# ปฏิกิริยาซูซูกิครอสคัปปลิงเร่งปฏิกิริยาด้วยอนุภาคระดับนาโนเมตรของแพลเลเดียมรองรับด้วยแคลเซียมคาร์บอเนต

นางสาวสุขุมาภรณ์ โชตินิธิกรกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาเคมี ภาควิชาเคมี
คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2559

# SUZUKI CROSS-COUPLING REACTION CATALYZED BY PALLADIUM NANOPARTICLES SUPPORTED ON CALCIUM CARBONATE

Miss Sukumaporn Chotnitikornkun

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Chemistry
Department of Chemistry
Faculty of Science
Chulalongkorn University
Academic Year 2016

| | |
|---|---|
| Thesis Title | SUZUKI CROSS-COUPLING REACTION CATALYZED BY PALLADIUM NANOPARTICLES SUPPORTED ON CALCIUM CARBONATE |
| By | Miss Sukumaporn Chotnitikornkun |
| Field of Study | Chemistry |
| Thesis Advisor | Associate Professor Sumrit Wacharasindhu, Ph.D. |
| Thesis Co-Advisor | Professor Mongkol Sukwattanasinitt, Ph.D. |

---

Accepted by the Faculty of Science, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

..............................................................Dean of the Faculty of Science
(Associate Professor Polkit Sangvanich, Ph.D.)

THESIS COMMITTEE

..............................................................Chairman
(Associate Professor Vudhichai Parasuk, Ph.D.)

..............................................................Thesis Advisor
(Associate Professor Sumrit Wacharasindhu, Ph.D.)

..............................................................Thesis Co-Advisor
(Professor Mongkol Sukwattanasinitt, Ph.D.)

..............................................................Examiner
(Associate Professor Voravee Hoven, Ph.D.)

..............................................................External Examiner
(Assistant Professor Kanok-on Rayanil, Ph.D.)

สุขุมาภรณ์ โชตินิธิกรกุล : ปฏิกิริยาซูซูกิครอสคัปปลิงเร่งปฏิกิริยาด้วยอนุภาคระดับนาโนเมตรของแพลเลเดียมรองรับด้วยแคลเซียมคาร์บอเนต (SUZUKI CROSS-COUPLING REACTION CATALYZED BY PALLADIUM NANOPARTICLES SUPPORTED ON CALCIUM CARBONATE) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ดร.สัมฤทธิ์ วัชรสินธุ์, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ศ. ดร.มงคล สุขวัฒนาสินิทธิ์, 86 หน้า.

งานวิจัยนี้รายงานการใช้ตัวเร่งปฏิกิริยาแพลเลเดียมรองรับบนแผ่นแคลเซียมคาร์บอเนตชนิดเดี่ยวหรือ Pd/ICCP ที่เป็นมิตรกับสิ่งแวดล้อมครั้งแรก จากเปลือกหอยของเสียเพื่อเป็นตัวเร่งปฏิกิริยาวิวิธพันธุ์ในปฏิกิริยาซูซูกิครอสคัปปลิงในวัฏภาคน้ำ ตัวเร่งปฏิกิริยา Pd/ICCP ถูกเตรียมจากวิธีอิมเพรกเนชัน-รีดักชันและพิสูจน์เอกลักษณ์อย่างครบถ้วนด้วยเทคนิค SEM, EDX, TEM และ ICP-OES ผลแสดงการกระจายตัวสูงของอนุภาคแพลเลเดียม (0) นาโนขนาด 5-8 นาโนเมตรบนตัวรองรับ ICCP ขนาด 3 ไมโครเมตรที่มีความเป็นระเบียบสูงและมีปริมาณแพลเลเดียม 5.5 % โดยน้ำหนัก สำหรับประสิทธิภาพการเร่งปฏิกิริยา การใช้ตัวเร่งปฏิกิริยา Pd/ICCP 2 เปอร์เซ็นต์โดยโมลเพียงพอกับการใช้โพแทสเซียมคาร์บอเนตเป็นเบสสำหรับปฏิกิริยาซูซูกิครอสคัปปลิงที่ใช้ตัวทำละลายที่มีน้ำเป็นองค์ประกอบในระบบตัวทำละลาย 2 ชนิด ได้แก่ ระบบตัวทำละลายผสมเอทานอลและน้ำอัตราส่วน (3:2) และระบบ CTAB และน้ำ ทั้งสองสภาวะประสบผลสำเร็จในการเร่งปฏิกิริยาระหว่างเอริลเฮไลด์ (ไอโอไดด์และโบรไมด์) ชนิดต่างๆ กับเอริลโบโรนิคแอซิดที่ 40 องศาเซลเซียสและให้ผลิตภัณฑ์ไบเอริลที่ร้อยละผลได้ 70-100 โดยไม่มีสารตั้งต้นเหลืออยู่ เมื่อเปรียบเทียบกับตัวเร่งปฏิกิริยา แพลเลเดียมบนแคลเซียมคาร์บอเนต (Pd/$CaCO_3$) แพลเลเดียมบนอนุภาคเปลือกหอยธรรมดา (Pd/SP) และแพลเลเดียมบนคาร์บอน (Pd/C) พบว่า Pd/ICCP มีประสิทธิภาพการใช้ซ้ำสูงสุดและพบการหลุดของโลหะต่ำสุด สามารถใช้ซ้ำได้ถึง 9 ครั้งด้วยร้อยละผลได้มากกว่า 80 ความสามารถในการเร่งปฏิกิริยาและการใช้ซ้ำที่สูงของตัวเร่งปฏิกิริยา Pd/ICCP อาจเกิดจากตัวรองรับ ICCP ที่มีความเป็นระเบียบสูงและการคีเลตที่แข็งแรงระหว่าง แพลเลเดียม (0) กับโปรตีนบนตัวรองรับ ICCP นอกจากนี้กระบวนการไมโครเวฟสามารถประยุกต์ใช้ในปฏิกิริยาซูซูกิที่ใช้ตัวเร่งปฏิกิริยา Pd/ICCP ได้ โดยลดเวลาในการทำปฏิกิริยาเหลือเพียง 5 นาที โดยไม่มีสารตั้งต้นเหลืออยู่ และตัวเร่งปฏิกิริยา Pd/ICCP สามารถประยุกต์ใช้ในปฏิกิริยาซูซูกิแบบต่อเนื่อง โดยการใช้ Pd/ICCP เพียง 0.5 เปอร์เซ็นต์โดยน้ำหนักสามารถขับเคลื่อนปฏิกิริยาจนสมบูรณ์ในเวลา 2 ชั่วโมง ดังนั้น Pd/ICCP จึงเป็นตัวเร่งปฏิกิริยาวิวิธพันธุ์ประสิทธิภาพสูงสำหรับปฏิกิริยาซูซูกิวัฏภาคน้ำในกระบวนการแบบกะแบบไหลต่อเนื่องและแบบไมโครเวฟ

| | | | |
|---|---|---|---|
| ภาควิชา | เคมี | ลายมือชื่อนิสิต | ................................................ |
| สาขาวิชา | เคมี | ลายมือชื่อ อ.ที่ปรึกษาหลัก | ................................................ |
| ปีการศึกษา | 2559 | ลายมือชื่อ อ.ที่ปรึกษาร่วม | ................................................ |

# # 5772181823 : MAJOR CHEMISTRY

KEYWORDS: PALLADIUM / HETEROGENEOUS CATALYST / SUZUKI CROSS-COUPLING / AQUEOUS SOLUTION / CALCIUM CARBONATE / ASIAN GREEN MUSSEL SHELL

SUKUMAPORN CHOTNITIKORNKUN: SUZUKI CROSS-COUPLING REACTION CATALYZED BY PALLADIUM NANOPARTICLES SUPPORTED ON CALCIUM CARBONATE. ADVISOR: ASSOC. PROF. SUMRIT WACHARASINDHU, Ph.D., CO-ADVISOR: PROF. MONGKOL SUKWATTANASINITT, Ph.D., 86 pp.

In this work, we report the first use of an eco-friendly palladium catalyst supported on individual calcium carbonate plates (Pd/ICCP) catalyst which has been made from shell waste to use as heterogeneous catalyst in aqueous Suzuki cross-coupling reaction. The Pd/ICCP is prepared from impregnation-reduction method and completely characterized by SEM, EDX, TEM, and ICP-OES techniques. The results indicate a high dispersion of palladium (0) nanoparticles (5-8 nm) on a highly uniform ICCP support (3 micrometer) providing palladium content of 5.5 %wt. For catalytic activity, the use of 2 mol% of Pd/ICCP is generally sufficient with potassium carbonate as a base for aqueous Suzuki cross-coupling reaction in two solvent systems including EtOH:$H_2O$ (3:2) and CTAB/$H_2O$. Both reaction conditions successfully catalyze the reaction between various aryl halides (iodide and bromide) and arylboronic acids at 40 $^{o}$C to give biaryl products in 70-100 % yields without remaining starting materials. In comparison with Pd/$CaCO_3$, Pd/SP and Pd/C, Pd/ICCP exhibits the highest reusability and lowest metal leaching. It can be reused up to nine times with NMR yield of more than 80% retained. The high catalytic activity and reusability of Pd/ICCP catalyst has been ascribed to the highly uniform ICCP support and strong chelation between Pd(0) and trace protein on ICCP support. Moreover, the microwave process has been successfully applied to Suzuki reaction using Pd/ICCP catalyst which can considerably reduce reaction time to only five minutes without left over starting material. Furthermore, Pd/ICCP catalyst can be adapted to the continuous-flow Suzuki reaction. The use of only 0.5%wt of Pd/ICCP can drive reaction completely within two hours of residence time. Therefore, Pd/ICCP is demonstrated to be a highly effective heterogeneous catalyst for aqueous Suzuki reaction in conventional batch, continuous-flow, and microwave processes.

| | | | |
|---|---|---|---|
| Department: | Chemistry | Student's Signature | ........................................ |
| Field of Study: | Chemistry | Advisor's Signature | ........................................ |
| Academic Year: | 2016 | Co-Advisor's Signature | ........................................ |

# ACKNOWLEDGEMENTS

First, I would like to express my sincere thankfulness to my advisor, Associate Professor Sumrit Wacharasindhu, Ph.D. and my co-advisor, Professor Mongkol Sukwattanasinitt, Ph.D. for worth opinion, guidance, and mercifulness throughout this research. Genuine gratefulness is also extended to Associate Professor Vudhichai Parasuk, Ph.D., Associate Professor Voravee P. Hoven, Ph.D., and Assistant Professor Kanok-on Rayanil, Ph.D., attending as the members of committee for their worth advices and comments.

Especially, I am grateful to the Thailand Research Fund (TRF-RSA5480004) and National Nanotechnology Center (NANOTEC), NSTDA, Ministry of Science and Technology, Thailand, through its program of the Center of Excellence Network. This work is also partially supported by a Grant for International Research Integration: Chula Research Scholar and the student scholarship were received from the His Royal Highness Crown Prince Maha Vajiralongkorn Scholarship from the Graduate School, Chulalongkorn University to commemorate the 72nd anniversary of his Majesty King Bhumibala Aduladeja and the 90th Anniversary Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund), which are gratefully acknowledged.

Finally, I would like to specially thank my family, Mr. Chawalit Takoon, MAPS group members including Mr. Trin Saetan, Ms. Supitcha Mitprapan, Ms. Nopparat Thavornsin, Ms. Kunnigar Vongnam, Ms. Piyamaporn Tangkasemsamran, Mr. Teeranon Tankam, Ms. Kanokthorn Boonkitpatarakul and friends for their inspiration, encouragement, and understanding. I would not be able to achieve this accomplishment without them.

## CONTENTS

Page

Page

# LIST OF SCHEMES

# LIST OF TABLES

# LIST OF EQUATIONS

# LIST OF FIGURES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ICCP | individual calcium carbonate plate |
| SP | simple grounded shell particle |
| Pd | palladium |
| $^{13}$C-NMR | carbon-13 nuclear magnetic resonance |
| $^{1}$H-NMR | proton nuclear magnetic resonance |
| $CDCl_3$ | deuterated chloroform |
| MHz | megahertz |
| **$\delta$** | chemical shift |
| s | singlet (NMR) |
| d | doublet (NMR) |
| t | triplet (NMR) |
| m | multiplet (NMR) |
| ***J*** | coupling constant |
| IR | infrared |
| ATR | attenuated total reflection |
| g | gram (s) |
| mg | milligram (s) |
| mL | milliliter (s) |
| mmol | millimole (s) |
| mM | millimolar |
| M | molar |
| W | watt |
| TLC | thin layer chromatography |
| h | hour (s) |
| $^{\circ}$C | degree Celsius |

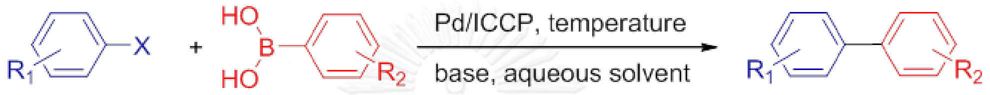
| | |
|---|---|
| equiv | equivalent (s) |
| % yield | percentage of yield |
| % wt | percentage by weight |
| EtOH | ethanol |
| CTAB | cetyltrimethylammonium bromide |
| TBAB | tetrabutylammonium bromide |
| CMC | critical micelle concentration |
| DIPA | diisopropylamine |

# CHAPTER I

# INTRODUCTION

## 1.1 Overview

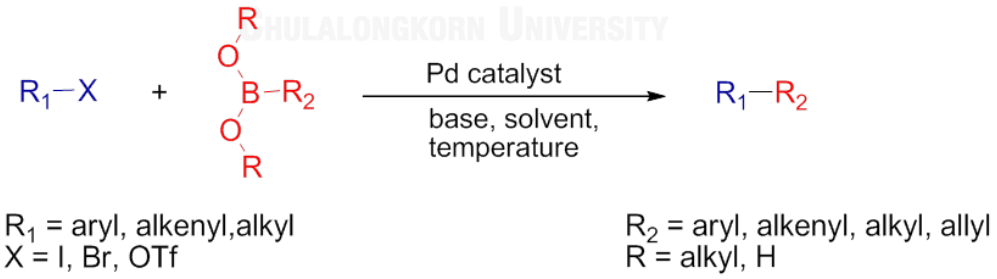
The palladium-catalyzed reactions are a powerful method for an organic synthesis, particularly carbon-carbon bond formation. One of the most popularly used protocols for palladium-catalyzed reaction is the Suzuki-cross-coupling reaction. It is the cross-coupling reaction between aryl halide and arylboronic acid to generate biaryl compounds [1]. Such products are very important as valuable intermediates for the synthesis of natural products, bioactive compounds, and organic materials [2-4]. Classically, the Suzuki reaction is carried under homogeneous palladium catalysts because of their high catalytic activity [5-7]. However, the separation and recovery of catalyst are very difficult causing the loss of expensive palladium catalyst and production of toxic metal waste [8]. To solve this problem, many researchers therefore have developed heterogeneous palladium catalyst for Suzuki cross-coupling reaction because of the ease of product isolation and reusability. Many solid matrices have been applied to support palladium catalyst for Suzuki cross-coupling reaction [9], for example Pd on graphene oxide [10], Pd on metal oxide [11], and Pd on carbon [12]. But for the first two catalysts, they require a multiple-step preparation, ligand, high reaction temperature and toxic organic solvent. In contrast, Pd on carbon is simple to prepare and inexpensive but it also has a pyrophoric problem. Avoiding the use of toxic organic solvents in organic synthesis is also a most significant aim in green chemistry [13], so many researchers attempt to use water as a solvent because it is widely available, low toxic, non-flammable solvent and facilitate to dissolve inorganic salts [14]. Recently, calcium carbonate was used as catalytic support for Stille [15] and Heck [16] cross-coupling reaction because of its safety and high abundance found in nature. Moreover, there are researches reported the use of calcium carbonate derived from shell particles as supported palladium catalyst in Heck [17] and Homo coupling reaction [18]. The utilization of this material is not only benefit in environmental aspect but also increasing the value of industry waste. In most recently, our group [19] and Lertvachirapaiboon and co-workers [20] have successfully prepared the individual calcium carbonate plate (ICCP) from Asian green mussel shell waste. It is really appropriate to use as catalytic support because of its high surface area from the natural aragonite structure. This palladium on individual calcium carbonate plate (Pd/ICCP) catalyst was successfully used in copper-free Sonogashira cross-coupling reaction [19]. To expand scope of our new catalytic support from shell waste, in this work, we develop the Suzuki cross-coupling reaction conducted in aqueous medium using our prepared Pd/ICCP catalyst (Scheme 1.1).



**Scheme 1.1** Synthesis of biaryl compound in Suzuki reaction

### 1.2 Introduction to Suzuki cross-coupling reaction

In 1979, Suzuki and his co-workers reported the palladium-catalyzed cross-coupling reaction between organohalide and organoborane in the presence of base, solvent, and homogeneous Pd catalyst such as $PdCl_2$(dppf), $Pd(PPh_3)_4$. This reaction was used to form carbon-carbon bonds to provide conjugated systems of alkenes, styrenes, or biaryl coupling product in good yield (Scheme 1.2) [21, 22].



**Scheme 1.2** General Suzuki cross-coupling reaction

Mechanistically, there are three steps for this catalytic cycle including oxidative addition, transmetallation, and reductive elimination as demonstrated in Figure 1.1 [9]. First, the catalytically active Pd(0) species **1** reacts with organohalide **2** to form an $[Pd(II)R_1X]$ specie **3** in an oxidative addition step. In general, this step is the rate-determining step of the reaction. Then, molecule of hydroxide or alkoxide base replaces the halide to give [Pd(II)$R_1$OH] intermediate **4**. While another substrate of organoborane **5** reacts with base to form reactive boronate complex **6** which is a stronger nucleophile. Second, an intermediate **4** reacts with boronate complex **6** via transmetallation to generate [Pd(II)$R_1R_2$] specie **8.** The final step is reductive elimination to give the coupling product **9** and restore the active palladium (0) catalyst into the catalytic cycle. This mechanism suggests that the base is essential for the catalytic cycle of the Suzuki reaction. The roles of base consist of the formation of palladium complex [Pd(II)$R_1$OH] and more reactive nucleophile of boronate complex in order to drive transmetallation step in catalytic cycle [23].

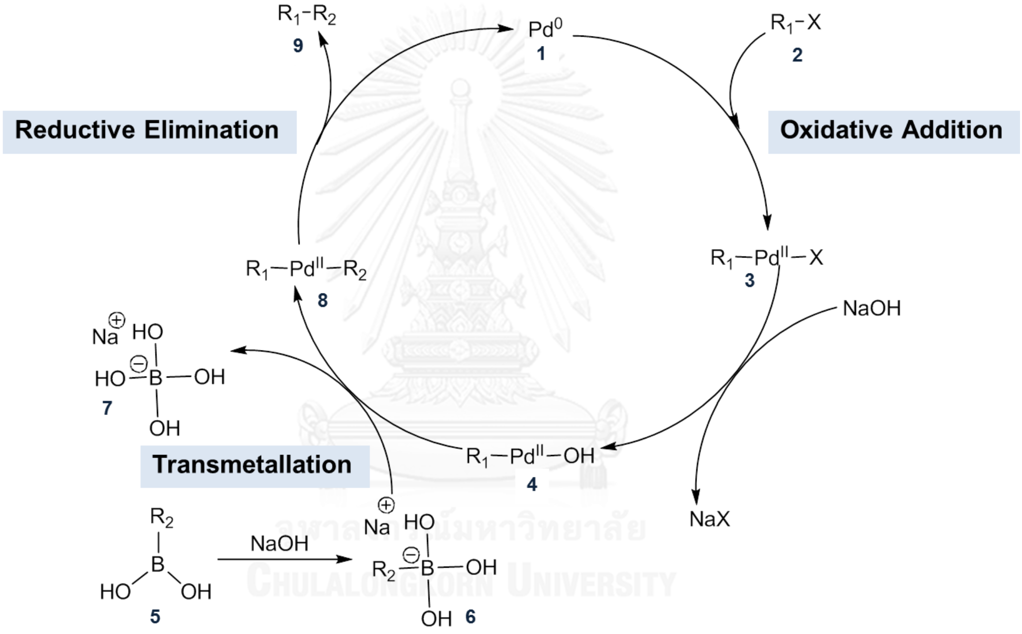
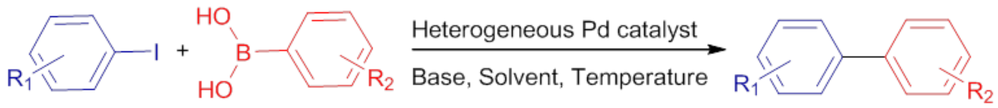


**Figure 1.1** Catalytic cycle of Suzuki cross-coupling reaction

### 1.3 Introduction to heterogeneous catalyst in Suzuki reaction

As mentioned above, there are some disadvantages for homogeneous catalyst, especially, the separation and reusability of catalyst. Therefore, it results in losing expensive palladium catalyst and producing toxic metal waste. To overcome these problems, the utilization of heterogeneous catalyst which is easy to separate and reuse is the best option in the aspect of atom economy and the environmental issue. Many solid matrices have been applied to support palladium catalyst for Suzuki cross-coupling reaction [9] such as Pd on metal oxide [11, 24], Pd on modified silica [25], Pd on clay [26], Pd on graphene oxide [10] and Pd on C [12] as shown in Scheme 1.3. These catalysts are divided into two groups including covalently attached ligand on catalytic support and directly physical adsorption of palladium on catalytic support.



X = I, Br

Heterogeneous Pd catalyst: Pd/C or Pd on KF/$Al_2O_3$ or $Fe_2O_3$-Pd-NHC complex or $SiO_2$/TEG/Pd or $Pd^{2+}$-sepiolite or GO-NHC-Pd

**Scheme 1.3** Suzuki cross-coupling reaction catalyzed by heterogeneous Pd catalyst

## 1.4 Organic chemistry in water

In the aspect of environmental pollution was caused by the use of volatile and highly inflammable organic solvents. Avoiding the use of toxic organic solvents in organic synthesis is also a most significant aim in green chemistry [13]. The replacement with water as solvent has been interested because water is termed as a “most green solvent” [27]. It is widely available, low toxic, economical, non-flammable solvent as well as facilitate to dissolve inorganic salts and reduce toxic organic waste [14]. Therefore, in this work, we aim to develop Suzuki cross-coupling reaction by using environmentally benign aqueous solvent. The use of benign chemical is one of concepts of sustainable chemistry [28].

## 1.5 Literature reviews

### 1.5.1 Suzuki cross-coupling reaction

In 2010, the Nobel prize in chemistry had been awarded to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki for their research on palladium-catalyzed cross coupling in organic synthesis [29] as shown in Figure 1.2. They have first developed a new efficient method to form carbon-carbon bond via palladium-catalyzed reaction namely Heck, Negishi, and Suzuki reactions.

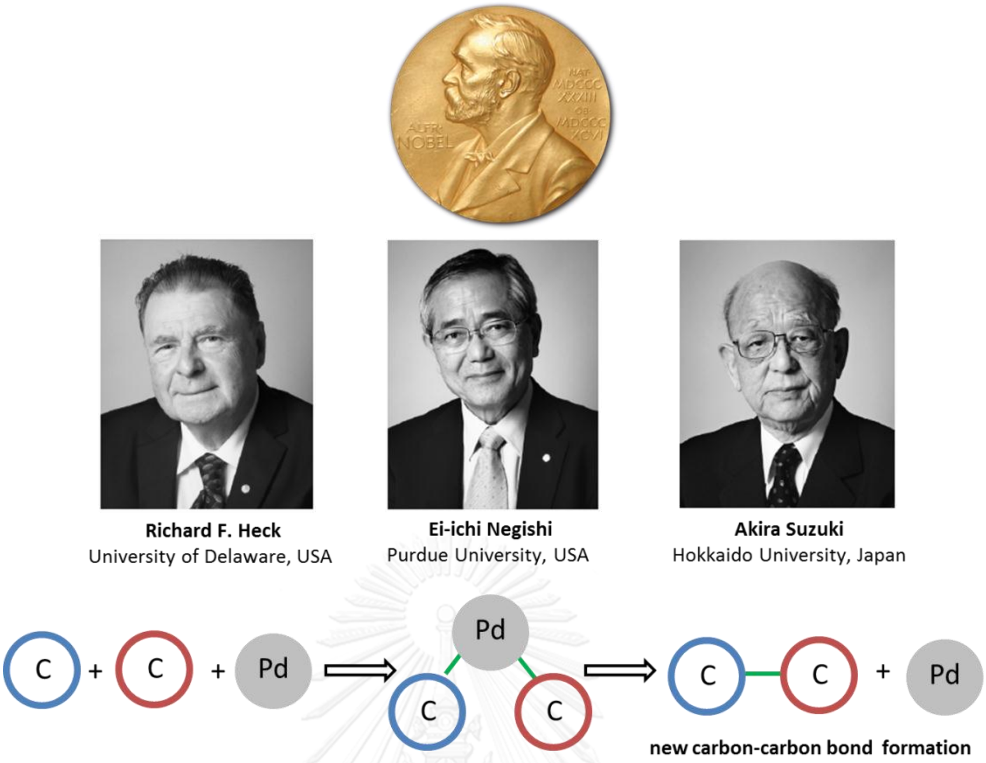
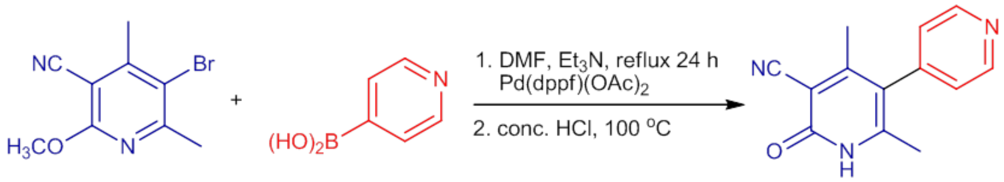
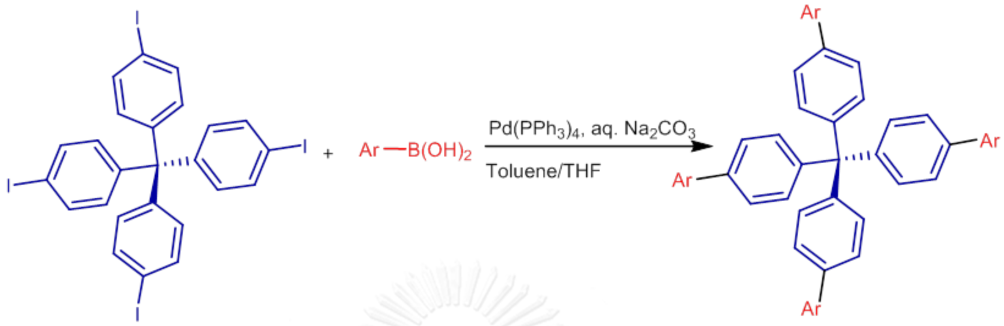


**Figure 1.2** Three scientists shared the 2010 Nobel Prize in chemistry for palladium-catalyzed cross coupling in organic synthesis

Among them Suzuki cross-coupling reaction is one of the most important palladium-catalyzed C-C bond formations. It is the coupling between aryl or vinyl halide (or triflate) with aryl or vinylboronic acid to generate the coupling product. The reaction name was first published in 1979 by Akira Suzuki. The reaction proceeds smoothly using a catalytic amount of palladium source such as Pd($PPh_3$)$_4$ as catalyst, base, and solvent [22]. According to the productivity of Suzuki reaction, such products are very important as valuable intermediates for the synthesis of natural products, bioactive compounds, and organic materials [2-4]. For instance, it was used in the synthesis of milrinone [30], which was applied as the cardiotonic drug for patients who have heart failure as shown in Scheme 1.4. Moreover, the Suzuki reaction was also used in the synthesis of tetraphenylmethane derivatives [4], which was applied as organic light-emitting diodes (OLEDs) as demonstrated in Scheme 1.5.



**Scheme 1.4** Suzuki reaction for synthesizing milrinone derivative



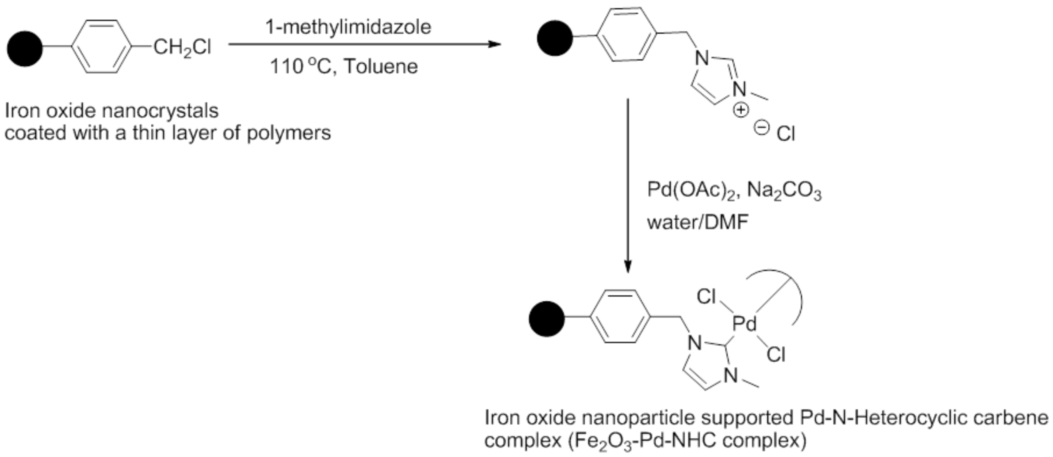
**Scheme 1.5** Suzuki reaction for synthesizing tetraphenylmethane derivatives

### 1.5.2 Suzuki reaction using heterogeneous catalyst

To solve the problems for the use of homogeneous palladium catalyst as mentioned in previous section. Many researchers reported the development of heterogeneous palladium catalysts to catalyze Suzuki cross-coupling reaction.

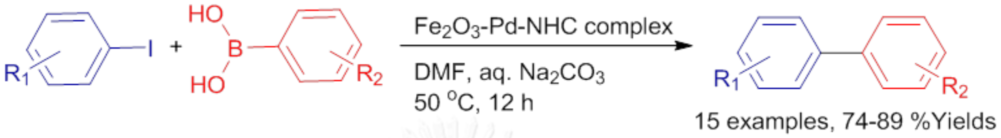
#### 1.5.2.1 Example on covalently attached ligand on catalytic support

In 2005, Stevens and co-workers [11] reported the preparation of iron oxide nanoparticle supported Pd-N-heterocyclic carbene complex ($Fe_2O_3$-Pd-NHC complex) catalyst as shown in Scheme 1.6.



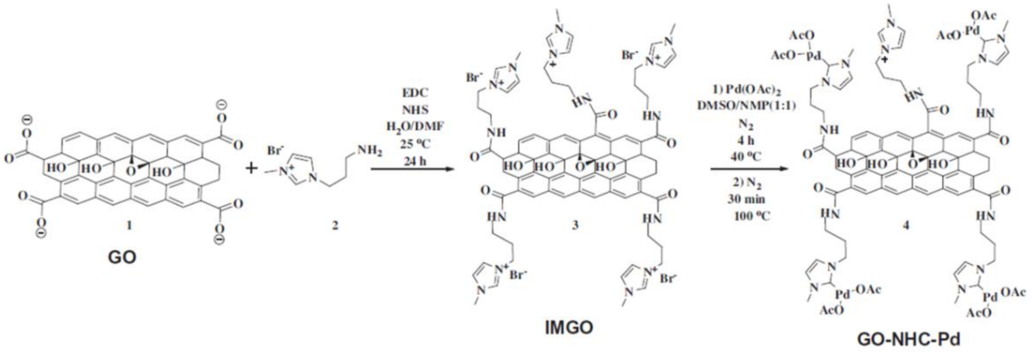
**Scheme 1.6** Preparation of $Fe_2O_3$ Nanoparticle-Supported Pd-NHC complex catalyst

It is stable and highly active heterogeneous palladium catalyst for Suzuki reactions. The $Fe_2O_3$-Pd-NHC complex catalyst was used with dimethylformamide as solvent and $Na_2CO_3$ as base to catalyze Suzuki reaction between aryl iodides and arylboronic acids (Scheme 1.7). The desired products were obtained in good to high yields. As the superparamagnetic property of this catalyst, it can be easily reused up to five times without significant loss of catalytic activity by applying a permanent magnet.



