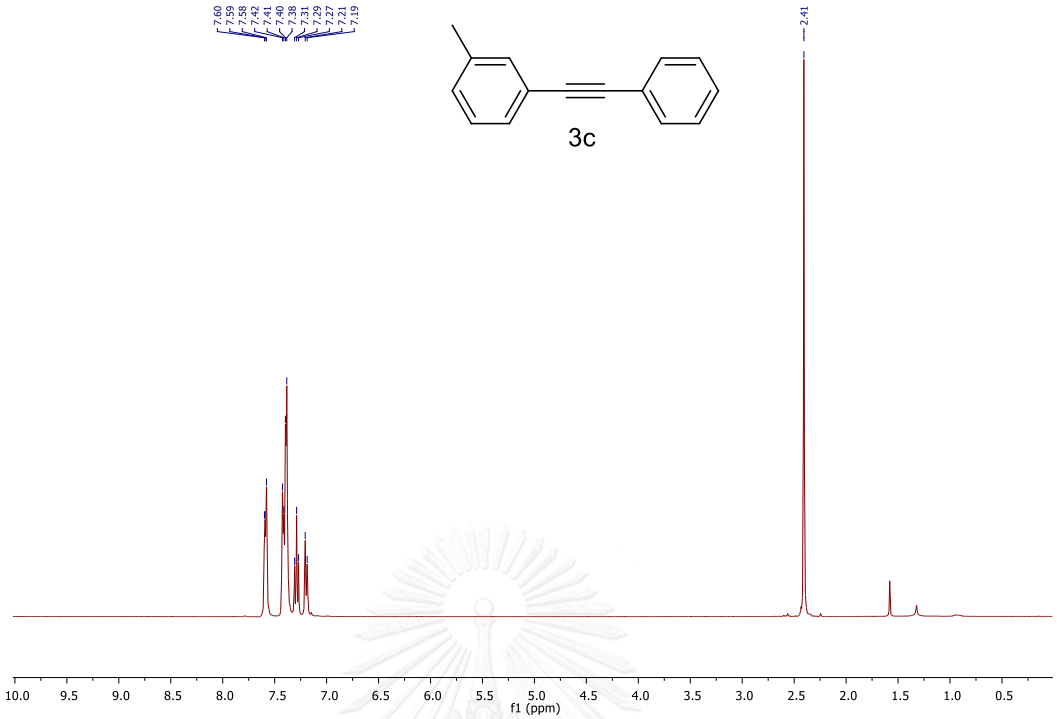


Figure A5 ^{1}H NMR spectrum of 3c ($CDCl_3$)

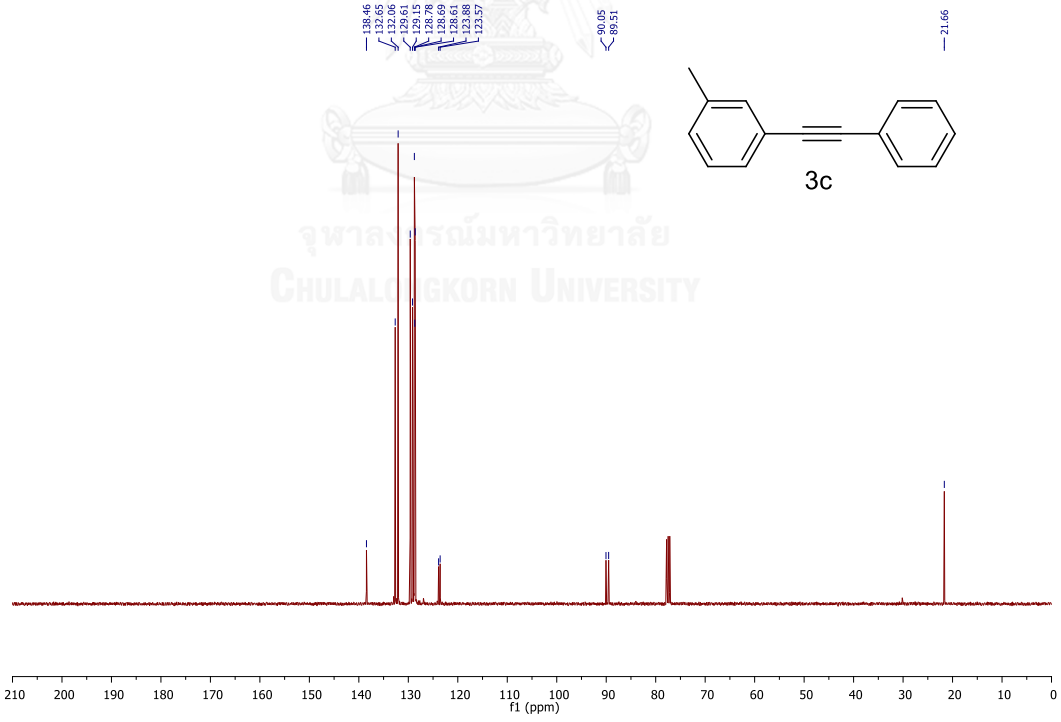


Figure A6 ^{13}C NMR spectrum of 3c (CDCl3)

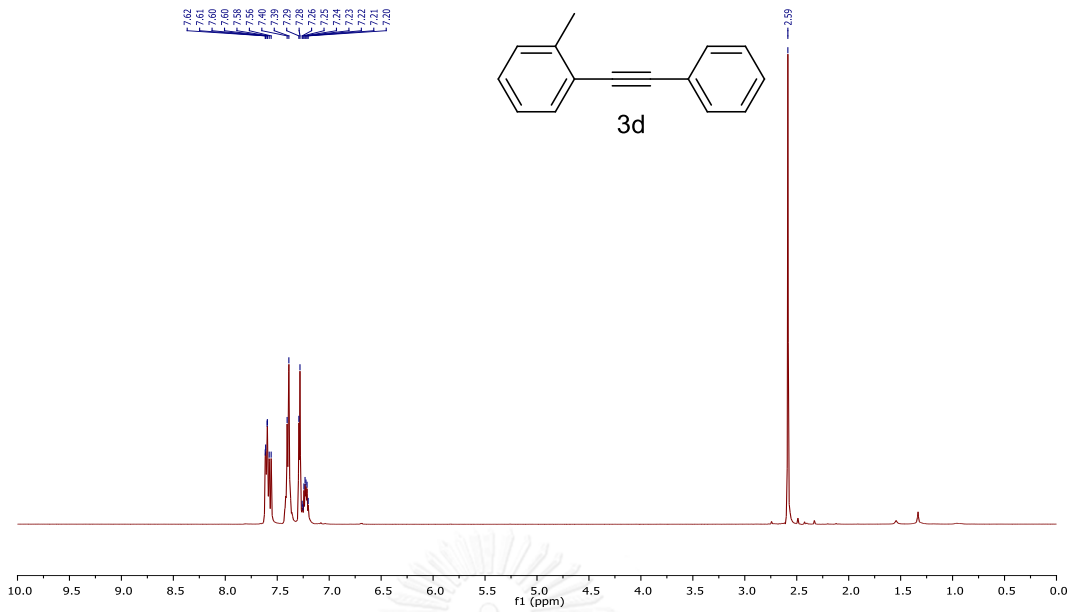


Figure A7 ^{1}H NMR spectrum of 3d ($CDCl_3$)

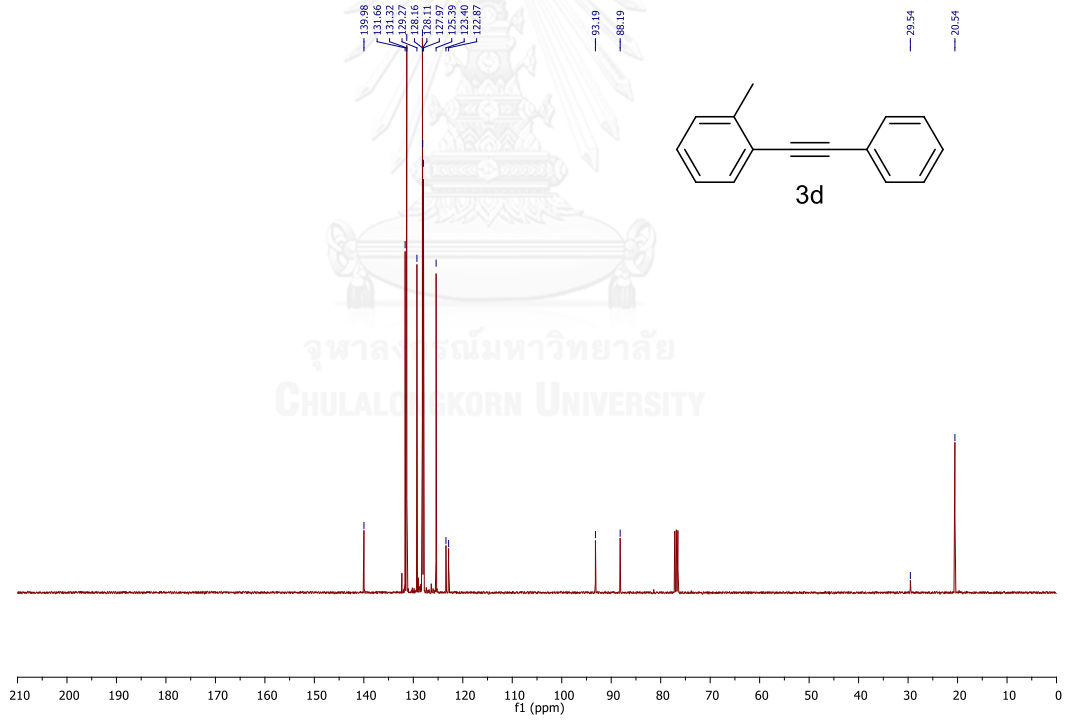


Figure A8 ^{13}C NMR spectrum of 3d ($CDCl_3$)

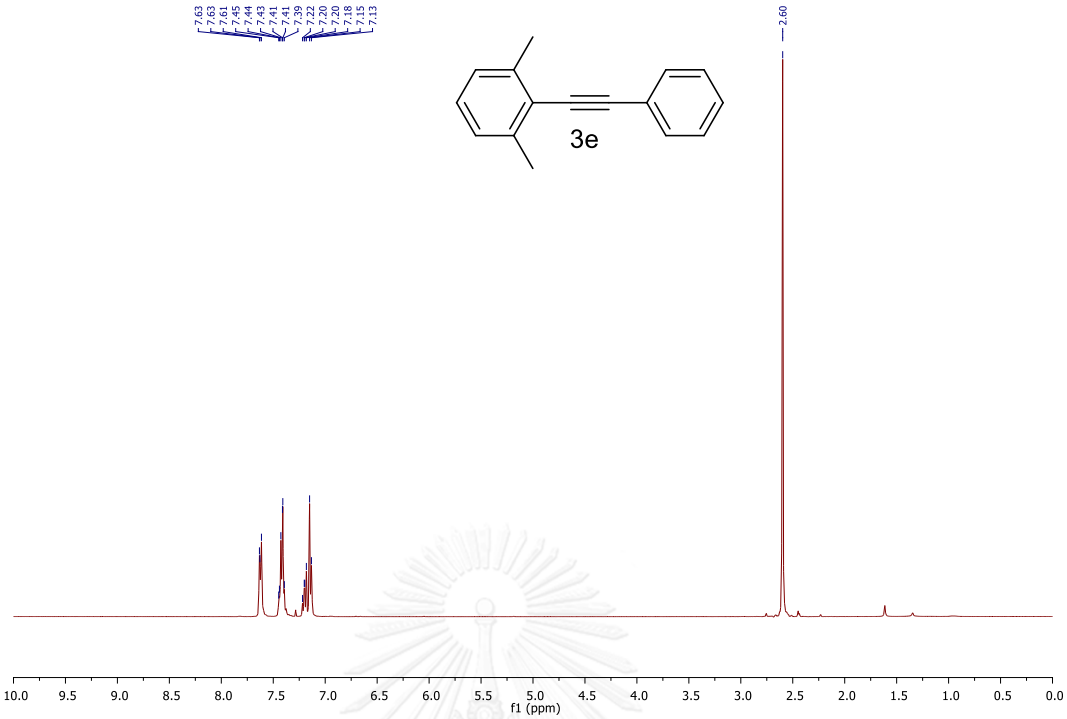


Figure A9 ^{1}H NMR spectrum of 3e ($CDCl_3$)

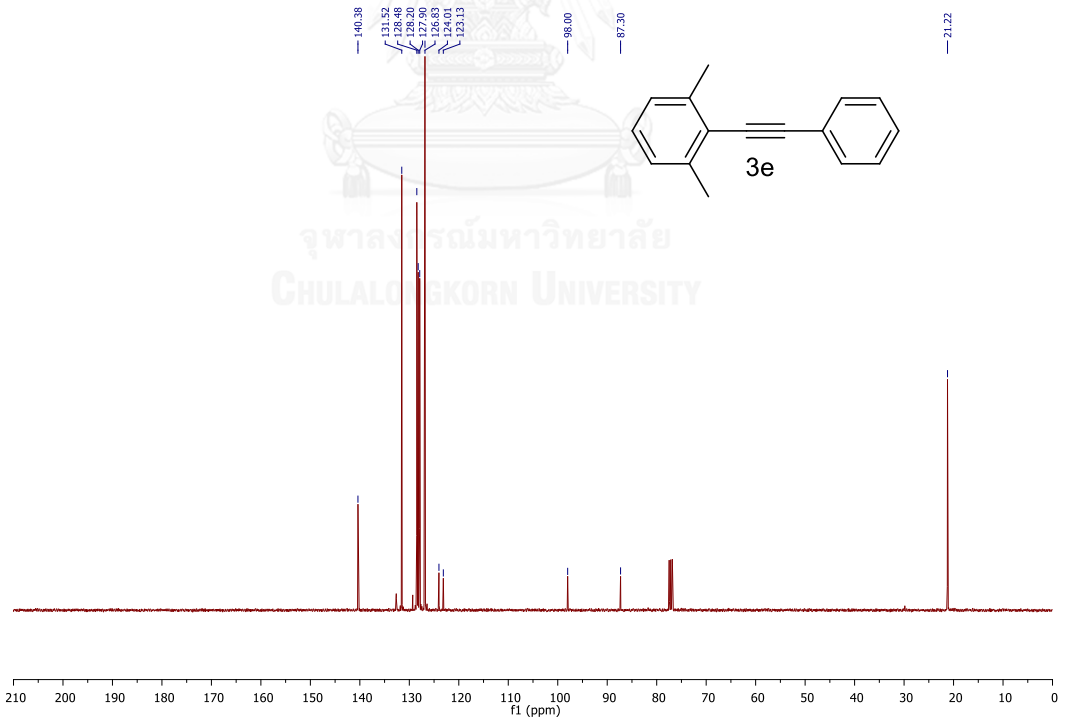


Figure A10 ^{13}C NMR spectrum of 3e ($CDCl_3$)

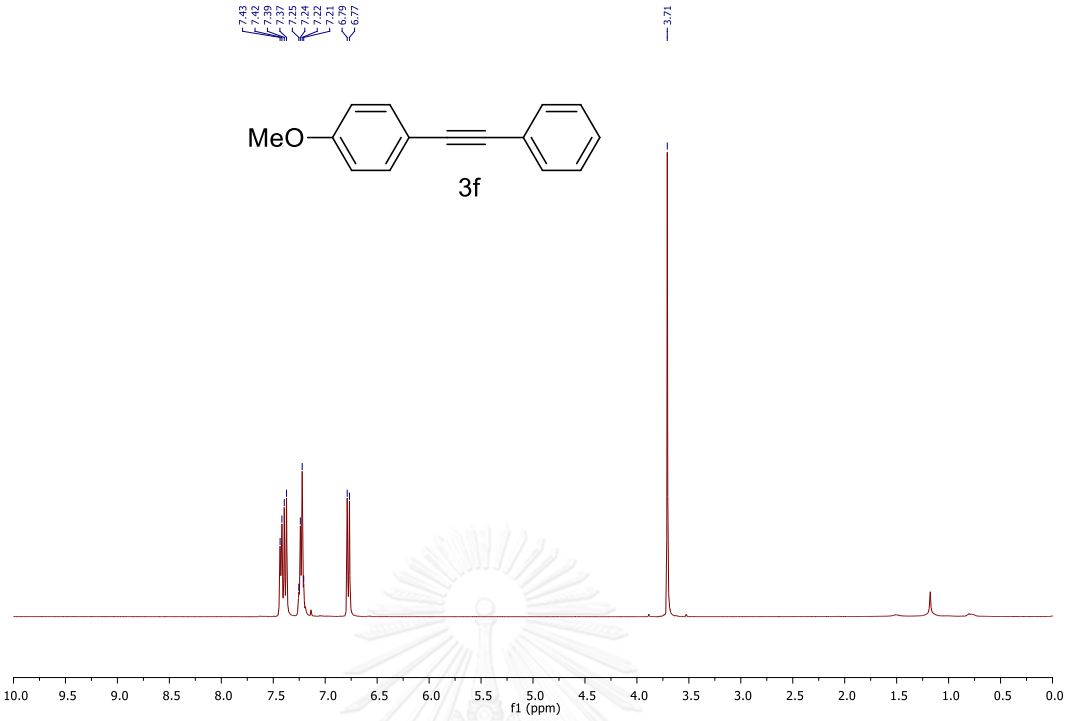


Figure A11 ^{1}H NMR spectrum of 3f ($CDCl_3$)

