공학석사학위논문

Preparation of Pd-NHC Catalyst Immobilized on γ-Alumina for Suzuki-Miyaura Cross-Coupling Reaction

감마-알루미나에 고정시킨 팔라듐-질소헤테로고리카벤 촉매를 이용한 스즈키-미야우라 짝지음 반응에 대한 연구

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서울대학교 대학원

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화학생물공학부
강 민 기

강민기의 공학석사학위논문을 인준함
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위 원 장 김 영 규 (인)

부위원장 이 윤 식 (인)

위 원 송 인 규 (인)

ABSTRACT

Preparation of Pd-NHC Catalyst Immobilized on γ-Alumina for Suzuki-Miyaura Cross-Coupling Reaction

Min-Ki Kang
School of Chemical and Biological Engineering
The Graduate School
Seoul National University

γ-Alumina (γ-aluminium oxide) supported palladium(II)-*N*-heterocyclic carbene (Pd-NHC) complex is one of the effective Suzuki-Miyaura cross-coupling catalysts in water dominant environment. NHCs are stable ligands in aqueous conditions, and they have been used for spectator ligands of Suzuki-Miyaura cross-coupling catalyst. γ-Alumina is one of the suitable solid supports due to its hydrophilicity and large surface area but has not been fully studied for Suzuki-Miyaura reaction. In this research, two kinds of 1-substituted imidazoles were synthesized as precursors of NHCs, and Pd-NHC complexes were prepared by using $Pd(OAc)_2$ and these precursors. Finally, the catalysts were prepared by immobilizing the Pd-NHC complexes on γ-alumina. The catalysts were characterized by X-ray photoelectron spectroscopy (XPS), scanning electron mictrscope (SEM), and inductively coupled plasma atomic emission spectroscopy (ICP-AES). The catalytic activity was investigated under various solvents and basic conditions via conventional heating or microwave heating methods. As a result, up to 99% yields were obtained from the reactions of aryl bromides with phenylboronic acid at 50°C for 2 h.

Keywords: ɣ-Alumina, Palladium, Heterogeneous Catalyst, Suzuki-Miyaura Reaction, Aqueous Environment

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LIST OF ABBREVIATIONS

DMF	*N,N'*-Dimethylformaldehyde
DMSO	Dimethylsulfoxide
EDS	Electron Dispersive Spectroscopy
ESCA	Electron Spectroscopy for Chemical Analysis
Et_3N	Triethylamine
FE-SEM	Field Emission Scanning Electron Microscopy
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectroscopy
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectroscopy
MC	Methylene Chloride
MeCN	Acetonitrile
MeOH	Methanol
NHC	*N*-Heterocyclic Carbene
NMR	Neclear Magnetic Resonance
Pd-NHC	Palladium *N*-Heterocyclic Carbene
$Pd(OAc)_2$	Palladium(II) Acetate
RBF	Round Bottom Flask
THF	Tetrahydrofuran
XPS	X-ray Photoelectron Spectroscopy

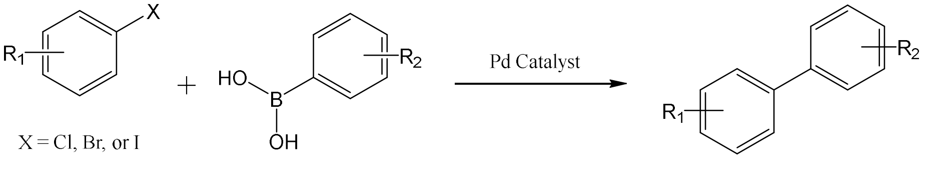
Preparation and Characterization of Pd-NHC Complex Immobilized on γ-Alumina for Heterogeneous Suzuki-Miyaura Cross-Coupling Catalyst

I. Introduction

I. 1. Suzuki-Miyaura Reaction in Water

The Suzuki-Miyaura reaction is palladium catalyzed cross-coupling reactions that forms carbon-carbon single bond under mild conditions (Scheme 1). Its biaryl products are used for preparing fine chemicals, medicine, polymers, and so on.[1]

Recently, as a part of green processess, various studies were performed using water as a solvent in Suzuki-Miyaura reaction.[2-6] Since one of the reaction's substrate is a phenylboronic acid its derivatives, which are quite soluble in water, the reaction can be proceeded in aqueous media if the catalyst is compatible with water. But there are some issues to be solved in Suzuki-Miyaura reaction in aqueous solution. First, the reaction should be proceeded under mild condition with aryl bromides and chlorides. Seconds, the amount of Pd metal should be low. To overcome these issues, a highly stable and active catalyst should be prepared.[1,7]



Scheme 1. Suzuki-Miyaura reaction.