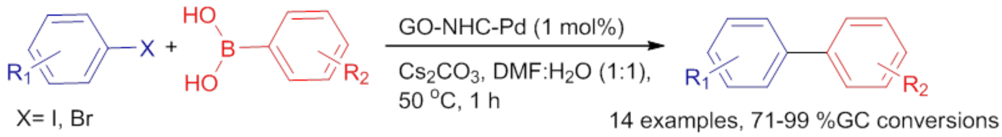
**Scheme 1.7** $Fe_2O_3$ Nanoparticle-Supported Pd-NHC complex catalyzed Suzuki coupling of aryl iodide with arylboronic acid

In 2014, Park and co-workers [10] prepared graphene oxide (GO) supported Pd-N-heterocyclic carbene complex (GO-NHC-Pd) catalyst as demonstrated in Scheme 1.8



**Scheme 1.8** Preparation of graphene oxide-supported Pd-NHC complex catalyst

This GO-NHC-Pd catalyst exhibited high stability and reactivity for Suzuki reaction. The coupling reaction between aryl halides with arylboronic acids using this catalyst, $Cs_2CO_3$ as base, DMF:$H_2O$ as solvent underwent within 1 hour at 50 °C (Scheme 1.9). The target products were obtained in good to high yields and GO-NHC-Pd catalyst can be reused up to five times without a loss of its catalytic activity.

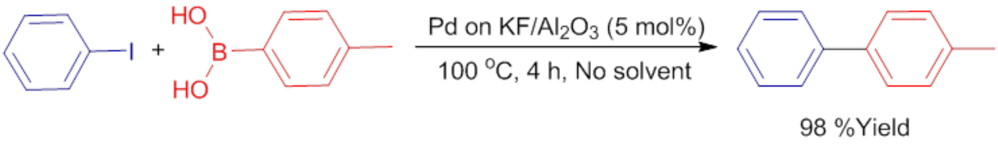


**Scheme 1.9** Graphene oxide supported Pd-NHC complex catalyzed Suzuki coupling of aryl halide with arylboronic acid

As the mentioned above, both catalysts including palladium on $Fe_2O_3$ nanoparticle-supported Pd-NHC complex, and palladium on graphene oxide (GO-NHC-Pd) have ligand that which is covalently attached to catalytic support. These catalysts therefore demonstrated high stability, catalytic activity, and reusability. However, they need difficult multiple-step preparation. Alternatively, there are many research reported on the development of heterogeneous catalyst that palladium directly adsorbed on support. The catalyst from this method is easily prepared which is suitable for large-scale synthesis.

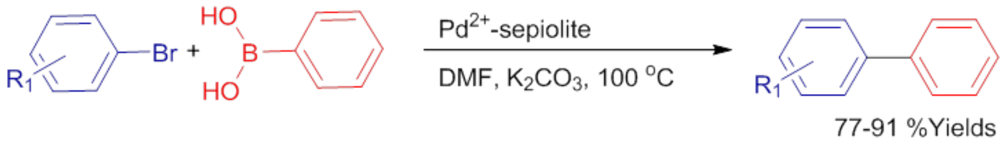
1.5.2.2 Example on heterogeneous palladium catalyst from direct physisorption

In 1999, Kabalka and co-workers [24] reported ligandless palladium(0) catalyst deposited on a commercial potassium fluoride-alumina mixture (Pd on $KF/Al_2O_3$) to catalyze solventless Suzuki reaction between iodobenzene and 4-methylphenylboronic acid (Scheme 1.10). KF was used as the most effective base for their reaction condition. The coupling product was obtained in excellent yield.



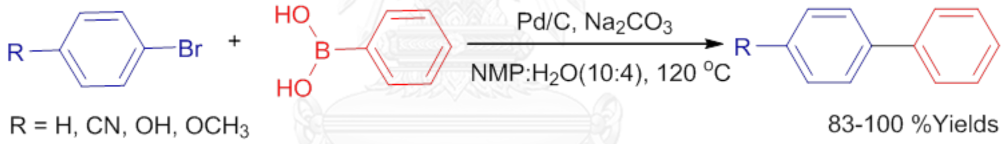
**Scheme 1.10** Palladium-doped $KF/Al_2O_3$ catalyzed solvent-free Suzuki coupling reaction

In 2002, Shimizu and co-workers [26] reported the simple preparation of sepiolite clay supported $Pd^{2+}$-complex immobilized catalyst ($Pd^{2+}$-sepiolite). This catalyst effectively catalyzed Suzuki reaction between aryl bromide and phenylboronic acid using $K_2CO_3$ as base in DMF at 100 °C (Scheme 1.11). The desired products were obtained in good to high yield. The catalyst can be reused up to two times without losing its activity.



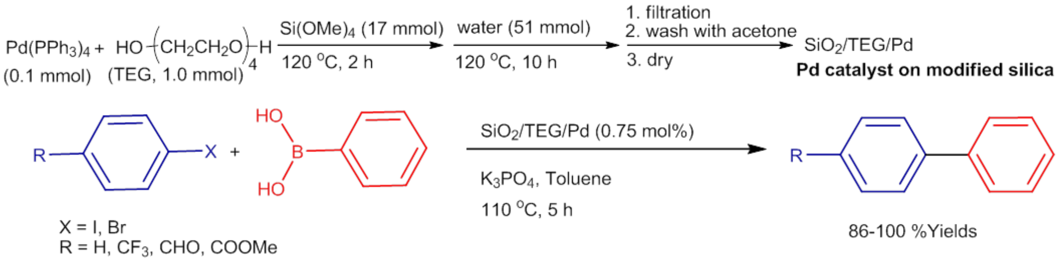
**Scheme 1.11** Sepiolite clay supported Pd (II) complex catalyzed Suzuki coupling reaction

In the same year, Heidenreich and co-workers [12] prepared a palladium on activated carbon catalyst. It is highly selective, active, and appropriate heterogeneous catalyst for Suzuki reaction. The Pd on C catalyst was used with $Na_2CO_3$ as base and mixed solvent of N-methyl-2-pyrrolidone and water to catalyze Suzuki reaction between aryl bromide and phenylboronic acid (Scheme 1.12). The desired biaryls were obtained in high yields and this catalyst could be isolated and reused by filtration.



**Scheme 1.12** Pd/C catalyzed Suzuki cross-coupling of aryl bromide with phenylboronic acid

In 2004, Kim and co-workers [25] reported an amorphous silica supported palladium nanoparticles ($SiO_2$/TEG/Pd) catalyst. It was prepared from $Pd(PPh_3)_4$ in a mixture of tetramethoxysilane and tetra(ethylene glycol), then encapsulated in a silica matrix. This efficient catalyst was applied in Suzuki reaction between aryl halides (iodide and bromide) and phenylboronic acid using $K_3PO_4$ as base in toluene at 110 °C (Scheme 1.13). The biaryl products were achieved in 86-100 %yields. Moreover, the $SiO_2$/TEG/Pd catalyst could be reused up to three times without losing catalytic activity.



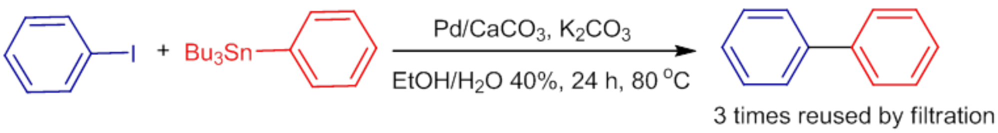
**Scheme 1.13** Preparation of $SiO_2$/TEG/Pd and using it as a catalyst in Suzuki reaction

As mentioned above, although palladium on metal oxide and palladium on modified silica have high catalytic activity for Suzuki cross coupling, but the method for synthesis of these supports require multi-step steps and expensive equipment. Alternatively, palladium on carbon was popularly applied as catalyst in large-scale synthesis [31] because of high catalytic efficiency, simple preparation and inexpensive support. However, the carbon support still has pyrophoric and leaching issues. Another widely used catalytic support for industrial process is calcium carbonate owing to its safety and high abundance found in nature. One of the most recognized Pd/$CaCO_3$ catalysts is “Lindlar catalyst” which is used in hydrogenation application. Due to its many advantages, several researchers initiatively apply calcium carbonate supported palladium to catalyze cross-coupling reaction recently.

### 1.5.3 Palladium-catalyzed cross coupling reaction using calcium carbonate as solid support

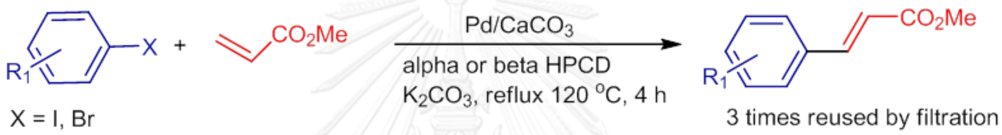
Calcium carbonate is not only large abundant material found in nature, but it is also stable, inexpensive, and non-pyrophoric. Such advantages, calcium carbonate is worth to be considered as an alternative support for heterogeneous palladium catalyst. Typically, palladium on calcium carbonate is known as Lindlar catalyst which is used for hydrogenation of alkynes to alkenes in chemical industry for fifty-one years [32]. Recently, it was used to catalyze carbon-carbon bond formation in Stille and Heck reactions, as shown below.

In 2007, Coelho and co-worker [15] first reported the use of Pd/$CaCO_3$ to catalyze the ligand-free Stille cross-coupling reaction as demonstrated in Scheme 1.14. Moreover, this catalyst could be reused up to three times by filtration without losing catalytic activity.



**Scheme 1.14** Stille reaction between iodobenzene and tributylphenyltin using Pd/CaCO$_3$ as a catalyst

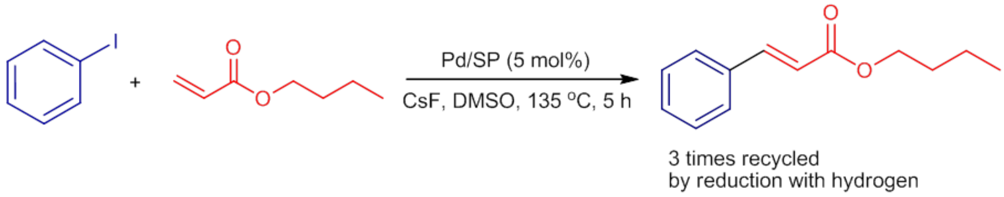
In the same year, Senra and co-workers [16] studied the use of Pd/CaCO$_3$ as a catalyst for phosphine-free Heck cross-coupling in aqueous solvent by using hydroxypropylated cyclodextrins (HPCD) as supramolecular hosts (Scheme 1.15). The hydrophobic internal cavity can collect the lipophilic organic reagents resulting in increasing solubility in aqueous solvent. Moreover, the Pd/CaCO$_3$ catalyst could be reused up to three times by filtration.



**Scheme 1.15** Phosphine-free Heck reaction between aryl halide and methyl acrylate

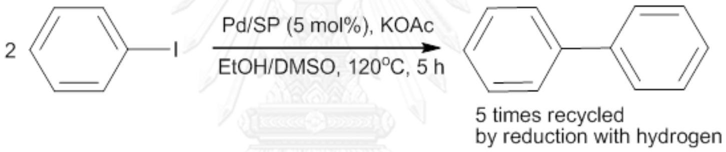
According to the above-mentioned researches, calcium carbonate supported palladium catalyst has high stability, catalytic activity and reusability in the several cross-coupling reactions. In recent year, the green and sustainable concepts are important criteria for reaction and catalyst design. To adapt such concept to the heterogeneous palladium catalyst, several researchers reported the use of bio-mineral, shell waste as catalytic support. Therefore, the utilization of shell waste as catalytic support is not only benefit in environmental aspect but also increasing the value of industry waste.

In 2010, Shen and co-workers [17] prepared a new heterogeneous palladium catalyst from pearl shell particles by grinding dried-shell and impregnating with Na$_2$PdCl$_2$ solution, after that reducing palladium (II) with hydrogen gas. They used the palladium supported on shell particles (Pd/SP) to catalyze the Heck cross-coupling reaction between iodobenzene and butyl acrylate as shown in Scheme 1.16. This Pd/SP catalyst demonstrated high stability and catalytic activity in this reaction with high yield and it can be recycled up three times by reduction with hydrogen.



**Scheme 1.16** Palladium on shell particles (Pd/SP) catalyzed Heck reaction between iodobenzene and butyl acrylate

Later, the same group [18] used the same catalyst (Pd/SP) to do the homocoupling reactions of iodobenzene as demonstrated in Scheme 1.17. Importantly, they also compared the catalytic activity and recyclability of Pd/SP with Pd/$CaCO_3$ and Pd/C. The Pd/SP catalyst has higher properties than Pd/$CaCO_3$ and Pd/C, and it can be recycled up five times by reduction with hydrogen. This was probably due to the chelation between palladium metal and the functional groups of protein on shell particles.



**Scheme 1.17** Homocoupling reaction of iodobenzene

Even though this palladium supported on shell particle (Pd/SP) catalyst was efficient enough to catalyze both of coupling reactions. However, its calcium carbonate is large and the morphology is non-uniform (Figure 1.3) due to physical grinding of shell particles. This might decrease catalytic activity, reproducibility, and recyclability.

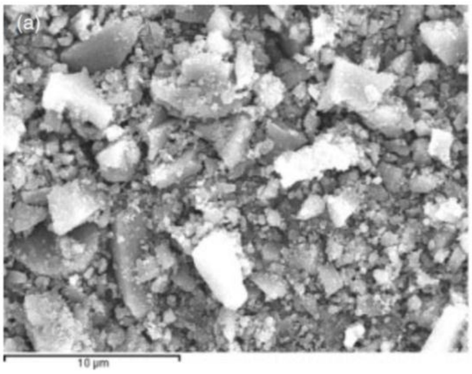


**Figure 1.3** TEM image of palladium supported on shell particle (Pd/SP) catalyst [17]

Recently, Lertvachirapaiboon and co-workers [20, 33] studied the structure of Asian green mussel shell waste. An Asian green mussel shell consists of slim aragonite calcium carbonate layers bounded by thin organic matrix layers including protein, chitin, polysaccharides, peptides and lipid. The removal of organic matrix between nacreous layers without destroying aragonite structure was performed by chemical treatment (Figure 1.4). It resulted in the uniform calcium carbonate plates. Moreover, calcium carbonate plate derived from mussel shell has smaller size than calcium carbonate from other shells at equal weights. This led to higher surface area of calcium carbonate plates. Therefore, calcium carbonate from mussel shell waste is indeed suitable as catalytic support.

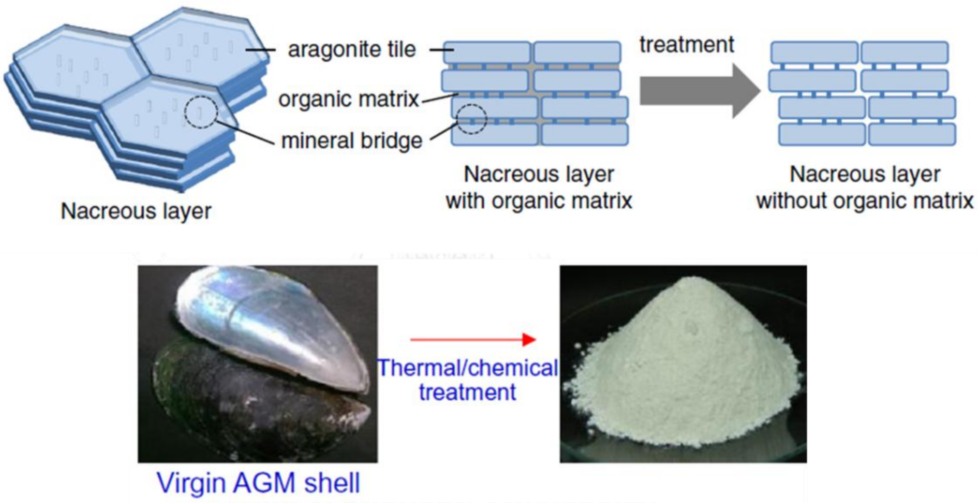


**Figure 1.4** The structure of Asian green mussel shell [33]

In 2016, our research group [19] has successfully prepared the novel individual calcium carbonate plates supported palladium (Pd/ICCP) catalyst from Asian green mussel shell waste using Lertvachirapaiboon method (Figure 1.5). With high surface area and highly uniform of Pd/ICCP, We also applied the Pd/ICCP catalyst to catalyze the Copper-free Sonogashira cross-coupling reaction between aryl iodides and terminal alkynes successfully. Our Pd/ICCP catalyst could be reused up to three times without losing its activity.

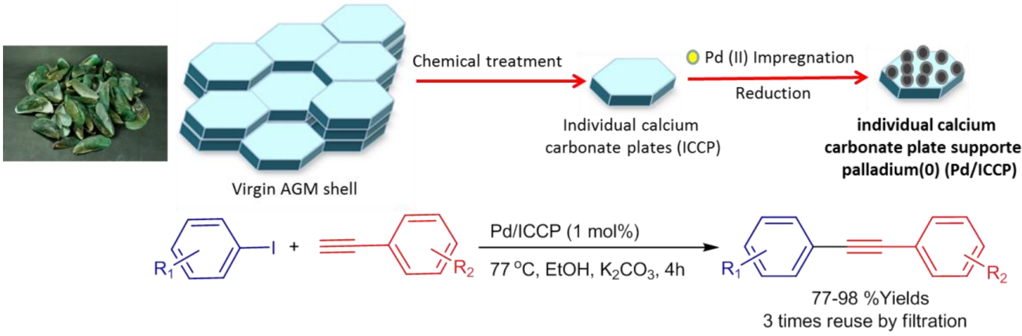
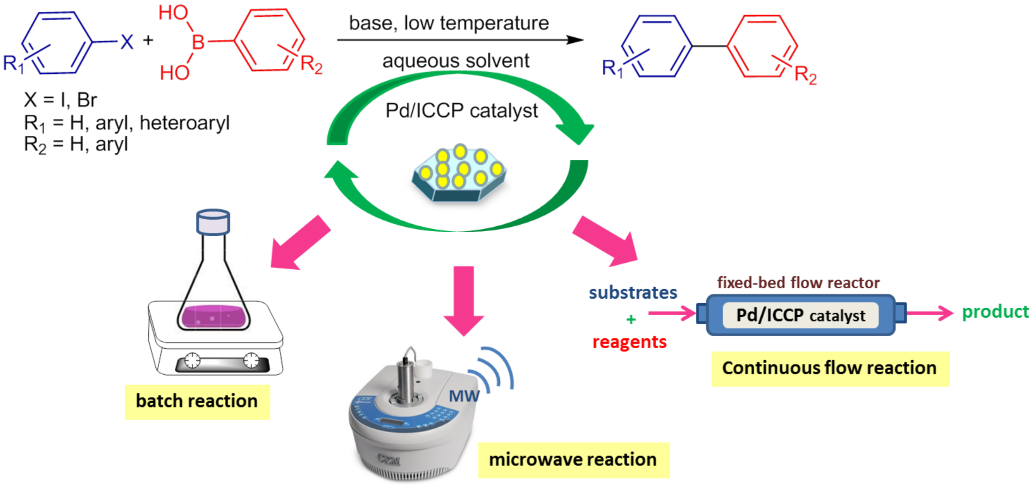


**Figure 1.5** Preparation of individual calcium carbonate plates supported palladium (Pd/ICCP) catalyst and the use of Pd/ICCP to catalyze Copper-free Sonogashira cross-coupling reaction

As mentioned above, our palladium on individual calcium carbonate plates (Pd/ICCP) catalyst has superior catalytic activity than commercial Pd/$CaCO_3$ and palladium on shell particle (Pd/SP) for palladium-catalyzed cross-coupling reaction. To demonstrate the high generality of our Pd/ICCP catalyst, we will apply our catalyst into more challenge reaction which is aqueous Suzuki cross-coupling reaction in traditional batch and continuous-flow reaction.

## 1.6 Objective of this research

In this research, we aim to use the individual calcium carbonate plate from Asian green mussel shell waste supported palladium (Pd/ICCP) catalyst to catalyze Suzuki cross-coupling reaction conducted in aqueous medium at low temperature as shown in Scheme 1.18. The effect of bases, solvent systems, and temperature will be screened for optimization condition. Moreover, substrate compatibility between aryl halides and arylboronic acids will also be investigated. The reusability and leaching test of Pd/ICCP catalyst will be also tested. Furthermore, we will apply microwave and continuous flow processes for Suzuki reaction using our Pd/ICCP catalyst.



**Scheme 1.18** Pd/ICCP catalyst catalyzed Suzuki cross-coupling reaction

# CHAPTER II
# EXPERIMENTAL

Total reagents were derived from commercial providers, including Merck® (Germany), Sigma-Aldrich and Fluka® (Switzerland), and were applied without additional purification. Overall solvents were circulated with nitrogen gas before usage in the reaction. Kieselgel F-254 pre-coated plastic TLC plates from EM Science were used for analytical thin-layer chromatography (TLC). An ultraviolet lamp with 254 nm was applied for visualization on TLC plates. Gel column chromatography was accomplished with silica gel (60 Å, 230-400 mesh) from ICN Silitech. The $^{1}H$ and $^{13}C$ NMR spectra were acquired on a Varian or Bruker NMR spectrometer, working at 400 MHz for $^{1}H$ and 100 MHz for $^{13}C$ nuclei in $CDCl_3$ solution. Chemical shifts of $^{1}H$ and $^{13}C$ NMR were cited in ppm relative to $CDCl_3$ ($\delta$ 7.26 ppm for $^{1}H$, $\delta$ 77.00 ppm for $^{13}C$). Coupling constants (*J*) were informed in unit of Hertz (Hz). The multiplicity of the signal was demonstrated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). The Asian green mussel shell waste was received from the fishing industry in Thailand. The palladium content of the prepared catalyst was determined by ICP-OES (Thermo Scientific, iCAP 6500). The morphology of Pd/ICCP was investigated using scanning electron microscope (SEM, JEOL JSM-6510A) at an operating voltage of 20 kV under a high vacuum mode with a secondary electron image (SEI) detector. TEM image of Pd/ICCP was obtained by transmission electron microscope (TEM, JEM-2100). The metal elemental composition of catalyst was determined using a built-in energy dispersive X-ray spectrometer (EDX). Whole ATR FT-IR spectra were received from 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 continuous flow reactions were performed in a microflow reactor (Syrris Asia, FRXTM Model) including hot plate, a solid phase packed bed reactor, syringe pump and pressurization. Microwave reactions were carried out in a CEM Discover microwave apparatus.

## 2.1 Preparation of tetrachloropalladic acid ($H_2PdCl_4$) solution

0.05 M of $H_2PdCl_4$ solution was prepared by dissolving palladium (II) chloride (0.89 g) in aqua regia (5 mL, a mixture of concentrated hydrochloric acid and nitric acid with a volume ratio of 3:1) and stirring at 100 $^{\circ}$C until palladium (II) chloride was totally dissolved. Then, heating of the solution was still continued until nearly dry and the solution was added into a 100 mL volumetric flask. After that, adjusting concentration of $H_2PdCl_4$ solution was carried out by pouring water.

## 2.2 Preparation of the individual calcium carbonate plates (ICCP)

ICCP powder was produced by the following procedure: Firstly, Asian green mussel (Perna viridis) shells were washed with water in order to eliminate other contaminants and dried at ambient temperature. Secondly, the dried mussel shells were baked at 300 $^{\circ}$C for 2 h and immersed in 30% (w/w) hydrogen peroxide solution under ultrasonic sonication for 24 h. Thirdly, filtration of the treated-shells was performed to become ICCP powder with 200 mesh filter size. Finally, ICCP powder was washed with water several times, then further dried under an ambient air and stored in a desiccator.

## 2.3 Preparation of the individual calcium carbonate plates supported palladium (Pd/ICCP) catalyst

Pd/ICCP (6.0 wt% Pd supported on individual calcium carbonate plates) was prepared by the following impregnation-reduction method: ICCP powder (5.0 g) was dispersed into $H_2PdCl_4$ aqueous solution (0.05 M, 56.4 mL) and the mixture was stirred until the color of solution changed from brown to colorless. Then the excess aqueous sodium borohydride ($NaBH_4$) solution (0.69 M, 10 mL) was gradually dropped over 20 min and stirred for 1 h. The white ICCP powder became black during the reduction process of palladium (II) to palladium (0). After that, the solution was centrifuged to separate the solid which was washed with water and dried at 100 $^{\circ}$C for 2 hours. Lastly, the dried solid was applied as the catalyst.

## 2.4 Determination of Palladium content of prepared catalyst by ICP-OES analysis

### 2.4.1 General process for preparation of sample.

The prepared Pd/ICCP catalyst (25.0 mg) and aqua regia (6.0 mL) were added in an oven-dried sealed tube equipped with a magnetic stirring bar. Then, stirring the mixture at 100 °C for 24 hours was executed. After cooling to ambient temperature, the mixture was decanted into 100 mL volumetric flask. Finally, adjusting concentration of palladium to 15 ppm was carried out by pouring water.

### 2.4.2 Calibration curve method.

Palladium standard stock solution for ICP analysis (1000 ppm) was applied for preparation of calibration curve between 1-25 ppm as shown in Figure 2.1

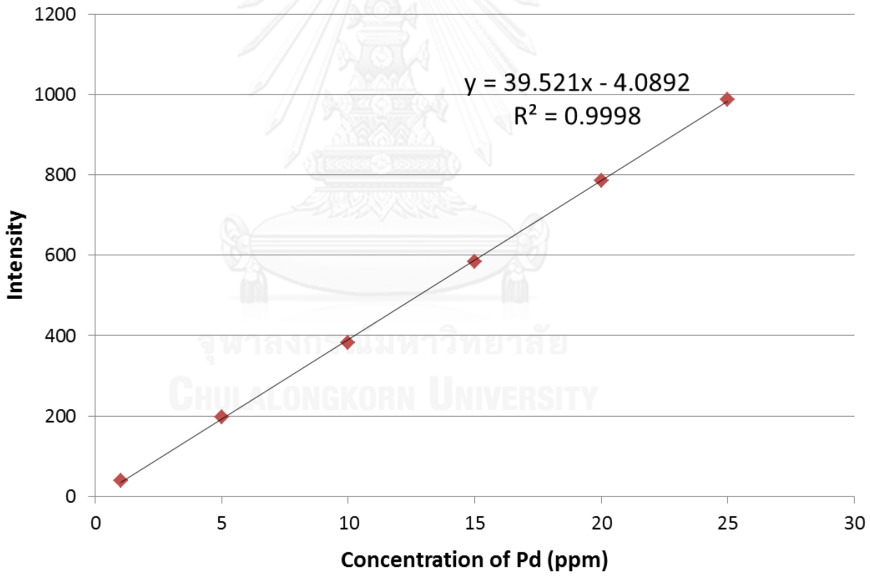


**Figure 2.1** Calibration curve of palladium standard solution

## 2.5 Determination of percent NMR yield of reaction mixture in Suzuki reaction between 4-iodoanisole and phenylboronic acid by $^1$H-NMR spectroscopy

### 2.5.1 General process for preparation of sample

After completed reaction, the reaction mixture was filtered and the solvent was evaporated under reduced pressure. Then, the crude reaction mixture was dissolved in $CDCl_3$ and analyzed by $^1$H-NMR spectroscopy in order to determine percent NMR yield.

### 2.5.2 Calculation of percent NMR yield of reaction mixture

The $^1$H-NMR spectrum of reaction mixture (Figure 2.2c) was used for calculating percent NMR yield of reaction mixture of Suzuki reaction between 4-iodoanisole and phenylboronic acid from Equation 2.1, where $Int_{product}$ and $Int_{substrate}$ are the intregrations of product and substrate, respectively. We selected the peak of 4-iodoanisole substrate in green frame (Figure 2.2a) and the peak of 4-methoxybiphenyl product in blue frame (Figure 2.2b) to determine percent NMR yield as shown in Figure 2.2.

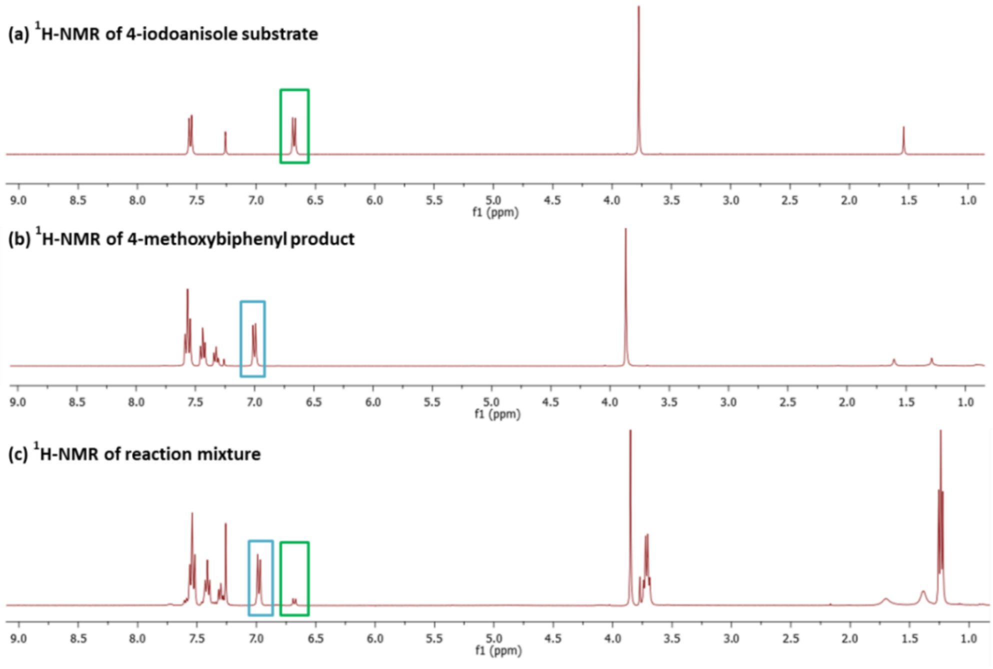


**Figure 2.2** $^1$H-NMR spectra of 4-iodoanisole substrate (a), 4-methoxybiphenyl product (b), and reaction mixture (c).

$$\%\text{NMR Yield} = \frac{\text{Int}_{\text{product}}}{\text{Int}_{\text{product}} + \text{Int}_{\text{substrate}}} \text{ X } 100$$

**Equation 2.1** Equation for determining the percent NMR yield of reaction mixture.

## 2.6 Optimization studies on the Suzuki cross-coupling reaction

### 2.6.1 Optimization of the reaction conditions

Effect of base: An oven-dried sealed tube was used as reaction container, after adding 4-iodoanisole (0.50 mmol), phenylboronic acid (0.75 mmol), the Pd/ICCP catalyst (0.01 mmol or 2 mol%), the base (1.50 mmol), and the mixed solvent of EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL), the sealed tube was transferred into a reaction chamber with a magnetic stirring bar. Then, the reaction mixture was stirred at 40 $^{\circ}$C under nitrogen for 12 hours. After cooling to ambient temperature, the reaction mixture was filtered and the solvent was evaporated under reduced pressure. Finally, the crude reaction mixture was dissolved in $CDCl_3$ to do $^1$H-NMR in order to determine percent NMR yield. The results were shown in Table 3.2.