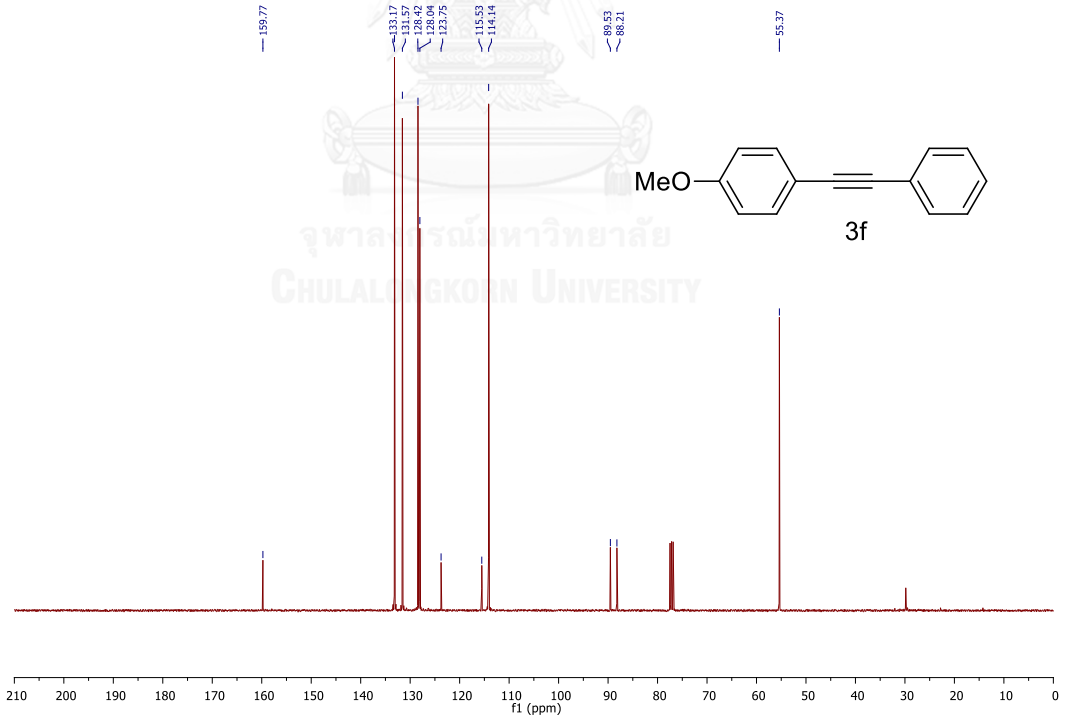


Figure A12 ^{13}C NMR spectrum of 3f ($CDCl_3$)

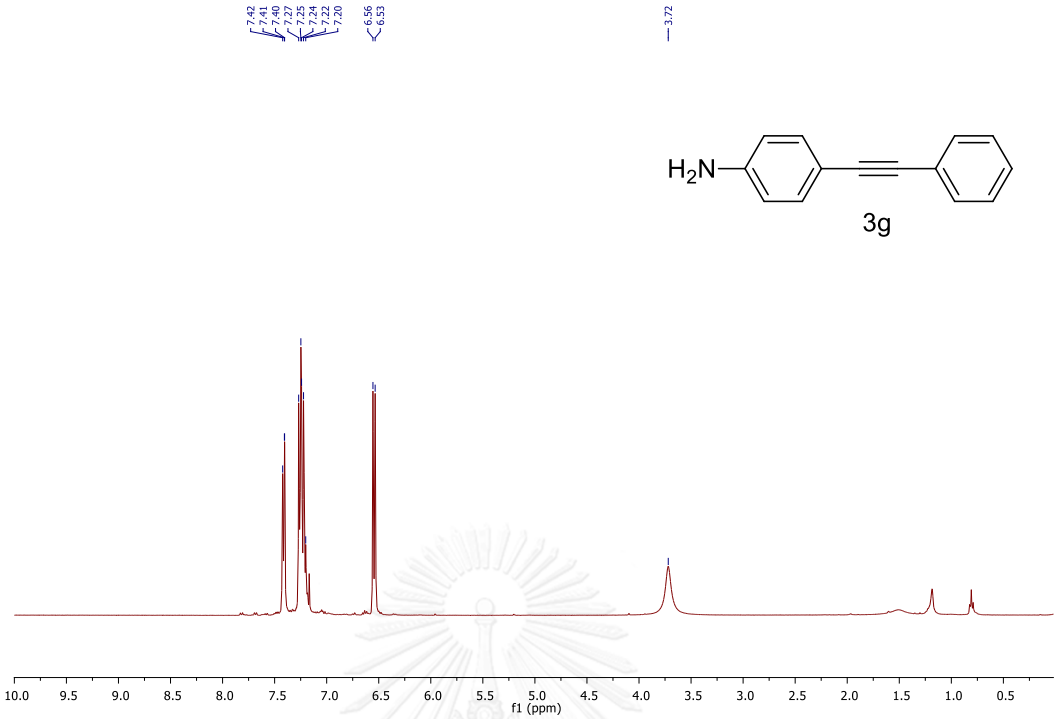


Figure A13 ^{1}H NMR spectrum of 3g ($CDCl_3$)

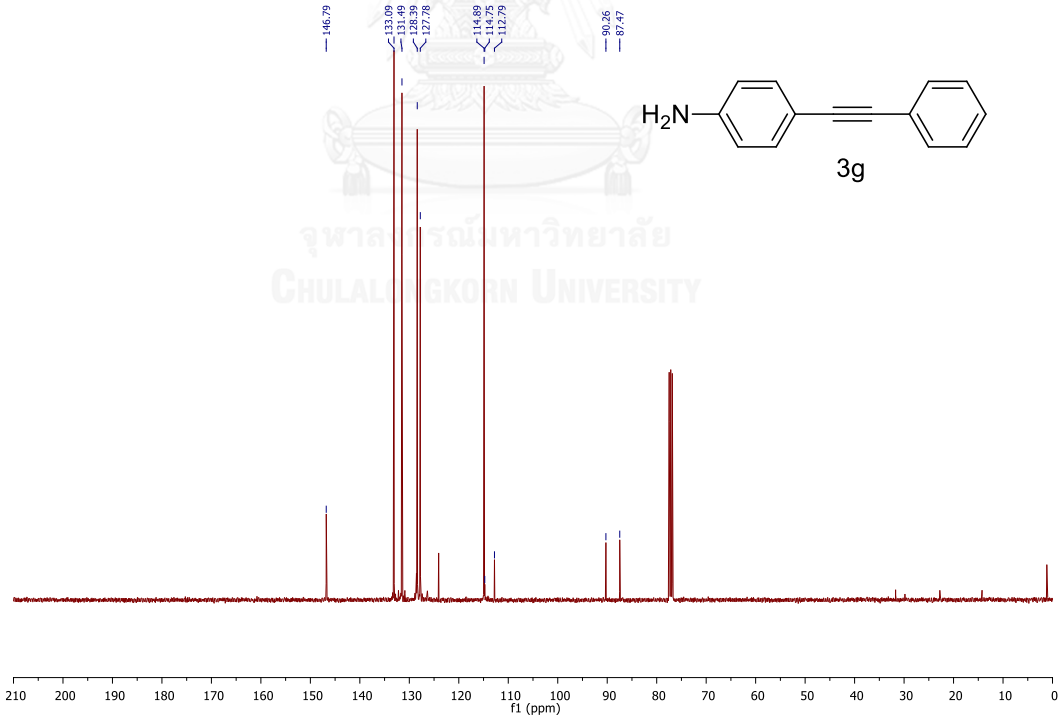


Figure A14 ^{13}C NMR spectrum of 3g ($CDCl_3$)

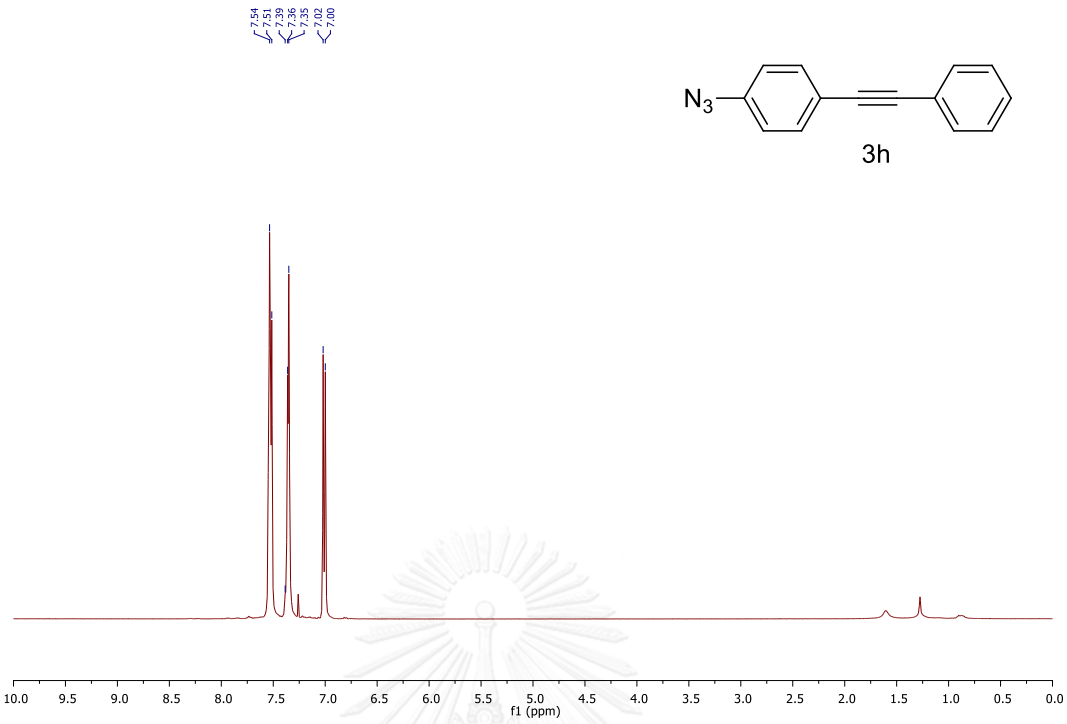


Figure A15 ^{1}H NMR spectrum of 3h ($CDCl_3$)

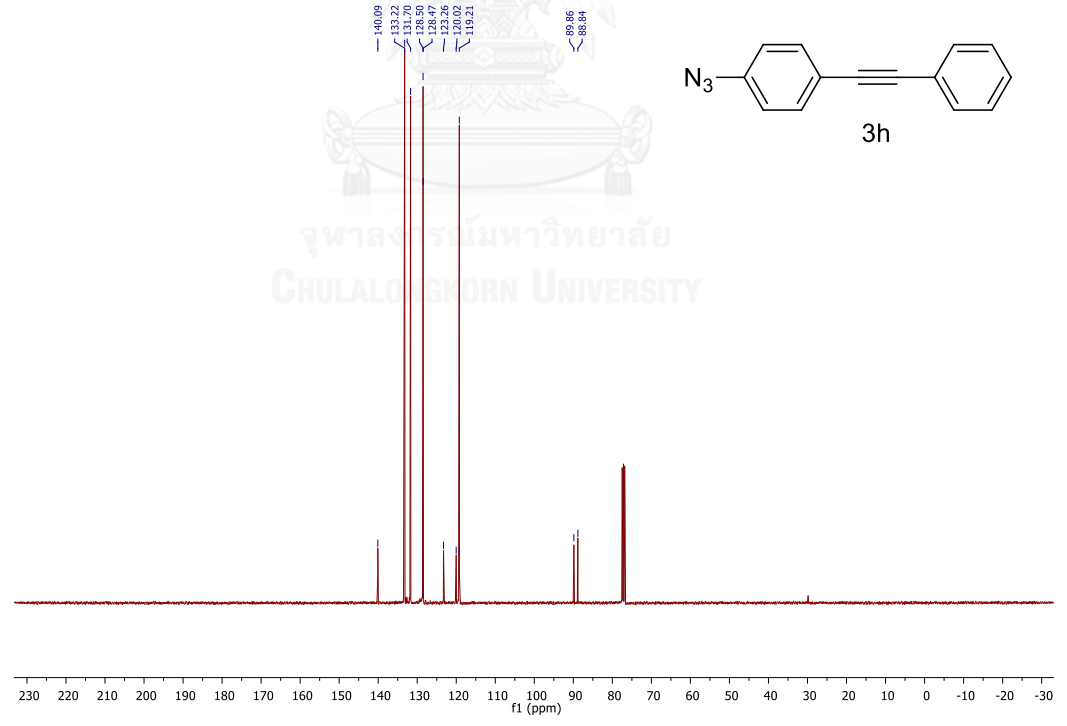


Figure A16 ^{13}C NMR spectrum of 3h ($CDCl_3$)

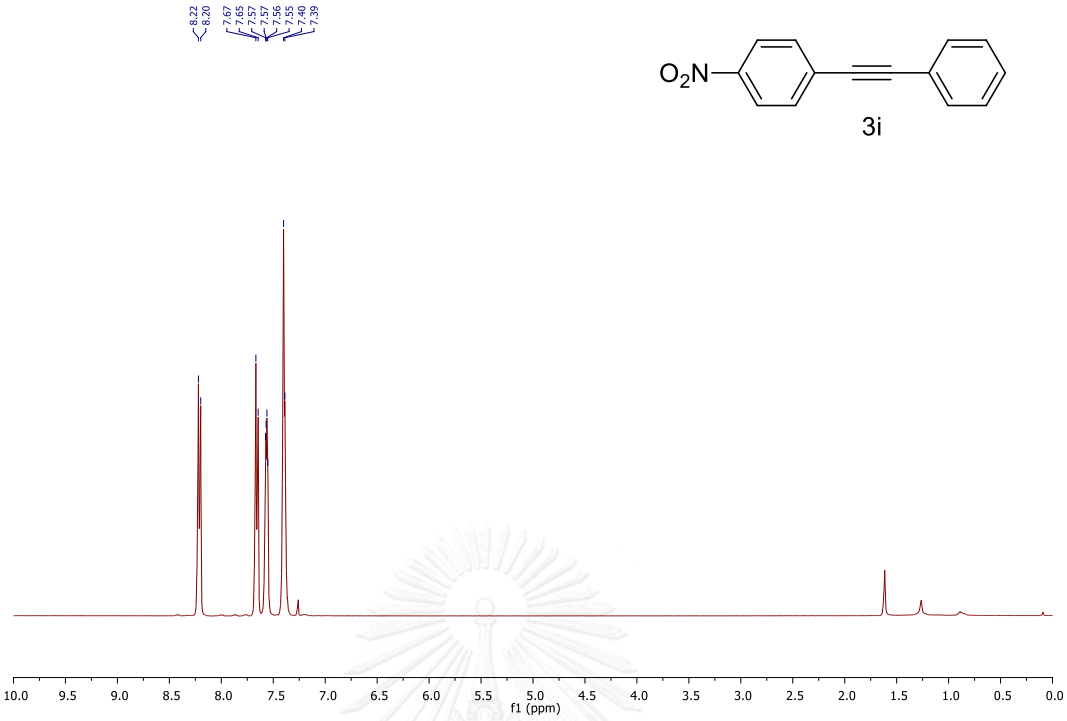


Figure A17 ^{1}H NMR spectrum of 3i ($CDCl_3$)

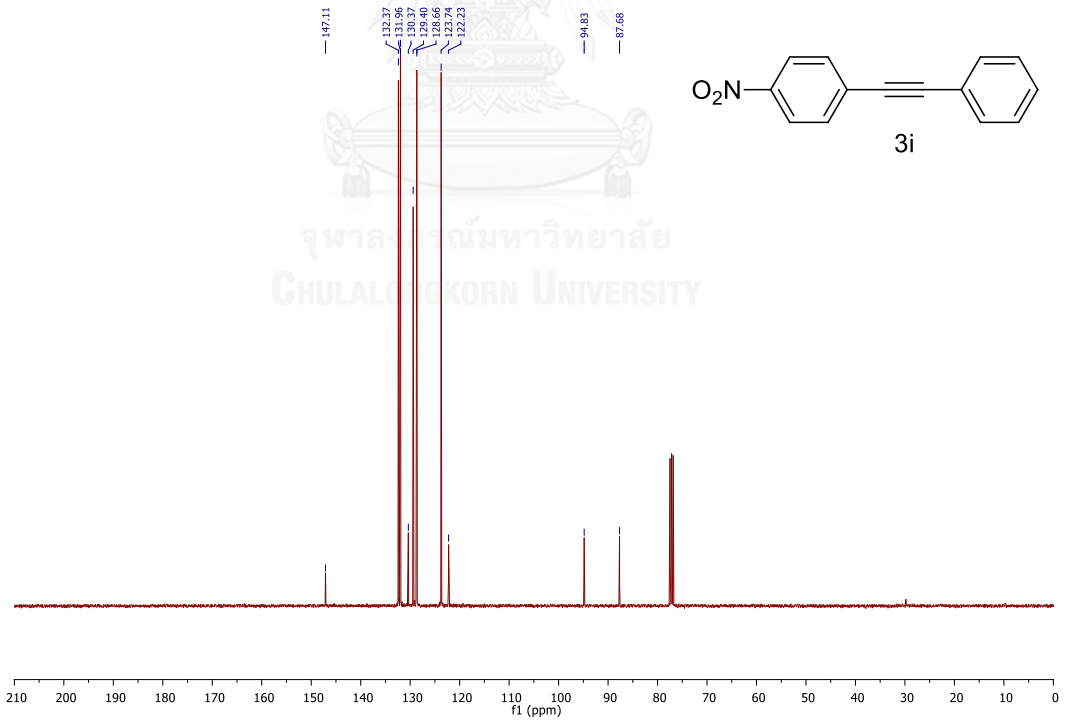


Figure A18 ^{13}C NMR spectrum of 3i ($CDCl_3$)