Based on the above study, we chose $K_2CO_3$ as a base and EtOH-$H_2O$ with a volume ratio of 3:2 as solvent and executed the reaction at room temperature and 40 $^{\circ}$C for a desired reaction time in order to look for the optimal reaction temperature and reaction time. The results in Table 3.4 indicated that decreasing the reaction temperature from 40 $^{\circ}$C to room temperature led to the lower NMR yield although the reaction was operated over 24 hours. Consequently, we selected 40 $^{\circ}$C for 12 hours as optimal reaction temperature and reaction time.

Effect of temperature and reaction time: An oven-dried sealed tube was used as reaction container, after adding 4-iodoanisole (0.50 mmol), phenylboronic acid (0.75 mmol), the Pd/ICCP catalyst (0.01 mmol or 2 mol%), $K_2CO_3$ (1.50 mmol), and the mixed solvent of EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL), the sealed tube was transferred into a reaction chamber with a magnetic stirring bar. Then, the reaction mixture was stirred at agreeing temperature under nitrogen for a desired reaction time. After cooling to ambient temperature, the reaction mixture was filtered and the solvent was evaporated under reduced pressure. Finally, the crude reaction mixture was dissolved in $CDCl_3$ to do $^1$H-NMR in order to determine percent NMR yield. The results were shown in Table 3.4.

Effect of solvent system: An oven-dried sealed tube was used as reaction container, after adding 4-iodoanisole (0.50 mmol), phenylboronic acid (0.75 mmol), the Pd/ICCP catalyst (0.01 mmol or 2 mol%), $K_2CO_3$ (1.50 mmol), and solvent (6.0 mL), the sealed tube was transferred into a reaction chamber with a magnetic stirring bar. Then, the reaction mixture was stirred at 40 $^{o}$C under nitrogen for 12 hours. After cooling to ambient temperature, the reaction mixture was filtered and extracted with dichloromethane. After that, the solvent was evaporated under reduced pressure. Finally, the crude reaction mixture was dissolved in $CDCl_3$ and analyzed by NMR spectroscopy in order to determine percent NMR yield. The results were shown in Table 3.5.

Base on above effect of the solvent systematic investigation in Table 3.5, we observed the low NMR yield of the reaction in neat water. We need to perform the Suzuki reaction in water by addition of cetyltrimethylammonium bromide (CTAB) in order to use as a phase transfer agent promoting the migration of organic substrate into the aqueous phase. Therefore, we performed the reaction by adding CTAB from 0 to 100 mol% in order to find the optimal amount of CTAB. These results indicated that the addition of 100 mol% of CTAB into water also led to complete NMR yield as shown in Figure 3.4.

Effect amount of cetyltrimethylammonium bromide (CTAB) in water: An oven-dried sealed tube was used as reaction container, after adding 4-iodoanisole (0.50 mmol), phenylboronic acid (0.75 mmol), the Pd/ICCP catalyst (0.01 mmol or 2 mol%), $K_2CO_3$ (1.50 mmol), different amount of CTAB (0-100 mol%) and water (6.0 mL), the sealed tube was transferred into a reaction chamber with a magnetic stirring bar. Then, the reaction mixture was stirred at 40 $^{o}$C under nitrogen for 12 hours. After cooling to ambient temperature, the reaction mixture was filtered to separate the Pd catalyst and was extracted with dichloromethane. Next, the solvent was evaporated under reduced pressure. Finally, the crude reaction mixture was dissolved in $CDCl_3$

and analyzed by NMR spectroscopy in order to determine percent NMR yield. The results were shown in Figure 3.4.

### 2.7 Substrate scope of the Suzuki cross-coupling reaction

2.7.1 General procedure **A** for screening aryl iodide via Suzuki cross-coupling reaction in the mixed solvent of EtOH and water using Pd/ICCP as catalyst

A mixture of aryl iodide (0.50 mmol), phenylboronic acid (0.75 mmol), potassium carbonate (1.5 mmol), the Pd/ICCP catalyst (0.01 mmol or 2 mol%) and EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) was added in oven-dried sealed tube and the reaction mixture was stirred at 40 $^{\circ}$C under nitrogen for 12 hours. After cooling to ambient temperature, filtration of the reaction mixture to separate Pd catalyst and evaporation of solvent were executed. Then the remainder was purified by silica column chromatography, eluting with hexane and dichloromethane to provide the desired product.

2.7.2 General procedure **B** for screening aryl halide and arylboronic acid via Suzuki cross-coupling reaction in CTAB and water as solvent system using Pd/ICCP as catalyst

A mixture of aryl halide (0.50 mmol), arylboronic acid (0.75 mmol), potassium carbonate (1.5 mmol), the Pd/ICCP catalyst (0.01 mmol or 2 mol%), cetyltrimethylammonium bromide (CTAB, 0.50 mmol) and water (6.0 mL) was added in oven-dried sealed tube and the reaction mixture was stirred at 40 $^{\circ}$C under nitrogen for 12 hours. After cooling to ambient temperature, filtration of the reaction mixture to separate Pd catalyst and extraction with dichloromethane were performed. Then the residue was purified by silica column chromatography with hexane and dichloromethane as the eluents to give the target product.

**Biphenyl [34] (3a):** Synthesized according to procedure **A** using iodobenzene (102 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3a** (63.2 mg, 0.41 mmol, 82%) as a white solid.

Synthesized according to procedure **B** using iodobenzene (102 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3a** (61.7 mg, 0.4 mmol, 80%) as a white solid.

Synthesized according to procedure **B** using bromobenzene (78.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3a** (58.6 mg, 0.38 mmol, 76%) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$): **δ** 7.64 – 7.56 (m, 4H), 7.49 – 7.40 (m, 4H), 7.40 – 7.32 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): **δ** 141.71, 129.21, 127.71, 127.63; IR (ATR, cm$^{-1}$): 3060, 3035, 1944, 1879, 1474, 1426, 1168, 1001.

**4-methylbiphenyl [34] (3b):** Synthesized according to procedure **A** using 4-iodotoluene (109 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-H$_2$O with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3b** (71.5 mg, 0.42 mmol, 85%) as a white solid.

Synthesized according to procedure **B** using 4-iodotoluene (109 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3b** (65.6 mg, 0.39 mmol, 78%) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$): **δ** 7.50 (d, $J$ = 7.6 Hz, 2H), 7.42 (d, $J$ = 8.0 Hz, 2H), 7.35 (t, $J$ = 7.6 Hz, 2H), 7.24 (t, $J$ = 7.4 Hz, 1H), 7.17 (d, $J$ = 7.6 Hz, 2H), 2.32 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): **δ** 141.65, 138.85, 137.47, 129.93, 129.16, 127.45, 127.43, 21.55; IR (ATR, cm$^{-1}$): 3051, 3031, 2922, 2848, 1483, 824, 753.

**3-methylbiphenyl [35] (3c):** Synthesized according to procedure **A** using 3-iodotoluene (109 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-H$_2$O with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3c** (80.8 mg, 0.48 mmol, 96%) as colorless to yellow liquid.

Synthesized according to procedure **B** using 3-iodotoluene (109 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3c** (61.4 mg, 0.36 mmol, 73%) as colorless to yellow liquid.

Synthesized according to procedure **B** using 3-bromotoluene (85.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3c** (63.1 mg, 0.38 mmol, 75%) as colorless to yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 7.64 (d, *J* = 7.2 Hz, 2H), 7.53 – 7.33 (m, 6H), 7.22 (d, *J* = 7.3 Hz, 1H), 2.48 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 141.52, 141.39, 138.43, 128.82, 128.79, 128.13, 128.11, 127.31, 127.28, 124.41, 21.67; IR (ATR, $cm^{-1}$): 3054, 3031, 2919, 2854, 1593, 1480, 788, 750, 695.

**2-methylbiphenyl [35] (3d):** Synthesized according to procedure **A** using 2-iodotoluene (109 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3d** (60.6 mg, 0.36 mmol, 72%) as a clear colorless liquid.

Synthesized according to procedure **B** using 2-iodotoluene (109 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3d** (58.9 mg, 0.35 mmol, 70%) as a clear colorless liquid.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 7.58 – 7.49 (m, 2H), 7.49 – 7.41 (m, 3H), 7.42 – 7.29 (m, 4H), 2.40 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 142.45, 142.41, 135.74, 130.74, 130.23, 129.63, 129.18, 128.50, 127.68, 127.19, 126.20, 20.88; IR (ATR, $cm^{-1}$): 3060, 3015, 2919, 2851, 1471, 1004, 750.

**2,6-dimethylbiphenyl [36] (3e):** Synthesized according to procedure **A** using 2,6-dimethyliodobenzene (116 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3e** (34.6 mg, 0.19 mmol, 38%) as yellow liquid. However, the reaction mixture was stirred at 70 °C under nitrogen for 12 hours.

Synthesized according to procedure **B** using 2,6-dimethyliodobenzene (116 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3e** (31.9 mg, 0.18 mmol, 35%) as yellow liquid. However, the reaction mixture was stirred at 70 °C under nitrogen for 12 hours.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 7.54 – 7.46 (m, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.31 – 7.12 (m, 5H), 2.11 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 142.33, 141.57, 136.49, 129.49, 128.86, 127.73, 127.47, 127.05, 21.28; IR (ATR, $cm^{-1}$): 3054, 3015, 2951, 2916, 2858, 1461, 1435, 1374, 1068, 1001.

**4-methoxybiphenyl [34] (3f):** Synthesized according to procedure **A** using 4-iodoanisole (92.1 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3f** (82.9 mg, 0.45 mmol, 90%) as a white solid.

Synthesized according to procedure **B** using 4-iodoanisole (92.1 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3f** (83.8 mg, 0.46 mmol, 91%) as a white solid.

Synthesized according to procedure **B** using 4-bromoanisole (93.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3f** (66.3 mg, 0.36 mmol, 72%) as a white solid.

Synthesized according to procedure **B** using iodobenzene (102 mg, 0.5 mmol), 4-methoxyphenylboronic acid (114 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB ( 182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3f** (88.4 mg, 0.48 mmol, 96%) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 7.64 – 7.57 (m, 4H), 7.48 (t, J = 7.2 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.04 (d, J = 7.3 Hz, 2H), 3.90 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 159.23, 140.89, 133.84, 128.76, 128.19, 126.77, 126.69, 114.27, 55.36; IR (ATR, $cm^{-1}$): 3070, 3031, 3005, 2957, 2935, 2832, 1603, 1519, 1480, 1245, 1197, 1184, 1033.

**4-nitrobiphenyl [37] (3g):** Synthesized according to procedure **A** using 1-iodo-4-nitrobenzene (124.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3g** (99.6 mg, 0.5 mmol, 100%) as a yellow solid.

Synthesized according to procedure **B** using 1-iodo-4-nitrobenzene (124.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB ( 182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3g** (92.6 mg, 0.46 mmol, 93%) as a yellow solid.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 8.30 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 8.9 Hz, 2H), 7.63 (d, *J* = 7.0 Hz, 2H), 7.54 – 7.41 (m, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 148.12, 139.29, 129.63, 129.38, 128.28, 127.86, 124.58; IR (ATR, $cm^{-1}$): 3073, 2829, 2439, 2359, 2037, 1986, 1931, 1590, 1506, 1339.

**4-phenylbenzaldehyde [37] (3h):** Synthesized according to procedure **A** using 4-iodobenzaldehyde (116 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3h** (90.2 mg, 0.5 mmol, 99%) as a white to light yellow solid.

Synthesized according to procedure **B** using 4-iodobenzaldehyde (116 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB ( 182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3h** (83.8 mg, 0.46 mmol, 92%) as a white to light yellow solid.

Synthesized according to procedure **B** using 4-bromobenzaldehyde (92.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3h** (78.4 mg, 0.43 mmol, 86%) as a white to light yellow solid.

Synthesized according to procedure **B** using iodobenzene (102 mg, 0.5 mmol), 4-formylphenylboronic acid (112.1 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3h** (79.3 mg, 0.44 mmol, 87%) as a white to light yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$): **δ** 10.06 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.53 – 7.45 (m, 2H), 7.45 – 7.39 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$): **δ** 192.25, 147.57, 140.11, 135.64, 130.65, 129.42, 128.87, 128.07, 127.76; IR (ATR, cm$^{-1}$): 3022, 2838, 2546, 1677, 1599, 1416, 1287.

**4-acetylbiphenyl [38] (3i):** Synthesized according to procedure **A** using 4-iodoacetophenone (123 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3i** (94.2 mg, 0.48 mmol, 96%) as off-white to beige powder.

Synthesized according to procedure **B** using 4-iodoacetophenone (123 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3i** (78.5 mg, 0.4 mmol, 80%) as off-white to beige powder.

Synthesized according to procedure **B** using 4-bromoacetophenone (99.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3i** (84.4 mg, 0.43 mmol, 86%) as off-white to beige powder.

$^1$H NMR (400 MHz, CDCl$_3$): **δ** 8.07 – 8.00 (m, 2H), 7.72 – 7.66 (m, 2H), 7.66 – 7.59 (m, 2H), 7.51 – 7.44 (m, 2H), 7.44 – 7.38 (m, 1H), 2.64 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): **δ** 198.15, 146.24, 140.30, 136.30, 129.40, 129.36, 128.68, 127.72, 127.67, 27.09; IR (ATR, cm$^{-1}$): 3073, 3009, 2970, 1673, 1603, 1249.

**4-phenylbenzonitrile [34] (3j):** Synthesized according to procedure **A** using 4-iodobenzonitrile (114.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3j** (89.6 mg, 0.5 mmol, 100%) as a beige crystalline powder.

Synthesized according to procedure **B** using 4-iodobenzonitrile (114.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3j** (86.0 mg, 0.48 mmol, 96%) as a beige crystalline powder.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 7.76 – 7.66 (m, 4H), 7.59 (d, *J* = 7.1 Hz, 2H), 7.52 – 7.40 (m, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 146.17, 139.68, 133.06, 129.58, 129.12, 128.21, 127.70, 119.37, 111.45; IR (ATR, cm$^{-1}$): 3060, 2916, 2224, 1603, 1480, 1393.

**4-(trifluoromethyl)–biphenyl [35] (3k):** Synthesized according to procedure **A** using 4-iodobenzotrifluoride (136 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3k** (88.9 mg, 0.40 mmol, 80%) as a white solid.

Synthesized according to procedure **B** using 4-iodobenzotrifluoride (136 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3k** (86.7 mg, 0.39 mmol, 78%) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 7.70 (s, 4H), 7.64 – 7.57 (m, 2H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.44 – 7.38 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 145.24, 140.27, 129.45, 128.65, 127.89, 127.75, 126.19, 126.15; IR (ATR, cm$^{-1}$): 3035, 2919, 2848, 1960, 1612, 1329, 1107, 1075.

**4-chlorobiphenyl [35] (3l):** Synthesized according to procedure **A** using 1-chloro-4-iodobenzene (119.2 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in

$EtOH-H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3l** (84.9 mg, 0.45 mmol, 90%) as a white solid.

Synthesized according to procedure **B** using 1-chloro-4-iodobenzene (119.2 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3l** (83.9 mg, 0.44 mmol, 89%) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 7.59 – 7.48 (m, 4H), 7.48 – 7.32 (m, 5H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 139.85, 139.53, 133.23, 128.74, 128.71, 128.22, 127.41, 126.82; IR (ATR, cm$^{-1}$): 3064, 3035, 2916, 2848, 1474, 1397, 1100, 997, 827, 756.

**4-fluorobiphenyl [35] (3m):** Synthesized according to procedure **A** using 1-fluoro-4-iodobenzene (111 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in $EtOH-H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3m** (75.8 mg, 0.44 mmol, 88%) as a white solid.

Synthesized according to procedure **B** using 1-fluoro-4-iodobenzene (111 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3m** (73.2 mg, 0.42 mmol, 85%) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 7.62 – 7.51 (m, 4H), 7.51 – 7.42 (m, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.21 – 7.08 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 163.75, 161.31, 140.25, 137.37, 128.85, 128.76, 128.68, 127.29, 127.20, 127.05, 115.74, 115.53; IR (ATR, cm$^{-1}$): 3060, 3041, 2922, 2851, 1895, 1599, 1512, 1480, 1236.

**1-phenylnaphthalene [35] (3n):** Synthesized according to procedure **A** using 1-iodonaphthalene (127.04 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in $EtOH-H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3n** (90.9 mg, 0.44 mmol, 89%) as a clear colorless viscous liquid.

Synthesized according to procedure **B** using 1-iodonaphthalene (127.04 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3n** (87.8 mg, 0.43 mmol, 86%) as a clear colorless viscous liquid.

Synthesized according to procedure **B** using iodobenzene (102 mg, 0.5 mmol), 1-naphthylboronic acid (129 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3n** (101.1 mg, 0.49 mmol, 99%) as a clear colorless viscous liquid.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 8.15 – 7.93 (m, 3H), 7.72 – 7.49 (m, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 140.91, 140.40, 133.96, 131.80, 130.19, 128.38, 127.75, 127.34, 127.04, 126.15, 125.87, 125.48; IR (ATR, cm$^{-1}$): 3051, 2919, 2854, 1590, 1493, 1393, 1014.

***p*-terphenyl [35] (3o):** Synthesized according to procedure **A** using 4-iodobiphenyl (140 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3o** (100.2 mg, 0.44 mmol, 87%) as a white solid.

Synthesized according to procedure **B** using 4-iodobiphenyl (140 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3o** (97.9 mg, 0.42 mmol, 85%) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): **δ** 7.69 (s, 4H), 7.66 (s, 2H), 7.64 (s, 2H), 7.47 (t, $J$ = 7.6 Hz, 4H), 7.37 (t, $J$ = 7.4 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 141.20, 140.62, 129.28, 127.97, 127.80, 127.52; IR (ATR, cm$^{-1}$): 3060, 3028, 1947, 1590, 1574, 1477.

**3-phenylpyridine [35] (3p):** Synthesized according to procedure **A** using 3-iodopyridine (102.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol) in EtOH-$H_2O$ with a volume ratio of 3:2 (6.0 mL) for 12 h to afford **3p** (55.9 mg, 0.36 mmol, 72%) as colorless oil.

Synthesized according to procedure **B** using 3-iodopyridine (102.5 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3p** (54.3 mg, 0.35 mmol, 70%) as colorless oil.

$^{1}$H NMR (400 MHz, $CDCl_3$): **δ** 8.76 (s, 1H), 8.49 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.29 – 7.24 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 148.29, 148.17, 137.79, 136.81, 134.55, 129.14, 128.20, 127.20, 123.68.

**3-nitrobiphenyl [34] (3q):** Synthesized according to procedure **B** using iodobenzene (102 mg, 0.5 mmol), 3-nitrophenylboronic acid (125.2 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3q** (93.6 mg, 0.47 mmol, 94%) as yellow crystalline powder. $^{1}$H NMR (400 MHz, $CDCl_3$): **δ** 8.44 (s, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.66 – 7.55 (m, 3H), 7.54 – 7.40 (m, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 149.12, 143.21, 139.00, 133.35, 130.07, 129.53, 128.91, 127.49, 122.36, 122.25; IR (ATR, $cm^{-1}$): 3086, 2845, 1976, 1519, 1496, 1348.

**4,4'-biphenyldicarboxaldehyde [39] (3r):** Synthesized according to procedure **B** using 4-iodobenzaldehyde (116.0 mg, 0.5 mmol), 4-formylphenylboronic acid (112.5 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3r** (105.1 mg, 0.5 mmol, 100%) as a white solid. $^{1}$H NMR (400 MHz, $CDCl_3$): **δ** 10.09 (s, 2H), 8.00 (d, *J* = 8.2 Hz, 4H), 7.81 (d, *J* = 8.2 Hz, 4H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 192.11, 146.05, 136.52, 130.83, 128.51; ESI-MS: m/z: ; IR (ATR, $cm^{-1}$): 2922, 2842, 2742, 1680, 1603, 1557, 1313, 1203, 1168.

**4'-methoxy-4-biphenylcarbaldehyde [40] (3s):** Synthesized according to procedure **B** using 4-iodoanisole (117 mg, 0.5 mmol), 4-formylphenylboronic acid (112.5 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3s** (98.7 mg, 0.46 mmol, 93%) as white to light yellow solid.

Synthesized according to procedure **B** using 4-iodobenzaldehyde (116 mg, 0.5 mmol), 4-methoxyphenylboronic acid (114 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3s** (99.8 mg, 0.47 mmol, 94%) as white to light yellow solid.

$^{1}$H NMR (400 MHz, $CDCl_3$): **δ** 10.03 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 191.91, 160.23, 146.85, 134.79, 132.13, 130.38, 128.57, 127.12, 114.59, 55.47; IR (ATR, $cm^{-1}$): 2964, 2848, 2761, 2018, 1673, 1596, 1294, 1252, 1181, 1033.

**4,4’-dimethoxybiphenyl [38] (3t):** Synthesized according to procedure **B** using 4-iodoanisole (117 mg, 0.5 mmol), 4-methoxyphenylboronic acid (114 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), potassium carbonate (207.3 mg, 1.5 mmol), CTAB (182.2 mg, 0.50 mmol) in water (6.0 mL) for 12 h to afford **3t** (107.1 mg, 0.5 mmol, 100%) as a white solid. $^{1}$H NMR (400 MHz, $CDCl_3$): **δ** 7.50 (d, *J* = 8.7 Hz, 4H), 6.98 (d, *J* = 8.7 Hz, 4H), 3.86 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$): **δ** 158.86, 133.63, 127.85, 114.32, 55.46; ESI-MS:m/z: ; IR (ATR, $cm^{-1}$): 2954, 2912, 2838, 1606, 1490, 1268, 1239, 1174, 1039.

## 2.8 Reusability test of Palladium catalysts

Figure 3.6 Comparison of reusability of palladium catalysts: A mixture of 4-iodoanisole (92.1 mg, 0.50 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), potassium carbonate (207.3 mg, 1.5 mmol), palladium catalyst (0.01 mmol), CTAB (182.2 mg, 0.50 mmol) and water (6.0 mL) was added in oven-dried sealed tube supplied with a magnetic stirring bar and the reaction mixture was stirred at 40 °C under nitrogen for 12 hours. After cooling to ambient temperature, centrifugation of the reaction mixture to separate the heterogeneous palladium catalyst was executed. Then, decanting the reaction mixture into round-bottom flask and extraction with dichloromethane were performed. After that, the solvent was evaporated under reduced pressure. Finally, the crude reaction mixture was dissolved in $CDCl_3$ and analyzed by $^{1}$H-NMR in order to determine percent NMR yield.

Furthermore, the reused palladium catalyst was washed with dichloromethane (3 times), water and acetone. After that, the catalyst was dried in a vacuum in order to remove the solvent before starting the next reaction.

### 2.9 Determination of Palladium leaching in the reaction mixture by ICP-OES analysis

Table 3.12 Comparing palladium leaching of catalysts in the reaction mixture: A mixture of 4-iodoanisole (92.1 mg, 0.50 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), potassium carbonate (207.3 mg, 1.5 mmol), the palladium catalyst (0.01 mmol or 2 mol%), CTAB (182.2 mg, 0.50 mmol) and water (6.0 mL) was added in oven-dried sealed tube supplied with a magnetic stirring bar and the reaction mixture was stirred at 40 °C under nitrogen for 12 hours. After finished reaction, filtration of the reaction mixture into 250 mL round-bottom flask was performed. Then, aqua regia (6.0 mL) was added into the reaction mixture in order to completely digest palladium catalyst. After that, the reaction mixture was stirred at 100 °C for 24 hours. After cooling to ambient temperature, the reaction solution was transferred to a 100 mL volumetric flask and adjusting volume was carried out by pouring water. The amount of palladium that leached into the reaction mixture was determined by ICP-OES analysis, followed the process in section 2.4.2.

### 2.10 Application of the Suzuki cross-coupling reaction

2.10.1 General procedure for synthesis of 4-methoxybiphenyl (**3f**) in microflow reaction

The mixture of reactants without catalyst of 4-iodoanisole (0.43 mmol), phenylboronic acid (0.64 mmol), and potassium carbonate (1.29 mmol) was added in the 250 mL Erlenmeyer flask and was dissolved in the mixed solvent of EtOH-$H_2O$ with a volume ratio of 3:2 (60 mL, 6 mL, and 12 mL for concentration of 7 mM, 70 mM, and 35 mM, respectively). Then, the mixture solution was transferred to a test tube sealed with septum under nitrogen flow, and the reaction mixture was performed in a microflow reactor as shown in Figure 2.3 by pumping the reactants mixture through the Pd/ICCP (0.1 or 0.5 %wt) packed-bed cartridge as a flow reactor at a certain flow rate, heated at 50 °C and then the reaction mixture was collected at residence time. After cooling to ambient temperature, the reaction mixture was evaporated the solvent under reduced pressure. Finally, the NMR yield was determined by using $^{1}$H-NMR.

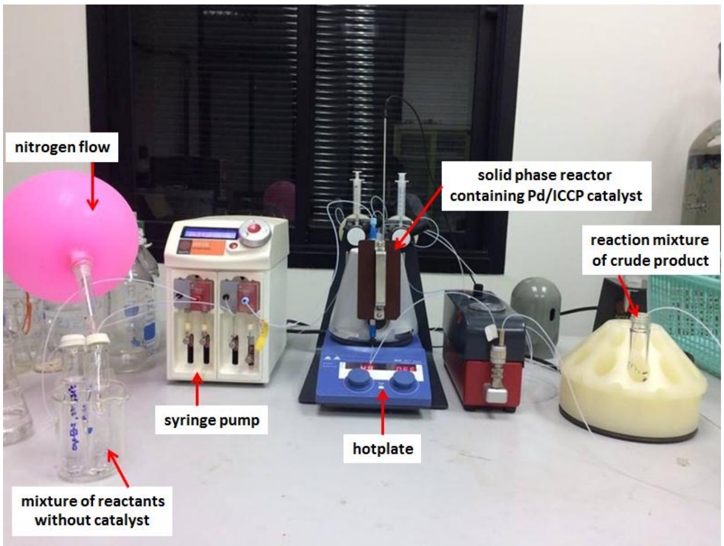


**Figure 2.3** Performing the continuous flow Suzuki reaction using a microflow reactor

2.10.2 General procedure for the Suzuki reaction under microwave irradiation

The mixture of aryl halide (0.50 mmol), phenylboronic acid (0.75 mmol), potassium carbonate (1.5 mmol), the Pd/ICCP catalyst (0.01 mmol or 2 mol%), CTAB (0.50 mmol) and water (2.0 mL) was added in a sealed glass microwave vial, and the reaction mixture was irradiated in a microwave equipment (CEM Discover) at 100 °C, 200 W for 5 min. After the reaction mixture was cooled to ambient temperature, the reaction mixture was filtered and extracted with dichloromethane. Then, the crude mixture was purified by silica column chromatography using hexane and dichloromethane as eluents to give the desired product.

# CHAPTER III

# RESULTS AND DISCUSSION

In this study, the calcium carbonate derived from waste Asian green mussel shell was applied as catalytic support. In general, An Asian green mussel shell consists of slim aragonite calcium carbonate layers bounded by thin organic matrix layers including protein, chitin, polysaccharides, peptides and lipid [33]. As already stated above, we hypothesized that the surface chitin and protein molecules on shell particles will stabilize the palladium metal nanoparticles. These will provide highly stable and reusable heterogeneous palladium catalyst. Based on previous literature [17, 18], the simple grounded shell particle (SP) was used as catalytic support for heterogeneous palladium catalyst in Heck and homocoupling reactions. Even though this catalyst is efficient enough to catalyze both reactions, however, the large and non-unified particle might decrease catalytic activity, reproducibility and recyclability. To improve the catalytic support from waste shell particle, we need to reduce the particle size of shell particle and convert them into a highly uniform structure. Recently, our group [19] and Lertvachirapaiboon and co-workers [20] successfully prepared catalytic support from waste shell having pseudo-hexagonal structure. This calcium carbonate plates are called "individual calcium carbonate plates or ICCP" due to its highly uniform structure. These catalysts were used in copper-free Sonogashira cross-coupling reaction [19]. To expand scope of our new catalytic support from shell particle, we will use Pd/ICCP to catalyze Suzuki cross-coupling reaction in batch and continuous-flow system.

## 3.1 Preparation of palladium supported on individual calcium carbonate plates (Pd/ICCP) catalyst

To begin with the Pd/ICCP and Pd/SP were prepared as illustrated in Figure 3.1. For preparation of ICCP, the dried mussel shells were immersed in 30% (w/w) hydrogen peroxide solution under ultrasonic sonication for 24 hours and were filtered with 200 mesh filter size. This method can dissolve and degrade the organic matrix between calcium carbonate plates in shell particles without destroying the aragonite structure to generate the support ICCP in white powder as shown in Figure 3.1b. On the other side, simple shell particles (SP) were prepared based on reported literature [18]. The dried-shell was ground and filtrated with 200 mesh filter size respectively, as elucidated in Figure 3.1a. Palladium nanoparticles were successfully embedded into both of ICCP and SP by impregnation of tetrachloropalladic acid ($H_2PdCl_4$) solution, followed by reduction of palladium (II) to generate palladium (0) nanoparticles with sodium borohydride ($NaBH_4$) solution. The appearance of Pd/ICCP and Pd/SP catalysts were depicted in Figure 3.1

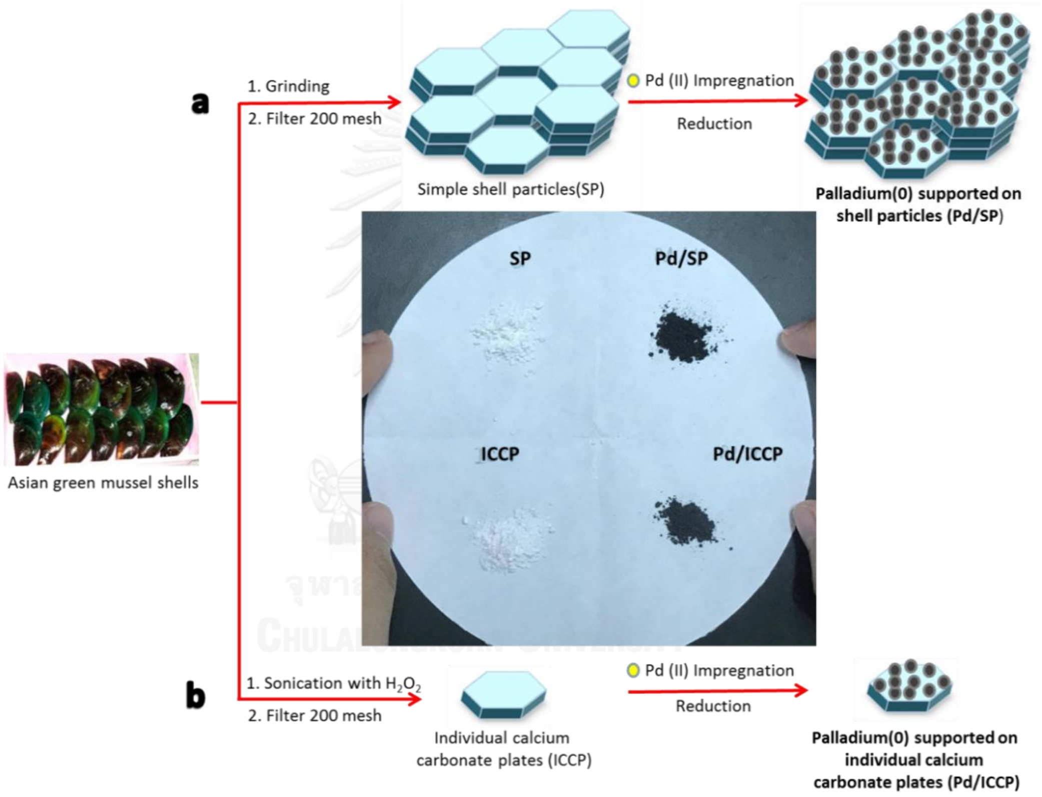


**Figure 3.1** The preparation of palladium on simple shell particle (Pd/SP) and individual calcium carbonate plates (Pd/ICCP) catalysts

## 3.2 Characterizations of Pd/ICCP

The prepared Pd/ICCP catalyst was fully characterized by SEM, EDX, TEM and ICP-OES as explained in the subsequent sections.

### 3.2.1 The morphology of Pd/ICCP catalyst

The morphological investigation of the prepared individual calcium carbonate plates deposited with palladium (Pd/ICCP) was carried out using the scanning electron microscope (SEM) demonstrating the single polygonal shaped particles with *ca.* 3 micrometer size (Figure 3.2a). This advised that the fragmentation of the mussel shell structure into the individual calcium carbonate plates (ICCP) is successful under our process. Moreover, the energy-dispersive X-ray spectroscopy (EDX) analysis showed the high dispersion of palladium (0) over the surface of individual calcium carbonate plates (ICCP) as seen in Figure 3.2b. Furthermore, our previous research [19] investigated the thickness of ICCP by SEM technique showing 300-400 nanometer of the ICCP thickness.

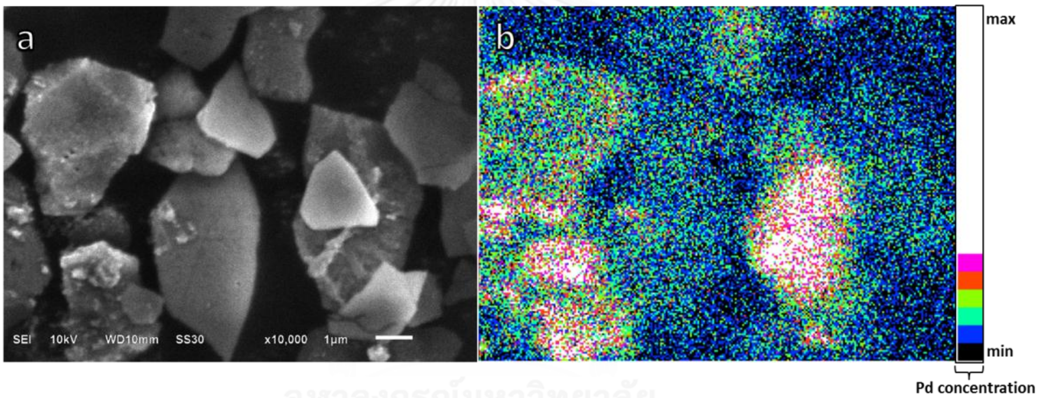


**Figure 3.2** (**a, b**) SEM and EDX images of palladium supported on individual calcium carbonate plates (Pd/ICCP) catalyst.

To investigate the morphology of palladium (0) on the ICCP support, we performed the transmission electron microscopy (TEM) analysis as shown in Figure 3.3. From the TEM image, it suggested that the palladium (0) is aggregated in nanostructure on the surface of the ICCP. The mean diameter with the black round shape of the palladium nanoparticles was approximately 5 to 8 nm. This result supports the formation of highly stable palladium nanoparticles on the surface of the ICCP.

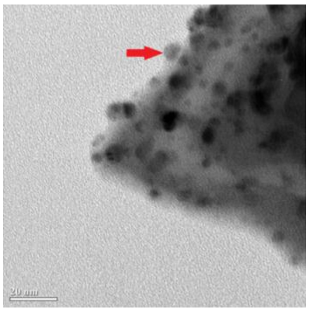


**Figure 3.3** TEM image of palladium supported on individual calcium carbonate plates (Pd/ICCP) catalyst. Arrow displayed Pd nanoparticles.

### 3.2.2 Determination of amount of palladium by ICP-OES analysis

The palladium content of the prepared Pd/ICCP catalyst was evaluated by inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis. Firstly, the calibration curve of the standard palladium solution was constructed to determine the palladium content on the Pd/ICCP catalyst (Figure 2.1). Similarly, the palladium contents of Pd/SP, Pd/$CaCO_3$ and Pd/C were measured under the same method in our previous research [19]. The exact palladium contents of Pd/ICCP, Pd/SP, Pd/$CaCO_3$ and Pd/C were measured as 5.5, 5.7, 4.3 and 6.9%wt on the average, respectively (Table 3.1). The expected and exact palladium contents in Pd/ICCP, Pd/SP and Pd/$CaCO_3$ catalysts were slightly different. These results are probably due to binding ability between Pd metal and surface of support. While in case of Pd/C, the significant loss of palladium content in this catalyst was observed. This is perhaps caused by the decomposition of palladium species under bench storage. The exact palladium amounts determined by ICP-OES will be applied in entirely studies.

**Table 3.1** Determination of amount of palladium in the catalysts

| Entry | Catalyst | Expected Palladium Content (%wt) | Exact Palladium Content[a] (%wt) |
|---|---|---|---|
| 1 | Pd/ICCP | 6.0 | 5.5 ± 0.1 |
| 2 | Pd/SP | 7.0 | 5.7 ± 0.1 |
| 3 | Pd/$CaCO_3$ | 5.0 | 4.3 ± 0.1 |
| 4 | Pd/C | 10.0 | 6.9 ± 0.3 |

[a] Percentage of exact palladium weight was determined by ICP-OES analysis.

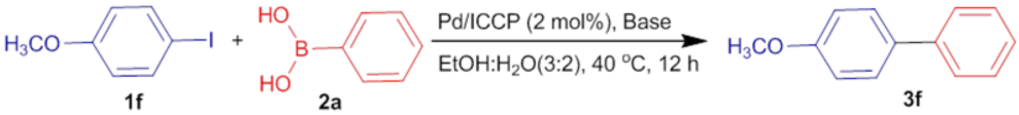
## 3.3 Optimization studies on the Suzuki cross-coupling reaction

To determine the catalytic activity of our Pd/ICCP catalyst, we challenge our investigation by choosing the most retarded aryl iodide substrate as 4-iodoanisole (**1f**) to react with phenylboronic acid (**2a**) to perform the Suzuki cross coupling reaction in the absence of ligand. The slow reaction of 4-iodoanisole (**1f**) is due to the strong electron donating group on the benzene ring which is sluggish the oxidative addition in the catalytic cycle. Therefore, if we obtained the optimal condition from this substrate, such condition should be applicable to others. In these studies, the reaction was monitored by $^1$H-NMR and %NMR yield was calculated as explained in Equation 2.1 and Figure 2.2. The influences of bases, reaction temperature, reaction time and solvent system were studied in the following part.

### 3.3.1 Screening type of bases

In this part, we used **1f** (92.1 mg, 0.50 mmol), **2a** (91.4 mg, 0.75 mmol), Pd/ICCP (19.4 mg, 0.01 mmol), base (1.5 mmol) and 6 mL of the mixed solvent of EtOH-$H_2O$ (3:2). Overall reactions were conducted at 40 $^oC$ for 12 hours in a sealed tube (Table 3.2). Among eight bases, DIPA, NaOH, KOH, $Cs_2CO_3$, and $K_2CO_3$ were testified to be excellent bases, providing the coupling product (**3f**) in 100% NMR Yields (Table 3.2, entries 5-9). While the reaction without base resulted in no reaction (Table 3.2, entry 1). This indicated that the base was necessary for the catalytic cycle of the Suzuki reaction.

**Table 3.2** Effect of base

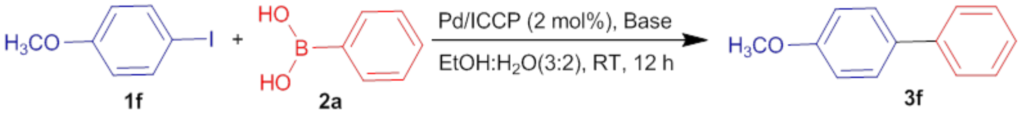


| Entry | Type of base | NMR Yield (%)[a] |
|---|---|---|
| 1 | No base | 0 |
| 2 | KOAc | 18 |
| 3 | Piperidine | 88 |
| 4 | TEA | 94 |
| 5 | DIPA | 100 |
| 6 | NaOH | 100 |
| 7 | KOH | 100 |
| 8 | $Cs_2CO_3$ | 100 |
| 9 | $K_2CO_3$ | 100 |

[a] Determined by $^1$H-NMR.

Due to the safety and the cost of material, we decided to focus on only three inorganic bases, including NaOH, KOH and $K_2CO_3$ to examine the Suzuki reaction of 4-iodoanisole (**1f**) at lower temperatures (room temperature) under the above condition. The results in Table 3.3 specified that all of reactions conducted at room temperature did not undergo complete NMR yields and the remaining starting material were observed in $^1$H-NMR. Those bases gave the comparable yields between 79-90%, but we decided to use $K_2CO_3$ for further investigation. The strong bases NaOH and KOH were deselected because they could generate the exothermic reaction in the large scale reaction. Therefore, we chose $K_2CO_3$ as a base and performed the reaction at 40 °C.

**Table 3.3** Comparing reactivity of the selected inorganic bases at room temperature



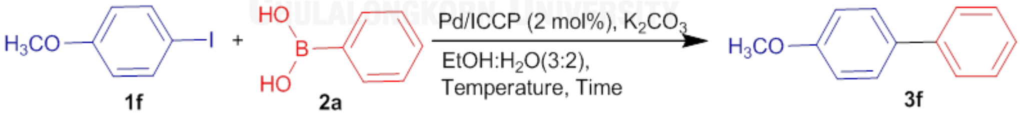
| Entry | Base | NMR Yield (%)[a] |
|---|---|---|
| 1 | NaOH | 79 |
| 2 | KOH | 87 |
| 3 | $K_2CO_3$ | 90 |

[a]Determined by $^1$H-NMR.

### 3.3.2 Temperature and reaction time

Based on the above study, we therefore selected $K_2CO_3$ as a base and EtOH-$H_2O$ as solvent to execute the reaction. Next, reaction temperature-dependent study of the Suzuki was investigated and the results were presented in Table 3.4. It indicated that reducing the reaction temperature from 40 °C to room temperature led to incomplete reaction. Even though the reaction was kept for 24 hours at room temperature, only 95% yield was observed. Therefore, we selected 40 °C for 12 hours as optimal reaction temperature and reaction time, which gave a 100% NMR yield (Table 3.4, entry 5).

**Table 3.4** Effect of temperature and reaction time



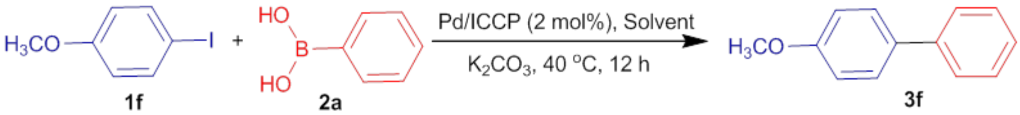
| Entry | Temperature (°C) | Time | NMR Yield (%)[a] |
|---|---|---|---|
| 1 | RT (32) | 12 | 90 |
| 2 | RT (32) | 24 | 95 |
| 3 | 40 | 3 | 94 |
| 4 | 40 | 6 | 96 |
| 5 | 40 | 12 | 100 |

[a]Determined by $^1$H-NMR.

### 3.3.3 Screening solvent system

Even though EtOH:$H_2O$ is a good solvent system for our reaction condition, however the use of neat water will be more beneficial to our methodology. Because the water is wide-available, inexpensive, low toxic solvent, and facilitate dissolving inorganic bases, so we try to test the Suzuki reactions in water. The results in Table 3.5 demonstrated that the reaction was obtained a 100 % NMR yield, when we used the mixed solvent of EtOH-$H_2O$ (3:2) (Table 3.5, entry 1). This was probably due to the high solubility between base and reactants, since the solute base in water could activate arylboronic acid escalating the reaction rate [41]. In the first attempt to perform the reaction in neat water, a poor NMR yield was obtained only 36% (Table 3.5, entry 2). Next, we try to improve the solubility by adding cationic surfactants including tetrabutylammonium bromide (TBAB) and cetyltrimethylammonium bromide (CTAB) into the water. Both surfactants were generally used as phase transfer agents in order to promote the migration of organic substrates into the aqueous phase [42]. The addition of TBAB (100 mol%) into water resulted in the significant enhancement of the NMR yield from 36% to 84% (Table 3.5, entry 3), and even more in case of CTAB (100 mol%) to 100% NMR yield without remaining starting material (Table 3.5, entry 4). These results confirm the necessary of surfactant to our Pd/ICCP catalysed Suzuki cross-coupling reaction. We hypothesized that the higher efficiency of CTAB over TBAB because of its higher hydrophobicity from non-polar alkyl chain. The long alkyl chain in CTAB facilitates the solvation of organic reagents in aqueous media.

**Table 3.5** Effect of solvent system



| Entry | Solvent | NMR Yield (%)[a] |
|---|---|---|
| 1 | EtOH:$H_2O$ (3:2) | 100 |
| 2 | $H_2O$ | 36 |
| 3 | $H_2O$, TBAB[b] | 84 |
| 4 | $H_2O$, CTAB[c] | 100 |

[a] Determined by $^1$H-NMR. [b] Tetrabutylammonium bromide (TBAB, 100 mol%) used as a phase transfer agent.

[c] Cetyltrimethylammonium bromide (CTAB, 100 mol%) used as a phase transfer agent.

### 3.3.4 Screening amount of CTAB in water

To study the effect of CTAB, the amounts of CTAB used in the reaction were varied in the range between 0 to 100 mol% and the results were summarized in Figure 3.4. We observed that the addition of CTAB at the critical micelle concentration (CMC, 2.79 mol%) into the water did not provide a complete reaction. However, 100% NMR yield of coupling product was acquired, in case of a 100 mol% of CTAB was added. According to Raman’s work [43], the arrangement of CTAB molecules was depended on CTAB concentration. At CMC point, CTAB molecules were arranged in spherical micelle form, while the arrangement of CTAB molecules in lamellar liquid crystal form was occurred at 100 mol% of CTAB. The reason, why lamellar liquid crystal form gives a better yield than in spherical micelle form, is still unclear to us.

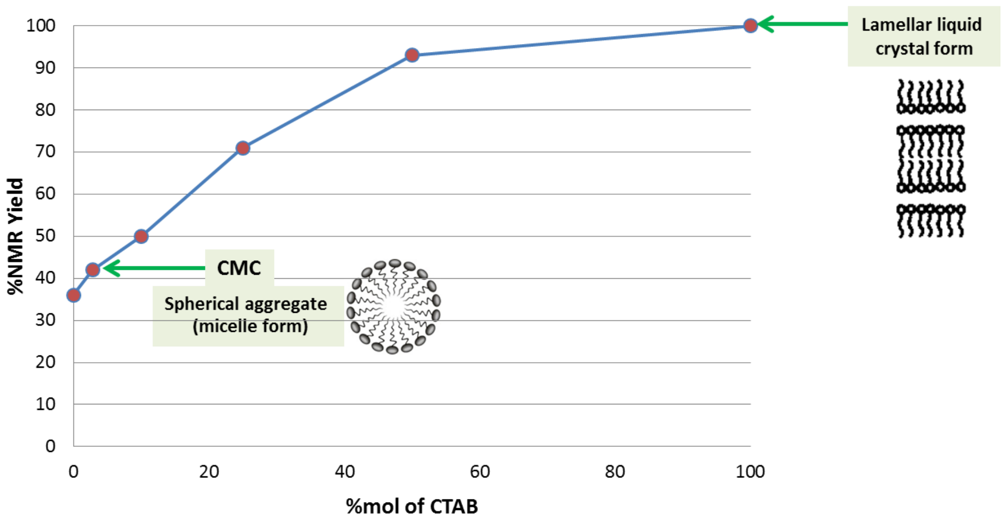


**Figure 3.4** Effect of amount of CTAB in water

In summary, our catalyst is suitable to carry Suzuki cross-coupling reaction in two solvent systems including EtOH:$H_2O$ and water/CTAB. Condition A which is the use of EtOH:$H_2O$ gave a single-phase solution before the addition of Pd/ICCP catalyst as shown in Figure 3.5a. Therefore, it is suitable for application in both batch and continuous flow Suzuki cross-coupling reaction. On the other hand, condition B which is the use of CTAB and water as a medium is indeed considered as the most green reaction condition. But it provided a multiple-phase solution (Figure 3.5b), which force us to perform the reaction in only conventional batch reaction.

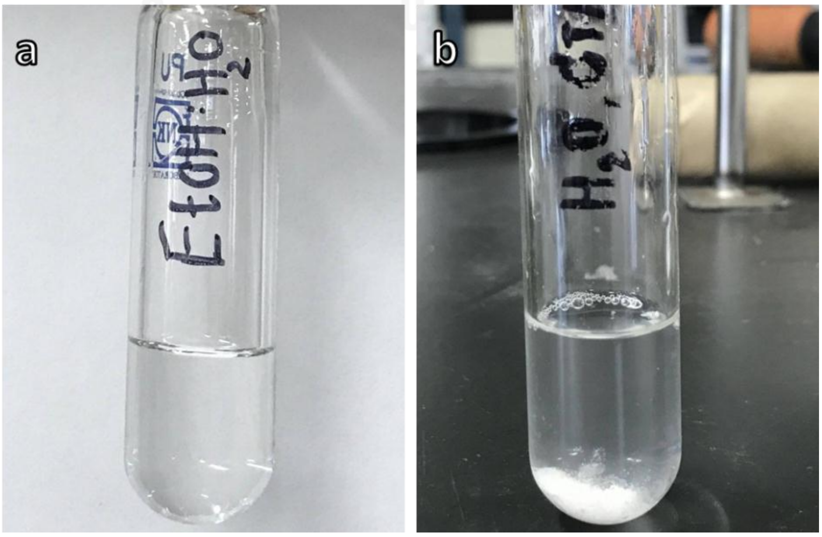


**Figure 3.5** Reactant solutions in **a**) mixed solvent of EtOH-$H_2O$ (3:2) **b**) CTAB/water before adding Pd/ICCP catalyst.

## 3.4 Substrate scope of the Suzuki reaction

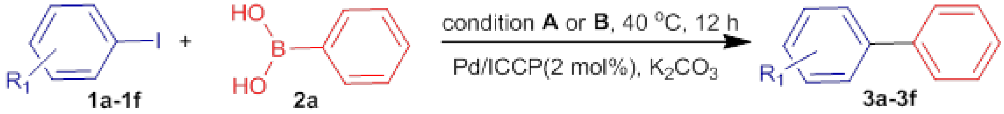
### 3.4.1 Substrate scope on aryl iodides

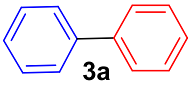
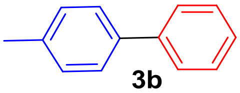
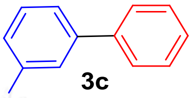
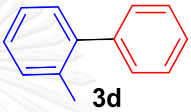
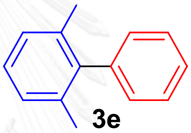
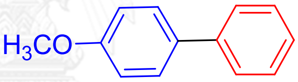
With the optimum conditions in hand, we afterward indicated the generalization of our process. The 2 mol% of Pd/ICCP catalyst was investigated toward the Suzuki reaction between aryl iodides (**1a-1p**) bearing various functional groups with phenylboronic acid (**2a**) under the condition A or B at 40 °C for 12 hours.

### 3.4.1.1 Aryl iodides bearing electron-donating groups (**1a-1f**)

The aryl iodides carrying electron donating group, comprising iodobenzene (**1a**), 4-iodotoluene (**1b**), 3-iodotoluene (**1c**), 2-iodotoluene (**1d**), 2,6-dimethyliodobenzene (**1e**), 4-iodoanisole (**1f**) were tested as representative substrates under the condition A and B (Table 3.6). Those substrates were nicely endured and the desired coupling products (**3a-3d**, **3f**) were obtained in good to high isolated yields after column purification without remaining starting materials. We would like to remark that these electron donating substituents were recognized as retarding groups in the oxidative addition step in the catalytic cycle resulting in reducing the reaction rate. Especially, the heteroatom in methoxy group could chelate with palladium metal in catalyst slowing the reaction rate [44]. The high yields from those substrates suggest the high catalytic performance of our Pd/ICCP catalyst. However, the cross-coupling reaction of 2,6-dimethyliodobenzene (**1e**) provided low yields of the target product (**3e**) in only 38% for condition A and 35% for condition B at 70 °C with remaining starting material (Table 3.6, entry 5). These are probably due to the steric hindrance of the aryl iodide substrate decreasing the rate of oxidative addition step.

**Table 3.6** Substrate scope: aryl iodide bearing electron donating group.



| Entry | Condition | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | A |  **3a** | 82 |
|  | B |  | 80 |
| 2 | A |  **3b** | 85 |
|  | B |  | 78 |
| 3 | A |  **3c** | 96 |
|  | B |  | 73 |
| 4 | A |  **3d** | 72 |
|  | B |  | 70 |
| 5 | A |  **3e** | 38[b] |
|  | B |  | 35[b] |
| 6 | A |  **3f** | 90 |
|  | B |  | 91 |

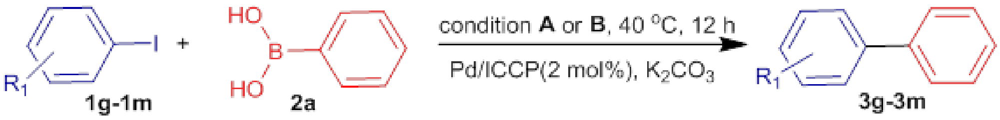
[a]Yield of the isolated product. [b]reaction was performed at 77 °C.

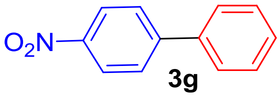
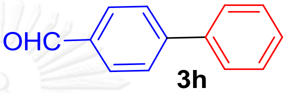
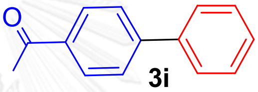
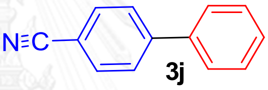
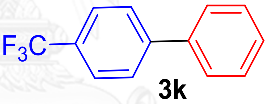
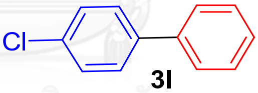
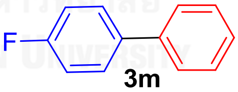
Contidion A: using EtOH-$H_2O$ (3:2) as solvent. Condition B: using CTAB and water as the solvent system.

### 3.4.1.2 Aryl iodides bearing electron-withdrawing groups (**1g-1m**)

The aryl iodide carrying electron-withdrawing groups such as nitro (**3g**), aldehyde (**3h**), acetyl (**3i**), nitrile (**3j**), trifluoromethyl (**3k**), chloro (**3l**), and fluoro groups (**3m**) were tested with phenylboronic acid (**2a**), and they underwent actively successful cross-coupling reaction without remaining starting materials under optimized condition A and B (Table 3.7). The desired biaryls (**3g-3m**) (Table 3, entries 1-7) were isolated in good to excellent yields after column purification and their structures were confirmed by $^{1}$H-NMR and $^{13}$C-NMR as shown in appendix section. These high yields in those particular substrates could be explained that the electron-withdrawing substituent on aryl iodide reduce bond strength of C-I bond resulting in accelerating oxidative addition step in the catalytic cycle [1]. Moreover, the other halide leaving groups such as chloro (**3l**) and fluoro groups (**3m**) which were carried out successfully without touching these leaving groups (Table 3.7, entries 6-7).

**Table 3.7** Substrate scope: aryl iodide bearing electron-withdrawing group.



| Entry | Condition | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | A |  **3g** | 100 |
|  | B |  | 93 |
| 2 | A |  **3h** | 99 |
|  | B |  | 92 |
| 3 | A |  **3i** | 96 |
|  | B |  | 80 |
| 4 | A |  **3j** | 100 |
|  | B |  | 96 |
| 5 | A |  **3k** | 80 |
|  | B |  | 78 |
| 6 | A |  **3l** | 90 |
|  | B |  | 89 |
| 7 | A |  **3m** | 88 |
|  | B |  | 85 |

[a]Yield of the isolated product.

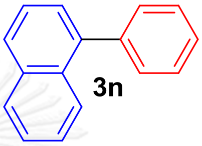
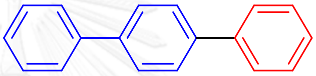
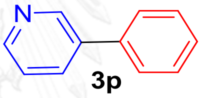
Contidion A: using EtOH-$H_2O$ (3:2) as solvent. Condition B: using CTAB and water as the solvent system.

### 3.4.1.3 Aryl iodides bearing heteroaromatic and polyaromatic groups (**1n-1p**)

The aryl iodides carrying heteroaromatic group, 3-iodopyridine (**1p**) and polyaromatic group, such as 1-iodonaphthalene (**1n**) and 4-iodobiphenyl (**1o**) were reacted with phenylboronic acid (**2a**) under the optimal conditions A and B as displayed in Table 3.8. We found that all aryl iodides (**1n-1p**) reacted completely to provide coupling products (**3n-3p**) in good to high isolated yields (Table 3.8, entries

1-3). We would like to note that the heteroatom in pyridine group is known to chelate with palladium metal but there is no effect in our reaction condition as seen in high isolated yields of  in product **3p** (Table 3.8, entry 3) [44].

**Table 3.8** Substrate scope: aryl iodide bearing heteroaromatic and polyaromatic groups

| Entry | Condition | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | A |  **3n** | 89 |
|  | B |  | 86 |
| 2 | A |  **3o** | 87 |
|  | B |  | 85 |
| 3 | A |  **3p** | 72 |
|  | B |  | 70 |

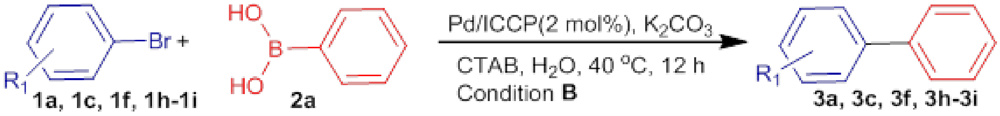
[a] Yield of the isolated product.

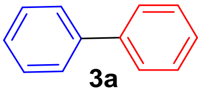
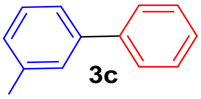
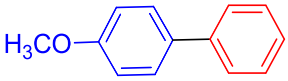
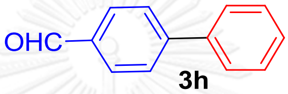
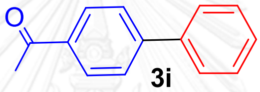
Contidion A: using EtOH-$H_2O$ (3:2) as solvent. Condition B: using CTAB and water as the solvent system.

### 3.4.2 Substrate scope on aryl bromides (**1a, 1c, 1f, 1h-1i**)

To expand the scope of the reaction into more challenge substrates, we also examined various aryl bromides (**1a, 1c, 1f, 1h-1i**) as coupling partners in the Suzuki reaction with phenylboronic acid (**2a**) in water (condition B). A panel of aryl bromides containing electron donating groups (**1a, 1c, 1f**) and electron withdrawing groups (**1h-1i**) underwent cross-coupling reactions successfully without the remaining starting material and the results were demonstrated in Table 3.9.

**Table 3.9** Substrate scope on aryl bromides



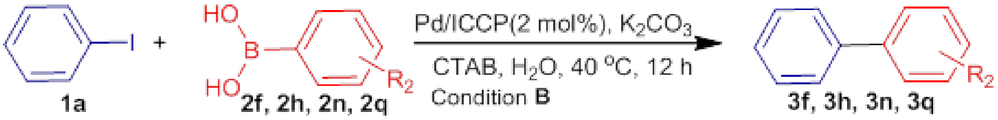
| Entry | Product | Yield (%)[a] |
|---|---|---|
| 1 |  **3a** | 76 |
| 2 |  **3c** | 75 |
| 3 |  **3f** | 72 |
| 4 |  **3h** | 86 |
| 5 |  **3i** | 86 |

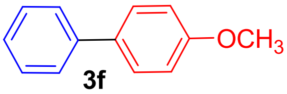
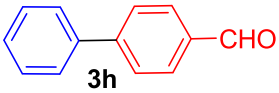
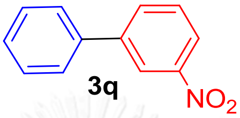
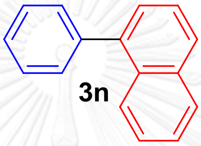
[a] Yield of the isolated product.

### 3.4.3 Substrate scope on arylboronic acid (**2f, 2h, 2n, 2q**)

From the above results, we are successful to couple various aryl halides substrate with phenylboronic acid **(2a)**. In this section, we would like to investigate the effect of substituents on arylboronic acid coupling partner. We chose 4-methoxyphenylboronic acid (**2f**), 4-formylphenylboronic acid (**2h**), 3-nitrophenylboronic acid (**2q**), and 1-naphthylboronic acid (**2n**) as representative for arylboronic acid substrates covering electron-donating, electron-withdrawing, and polyaromatic groups, respectively. These arylboronic acids (**2f, 2h, 2n, 2q**) underwent successful Suzuki cross-coupling reaction with iodobenzene (**1a**) under optimal condition B and the results were concluded in Table 3.10. We acquired the desired biaryls (**3f, 3h, 3n, 3q**) in high isolated yields after column purification (Table 3.10, entries 1-4).

**Table 3.10** Substrate scope on arylboronic acid



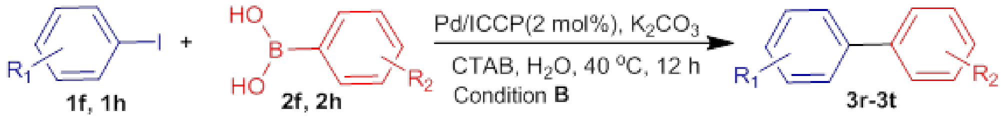
| Entry | Product | Yield (%)[a] |
|---|---|---|
| 1 |  **3f** | 96 |
| 2 |  **3h** | 87 |
| 3 |  **3q** | 94 |
| 4 |  **3n** | 99 |

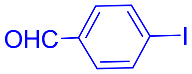
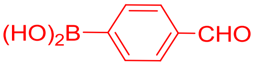
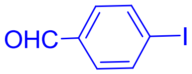
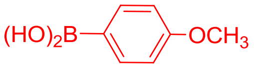
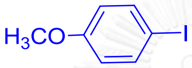
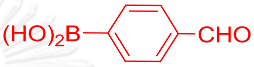
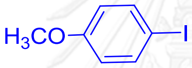
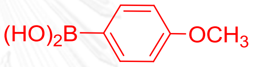
[a]Yield of the isolated product.

### 3.4.4 Substrate scope on both aryl iodide (1f, 1h) and arylboronic acid (2f, 2h)

Next, we would like to investigate substrate compatibility of substituents on both aryl iodide and arylboronic acid. Both of coupling partners carrying electron donating such as methoxy group (**1f**, **2f**) and electron-withdrawing groups such as aldehyde group (**1h**, **2h**) underwent Suzuki cross-coupling reaction under optimized condition B. We observed that these coupling products (**3r-3t**) were also received in excellent isolated yields without remaining starting materials as shown in Table 3.11.