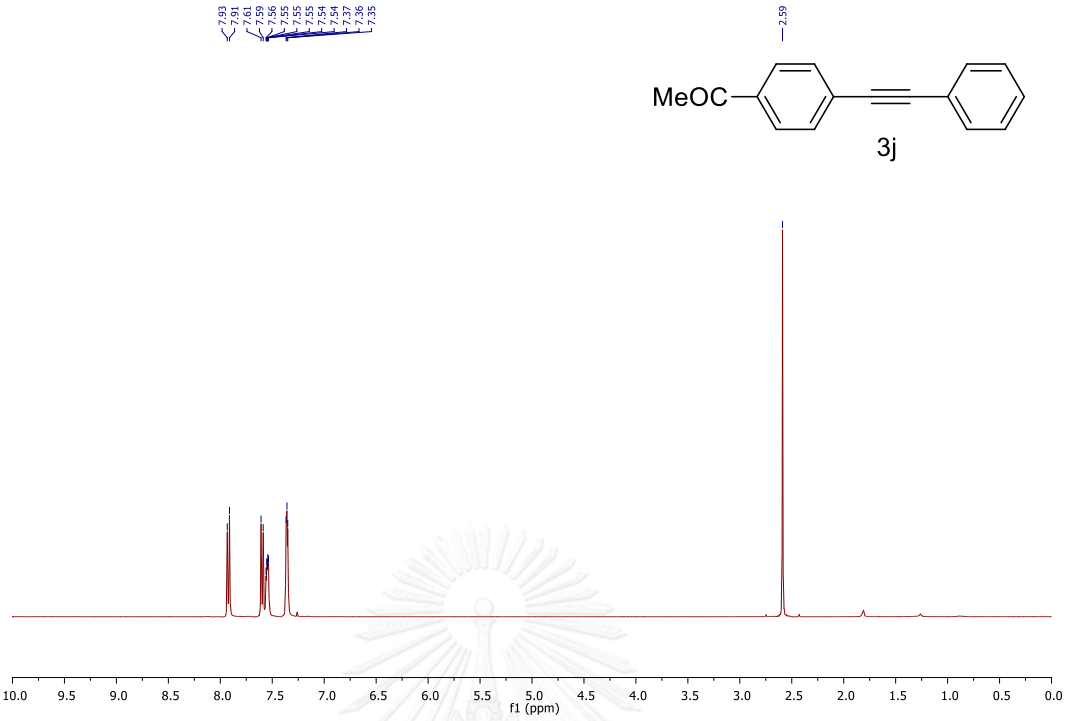


Figure A19 ^{1}H NMR spectrum of 3j ($CDCl_3$)

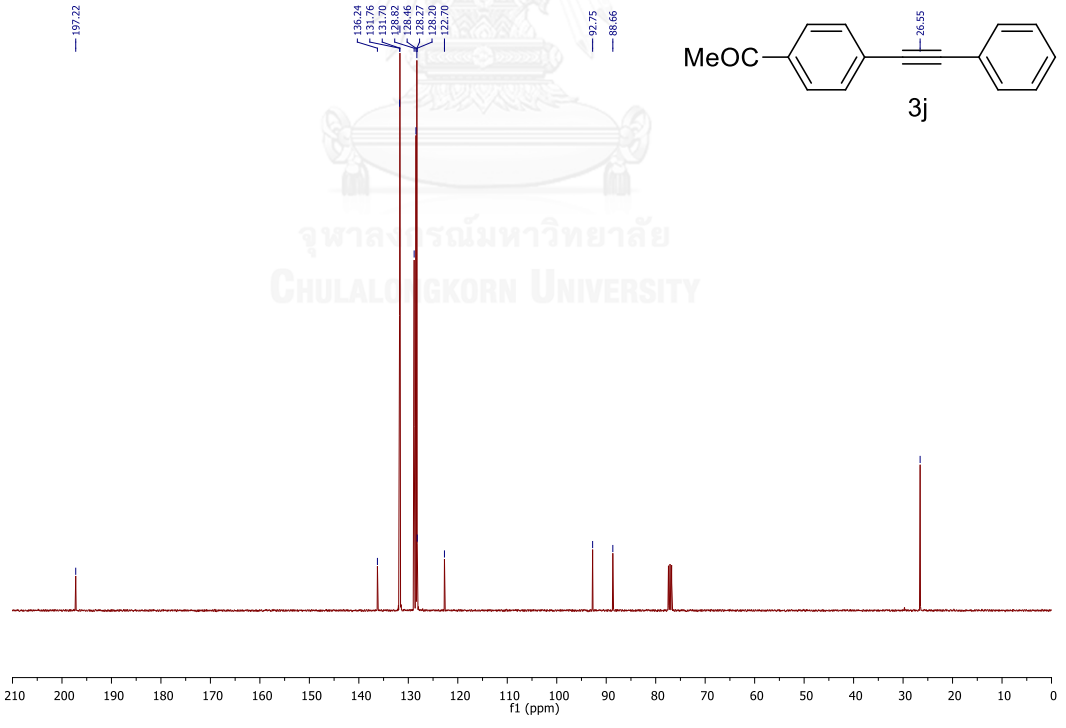


Figure A20 ^{13}C NMR spectrum of 3j ($CDCl_3$)

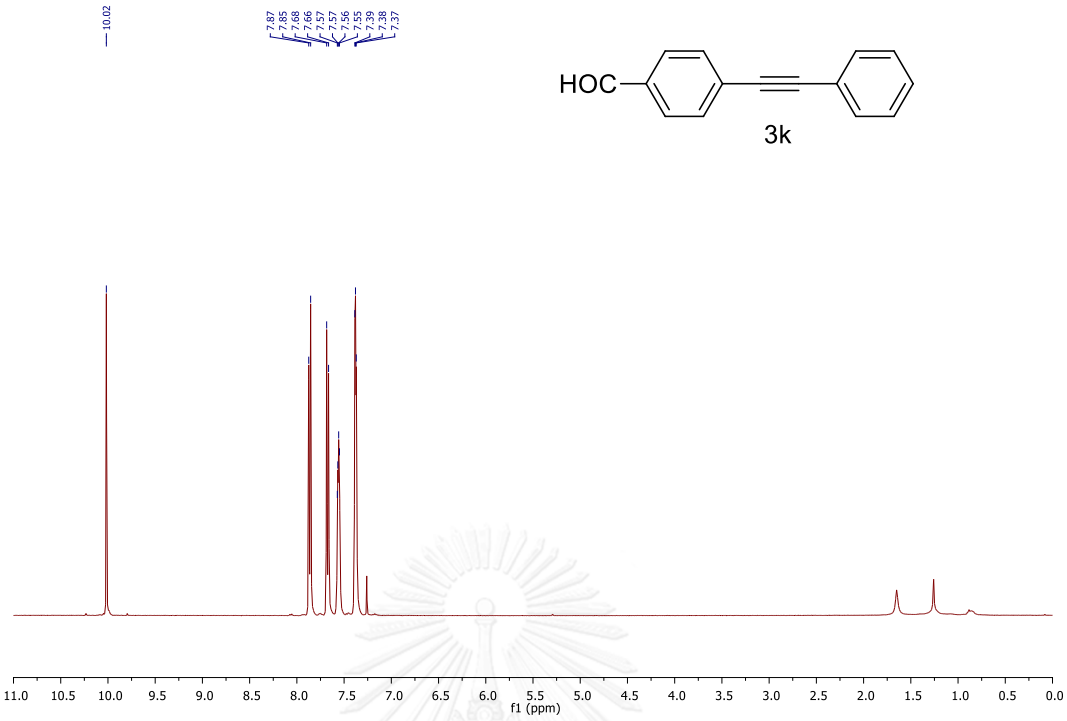


Figure A21 ^{1}H NMR spectrum of 3k ($CDCl_3$)

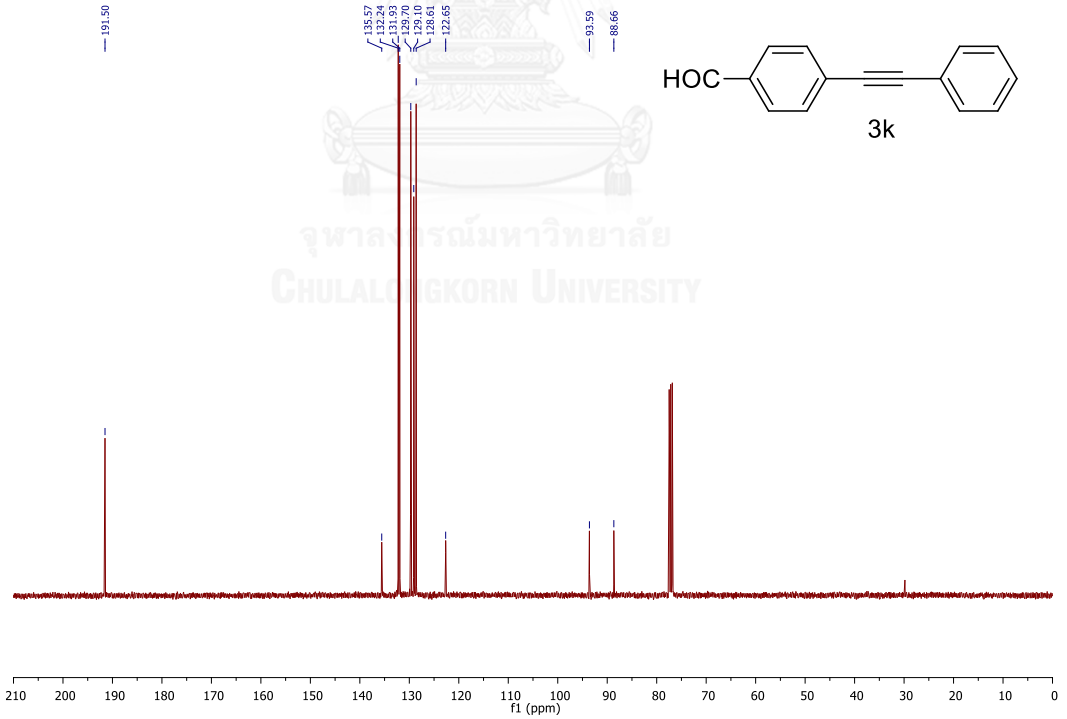


Figure A22 ^{13}C NMR spectrum of 3k ($CDCl_3$)

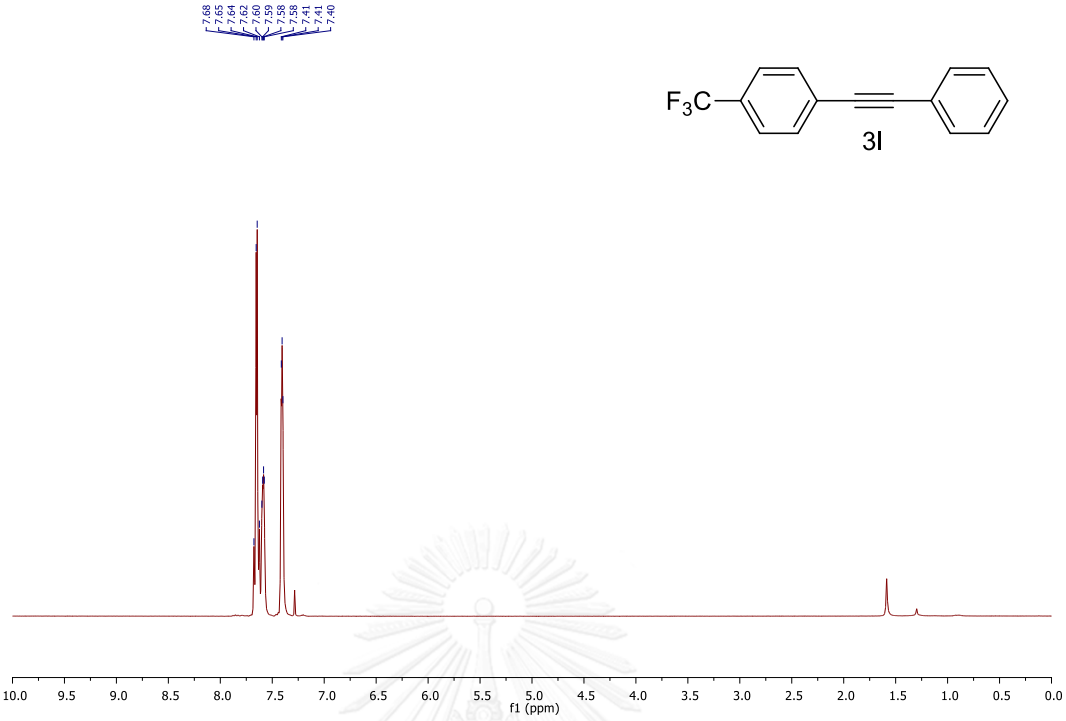


Figure A23 ^{1}H NMR spectrum of 3l ($CDCl_3$)

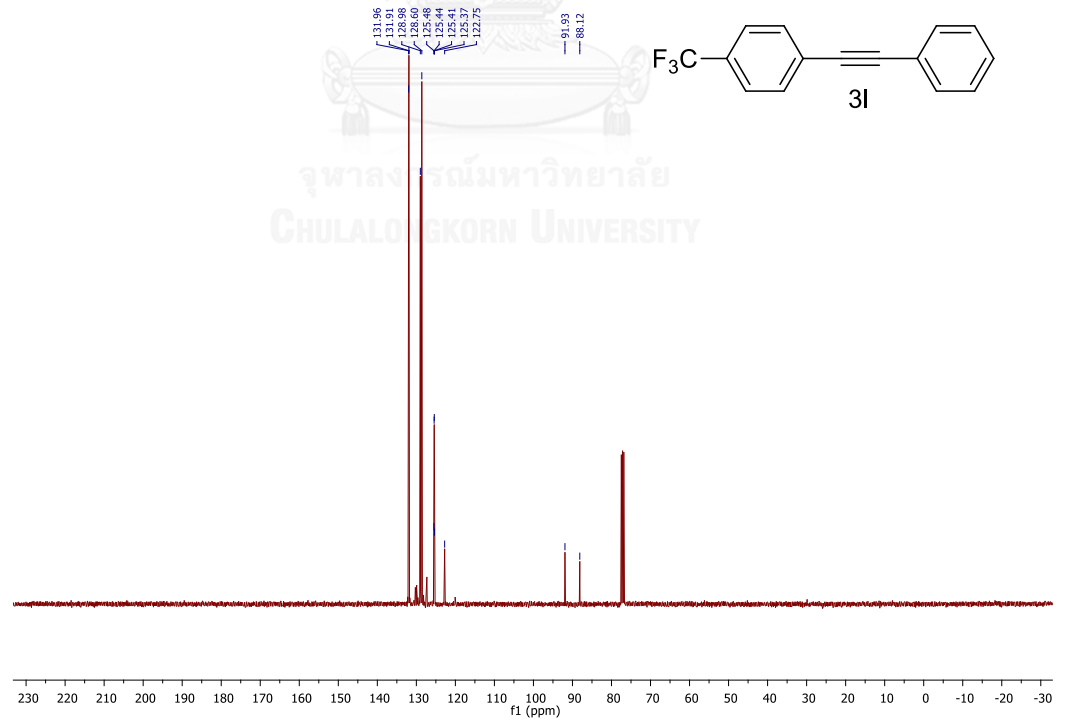


Figure A24 ^{13}C NMR spectrum of 3l ($CDCl_3$)

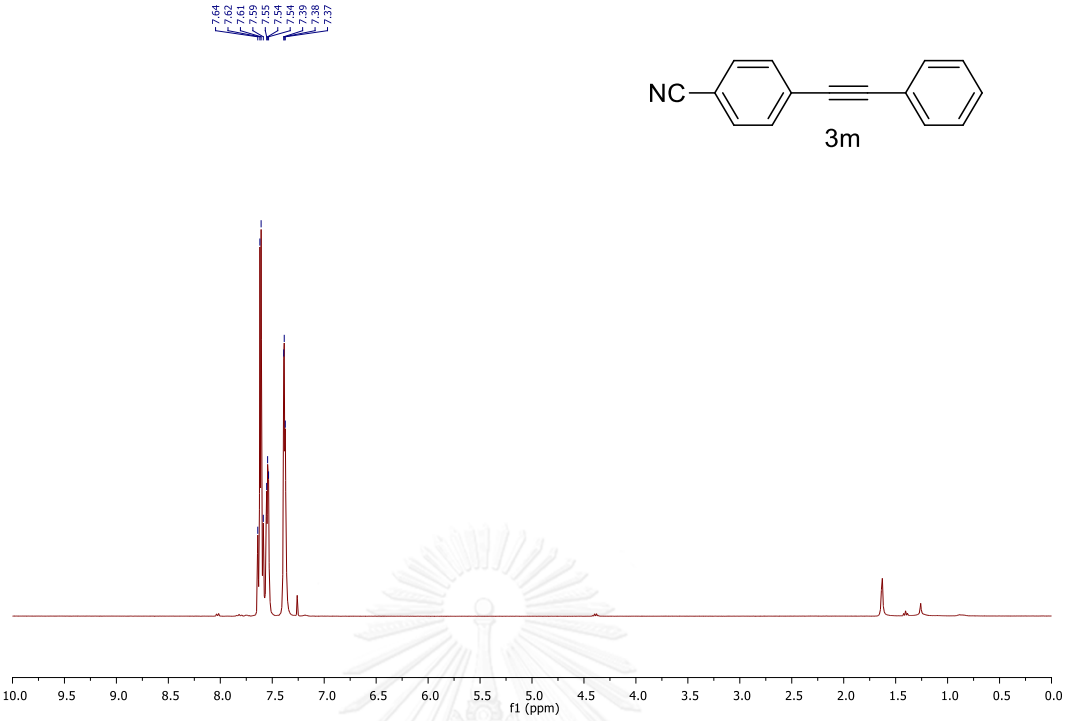


Figure A25 ^{1}H NMR spectrum of 3m ($CDCl_3$)

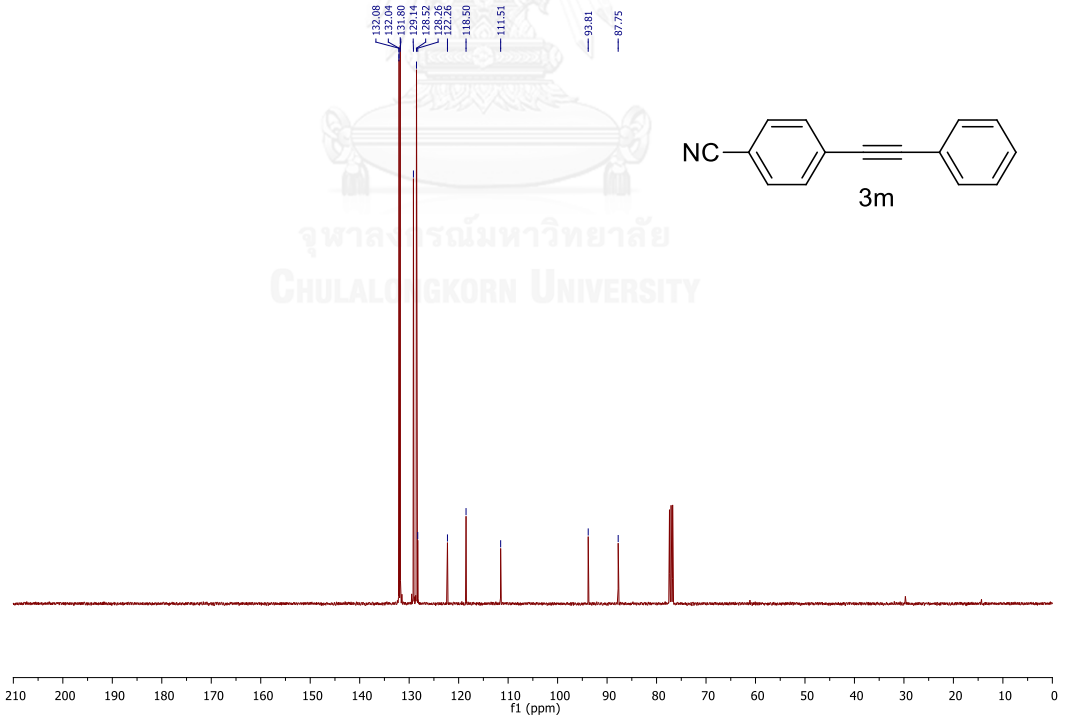


Figure A26 ^{13}C NMR spectrum of 3m ($CDCl_3$)

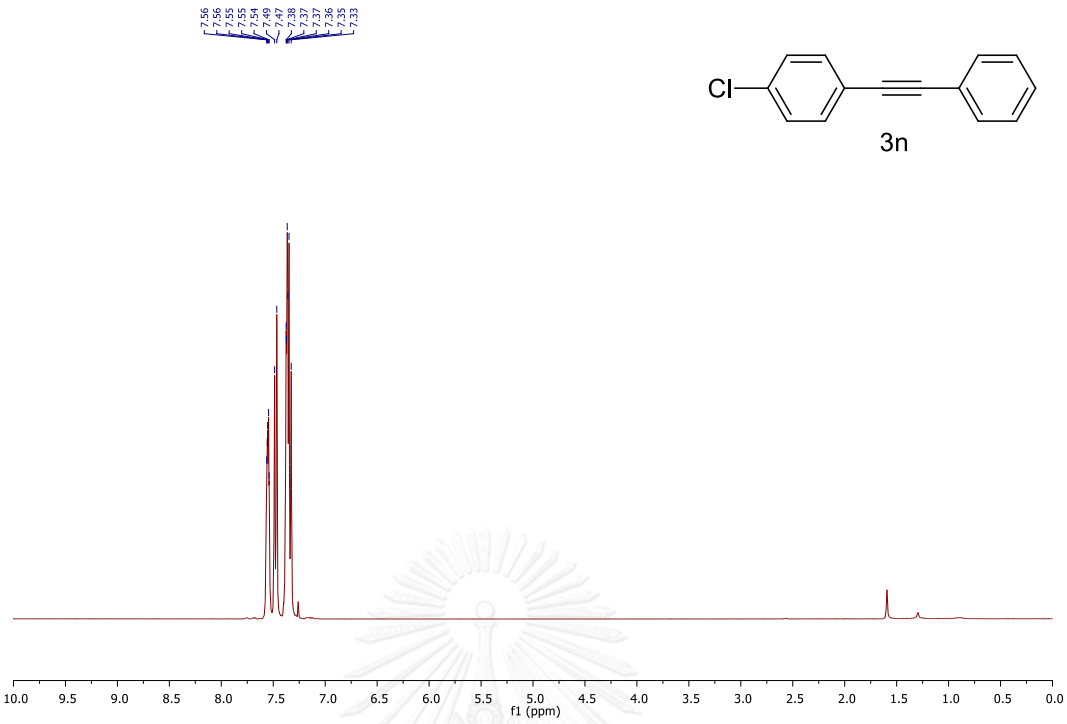


Figure A27 ^{1}H NMR spectrum of 3n ($CDCl_3$)

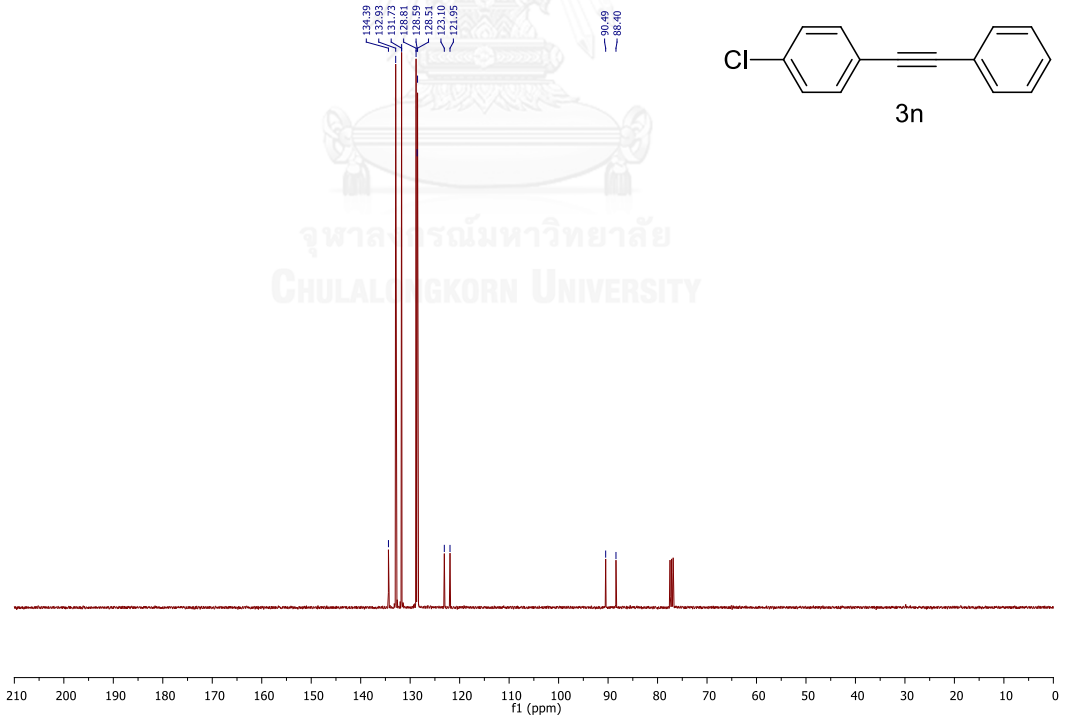


Figure A28 ^{13}C NMR spectrum of 3n ($CDCl_3$)

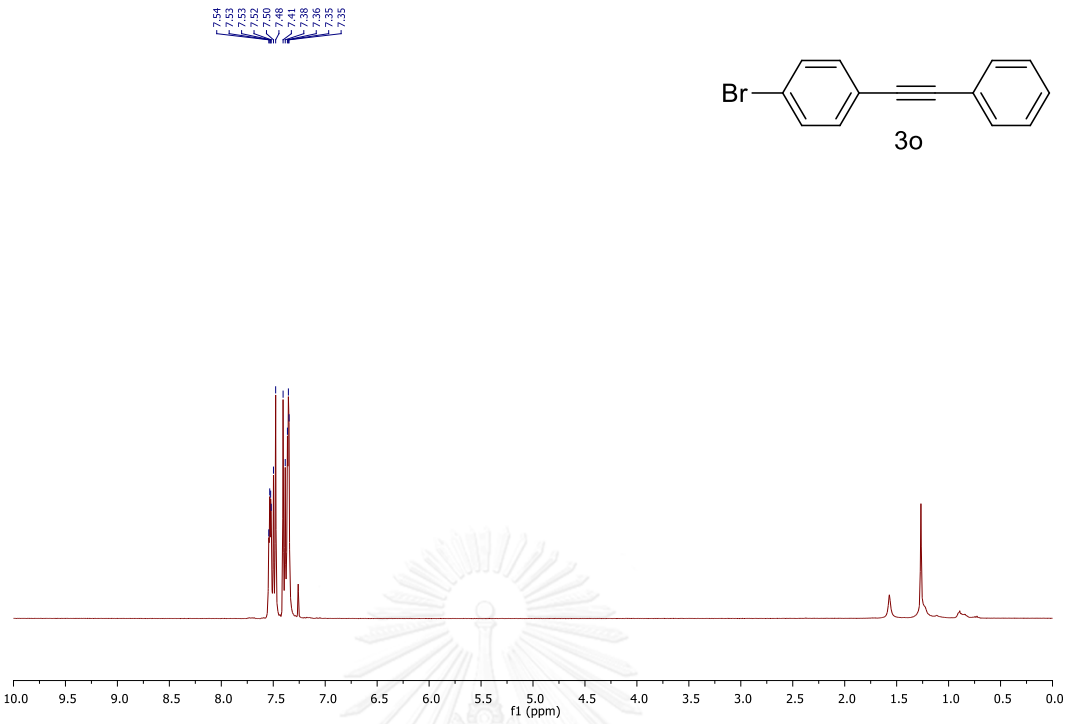


Figure A29 ^{1}H NMR spectrum of 3o ($CDCl_3$)

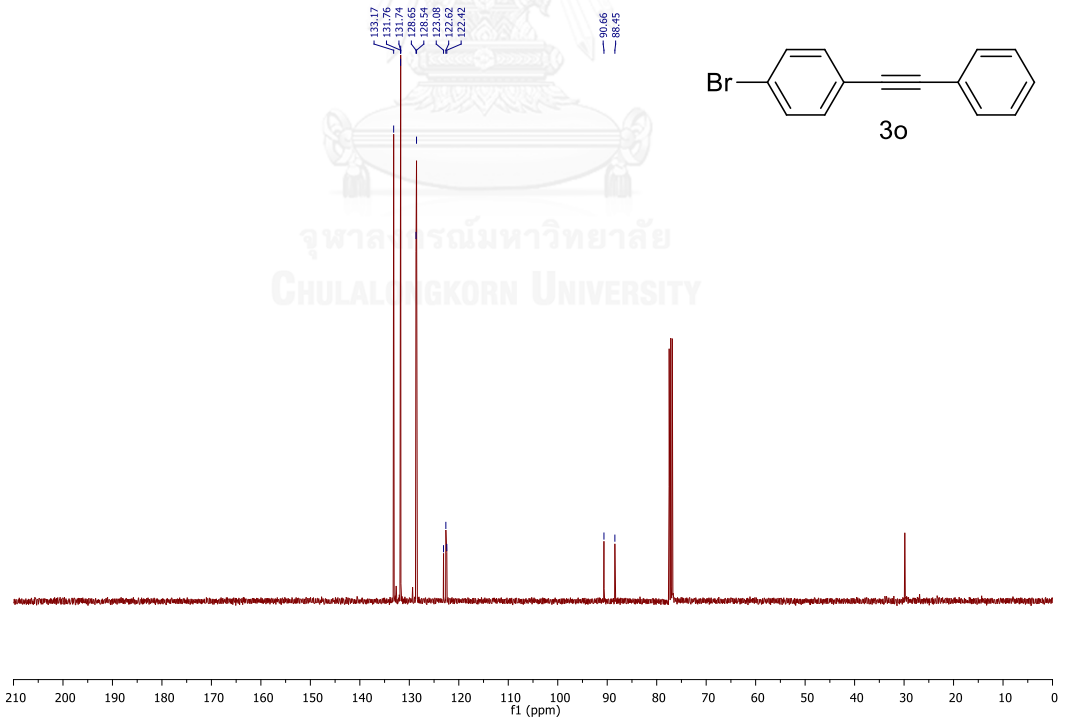


Figure A30 ^{13}C NMR spectrum of 3o ($CDCl_3$)

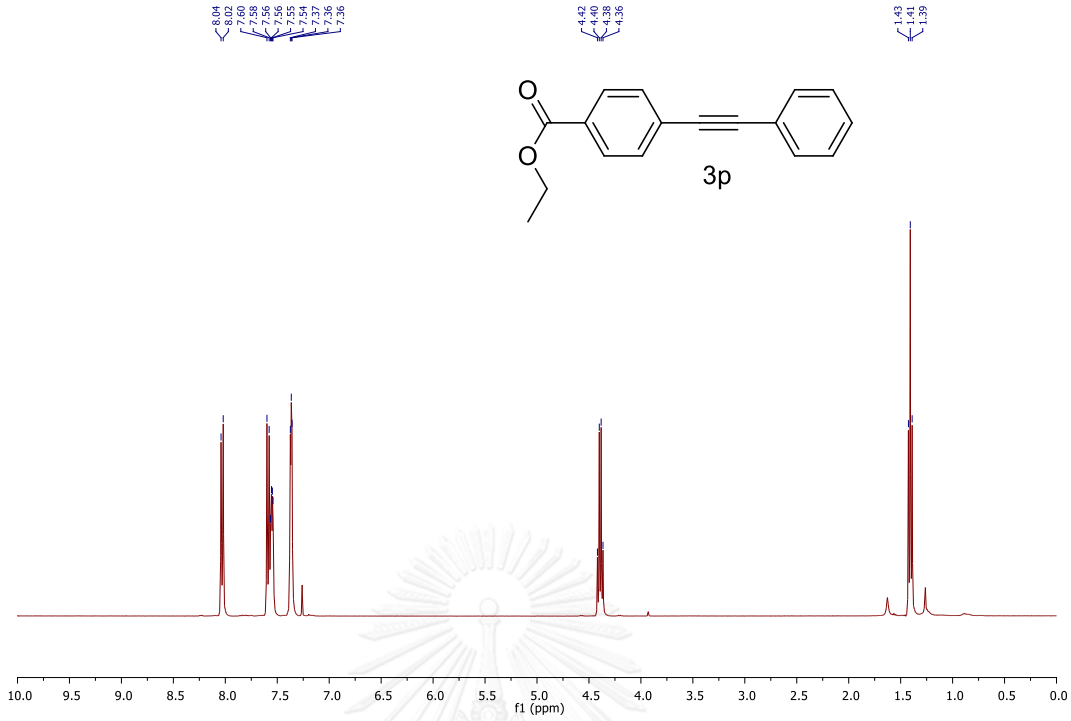


Figure A31 ^{1}H NMR spectrum of 3p ($CDCl_3$)