**Table 3.11** Substrate scope: substituents on both aryl iodide and arylboronic acid



| Entry | Aryl iodide | Arylboronic acid | Yield (%)[a] |
|---|---|---|---|
| 1 | <br>**1h** | <br>**2h** | 100 |
| 2 | <br>**1h** | <br>**2f** | 94 |
| 3 | <br>**1f** | <br>**2h** | 93 |
| 4 | <br>**1f** | <br>**2f** | 100 |

[a]Yield of the isolated product.

## 3.5 Reusability and catalytic activity of Pd/ICCP, Pd/$CaCO_3$, Pd/SP and Pd/C catalysts

To investigate the reusability of palladium catalysts, we performed the Suzuki reactions between 4-iodoanisole (**1f**) and phenylboronic acid (**2a**) using our prepared Pd/ICCP catalyst and compare with other three catalysts including Pd/$CaCO_3$, Pd/SP and Pd/C. The cross-coupling reactions of each palladium catalyst were carried out for fourteen consecutive runs and monitored by NMR spectroscopy. The reactions were performed in water following procedure in section 2.7 (condition B). To reuse palladium catalysts in each run, they were washed with dichloromethane, water and acetone to eliminate the adsorbed organic reagents and the remaining salts. Then, used catalysts were dried in vacuum before using for the next run without any chemical treatment or heating. The results were inferred in Figure 3.6. The reusability of investigated catalysts was found in order of Pd/ICCP > Pd/$CaCO_3$ > Pd/SP > Pd/C catalysts. The Pd/C catalyst had significant loss of catalytic activity since fourth cycle, which was probably due to weak interaction between palladium species and carbon support led to a high palladium leaching into the reaction mixture. In the similar way, the reusable efficiency of Pd/SP catalyst was significantly lost since eighth run, which was probably because of having low surface area of SP support from large size of shell particle resulted in poor binding efficiency between support and metal. From histogram in Figure 3.6, it's clearly showed that Pd/ICCP and Pd/$CaCO_3$ are the best catalysts in this work maintaining more than 80 %yield for nine and eight rounds, respectively. Moreover, in every runs, the reusability of Pd/$CaCO_3$ was slightly lower than Pd/ICCP as seen by NMR monitor in range of between 5 and 10 %yield. This suggested that Pd/ICCP has better reusability over commercial Pd/$CaCO_3$. This is probably due to the deficiency of organic protein in the surface of $CaCO_3$ support bringing about having higher palladium leaching than Pd/ICCP. While the highest reusability of Pd/ICCP catalyst was probably due to the chelation between the palladium metal and the surface protein and chitin molecules on the shell particles supports [18], along with the high surface area of ICCP support.

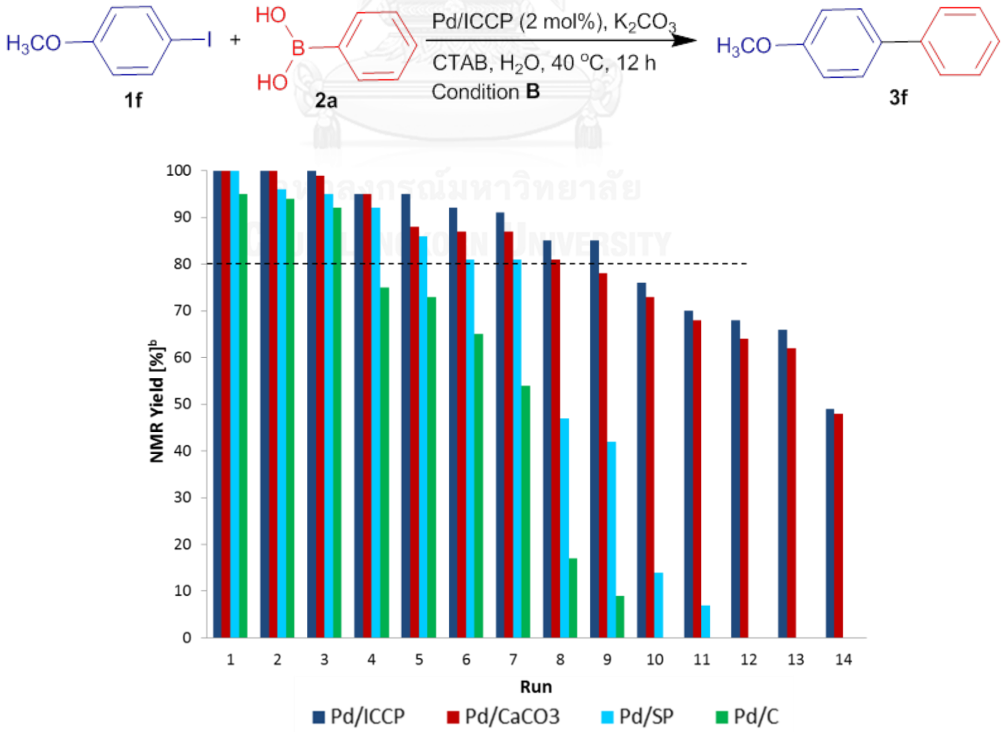


**Figure 3.6** Comparison of reusability of palladium catalysts

### 3.6 Determination of Palladium leaching content by ICP-OES analysis

Metal leaching was another important aspect to quantify whether these processes are environmentally-friendly or not. To determine the palladium content, after the first run, the reaction mixtures from Pd/ICCP, Pd/SP, Pd/$CaCO_3$, and Pd/C were determined by ICP-OES analysis and the results were concluded in Table 3.12. The highest palladium leaching content was found in case of the reaction from Pd/C. This might be because of weak interaction between palladium species with surface of carbon support. However, the palladium leachings in the reaction mixture from Pd/ICCP, Pd/SP, and Pd/$CaCO_3$ were detected in the range between 3.7 and 4.6 %wt. Their low leaching of palladium in those catalysts might be due to their electrostatic force between the partial negative charge of palladium nanoparticles with the positive charge of calcium cation on $CaCO_3$ [45] resulting in strong attachment of palladium nanoparticles on surface of $CaCO_3$ support. Moreover, the superior property of Pd/ICCP and Pd/SP is the extra chelation between palladium species and functional group of protein on the surface of shell support [18]. Furthermore, the SP support of Pd/SP has rough surface from aggregated multiple plates as predicted (Figure 3.7). This resulted in having slightly higher palladium leaching than Pd/ICCP, which has smooth surface on ICCP support. Therefore, the Pd/ICCP catalyst is the best choice for low metal leaching heterogeneous Pd catalyst with high catalytic activity and reusability.

**Table 3.12** Comparing palladium leaching of catalysts in the reaction mixture

| Catalysts | Palladium leaching (%wt)[a] |
|---|---|
| Pd/ICCP | 3.7 |
| Pd/$CaCO_3$ | 4.6 |
| Pd/SP | 4.0 |
| Pd/C | 12.5 |

[a] Determined by ICP-OES from crude after first run.

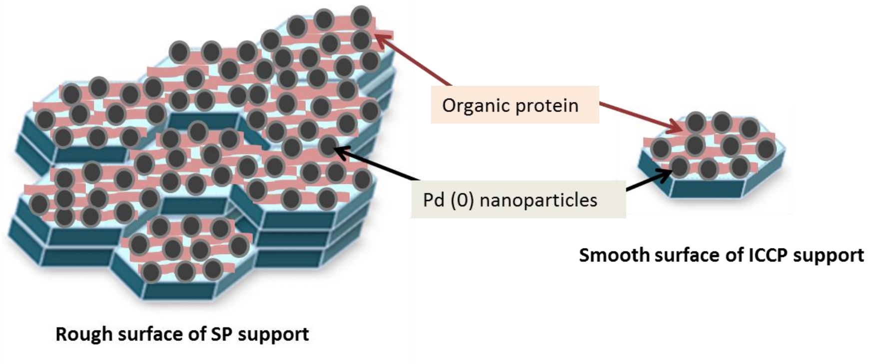


**Figure 3.7** Illustration of binding mechanism between SP and ICCP supported palladium nanoparticles

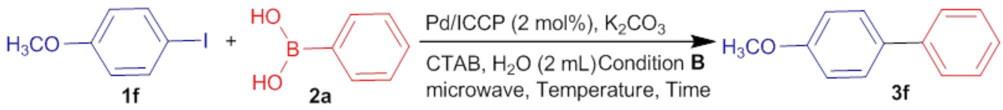
### 3.7 Microwave-assisted Suzuki cross-coupling reaction using Pd/ICCP catalyst

Commonly, the use of microwave resulted in the reduction of reaction times and side reactions, and the addition of yields, along with the improvement of reproducibility [46]. Currently, the microwave-assisted Suzuki cross-coupling reaction can be considered as a proficient synthetic methodology. For example, Sharma and co-workers reported that the synthesis of biaryl-containing polyaromatic hydrocarbon underwent successful cross-coupling reaction under microwave irradiation at 120 °C for 20 min [47]. Later, Chang and co-workers reported that the microwave-assisted Suzuki reactions of aryl iodides were carried out in the presence of heterogeneous palladium catalyst at 120 °C for 10 min and the target product were obtained in high yields [48]. These literatures suggested that the Suzuki reaction was facilitated under microwave irradiation by spending a few reaction times. Therefore, from the benefits of microwave operation, we applied microwave chemistry to Suzuki cross-coupling reaction using our prepared Pd/ICCP catalyst.

#### 3.7.1 Optimization of the reaction condition using microwave apparatus

In this section, we studied the effect of temperature and reaction time of the Suzuki reactions between 4-iodoanisole (**1f**) and phenylboronic acid (**2a**) under microwave irradiation. We used 2 mol% of Pd/ICCP as catalyst, $K_2CO_3$ as a base in CTAB and water as the solvent system to perform the reactions in 200 w of microwave apparatus at 80 °C and 100 °C. The results in Table 3.13 indicated that the complete NMR yields were obtained when the reactions were conducted at 100 °C in 5, 10, and 15 minutes (Table 3.13, entries 2-4). Therefore, we selected 100 °C for 5 minutes as the optimal condition for Suzuki reaction under microwave irradiation.

**Table 3.13** Optimization studies on Suzuki reaction under microwave irradiation



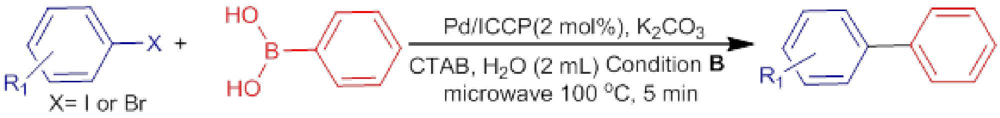
| Entry | Temperature (°C) | Time (min) | NMR Yield (%)[a] |
|---|---|---|---|
| 1 | 80 | 15 | 93 |
| 2 | 100 | 5 | 100 |
| 3 | 100 | 10 | 100 |
| 4 | 100 | 15 | 100 |

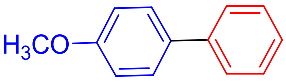
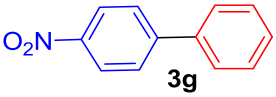
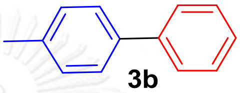
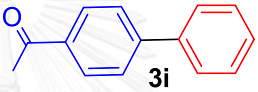
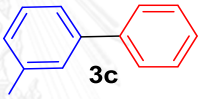
[a]Determined by $^1$H-NMR.

### 3.7.2 Substrate scope on aryl halides under microwave irradiation

After identify the optimum condition in microwave processing, various kinds of aryl iodide and aryl bromide (**1b-1c**, **1f-1g**, **1i**) were subjected to the reaction condition. Both of aryl iodides and aryl bromides with electron donating groups, including methyl (**1b-1c**) and methoxy groups (**1f**), and electron withdrawing groups, comprising nitro (**1g**), acetyl groups (**1i**) underwent successful cross-coupling reactions with phenylboronic acid (**2a**) under microwave irradiation at 100 °C for 5 minutes. These coupling products (**3b-3c, 3f-3g, 3i**) were also obtained in good to high isolated yields after column purification (Table 3.14, entries 1-5) without remaining starting materials.

**Table 3.14** Suzuki reaction of aryl halides with phenylboronic acid under microwave irradiation



| Entry | X=I or Br | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | I |  **3f** | 80 |
| | Br | | 79 |
| 2 | I |  **3g** | 88 |
| 3 | I |  **3b** | 88 |
| 4 | Br |  **3i** | 92 |
| 5 | Br |  **3c** | 75 |

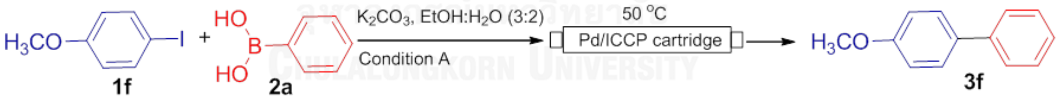
[a]Yield of the isolated product.

## 3.8 Continuous flow Suzuki cross-coupling reaction using Pd/ICCP catalyst

To expand our heterogeneous catalyst in Suzuki reaction to industry aspect, we therefore turn our attention to apply our reaction into continuous flow process. There are two main benefits in flow chemistry, which consisted of increasing mass transfer and heat transfer leading to the enhancement of reaction rate. Therefore, such process is suitable for a large-scale synthesis of biaryl derivatives in chemical industry in term of improving yield and reproducibility [49, 50]. In this study, we combined the usage of a solid-phase packed bed reactor containing our prepared Pd/ICCP catalyst [51]. This could enhance interfacial contact between organic reagents and palladium catalyst resulting in enhancement of the reaction efficiency [52]. Our prepared Pd/ICCP catalyst was also applied to Suzuki cross-coupling reaction between 4-iodoanisole (**1f**) and phenylboronic acid (**2a**) as model substrates under optimal condition A using $K_2CO_3$ as base in the mixed solvent of EtOH-$H_2O$

(3:2) behaving as single-phase solution which prevents the blockage of flow reactor. All reactions were performed at 50 °C by using the procedure in section 2.9.1 and were monitored by NMR in order to find the optimal condition. To determine the optimal condition having high production rate and low catalyst loading, we therefore conducted the continuous flow reactions with studying three reaction variables, including reaction concentration (7, 70 and 35 mM), catalyst loading (0.1 %wt and 0.5 %wt) and residence time (2, 4, and 8 hours) and the results were summarized in Table 3.15. In case of 0.5%wt catalyst loading with the concentration 7 mM, the 100% conversions were received in both 2 and 4 hours of residence time (Table 3.15, entries 1-2). Moreover, when increase concentration up to 70 mM, the 100% conversion was also obtained (Table 3.15, entry 3). On the other hand, decrease of catalyst loading to 0.1%wt requires longer residence time. It needs at least 8 hours of residence time at 7 mM to obtain full conversion (Table 3.15, entry 4). We also observed the blockage of reactor in high concentration with low flow rate (Table 3.15, entries 6-7). Based on these results, we conclude that at 70 mM with 0.5%wt and residence time of 2 hours is the optimal condition for continuous flow Suzuki reaction using our Pd/ICCP catalyst.

**Table 3.15** Suzuki reaction of 4-iodoanisole using a microflow reactor



| Entry | Concentration (mM) | Loading of Pd catalysts (%wt) | Flow rate (μL/min) | Residence time (h) | NMR Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | 7 | 0.5 | 5.7 | 4 | 100 |
| 2 | 7 | 0.5 | 11.5 | 2 | 100 |
| 3 | 70 | 0.5 | 13.3 | 2 | 100 |
| 4 | 7 | 0.1 | 2.9 | 8 | 100 |
| 5 | 7 | 0.1 | 5.9 | 4 | 68 |
| 6 | 70 | 0.1 | 3 | 8 | blocking of reactor |
| 7 | 35 | 0.1 | 3 | 8 | blocking of reactor |

[a] Determined by $^1$H-NMR.

# CHAPTER IV

# CONCLUSIONS

In summary, a new heterogeneous palladium catalyst supported on individual calcium carbonates plates (Pd/ICCP) from Asian green mussel shell waste has been prepared successfully. The catalyst has been demonstrated to be highly reactive and reusable for the ligand free Suzuki cross-coupling reaction in aqueous medium at low temperatures. It can be reused up to nine times without a significant loss of its catalytic activity with negligible Pd leaching content. The high catalytic activity and reusability of Pd/ICCP catalyst may be due to a highly uniform structure of ICCP support and the strong chelation between Pd(0) and protein on surface of support. Importantly, our finding turns the shell waste from fishery industry into a high value catalytic support to catalyze the green synthesis of biaryl derivatives in aqueous medium. Moreover, our catalyst can be adapted to microwave process and continuous flow Suzuki reaction which is appropriate for a large-scale synthesis of biaryls in chemical industry.

# REFERENCES

[1] Miyaura, N. and Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. Chemical Reviews 95(7) (1995): 2457-2483.

[2] Fihri, A., Meunier, P., and Hierso, J.-C. Performances of symmetrical achiral ferrocenylphosphine ligands in palladium-catalyzed cross-coupling reactions: A review of syntheses, catalytic applications and structural properties. Coordination Chemistry Reviews 251(15–16) (2007): 2017-2055.

[3] Cepanec, I. Chapter 5 - The Suzuki-Miyaura reaction. in Synthesis of Biaryls, pp. 139-207. Oxford: Elsevier Science Ltd, 2004.

[4] Kotha, S. and Lahiri, K. Expanding the Diversity of Polycyclic Aromatics Through a Suzuki–Miyaura Cross-Coupling Strategy. European Journal of Organic Chemistry 2007(8) (2007): 1221-1236.

[5] Sliger, M.D., Broker, G.A., Griffin, S.T., Rogers, R.D., and Shaughnessy, K.H. Di-t-butyl(ferrocenylmethyl)phosphine: air-stability, structural characterization, coordination chemistry, and application to palladium-catalyzed cross-coupling reactions. Journal of Organometallic Chemistry 690(6) (2005): 1478-1486.

[6] Smith, R.C., Woloszynek, R.A., Chen, W., Ren, T., and Protasiewicz, J.D. Suzuki reactions catalyzed by palladium complexes bearing the bulky (2,6-dimesitylphenyl)dimethylphosphine. Tetrahedron Letters 45(45) (2004): 8327-8330.

[7] Kolodziuk, R., Penciu, A., Tollabi, M., Framery, E., Goux-Henry, C., Iourtchenko, A., and Sinou, D. Palladium-catalyzed Suzuki cross-coupling of aryl halides with aryl boronic acids in the presence of glucosamine-based phosphines. Journal of Organometallic Chemistry 687(2) (2003): 384-391.

[8] 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.

[9] Yin and Liebscher, J. Carbon−Carbon Coupling Reactions Catalyzed by Heterogeneous Palladium Catalysts. Chemical Reviews 107(1) (2007): 133-173.

[10] Park, J.H., Raza, F., Jeon, S.-J., Kim, H.-I., Kang, T.W., Yim, D., and Kim, J.-H. Recyclable N-heterocyclic carbene/palladium catalyst on graphene oxide for the aqueous-phase Suzuki reaction. Tetrahedron Letters 55(23) (2014): 3426-3430.

[11] Stevens, P.D., Fan, J., Gardimalla, H.M.R., Yen, M., and Gao, Y. Superparamagnetic Nanoparticle-Supported Catalysis of Suzuki Cross-Coupling Reactions. Organic Letters 7(11) (2005): 2085-2088.

[12] 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.

[13] Seyler, C., Capello, C., Hellweg, S., Bruder, C., Bayne, D., Huwiler, A., and Hungerbühler, K. Waste-Solvent Management as an Element of Green Chemistry:  A Comprehensive Study on the Swiss Chemical Industry. Industrial & Engineering Chemistry Research 45(22) (2006): 7700-7709.

[14] Polshettiwar, V., Decottignies, A., Len, C., and Fihri, A. Suzuki–Miyaura Cross-Coupling Reactions in Aqueous Media: Green and Sustainable Syntheses of Biaryls. ChemSusChem 3(5) (2010): 502-522.

[15] 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/CaCO3 as catalyst reservoir. Tetrahedron Letters 48(43) (2007): 7671-7674.

[16] 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.

[17] Shen, Y.-M., Du, Y.-J., Zeng, M.-F., Zhi, D., Zhao, S.-X., Rong, L.-M., Lv, S.-Q., Du, L., and Qi, C.-Z. Heck reaction catalyzed by a recyclable palladium supported on shell powder. Applied Organometallic Chemistry 24(9) (2010): 631-635.

[18] Zeng, M., Du, Y., Qi, C., Zuo, S., Li, X., Shao, L., and Zhang, X.-M. An efficient and recyclable heterogeneous palladium catalyst utilizing naturally abundant pearl shell waste. Green Chemistry 13(2) (2011): 350-356.

[19] Saetan, T., Lertvachirapaiboon, C., Sanong, E., Sukwattanasinitt, M., and Wacharasindhu, S. Pd Nanoparticles immobilized on individual calcium carbonate plate derived from mussel shell waste: An eco-friendly catalyst for copper-free Sonogashira coupling reaction. Chemistry – An Asian Journal: n/a-n/a.

[20] 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.

[21] Miyaura, N., Yamada, K., and Suzuki, A. A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. Tetrahedron Letters 20(36) (1979): 3437-3440.

[22] Suzuki, A. Synthetic studies via the cross-coupling reaction of organoboron derivatives with organic halides. Pure and Applied Chemistry 63(3) (1991): 419.

[23] Amatore, C., Jutand, A., and Le Duc, G. Kinetic Data for the Transmetalation/Reductive Elimination in Palladium-Catalyzed Suzuki–Miyaura Reactions: Unexpected Triple Role of Hydroxide Ions Used as Base. Chemistry – A European Journal 17(8) (2011): 2492-2503.

[24] Kabalka, G.W., Pagni, R.M., and Hair, C.M. Solventless Suzuki Coupling Reactions on Palladium-Doped KF/Al2O3. Organic Letters 1(9) (1999): 1423-1425.

[25] Kim, N., Kwon, M.S., Park, C.M., and Park, J. One-pot synthesis of recyclable palladium catalysts for hydrogenations and carbon–carbon coupling reactions. Tetrahedron Letters 45(38) (2004): 7057-7059.

[26] Shimizu, K.-i., Kan-no, T., Kodama, T., Hagiwara, H., and Kitayama, Y. Suzuki cross-coupling reaction catalyzed by palladium-supported sepiolite. Tetrahedron Letters 43(32) (2002): 5653-5655.

[27] Hartonen, K. and Riekkola, M.-L. Chapter 2 - Water as the First Choice Green Solvent A2 - Pena-Pereira, Francisco. in Tobiszewski, M. (ed.)The Application of Green Solvents in Separation Processes, pp. 19-55: Elsevier, 2017.

[28] Blum, C., Bunke, D., Hungsberg, M., Roelofs, E., Joas, A., Joas, R., Blepp, M., and Stolzenberg, H.-C. The concept of sustainable chemistry: Key drivers for the transition towards sustainable development. Sustainable Chemistry and Pharmacy 5 (2017): 94-104.

[29] Colacot, T.J. The 2010 Nobel Prize in Chemistry: Palladium-Catalysed Cross-Coupling. Platinum Metals Review 55(2) (2011): 84-90.

[30] Thompson, W.J., Jones, J.H., Lyle, P.A., and Thies, J.E. An efficient synthesis of arylpyrazines and bipyridines. The Journal of Organic Chemistry 53(9) (1988): 2052-2055.

[31] Dantas Ramos, A.L., Alves, P.d.S., Aranda, D.A.G., and Schmal, M. Characterization of carbon supported palladium catalysts: inference of electronic and particle size effects using reaction probes. Applied Catalysis A: General 277(1–2) (2004): 71-81.

[32] Wang, Z. Lindlar Hydrogenation. in Comprehensive Organic Name Reactions and Reagents: John Wiley & Sons, Inc., 2010.

[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.

[34] Yang, J. and Wang, L. Synthesis and characterization of dinuclear NHC-palladium complexes and their applications in the Hiyama reactions of aryltrialkyoxysilanes with aryl chlorides. Dalton Transactions 41(39) (2012): 12031-12037.

[35] Li, L., Wang, J., Zhou, C., Wang, R., and Hong, M. pH-Responsive chelating N-heterocyclic dicarbene palladium(ii) complexes: recoverable precatalysts for Suzuki-Miyaura reaction in pure water. Green Chemistry 13(8) (2011): 2071-2077.

[36] Wang, P., Cai, J., Chen, J., and Ji, M. Agarose-Alumina Composite Supported Palladium Catalyst for Suzuki Coupling Reactions. Journal of the Brazilian Chemical Society 26 (2015): 748-754.

[37] Borah, R.K., Saikia, H.J., Mahanta, A., Das, V.K., Bora, U., and Thakur, A.J. Biosynthesis of poly(ethylene glycol)-supported palladium nanoparticles using Colocasia esculenta leaf extract and their catalytic activity for Suzuki-Miyaura cross-coupling reactions. RSC Advances 5(89) (2015): 72453-72457.

[38] Srinivas, K., Srinivas, P., Prathima, P.S., Balaswamy, K., Sridhar, B., and Rao, M.M. Thiopseudourea ligated palladium complexes: synthesis, characterization and application as catalysts for Suzuki-Miyaura, Sonogashira, Heck and Hiyama reactions. Catalysis Science & Technology 2(6) (2012): 1180-1187.

[39] Nguyen, H.L., Vu, T.T., Le, D., Doan, T.L.H., Nguyen, V.Q., and Phan, N.T.S. A Titanium–Organic Framework: Engineering of the Band-Gap Energy for Photocatalytic Property Enhancement. ACS Catalysis 7(1) (2017): 338-342.

[40] Mao, S.-L., Sun, Y., Yu, G.-A., Zhao, C., Han, Z.-J., Yuan, J., Zhu, X., Yang, Q., and Liu, S.-H. A highly active catalytic system for Suzuki-Miyaura cross-coupling reactions of aryl and heteroaryl chlorides in water. Organic & Biomolecular Chemistry 10(47) (2012): 9410-9417.

[41] Xiao, Q., Sarina, S., Jaatinen, E., Jia, J., Arnold, D.P., Liu, H., and Zhu, H. Efficient photocatalytic Suzuki cross-coupling reactions on Au-Pd alloy nanoparticles under visible light irradiation. Green Chemistry 16(9) (2014): 4272-4285.

[42] Wang, F., Li, C., Chen, H., Jiang, R., Sun, L.-D., Li, Q., Wang, J., Yu, J.C., and Yan, C.-H. Plasmonic Harvesting of Light Energy for Suzuki Coupling Reactions. Journal of the American Chemical Society 135(15) (2013): 5588-5601.

[43] Raman, N.K., Anderson, M.T., and Brinker, C.J. Template-Based Approaches to the Preparation of Amorphous, Nanoporous Silicas. Chemistry of Materials 8(8) (1996): 1682-1701.

[44] 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.

[45] Islam, K.N., Bakar, M.Z.B.A., Noordin, M.M., Hussein, M.Z.B., Rahman, N.S.B.A., and Ali, M.E. Characterisation of calcium carbonate and its polymorphs from cockle shells (Anadara granosa). Powder Technology 213(1–3) (2011): 188-191.

[46] Kappe, C.O. Controlled Microwave Heating in Modern Organic Synthesis. Angewandte Chemie International Edition 43(46) (2004): 6250-6284.

[47] Sharma, A.K., Gowdahalli, K., Krzeminski, J., and Amin, S. Microwave-Assisted Suzuki Cross-Coupling Reaction, a Key Step in the Synthesis of Polycyclic Aromatic Hydrocarbons and Their Metabolites. The Journal of Organic Chemistry 72(23) (2007): 8987-8989.

[48] Chang, W., Chae, G., Jang, S.R., Shin, J., and Ahn, B.J. An efficient microwave-assisted Suzuki reaction using Pd/MCM-41 and Pd/SBA-15 as catalysts in solvent-free condition. Journal of Industrial and Engineering Chemistry 18(2) (2012): 581-585.

[49] Mateos, C., Rincón, J.A., Martín-Hidalgo, B., and Villanueva, J. Green and scalable procedure for extremely fast ligandless Suzuki–Miyaura cross-coupling reactions in aqueous IPA using solid-supported Pd in continuous flow. Tetrahedron Letters 55(27) (2014): 3701-3705.

[50] Newman, S.G. and Jensen, K.F. The role of flow in green chemistry and engineering. Green Chemistry 15(6) (2013): 1456-1472.

[51] Mitprapan, S. Continuous Flow Suzuki Cross-Coupling Reaction Catalyzed By Palladium Supported On $CaCO_3$ Derived From Mussel Shells. Bachelor's degree, Department of Chemistry Chulalongkorn University, Academic Year 2016.

[52] Shang, M., Noël, T., Wang, Q., and Hessel, V. Packed-Bed Microreactor for Continuous-Flow Adipic Acid Synthesis from Cyclohexene and Hydrogen Peroxide. Chemical Engineering & Technology 36(6) (2013): 1001-1009.