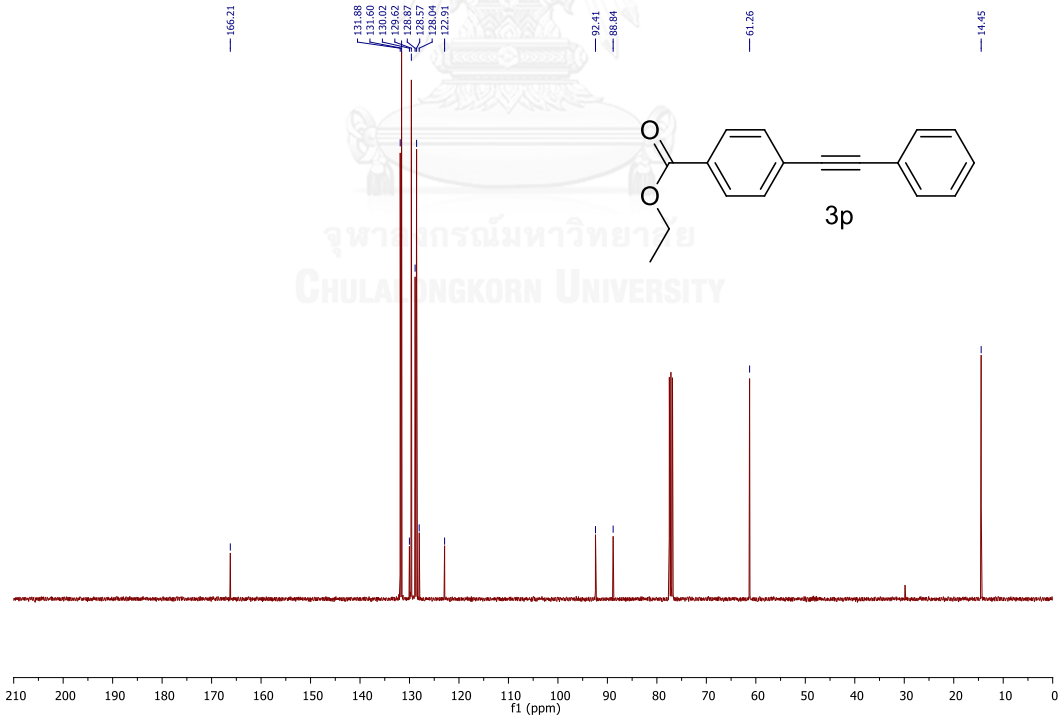


Figure A32 ^{13}C NMR spectrum of 3p ($CDCl_3$)

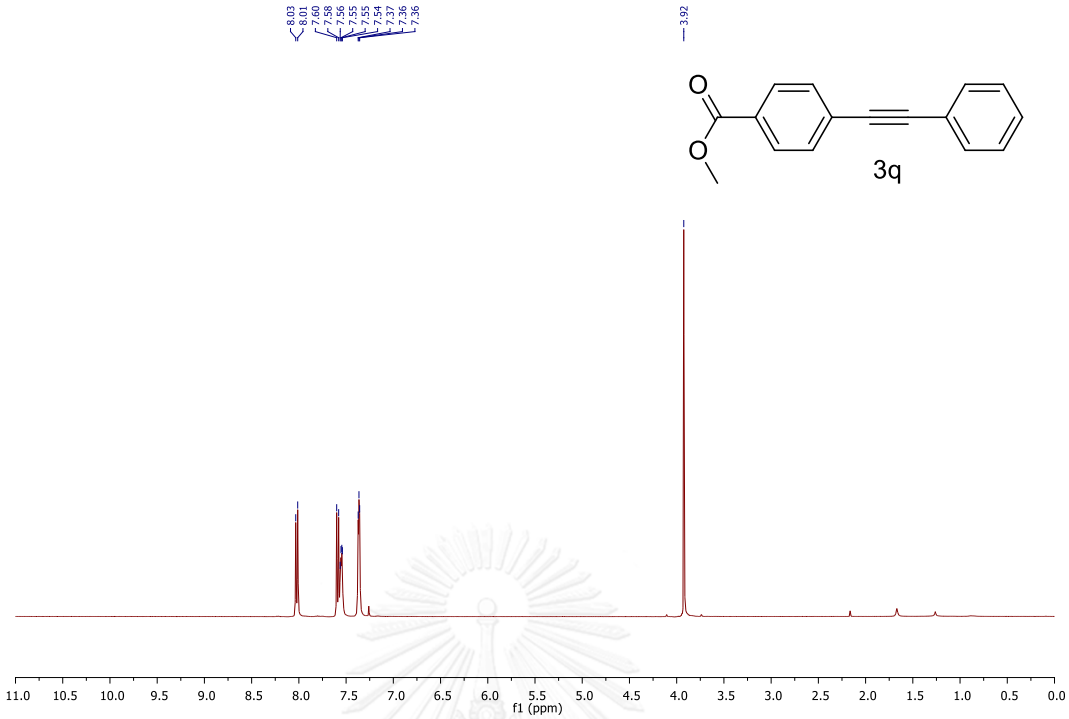


Figure A33 ^{1}H NMR spectrum of 3q ($CDCl_3$)

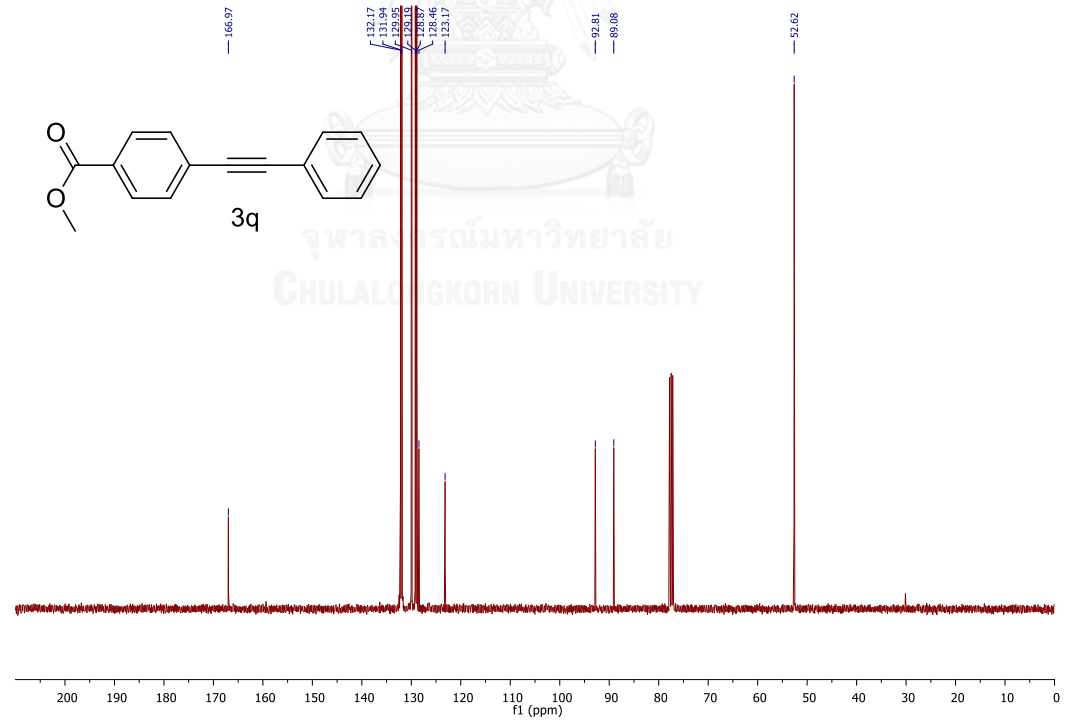


Figure A34 ^{13}C NMR spectrum of 3q ($CDCl_3$)

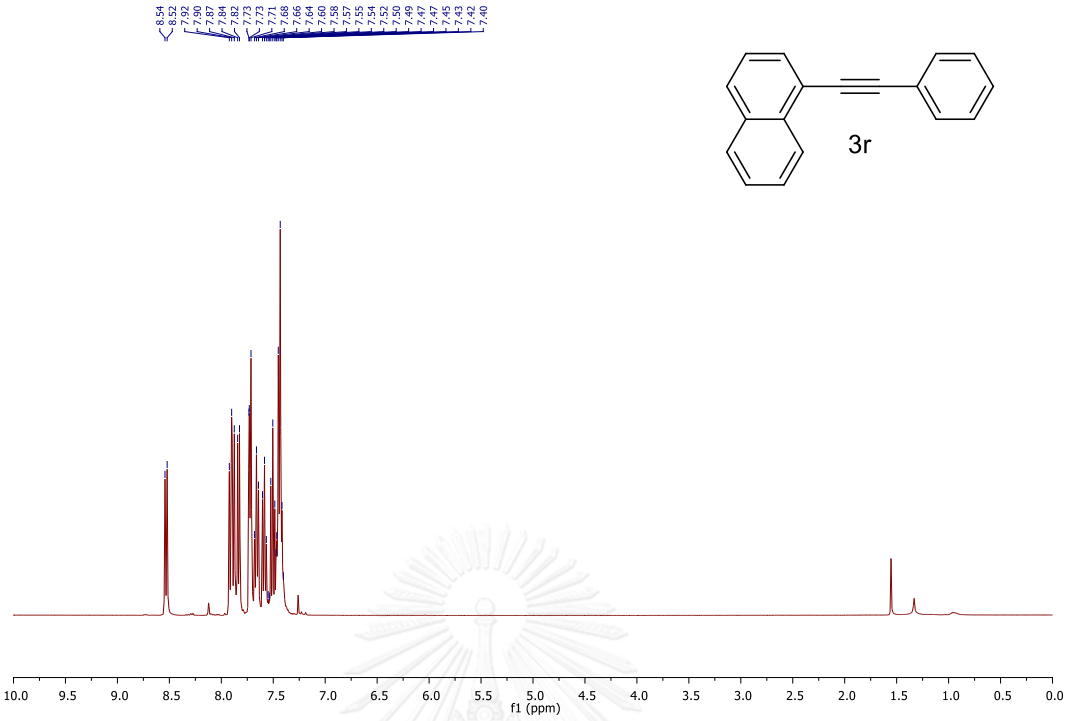


Figure A35 ^{1}H NMR spectrum of 3r ($CDCl_3$)

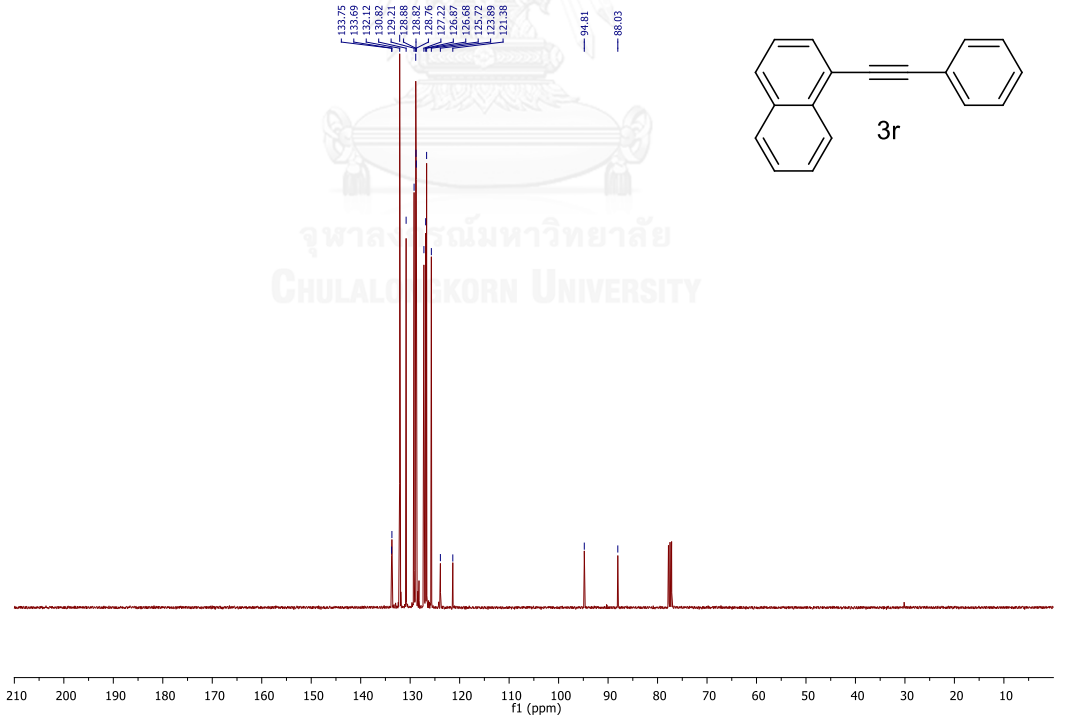


Figure A36 ^{13}C NMR spectrum of 3r ($CDCl_3$)

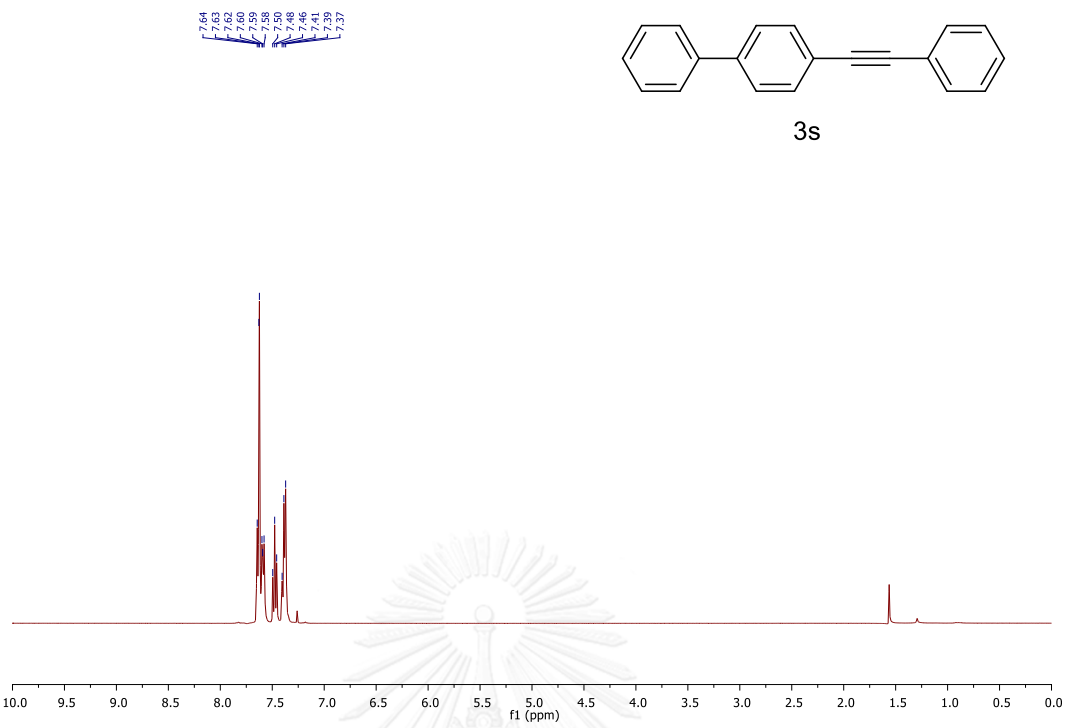


Figure A37 ^{1}H NMR spectrum of 3s ($CDCl_3$)

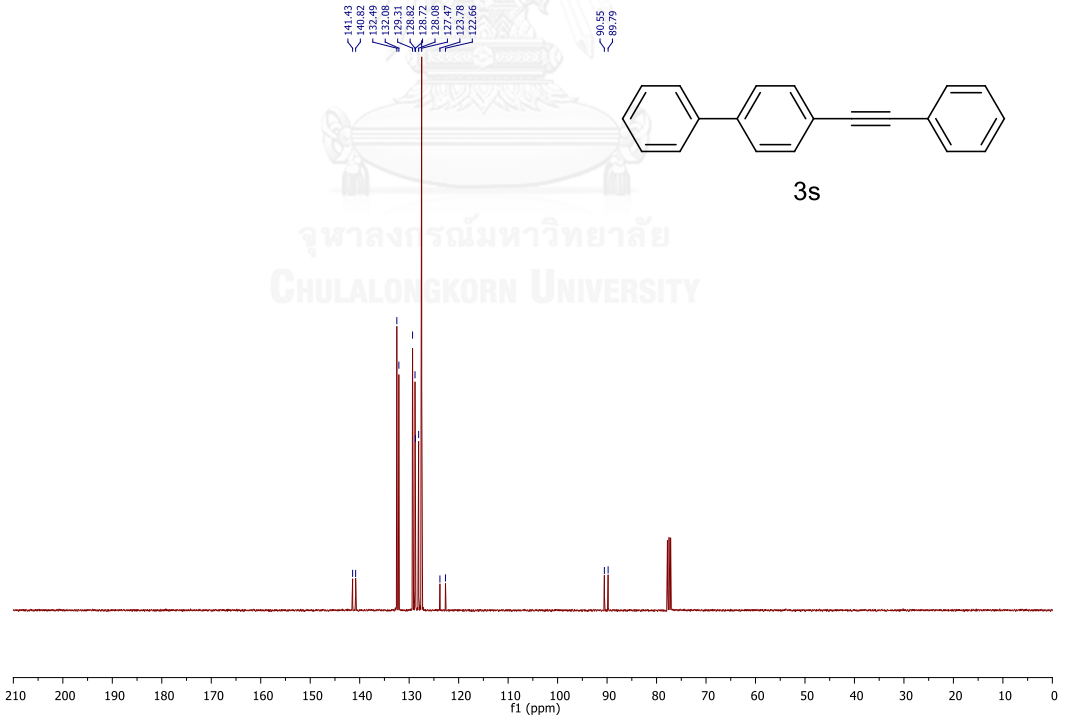


Figure A38 ^{13}C NMR spectrum of 3s ($CDCl_3$)