# APPENDIX

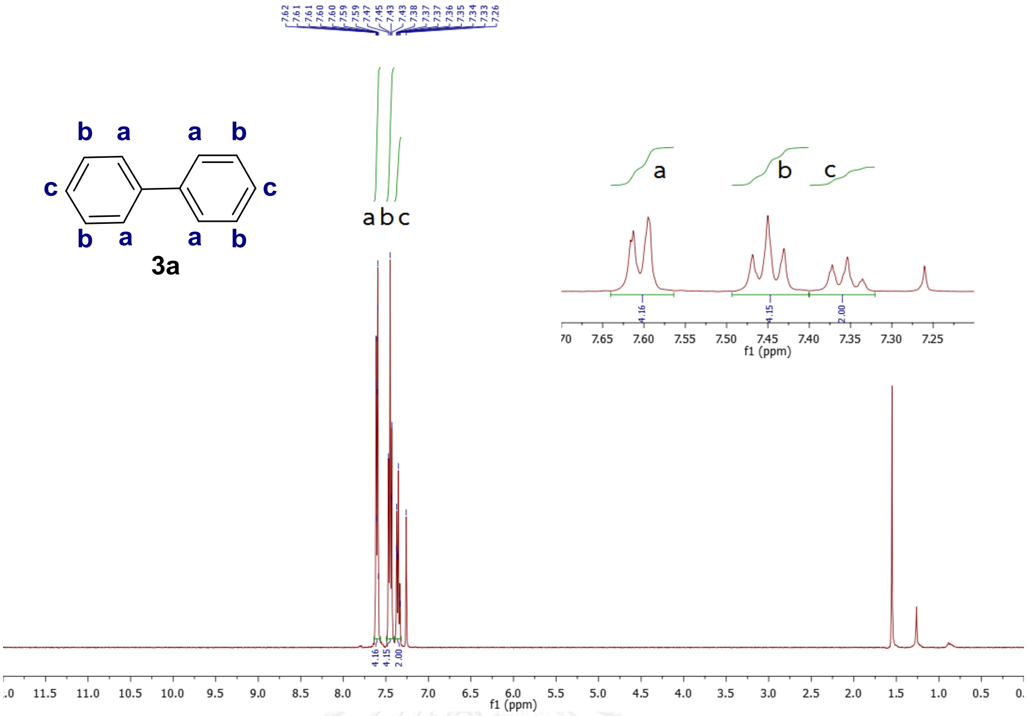


Figure A1 $^1$H NMR spectrum of **3a** ($CDCl_3$)

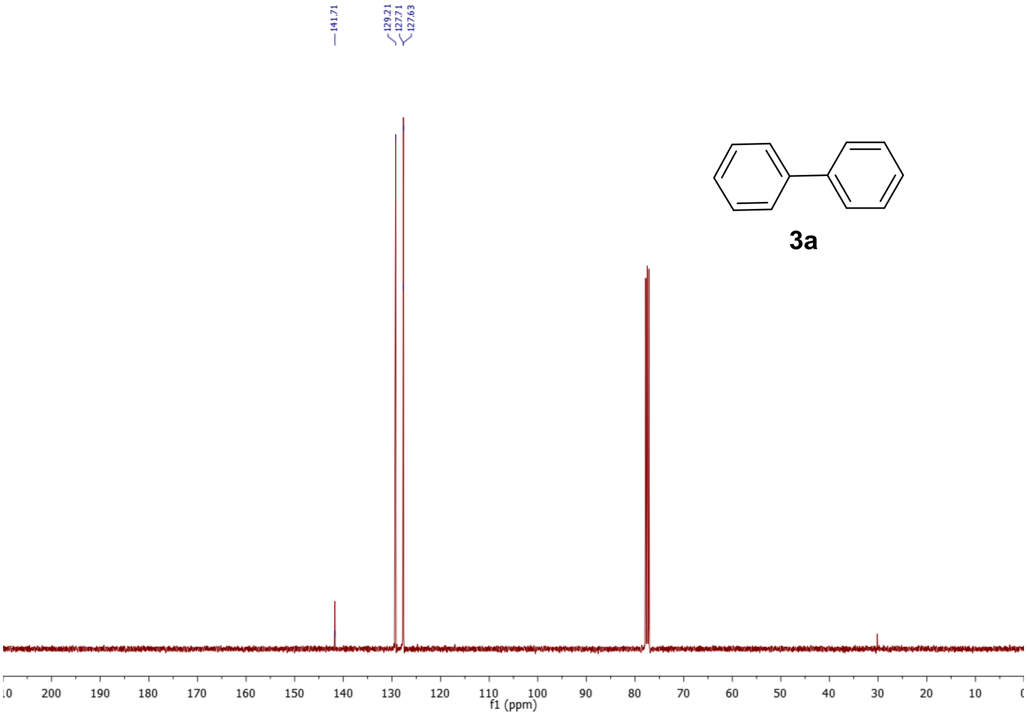


Figure A2 $^{13}$C NMR spectrum of **3a** ($CDCl_3$)

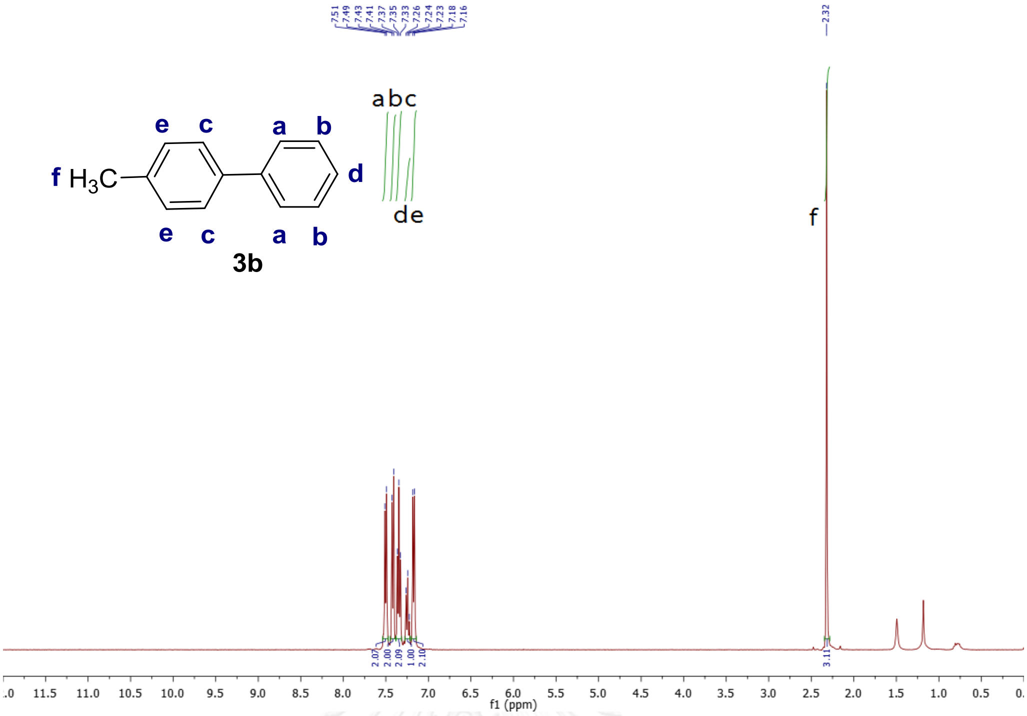


Figure A3 $^{1}$H NMR spectrum of **3b** ($CDCl_3$)

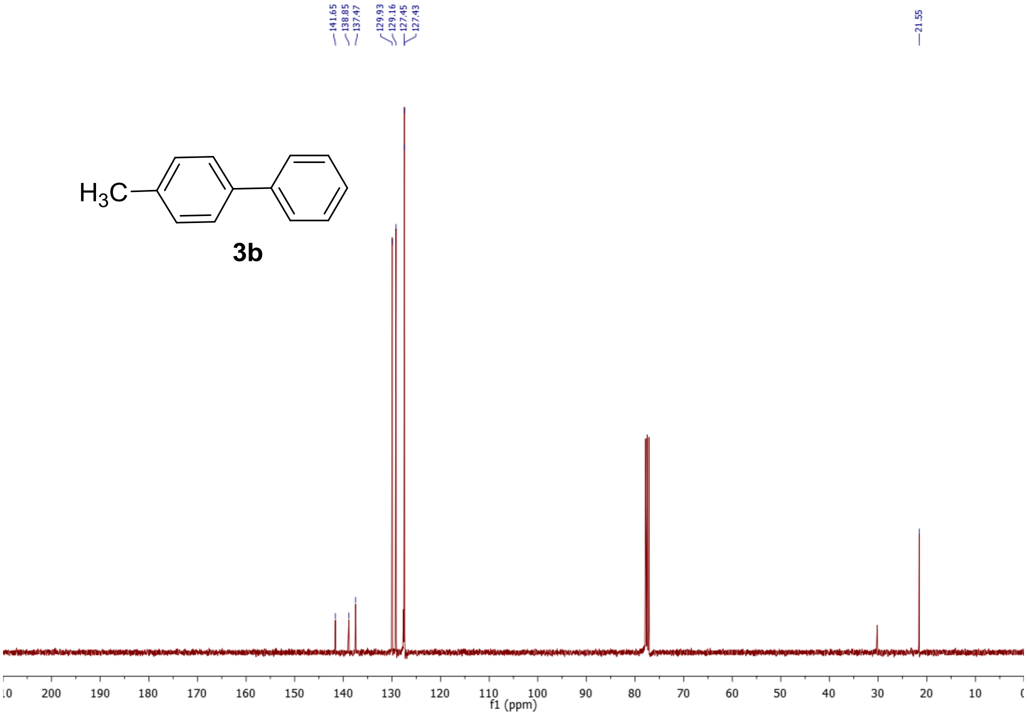


Figure A4 $^{13}$C NMR spectrum of **3b** ($CDCl_3$)

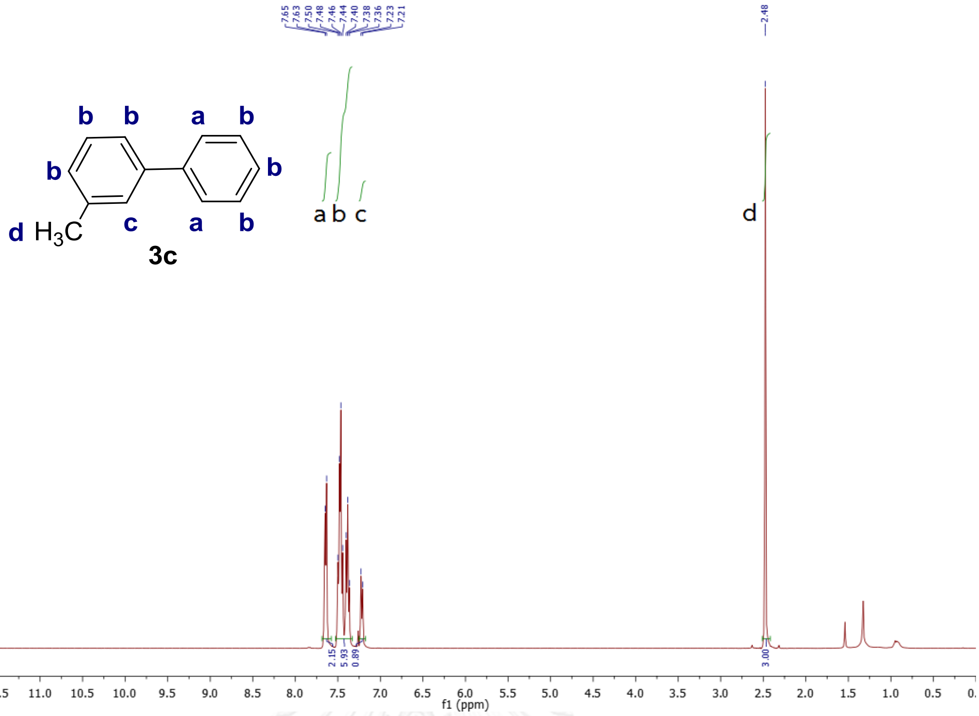


Figure A5 $^{1}$H NMR spectrum of **3c** ($CDCl_3$)

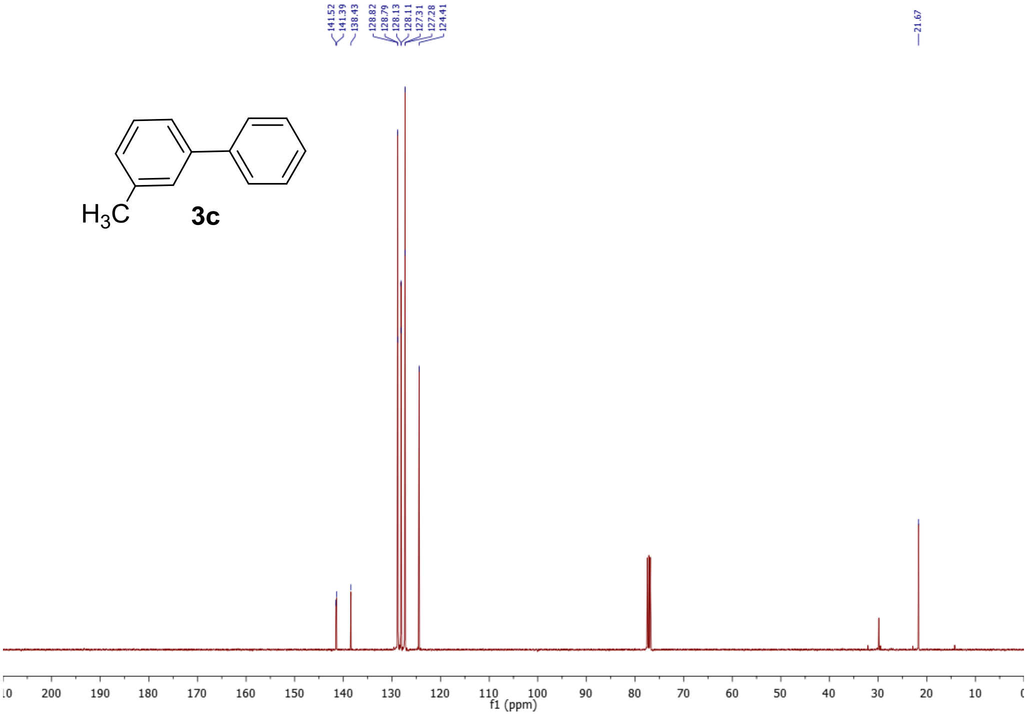


Figure A6 $^{13}$C NMR spectrum of **3c** ($CDCl_3$)

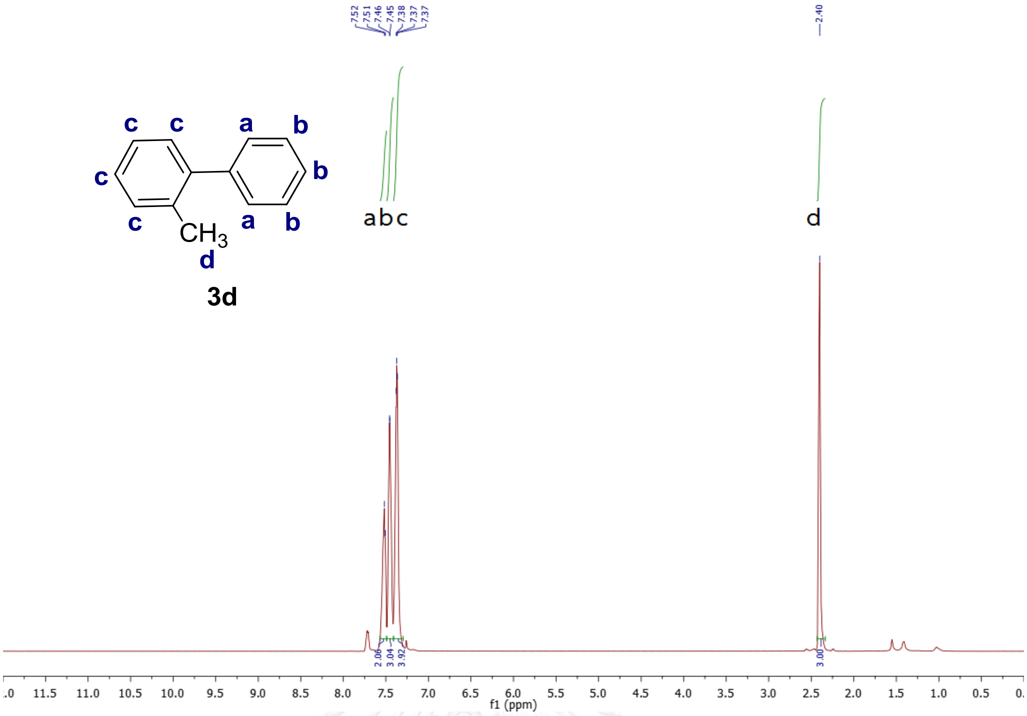


Figure A7 $^{1}$H NMR spectrum of **3d** (CDCl$_3$)

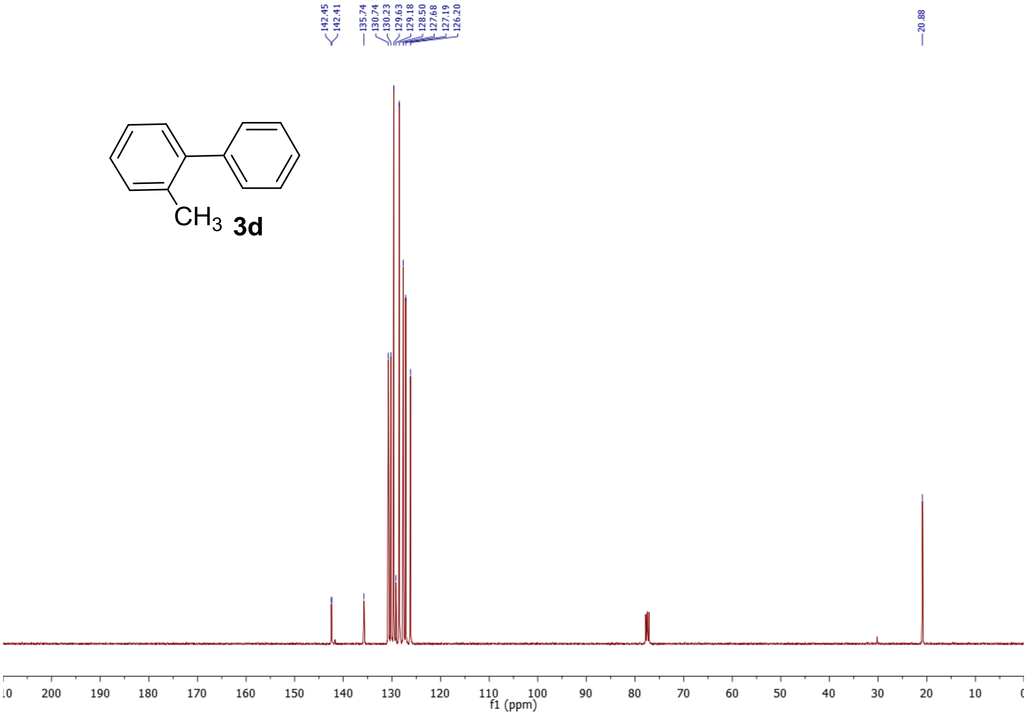


Figure A8 $^{13}$C NMR spectrum of **3d** (CDCl$_3$)

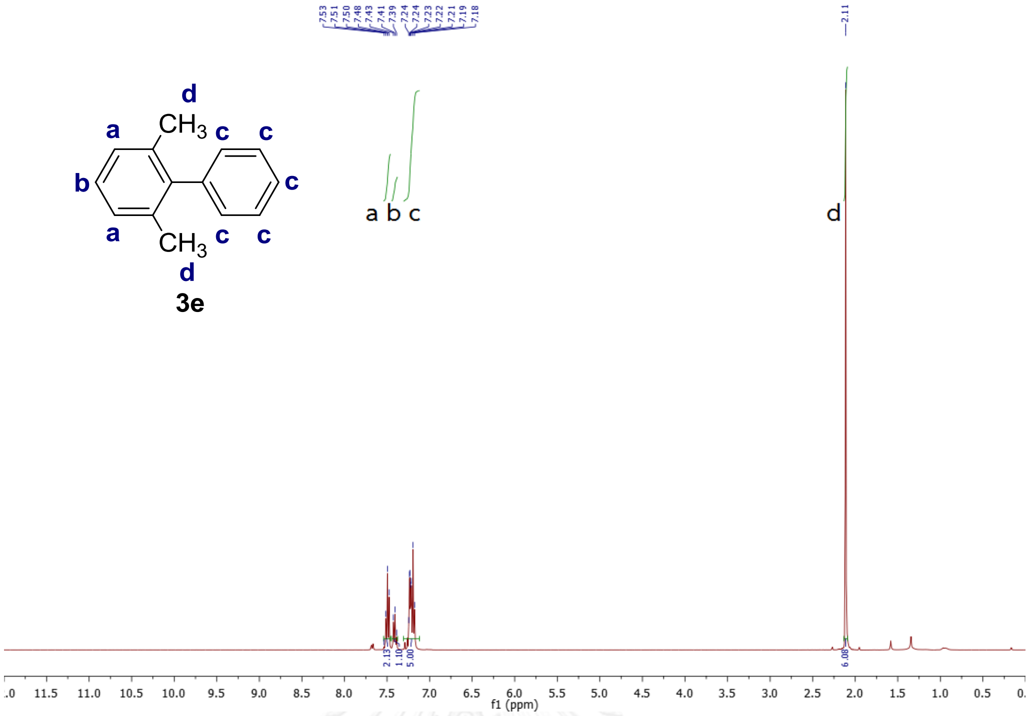


Figure A9 $^{1}$H NMR spectrum of **3e** ($CDCl_3$)

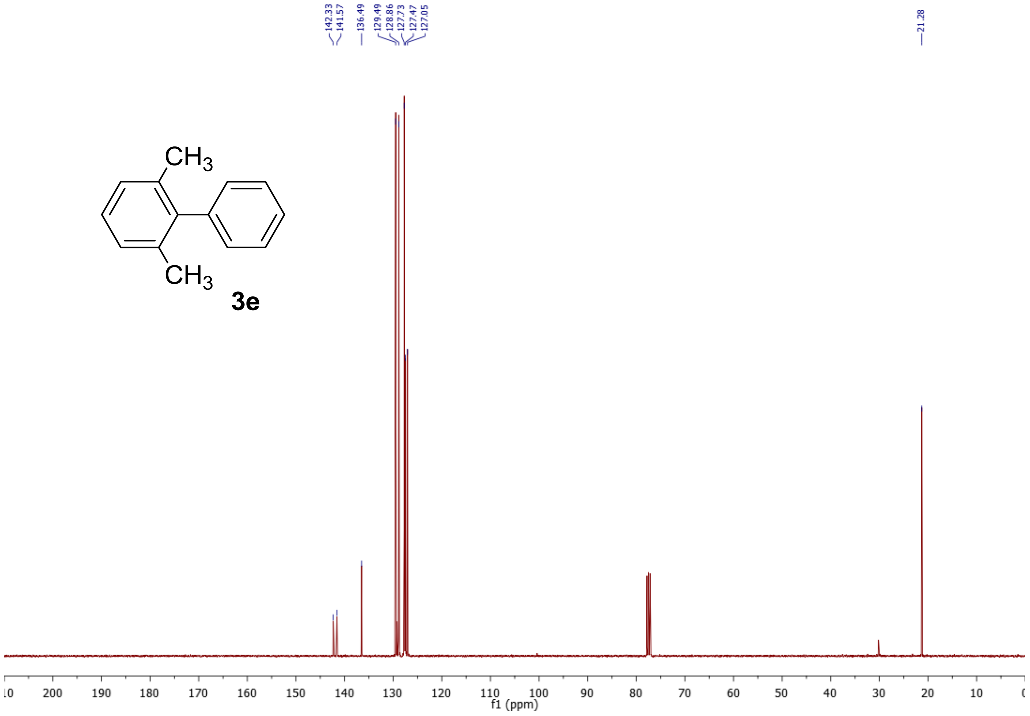


Figure A10 $^{13}$C NMR spectrum of **3e** ($CDCl_3$)

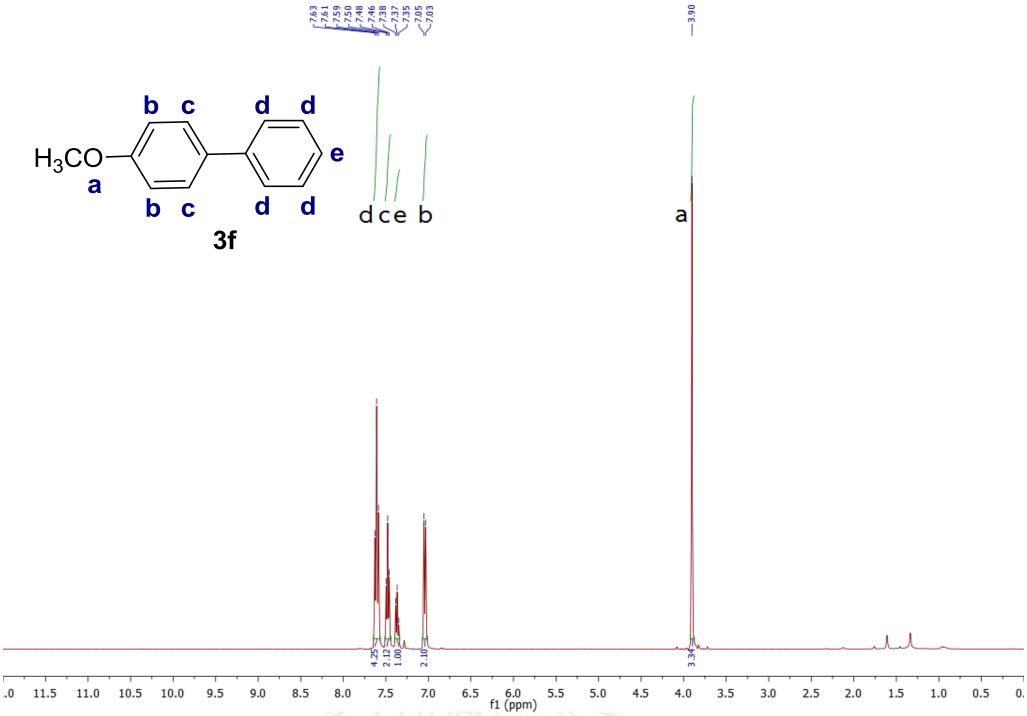


Figure A11 $^1$H NMR spectrum of **3f** ($CDCl_3$)

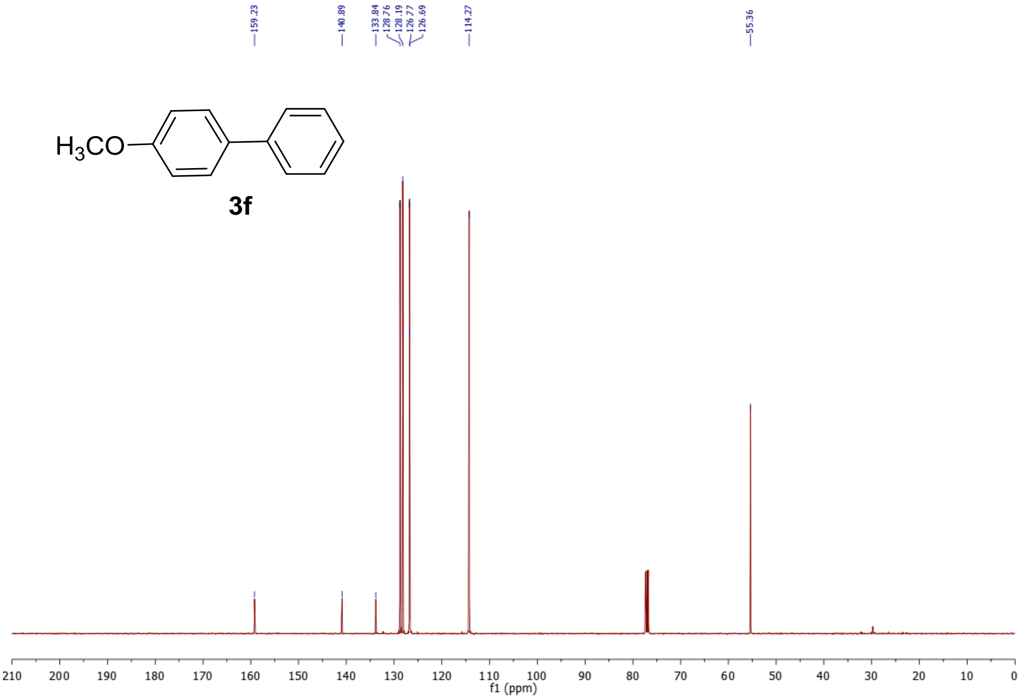


Figure A12 $^{13}$C NMR spectrum of **3f** ($CDCl_3$)

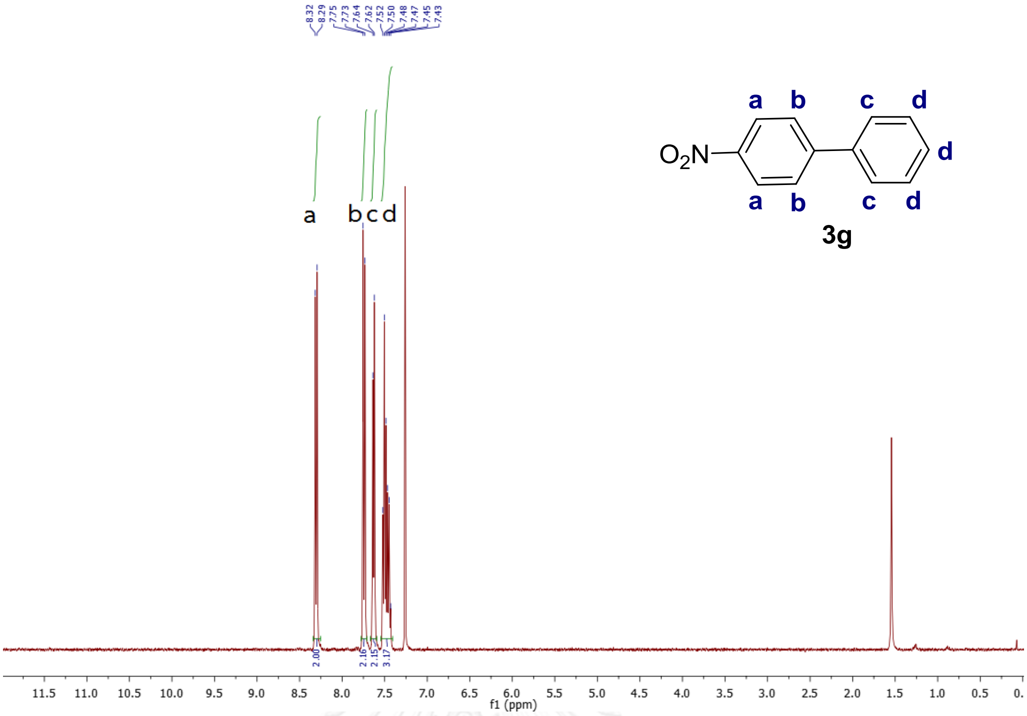


**Figure A13** $^{1}$H NMR spectrum of **3g** ($CDCl_3$)

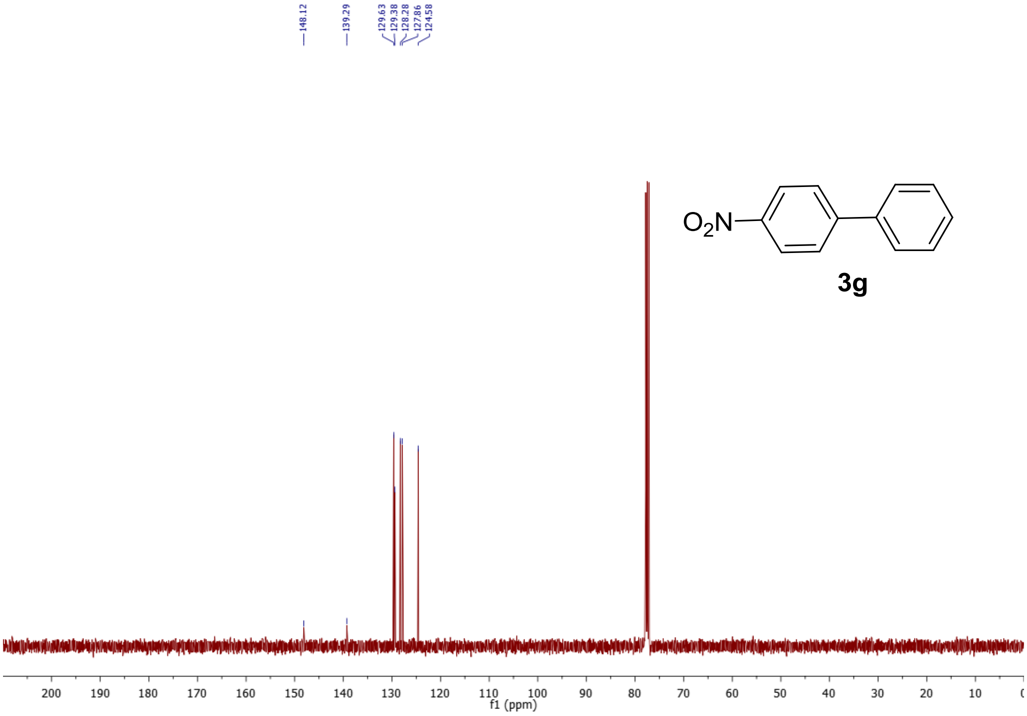


**Figure A14** $^{13}$C NMR spectrum of **3g** ($CDCl_3$)

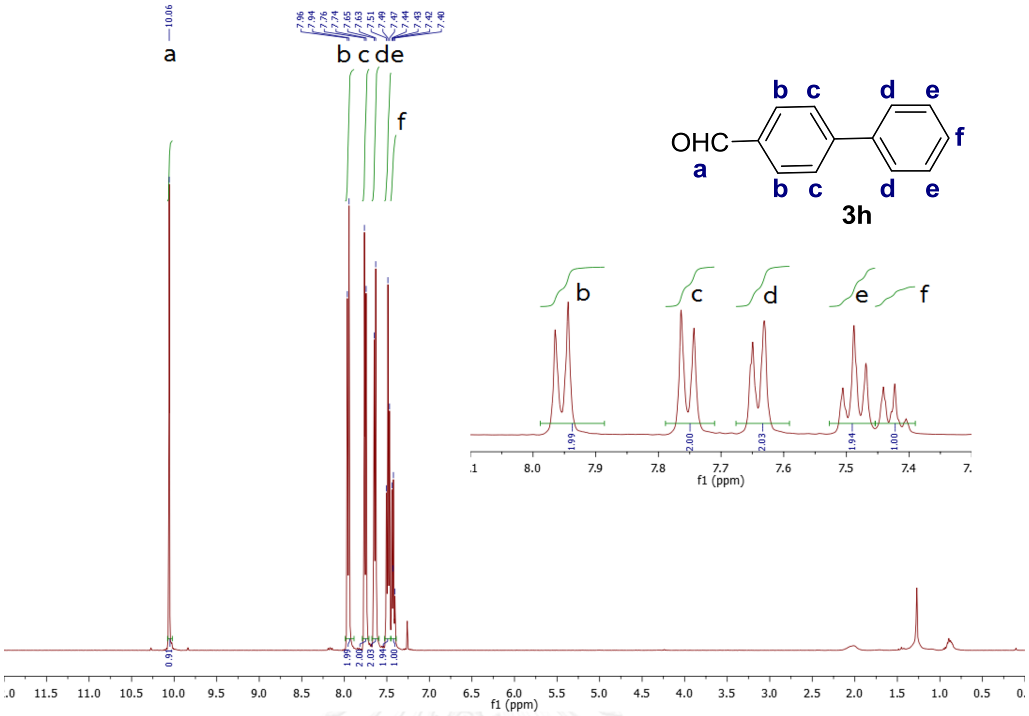


Figure A15 $^{1}$H NMR spectrum of **3h** ($CDCl_3$)