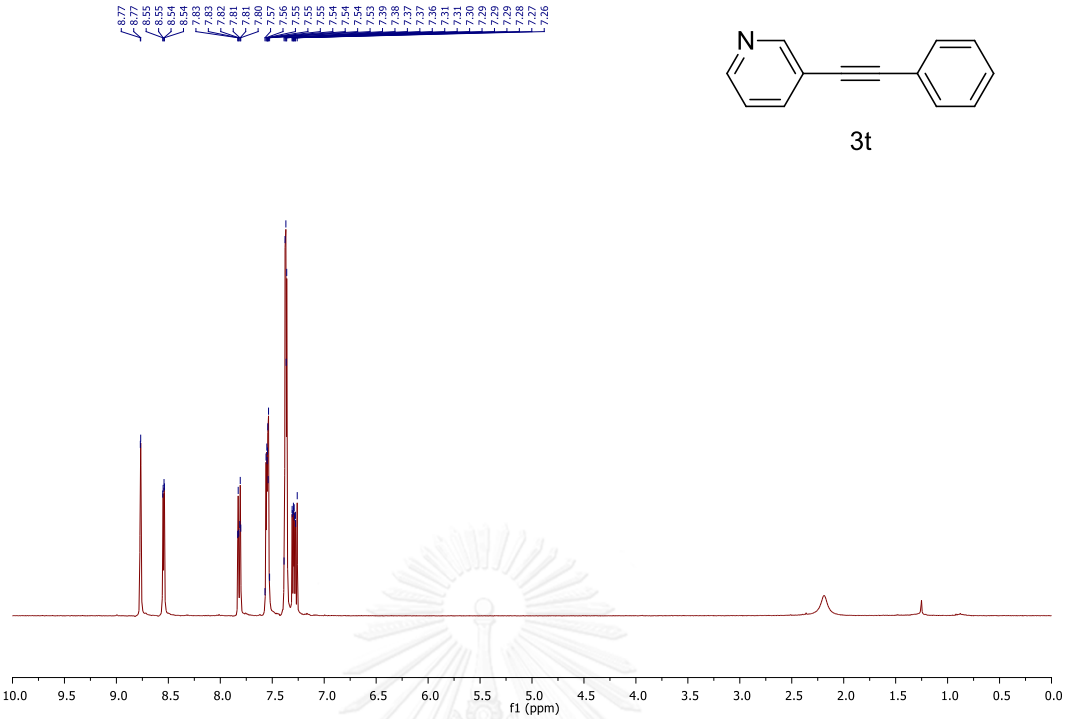


Figure A39 ^{1}H NMR spectrum of 3t ($CDCl_3$)

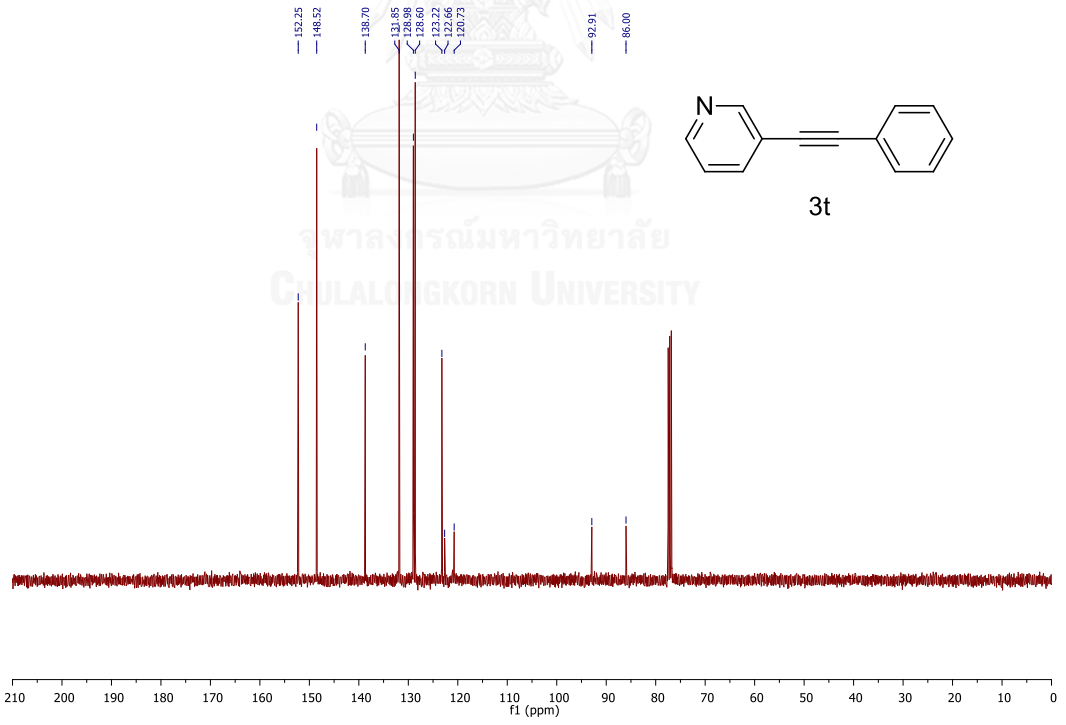


Figure A40 ^{13}C NMR spectrum of 3t ($CDCl_3$)

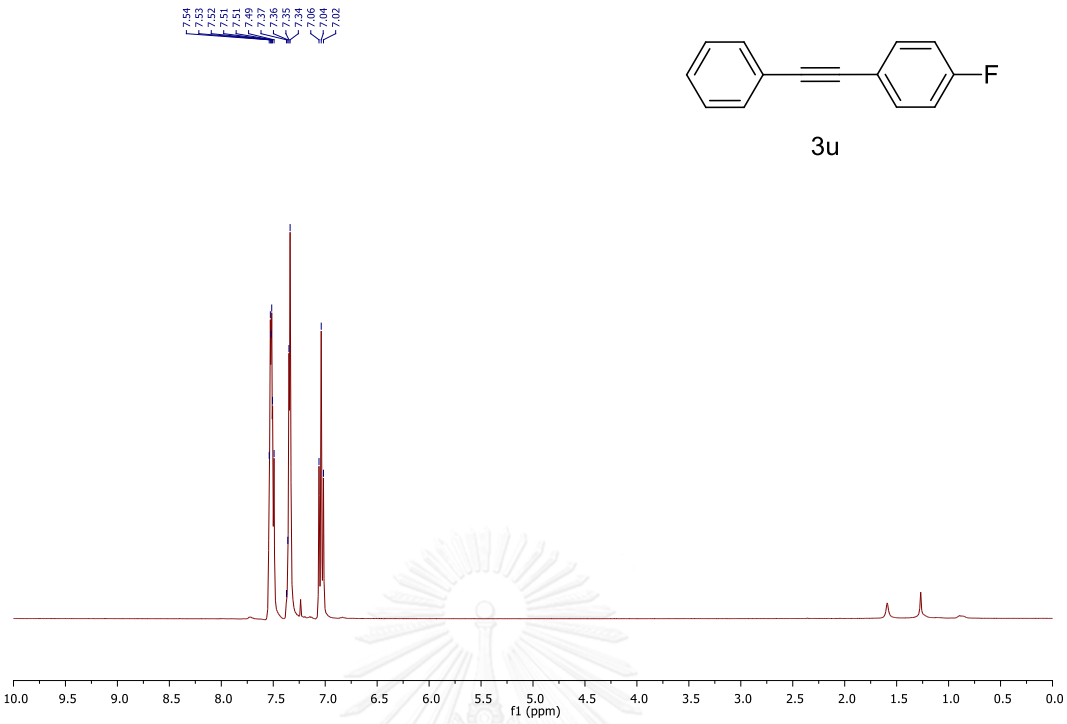


Figure A41 ^{1}H NMR spectrum of 3u ($CDCl_3$)

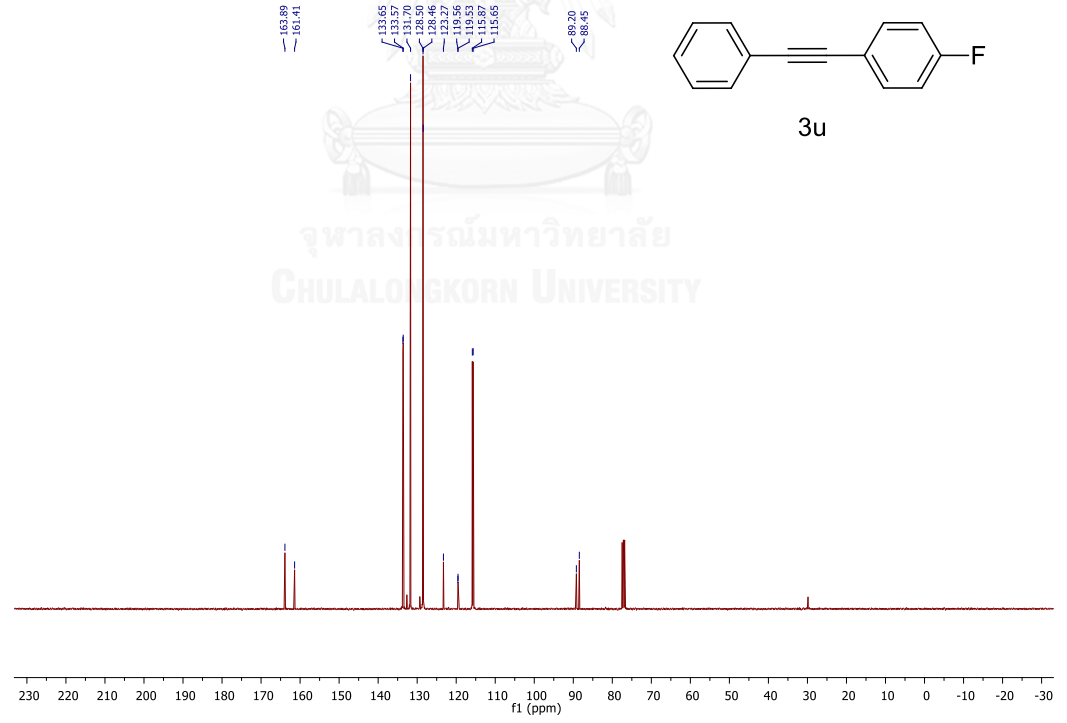


Figure A42 ^{13}C NMR spectrum of 3u ($CDCl_3$)

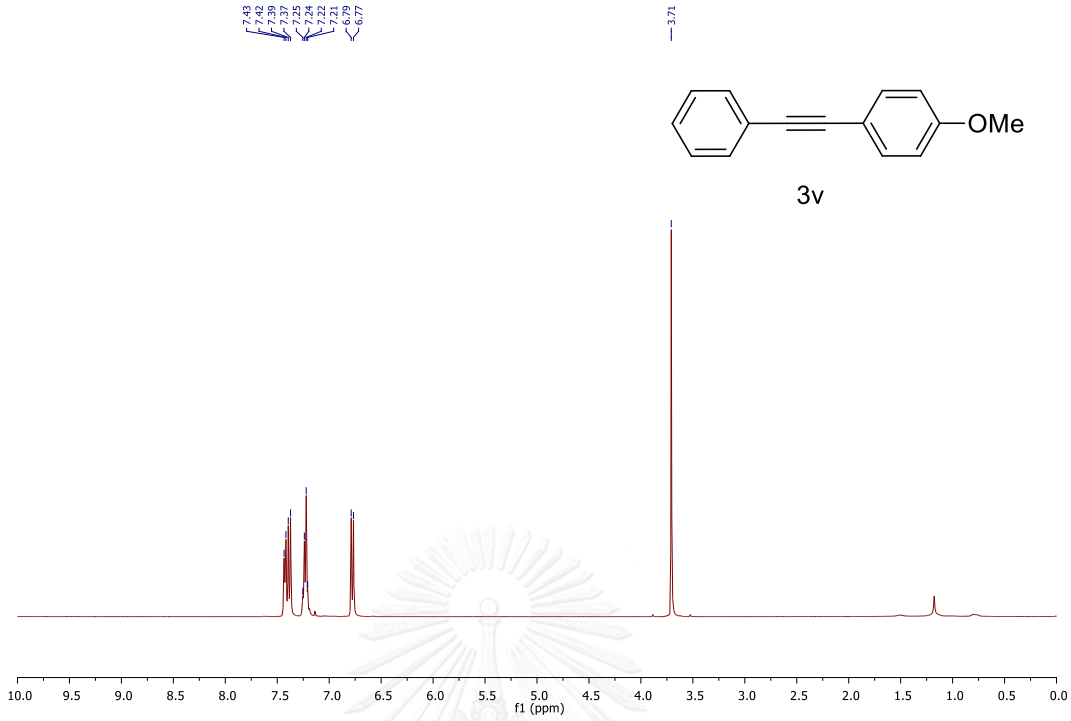


Figure A43 ^{1}H NMR spectrum of 3v ($CDCl_3$)

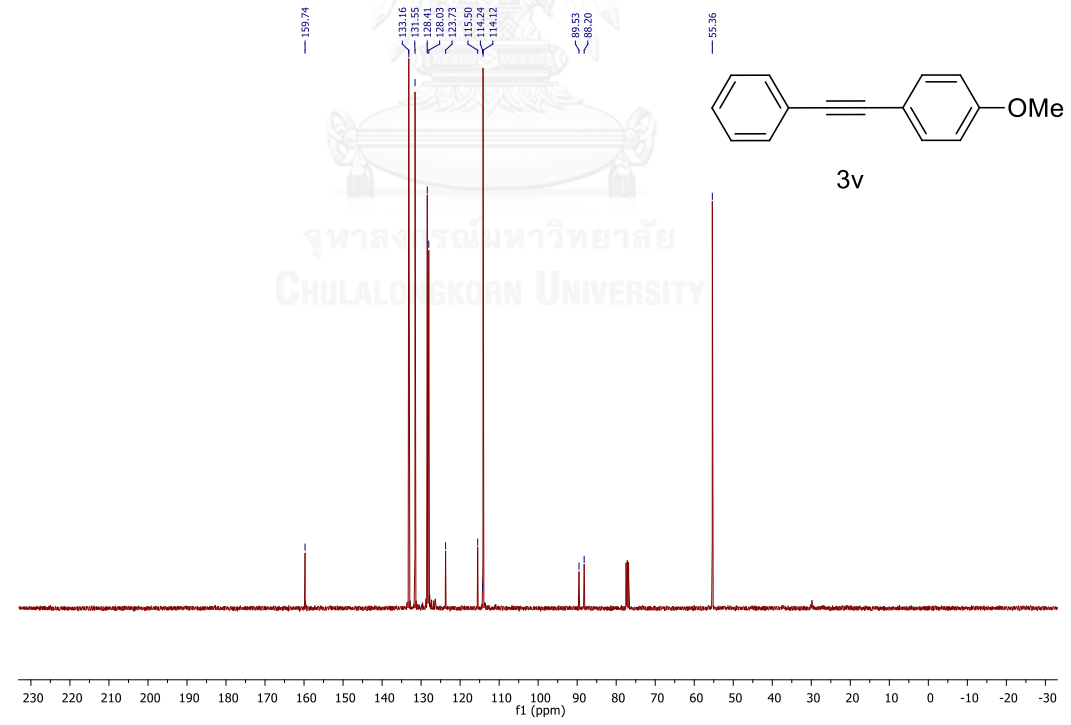


Figure A44 ^{13}C NMR spectrum of 3v ($CDCl_3$)