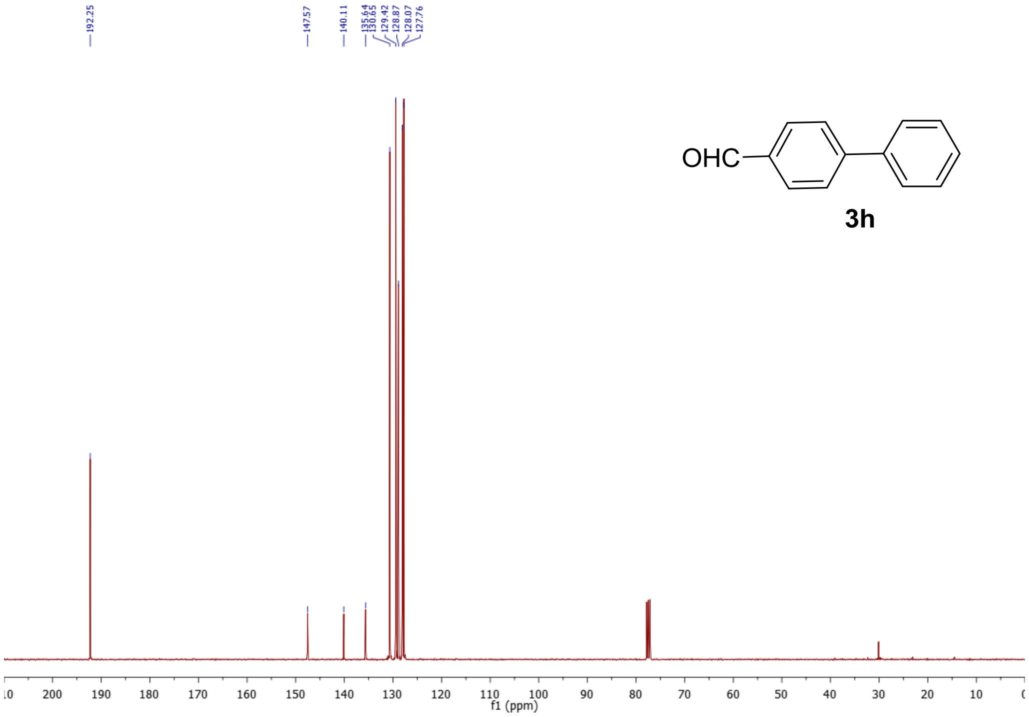


Figure A16 $^{13}$C NMR spectrum of **3h** ($CDCl_3$)

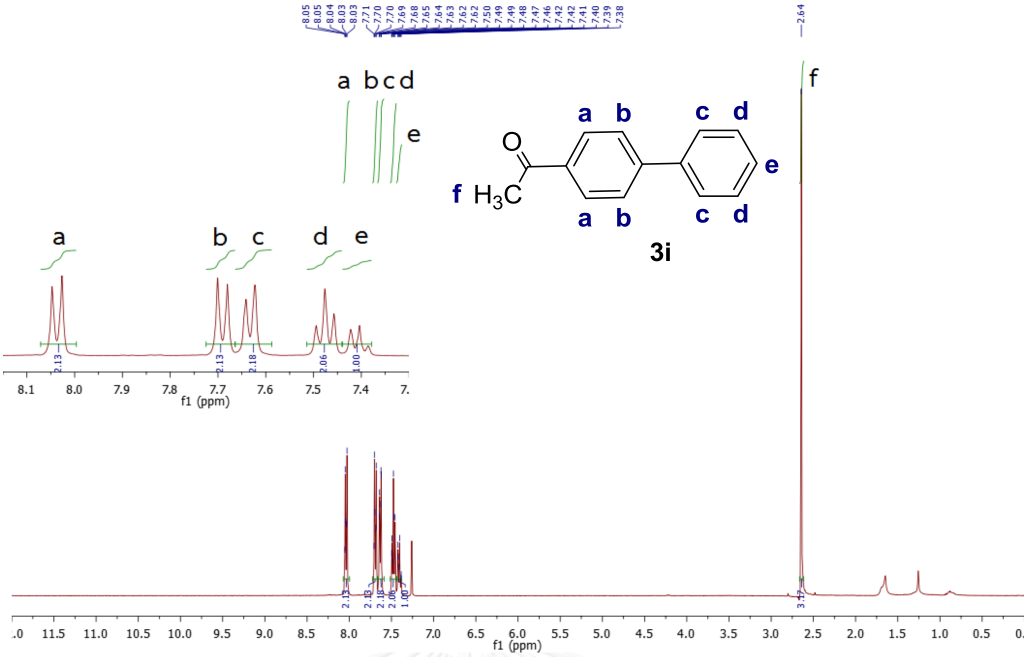


Figure A17 $^{1}$H NMR spectrum of **3i** ($CDCl_3$)

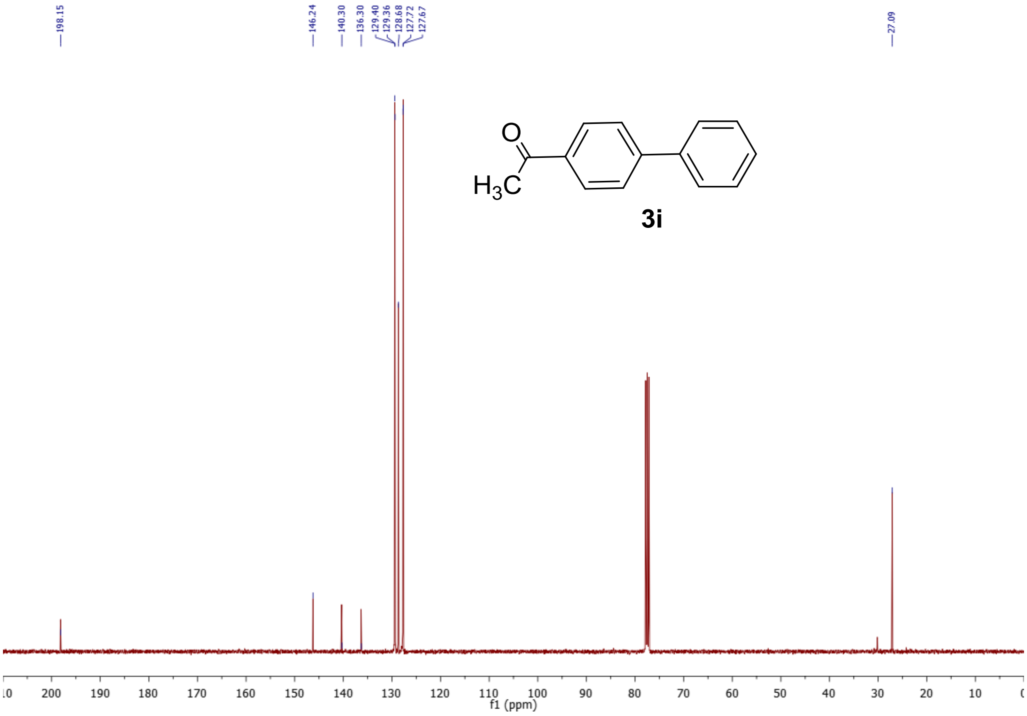


Figure A18 $^{13}$C NMR spectrum of **3i** ($CDCl_3$)

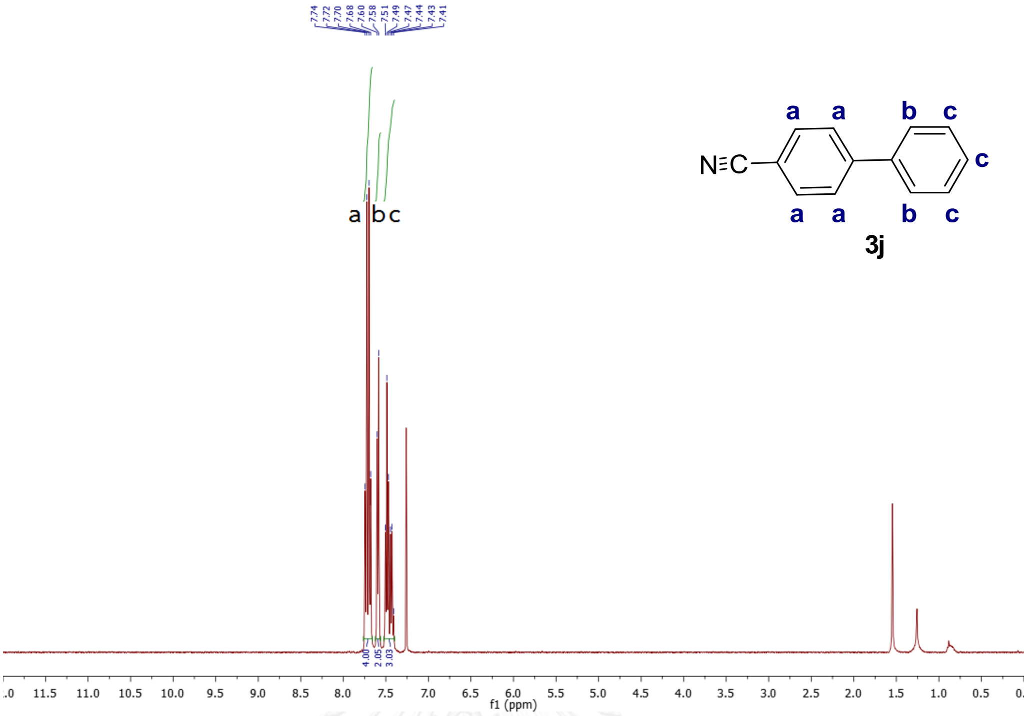


Figure A19 $^1$H NMR spectrum of **3j** ($CDCl_3$)

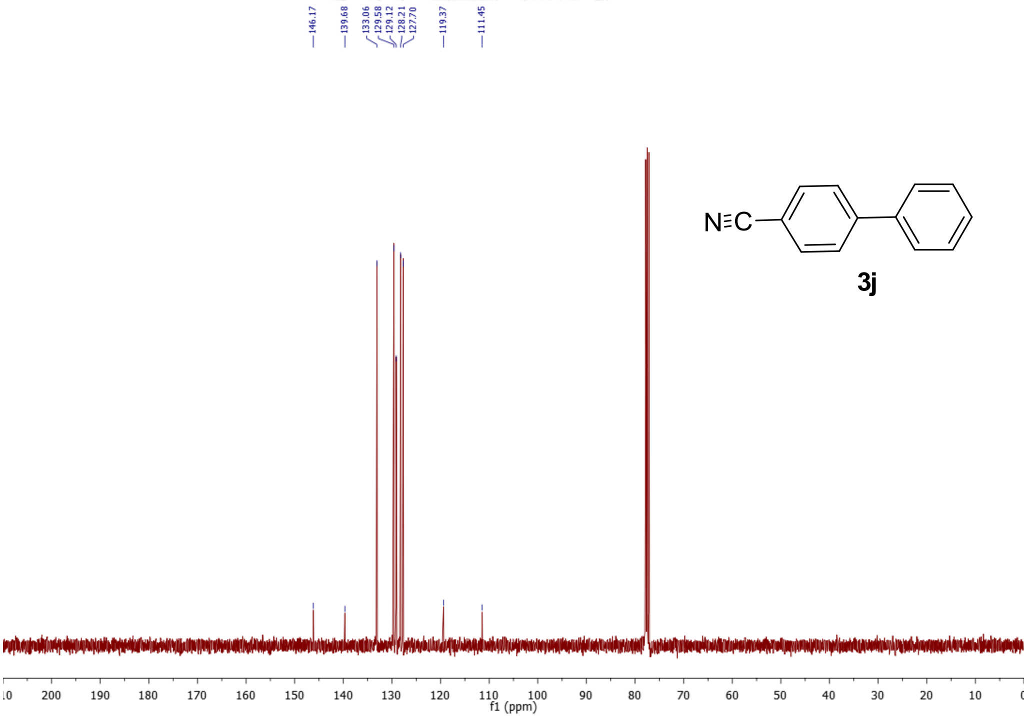


Figure A20 $^{13}$C NMR spectrum of **3j** ($CDCl_3$)

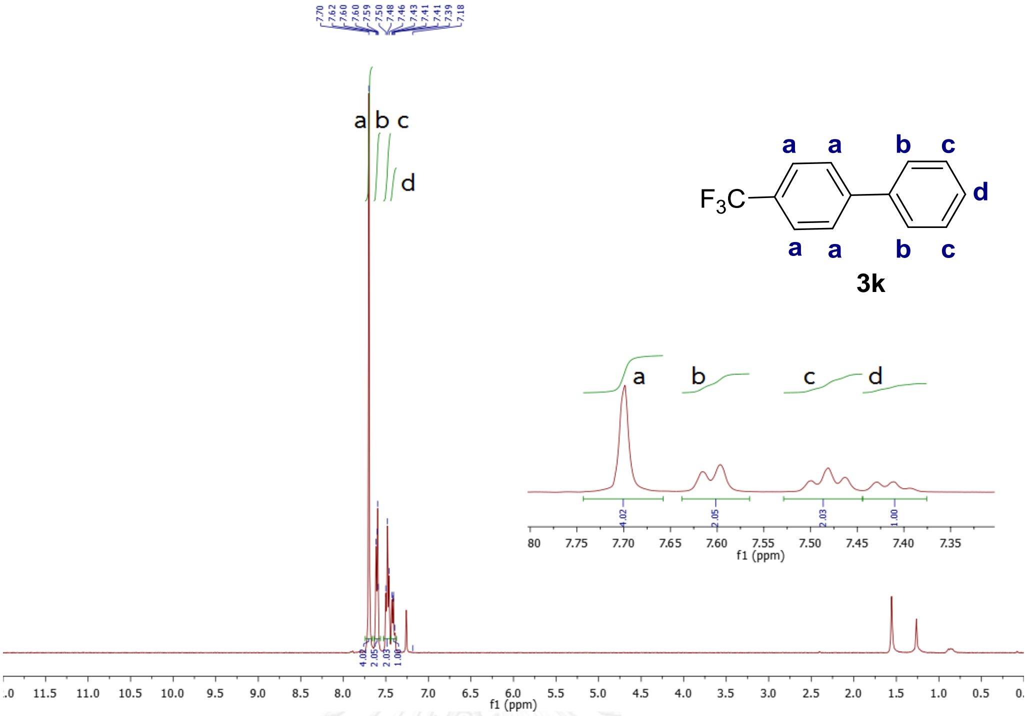


Figure A21 $^{1}$H NMR spectrum of **3k** (CDCl$_3$)

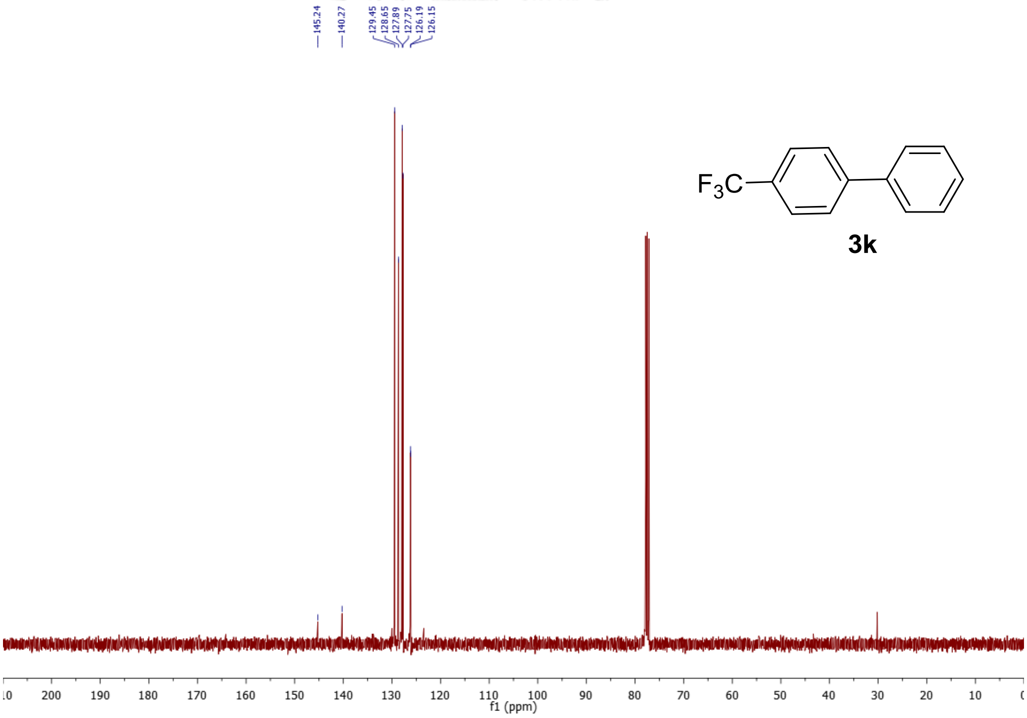


Figure A22 $^{13}$C NMR spectrum of **3k** (CDCl$_3$)

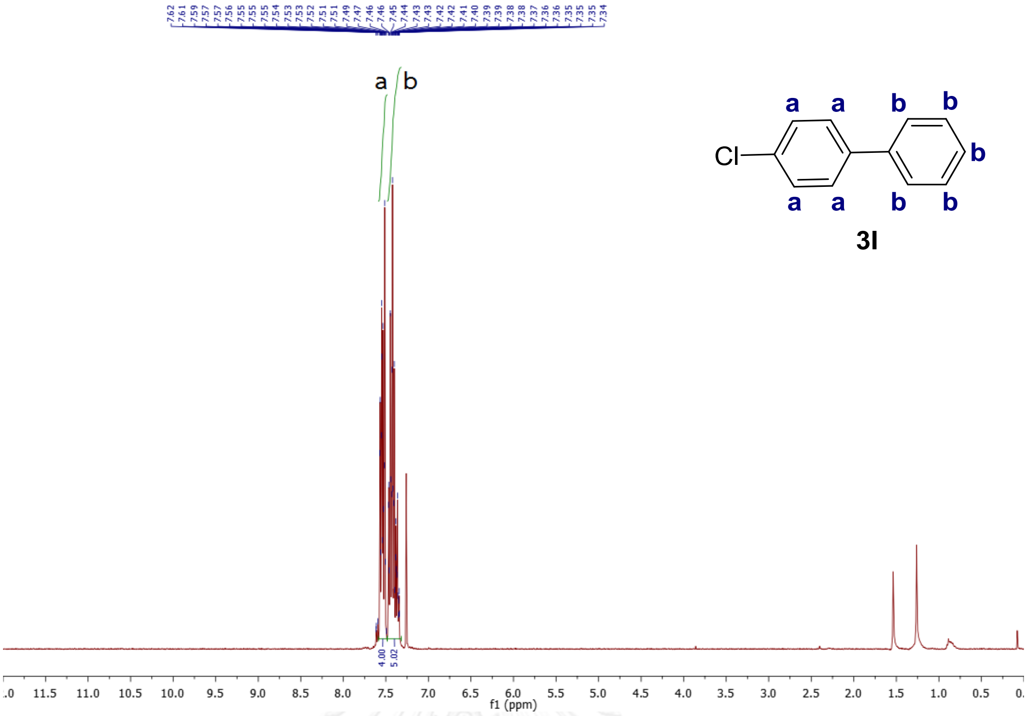


**Figure A23** $^1$H NMR spectrum of **3l** ($CDCl_3$)

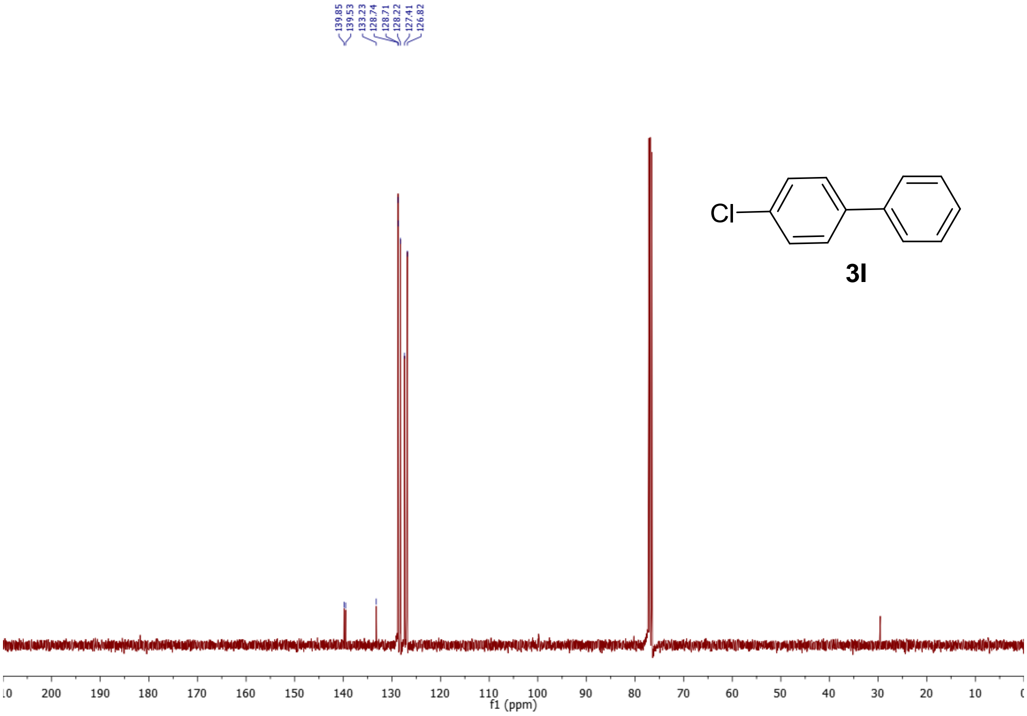


**Figure A24** $^{13}$C NMR spectrum of **3l** ($CDCl_3$)

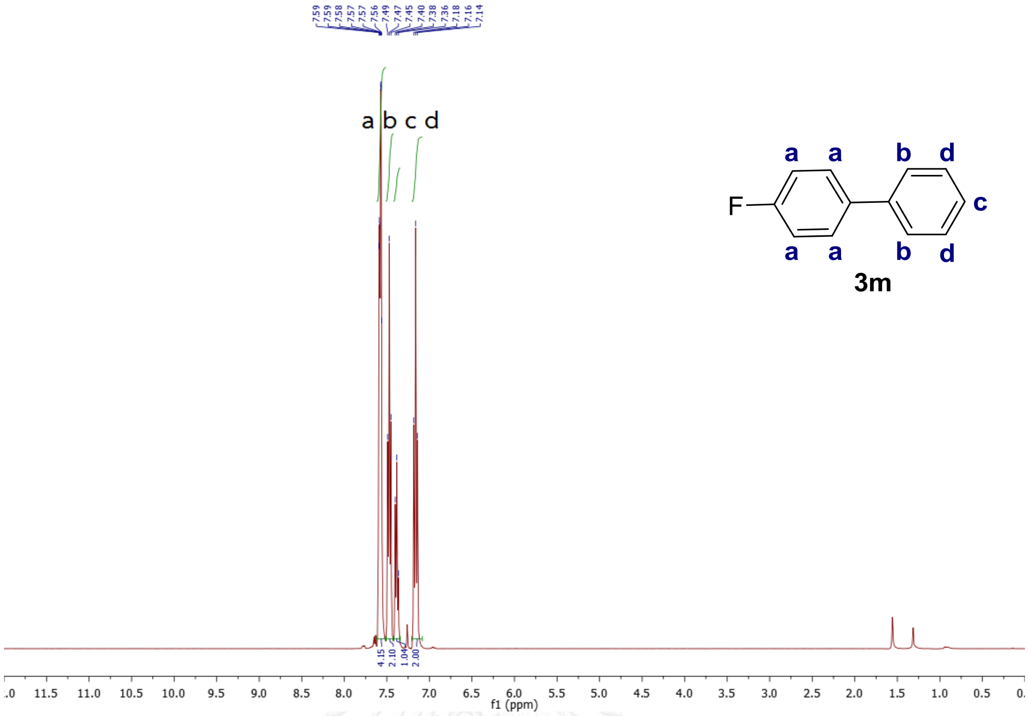


Figure A25 $^{1}$H NMR spectrum of **3m** ($CDCl_3$)

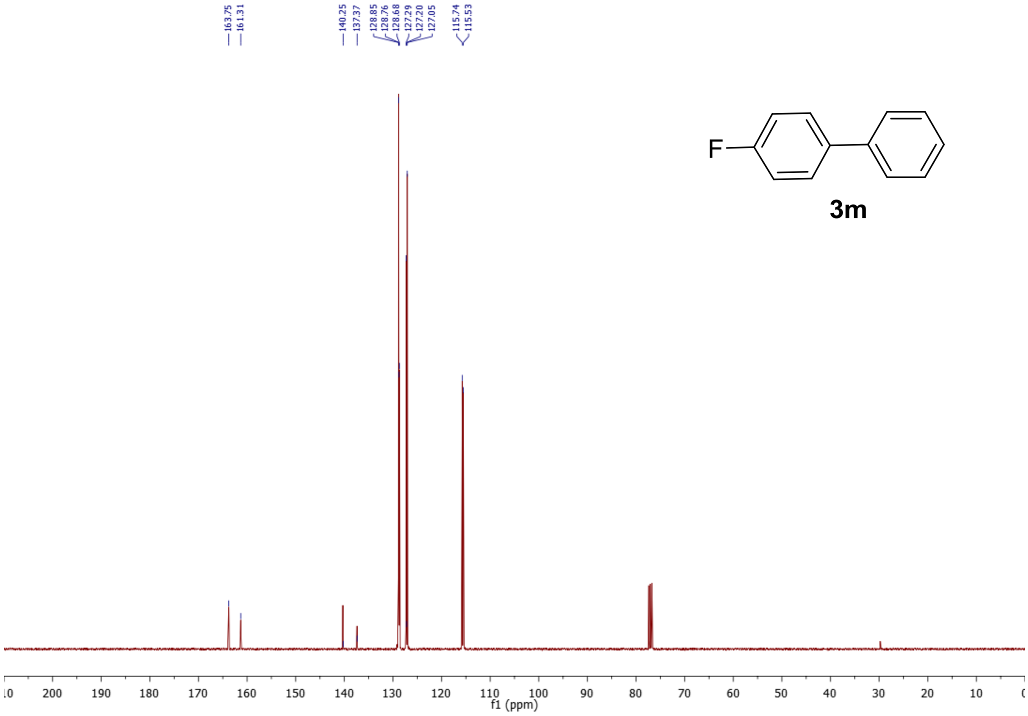


Figure A26 $^{13}$C NMR spectrum of **3m** ($CDCl_3$)