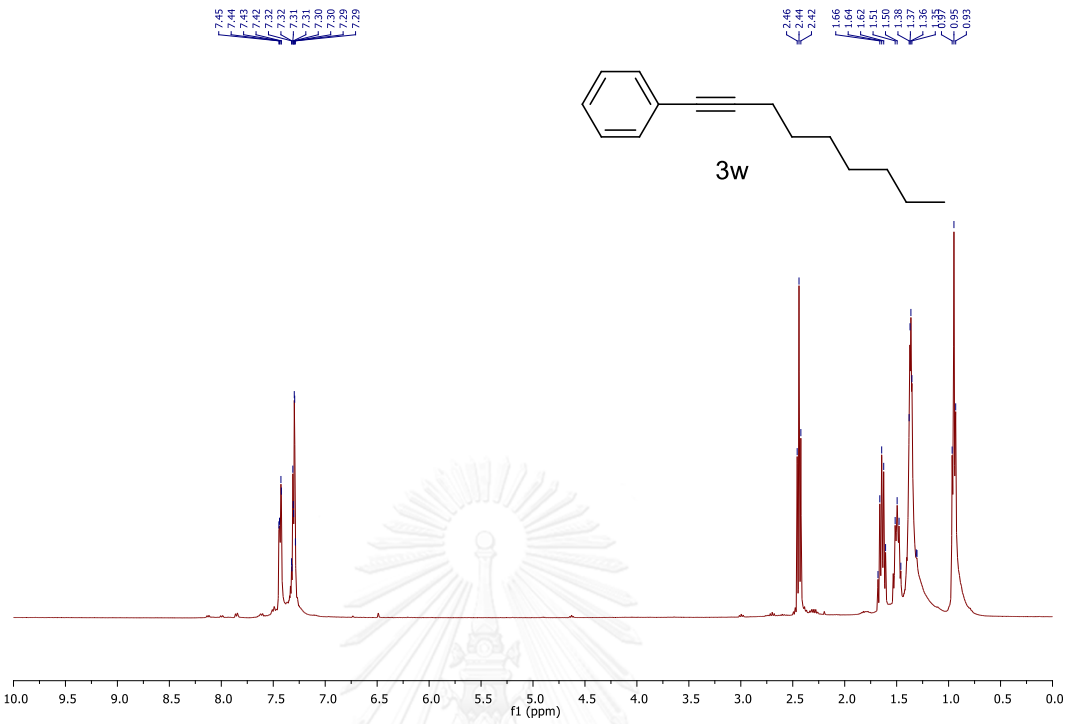


Figure A45 ^{1}H NMR spectrum of 3w ($CDCl_3$)

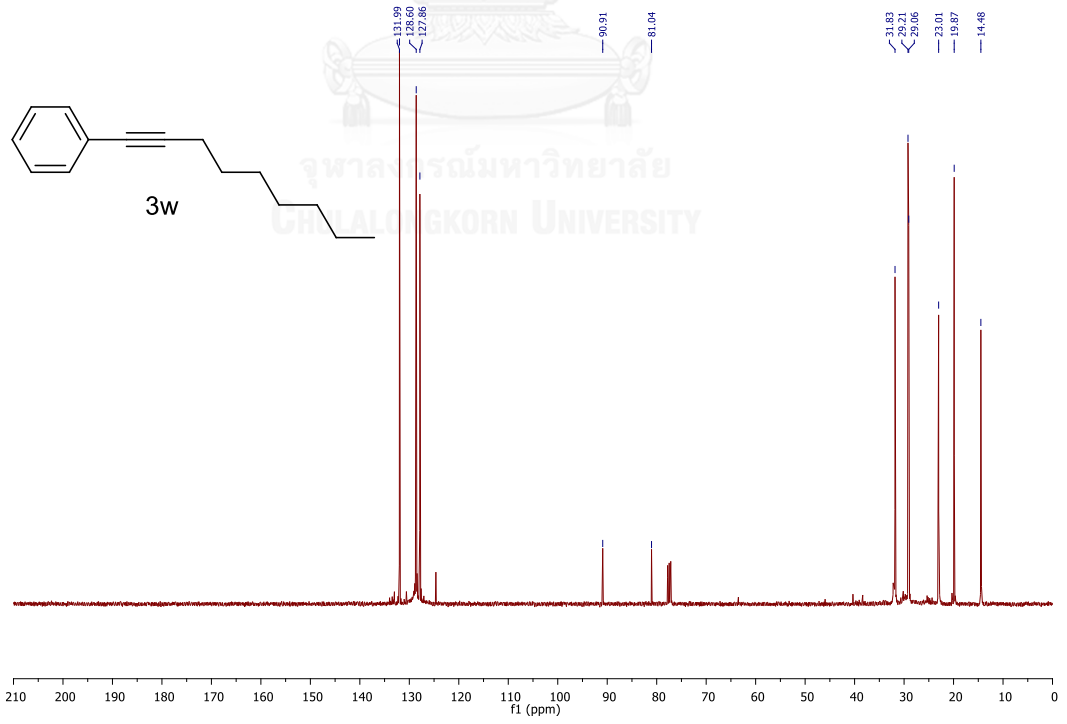


Figure A46 ^{13}C NMR spectrum of 3w ($CDCl_3$)

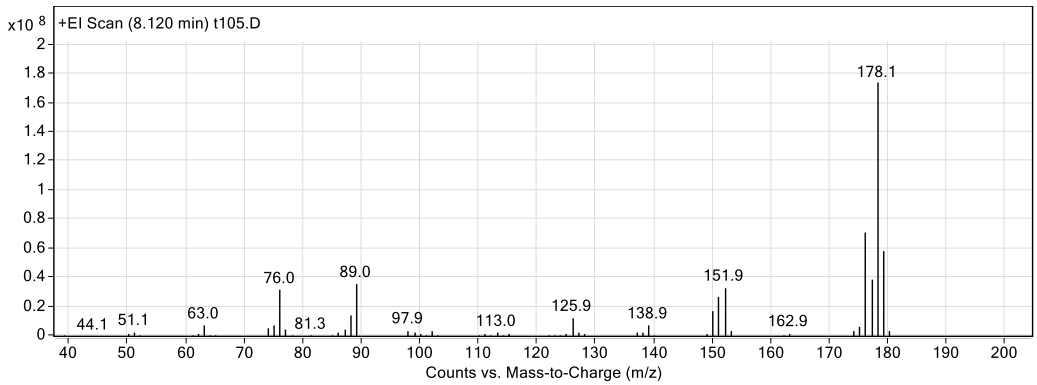


Figure B1 GC-MS spectrum of 3a

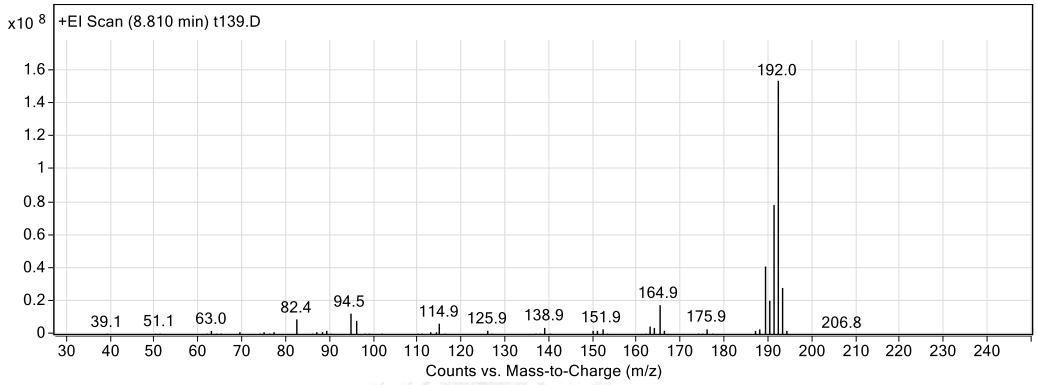


Figure B2 GC-MS spectrum of 3b

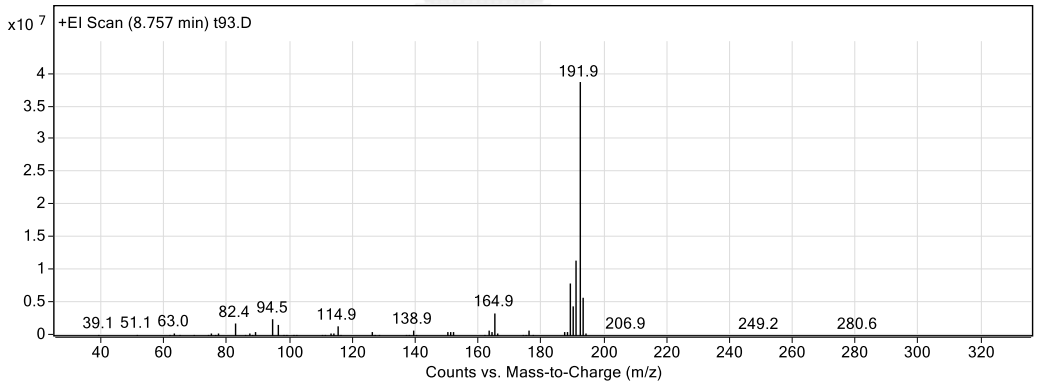


Figure B3 GC-MS spectrum of 3c

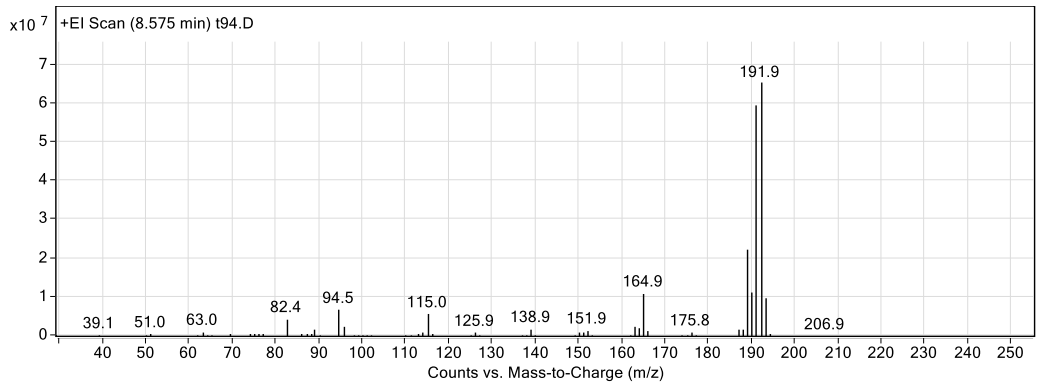


Figure B4 GC-MS spectrum of 3d

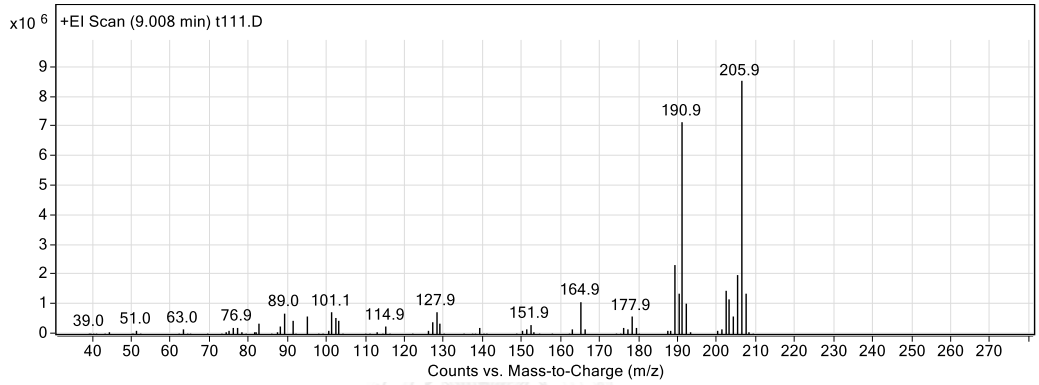


Figure B5 GC-MS spectrum of 3e

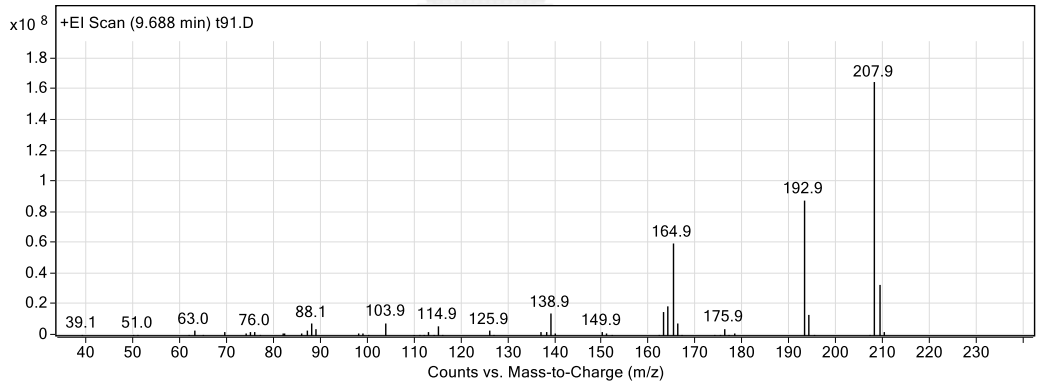


Figure B6 GC-MS spectrum of 3f

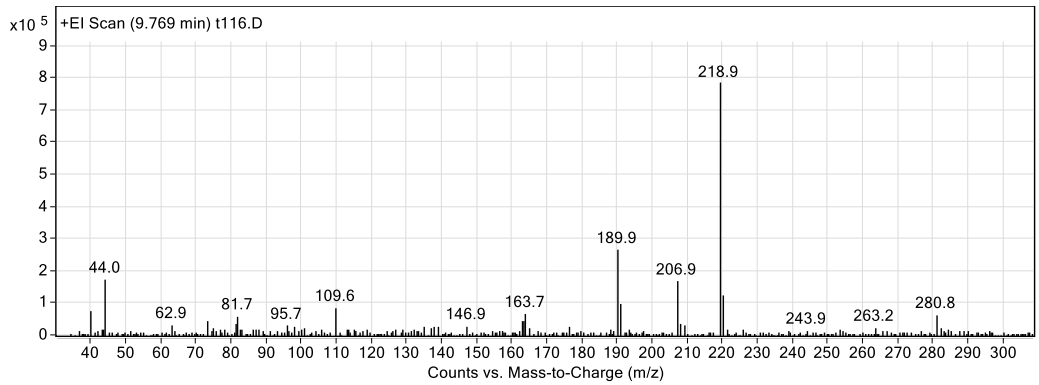


Figure B7 GC-MS spectrum of 3g

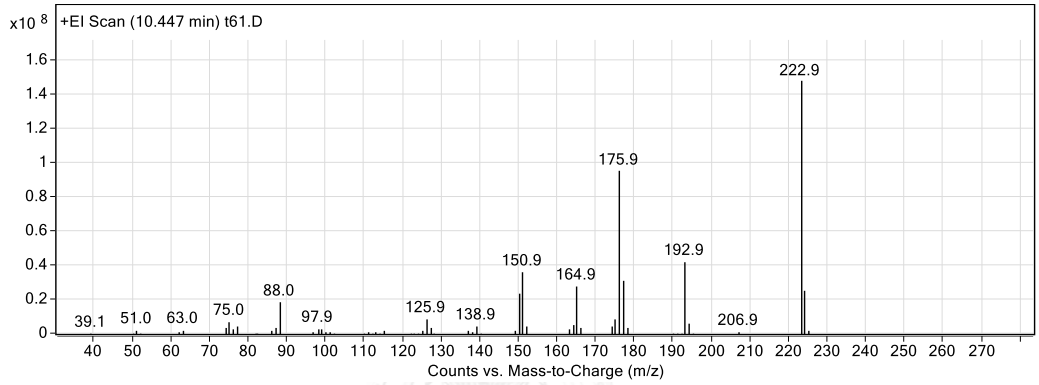


Figure B8 GC-MS spectrum of 3i

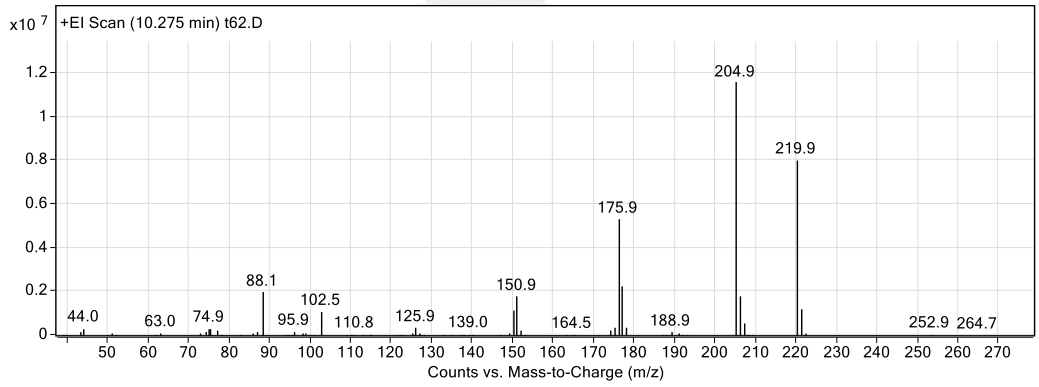


Figure B9 GC-MS spectrum of 3j

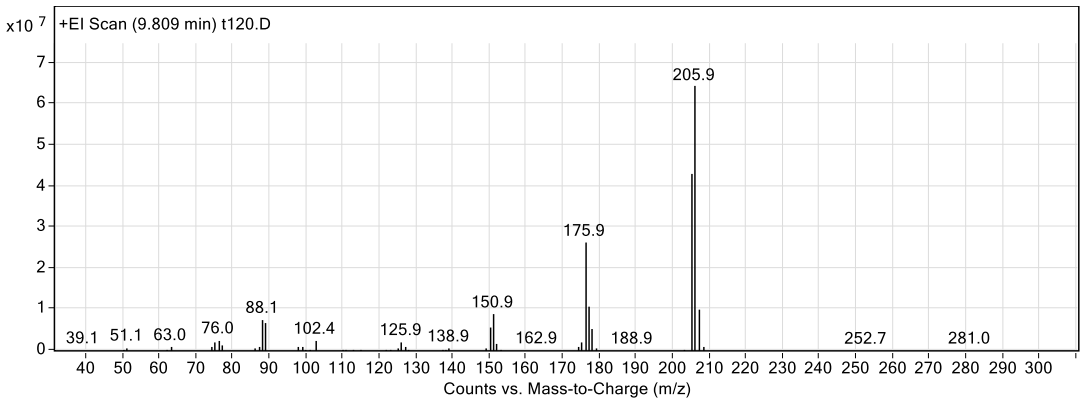


Figure B10 GC-MS spectrum of 3k

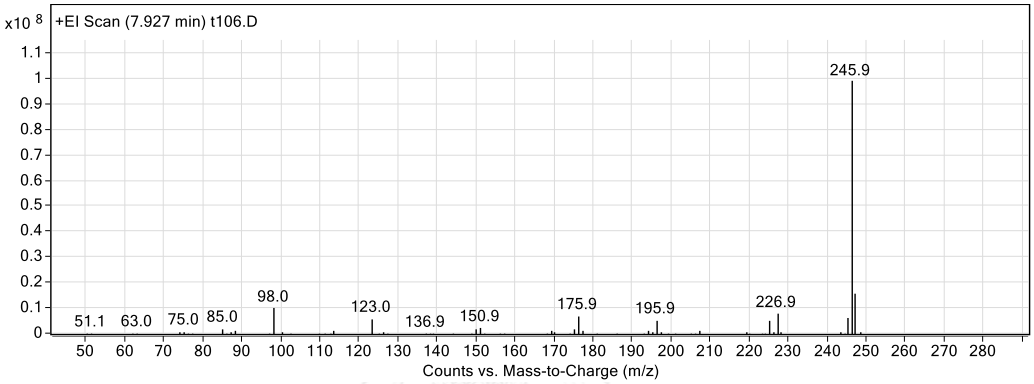


Figure B11 GC-MS spectrum of 3l

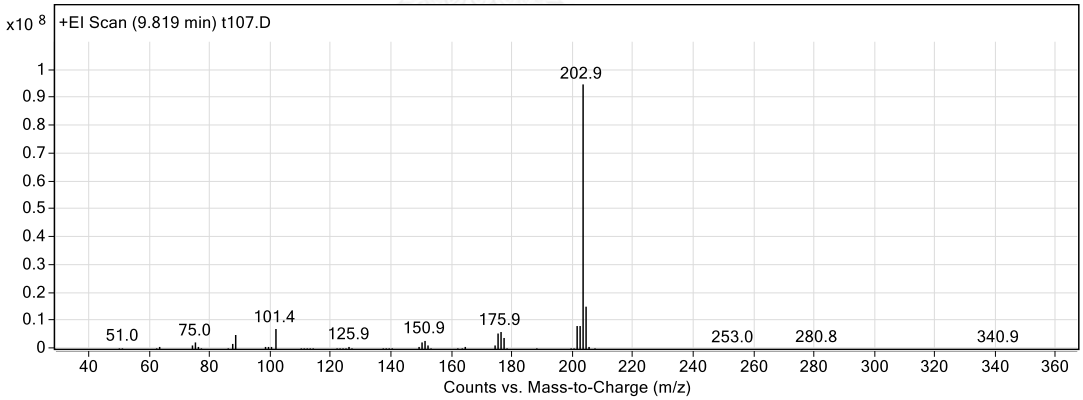


Figure B12 GC-MS spectrum of 3m

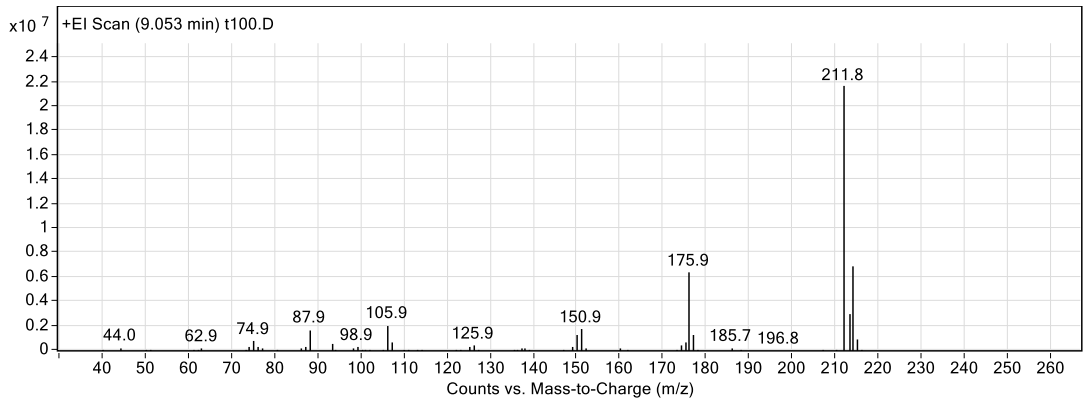


Figure B13 GC-MS spectrum of 3n

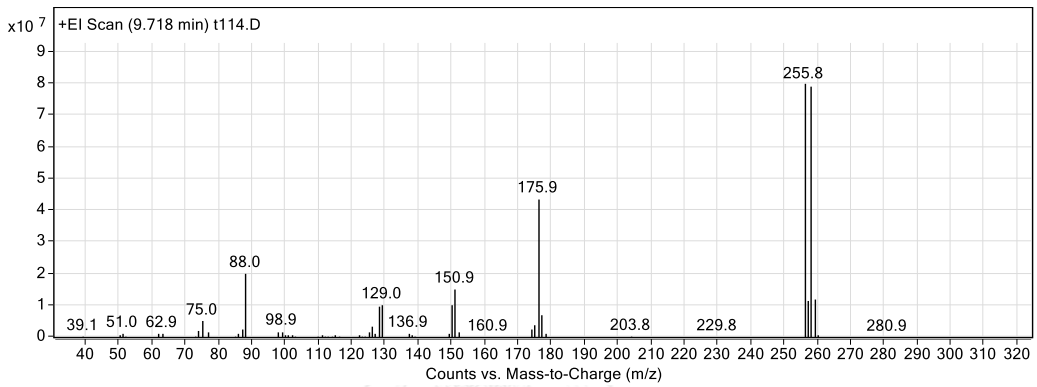


Figure B14 GC-MS spectrum of 3o

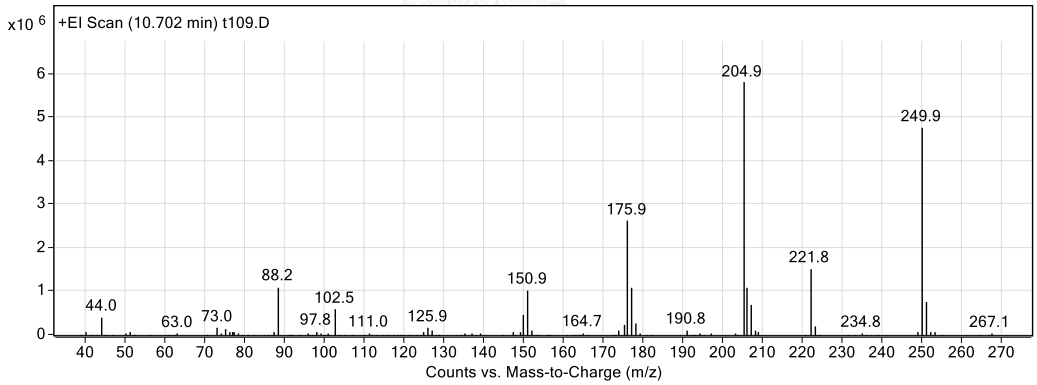


Figure B15 GC-MS spectrum of 3p

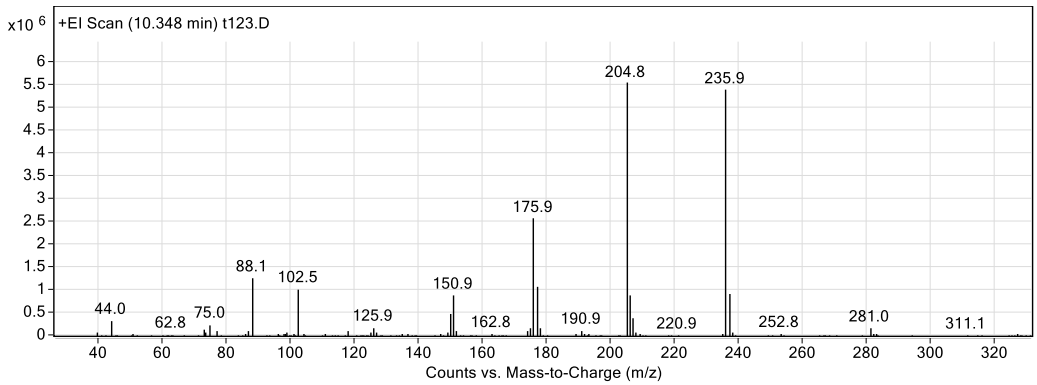


Figure B16 GC-MS spectrum of 3q

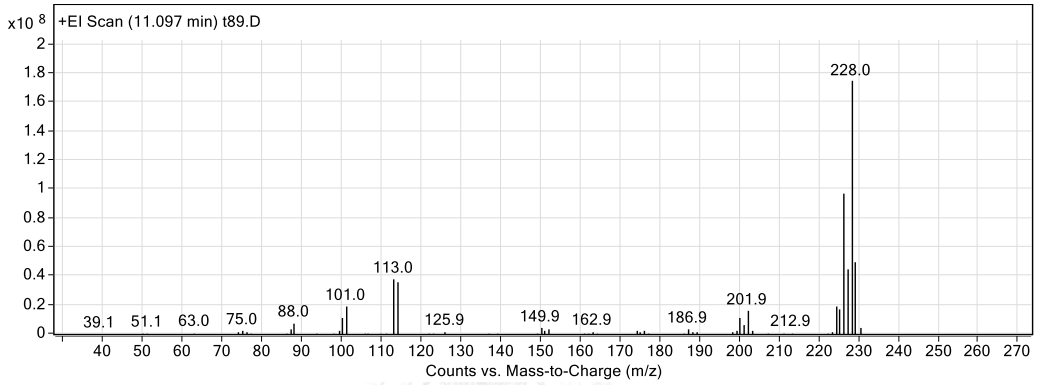


Figure B17 GC-MS spectrum of 3r

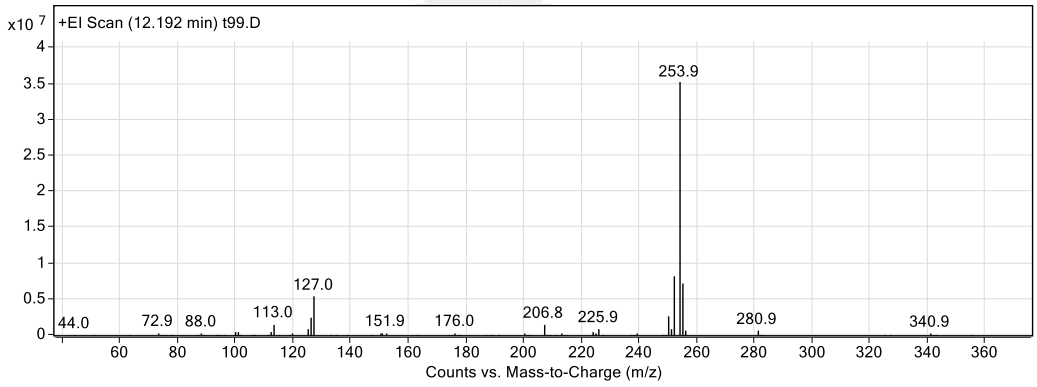


Figure B18 GC-MS spectrum of 3s

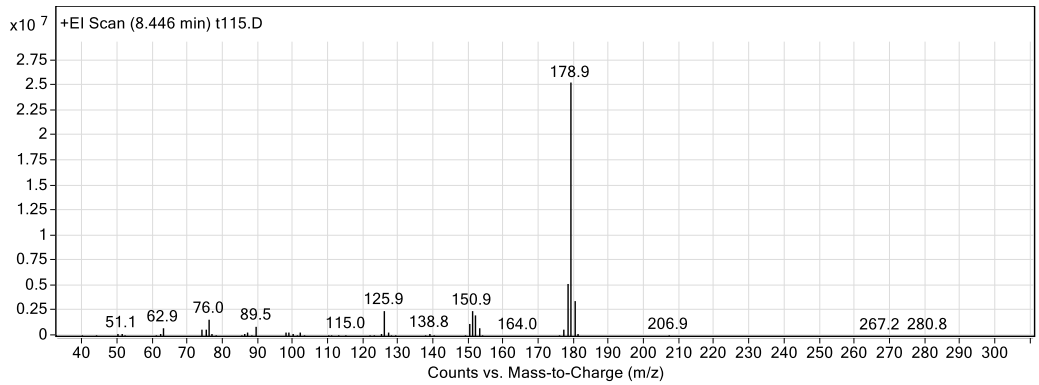


Figure B19 GC-MS spectrum of 3t

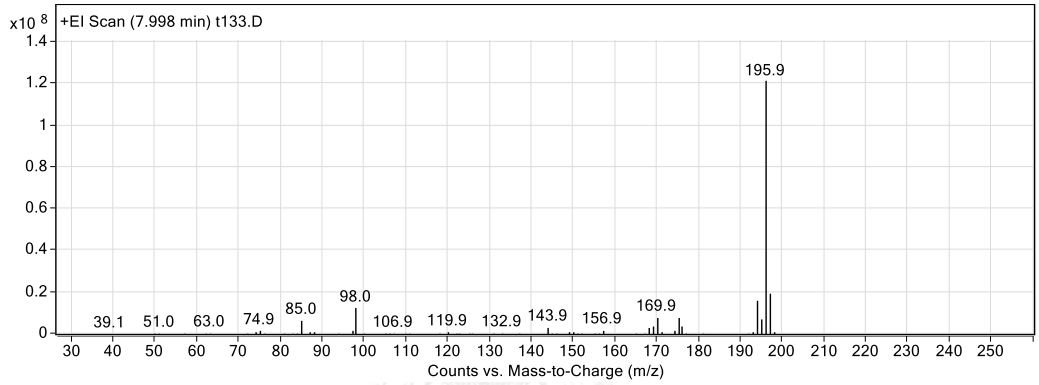


Figure B20 GC-MS spectrum of 3u

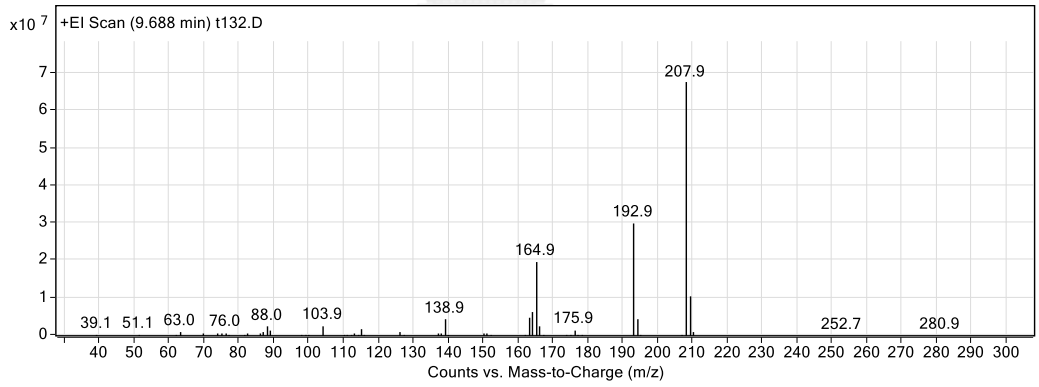


Figure B21 GC-MS spectrum of 3v

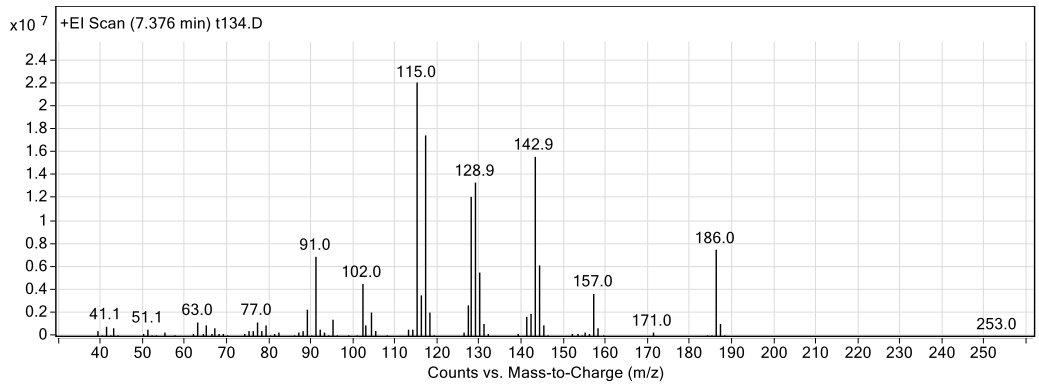


Figure B22 GC-MS spectrum of 3w

VITA

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