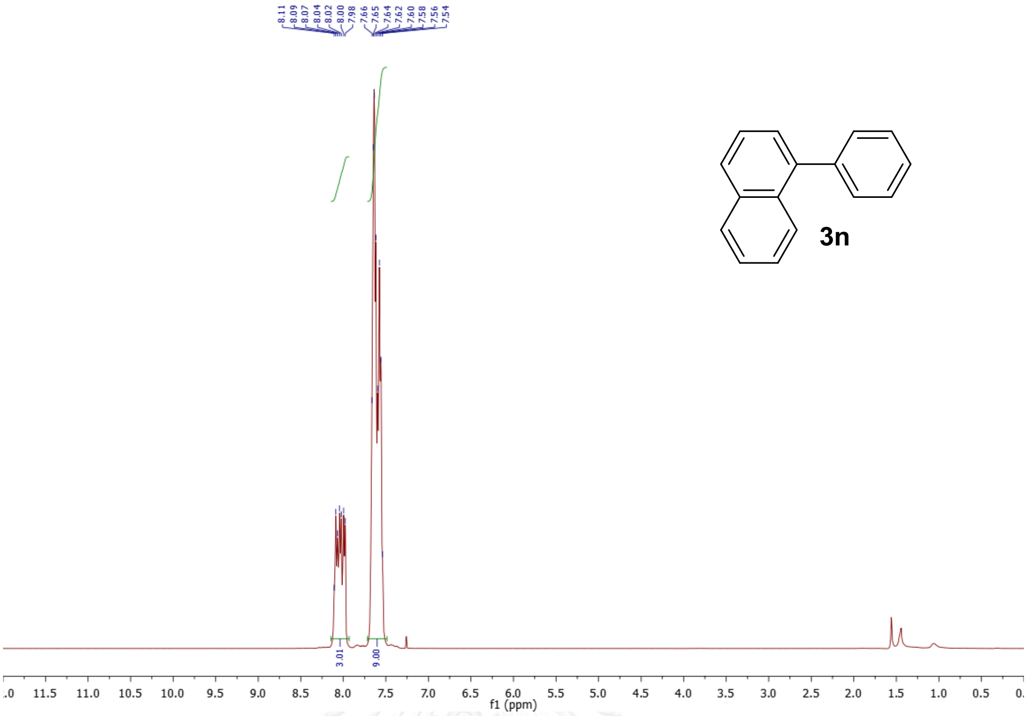


**Figure A27** $^1$H NMR spectrum of **3n** ($CDCl_3$)

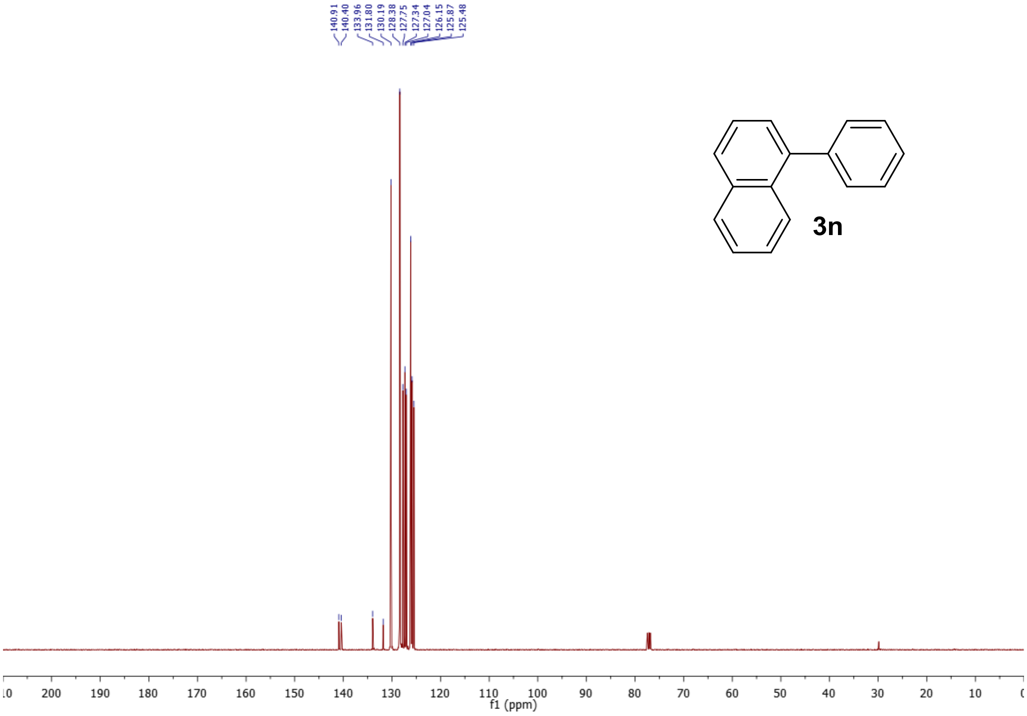


**Figure A28** $^{13}$C NMR spectrum of **3n** ($CDCl_3$)

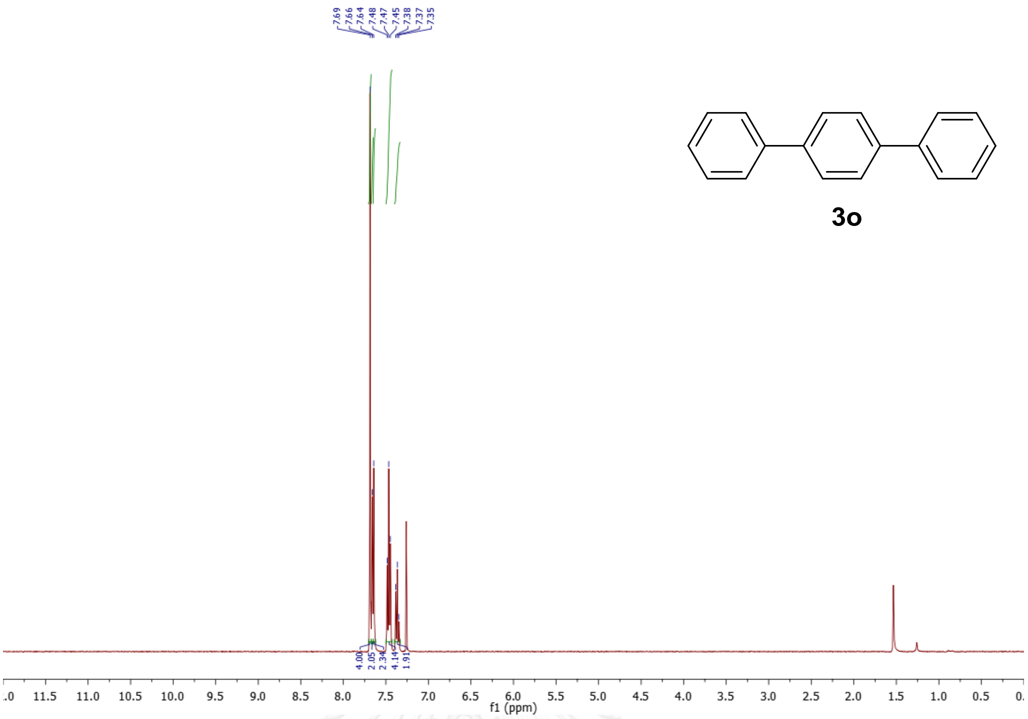


Figure A29 $^{1}$H NMR spectrum of **3o** ($CDCl_3$)

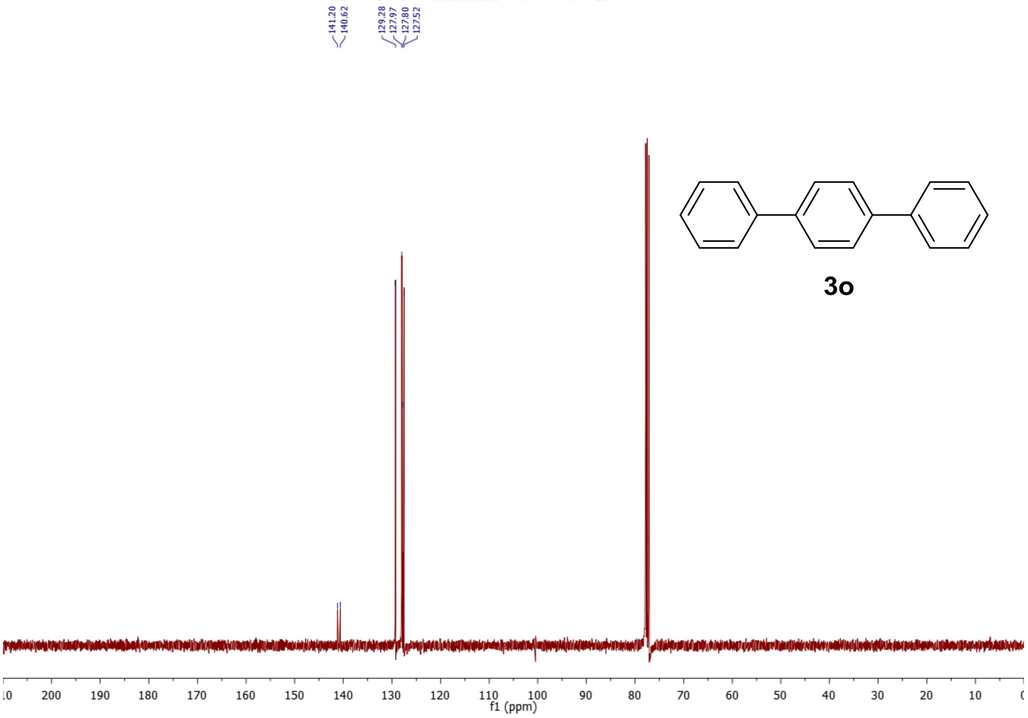


Figure A30 $^{13}$C NMR spectrum of **3o** ($CDCl_3$)

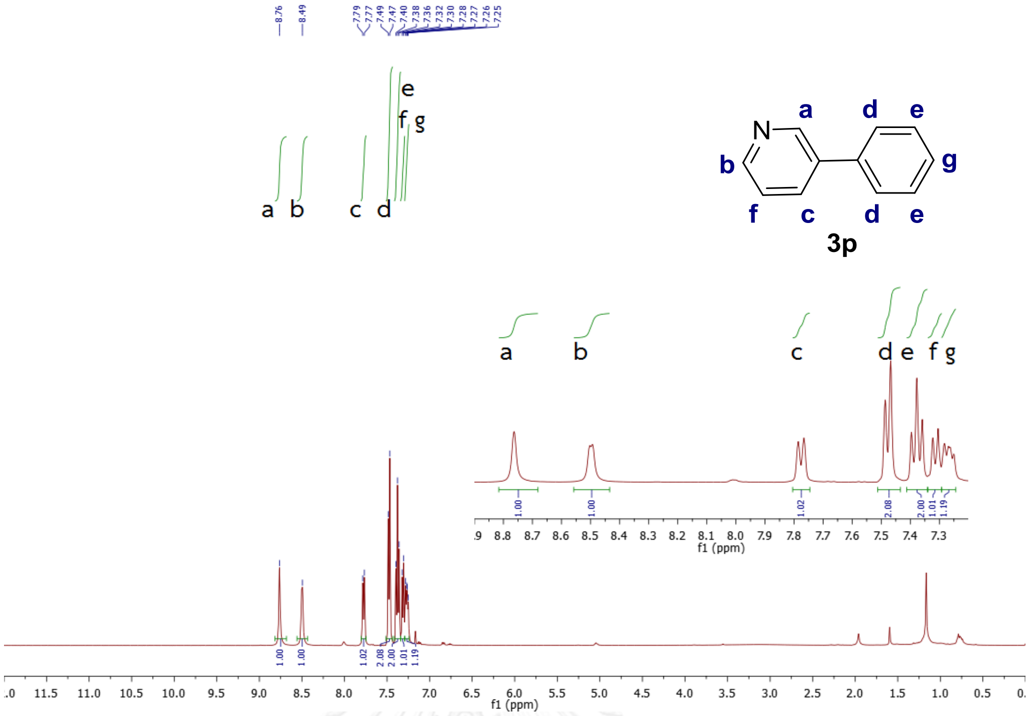


Figure A31 $^{1}$H NMR spectrum of **3p** ($CDCl_3$)

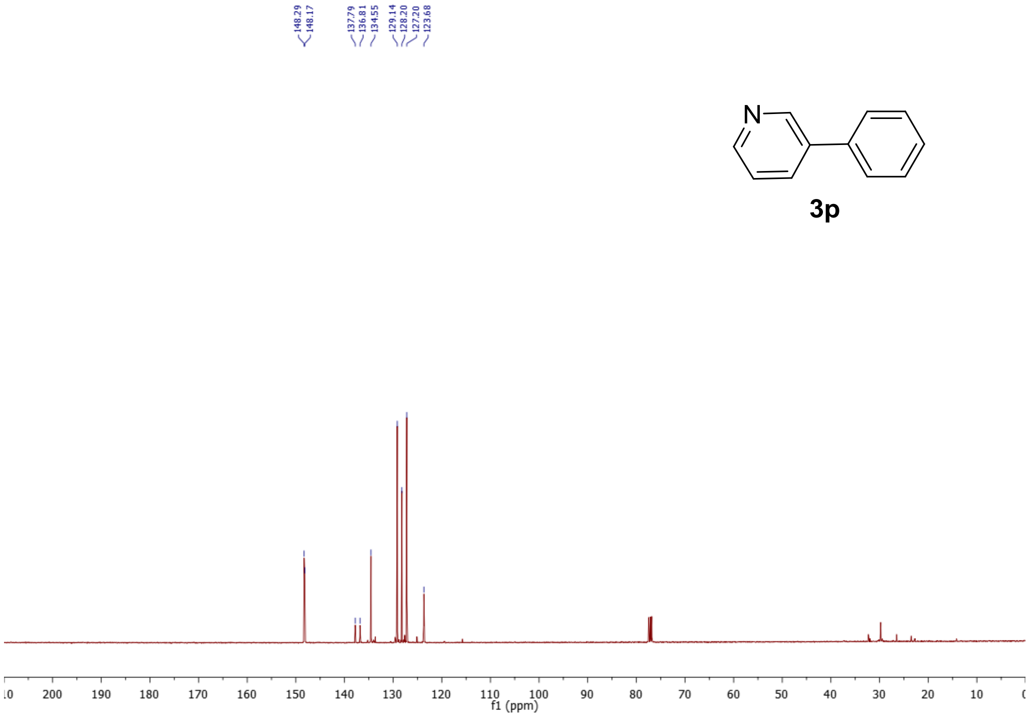


Figure A32 $^{13}$C NMR spectrum of **3p** ($CDCl_3$)

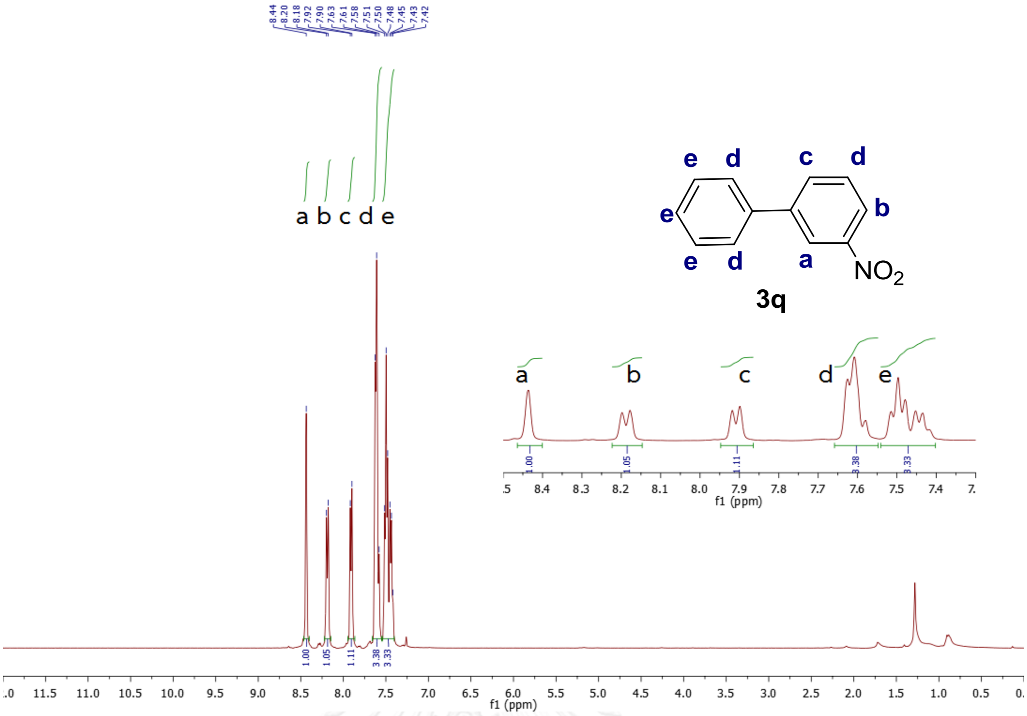


Figure A33 $^{1}$H NMR spectrum of **3q** ($CDCl_3$)

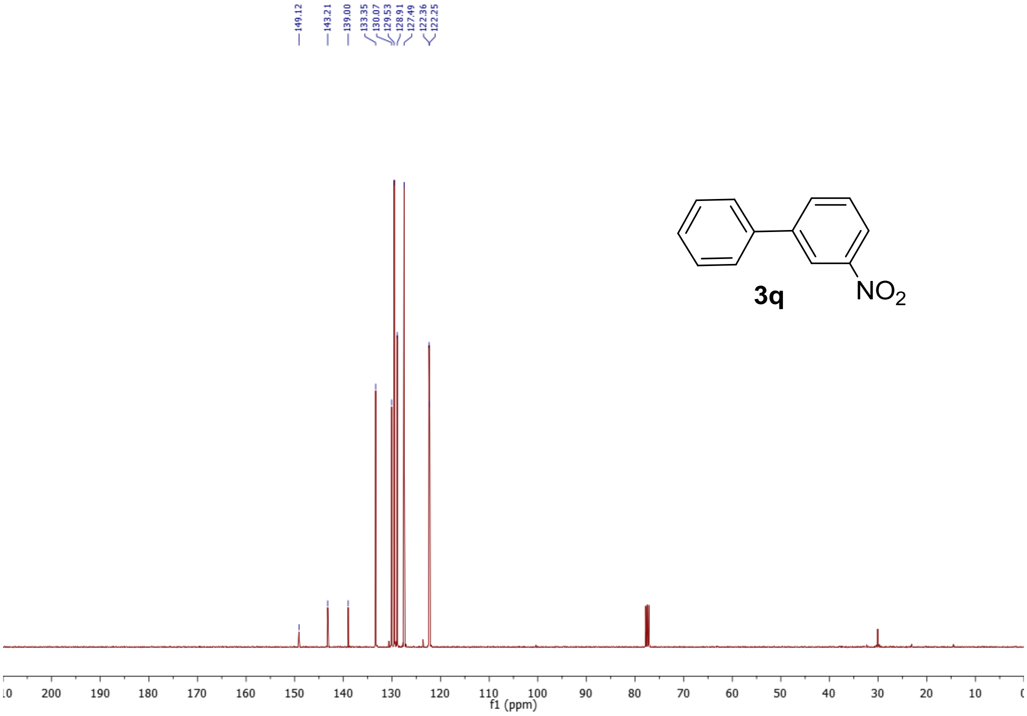


Figure A34 $^{13}$C NMR spectrum of **3q** ($CDCl_3$)

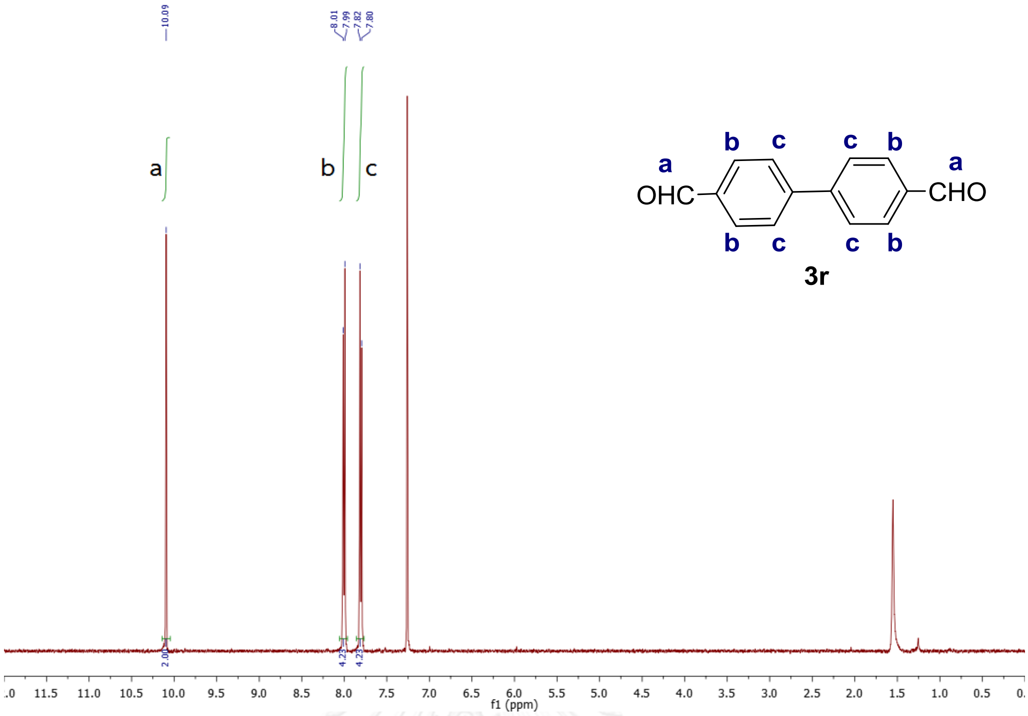


Figure A35 $^1$H NMR spectrum of **3r** ($CDCl_3$)

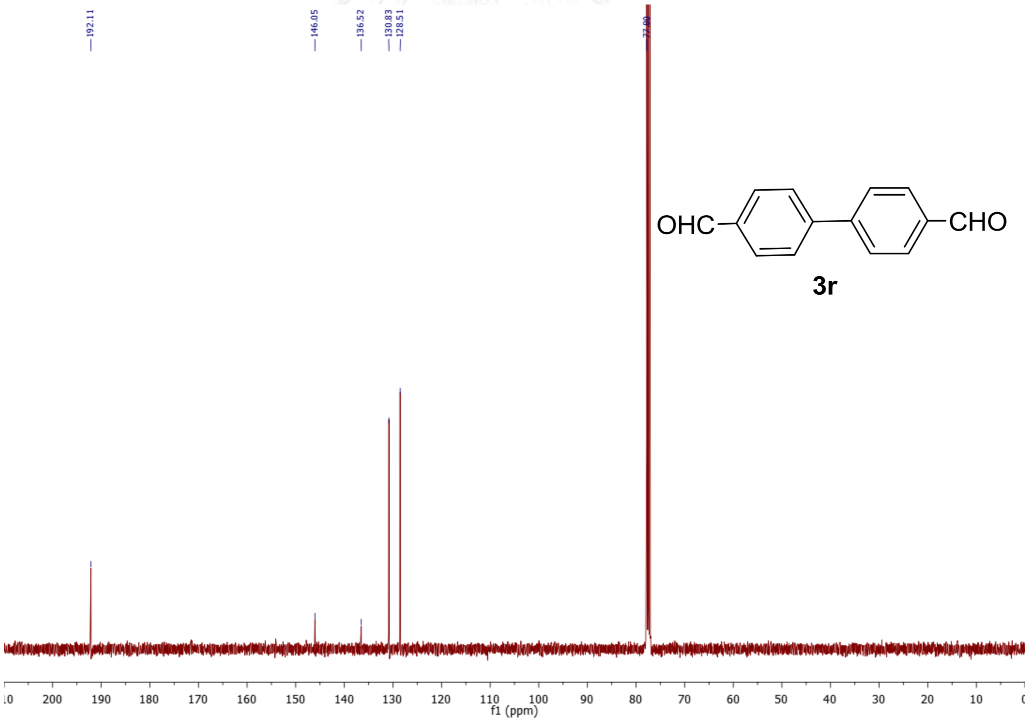


Figure A36 $^{13}$C NMR spectrum of **3r** ($CDCl_3$)

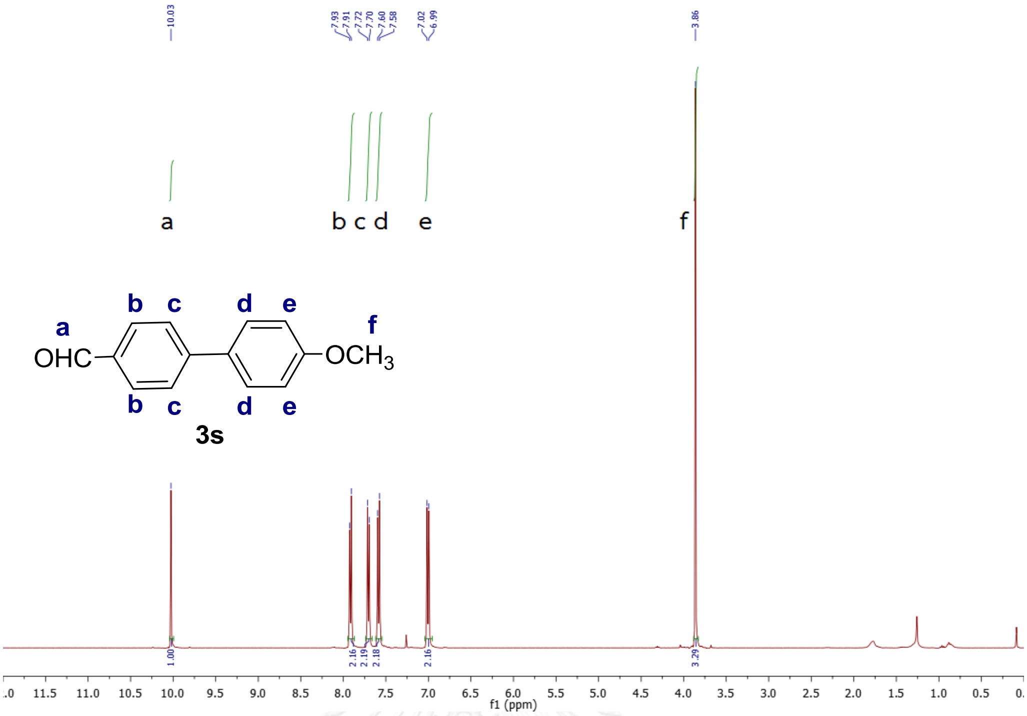


Figure A37 $^{1}$H NMR spectrum of **3s** ($CDCl_3$)

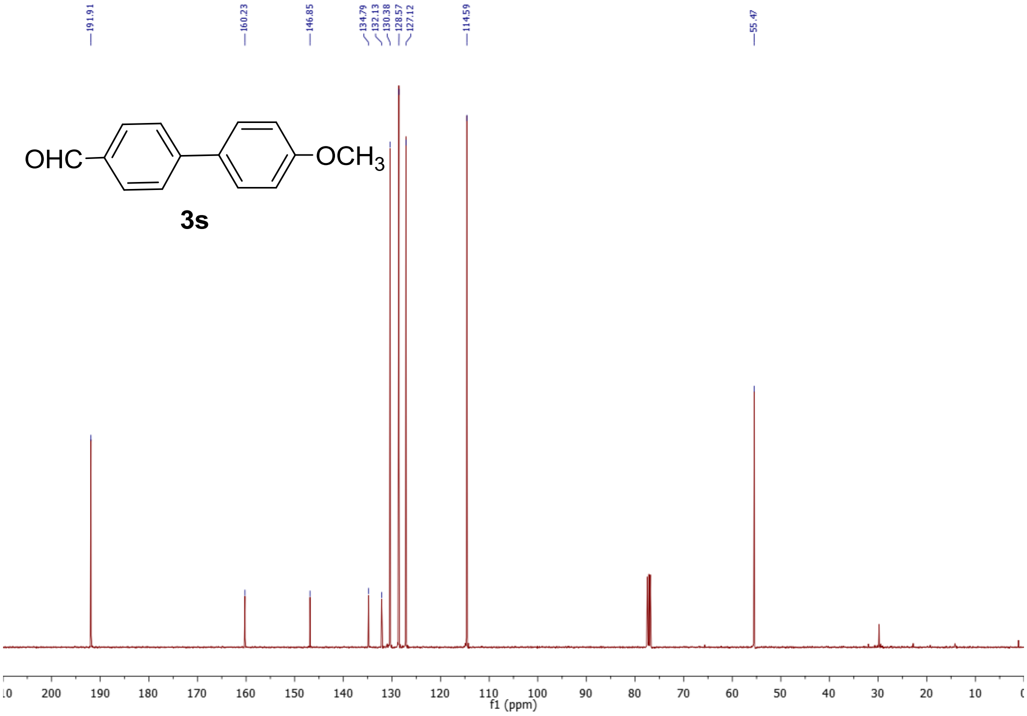


Figure A38 $^{13}$C NMR spectrum of **3s** ($CDCl_3$)

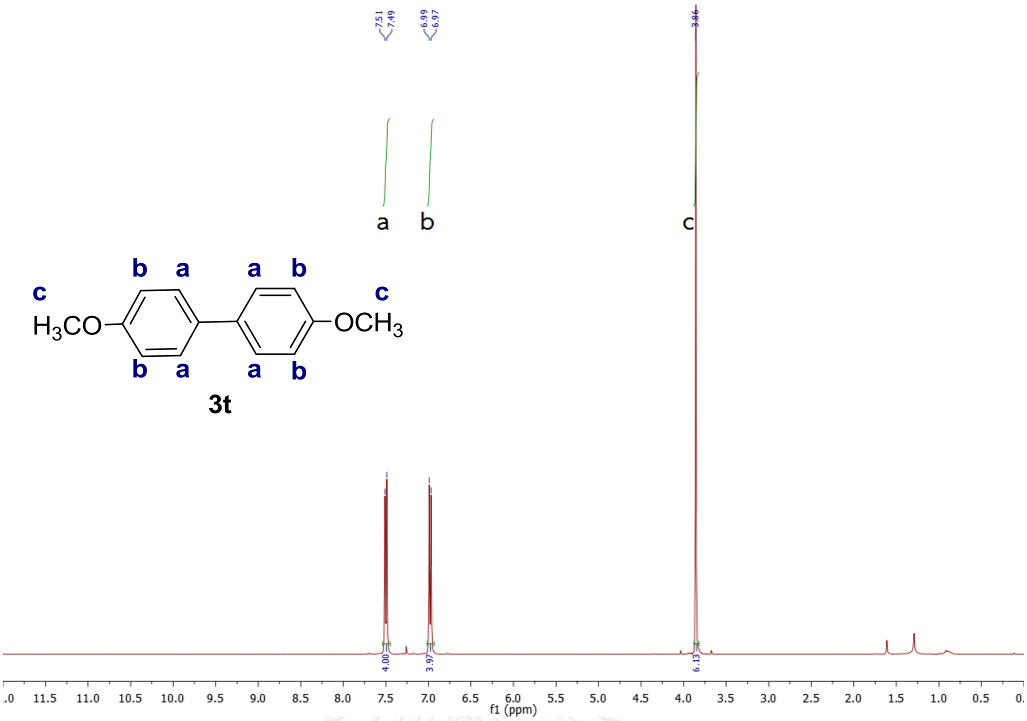


**Figure A39** $^{1}$H NMR spectrum of **3t** ($CDCl_3$)

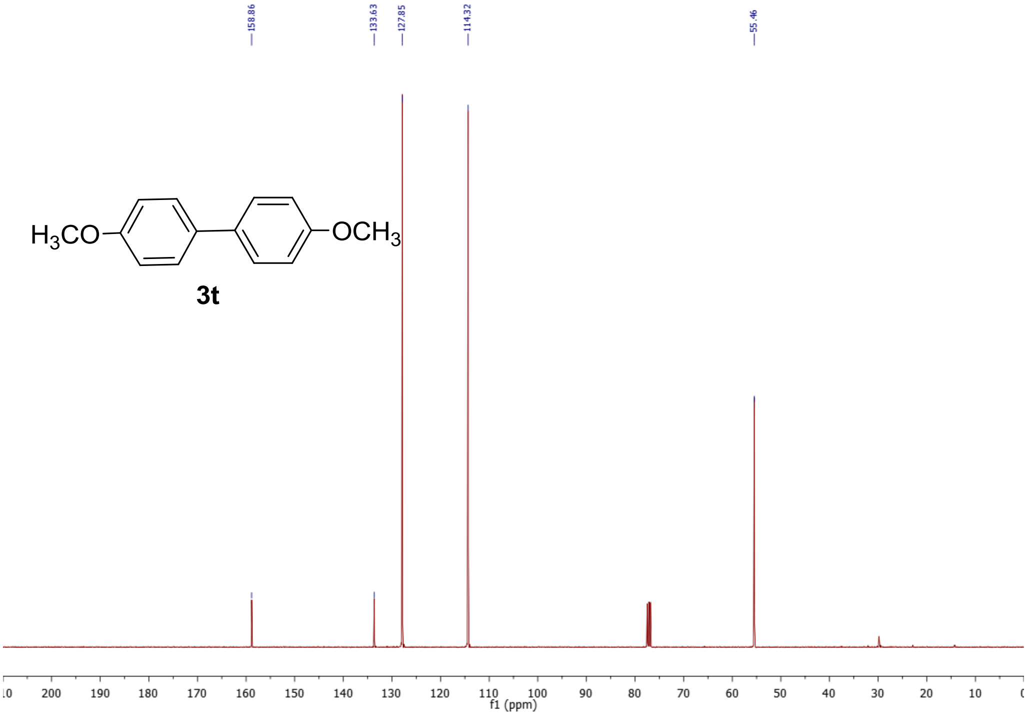


**Figure A40** $^{13}$C NMR spectrum of **3t** ($CDCl_3$)

# VITA

Miss Sukumaporn Chotnitikornkun was born on May 15, 1992 in Phetchaburi, Thailand. She achieved a Bachelor’s Degree of Science in Chemistry from Chulalongkorn University in 2014. Then, she began a Master’s Degree in Chemistry program at Chulalongkorn University. She had presented her research on “Heterogeneous Suzuki cross-coupling reaction in water catalyzed by palladium nanoparticles supported on individual calcium carbonate plates derived from mussel shell particle” in The 5th Thailand International Nanotechnology Conference (NanoThailand 2016) by oral presentation.

Her address is 73/25, Village No.3 Phetchaburi-banlam Road, Bankum Sub-district, Muang District, Phetchaburi, 76000, Thailand, Tel. 089-8993418.