I. 2. Pd-NHC Complex in Suzuki-Miyaura Reaction

Stable ligand-palladium complex such as Pd-NHC that is not easily decomposed by water is highly desirable in Suzuki-Miyaura reaction. Since Pd-NHC complex was first introduced by Herrmann et al.,[8] it has been used for various cross-coupling reactions such as Heck,[9,10] Sonogashira,[11,12] Suzuki,[13,14] Negishi,[15,16] and Stille[17,18] reactions due to its great catalytic activity and stability. Its superior property comes from the electron donating characteristics of NHC ligand that increase the electron density of central palladium.[19] Although NHC is very basic in aqueous media because of its electron donating property,[1,20] it is stable as Pd-NHC complex because of the formation of strong bond between the metal and NHC than proton and NHC.[21] These features make NHC a good spectator ligand even in water.

In Suzuki-Miyaura reaction, NHC in Pd-NHC complex promotes the catalytic cycle of the reaction that consists of three steps; oxidative addition, transmetalation and reductive elimination.[22,23] The electron richness of NHC lowers the energy barrier of the oxidative addition, which is the rate determining step, and facilitates the overall reaction.[19] The bulkiness of *N*-substituents not only helps the reductive elimination via repulsive force between bulky groups but also stablize the transition state of the oxidative addition intermediate.[24]

I. 3. Heterogenous Pd-NHC Suzuki-Miyaura Catalyst

Many attempts have been tried to develope greener chemistry by converting homogeneous catalytic systems into heterogeneous catalytic systems.[25-28] In spite of outstanding catalytic performance and stability, homogeneous Pd-NHC catalyst contains palladium heavy metals that can cause environmental problems when they are released. Difficulties in the recovery of the used catalysts led to the development of heterogeneous catalysts.[28] However, heterogeneous catalysts usually suffer from poor performance because the support for heterogeneous catalysts limits the accessibility of the active sites during the coupling reaction.[1] The limitation reduces efficient collision between the substrate molecules and the metal active sites, and lowers the activity of the catalys. Therefore, it is necessary to develop a highly effective heterogeneous catalyst.

I. 4. γ-Alumina as a Catalyst Support

In order to improve the activity of heterogeneous catalyst, it is important to select an appropriate support which can afford high activity, stability and accessibility of the active sites. From this point of view, γ-alumium oxide can be a good candidate as a support for the following reasons. It has highly mesoporous structure which can give a large surface area (around 200 m^2/g),[29,30] surface hydroxyl groups to immobilize the Pd-NHC complexes,[29,31] and hydrophilic surface[31] which enhances the accessibility of active sites in water environment. Its surface is hydrolyzed to bayerite over time in water, but it takes from few days to few months, which can be considered not so critical.[32] Thus, γ-alumina is rather stable in aqueos environment. In spite of these strong points as a catalytic support, γ-alumina has not drawn so much attention except in some cases.[33,34]

I. 5. Microwave-Assisted Suzuki-Miyaura Reaction

For acceleration of Suzuki-Miyaura reaction, the initial induction time should be reduced. The induction time mainly includes the activation time of Pd(II) to Pd(0) and the time interval in reaching the steady state temperature to develop full activity of the catalyst.[16,35] In a lab scale oil bath heating, significant temperature gradient occurs due to heat diffusion between outer and inner part of the reaction vessel before attaining the steady state.[36,37] This causes an initial induction time and reduces the reaction rate. On the other hand, microwave reactor does not rely on heat diffusion but uses irradiation of electromagnetic wave for heating. Microwave simultaneously heats the entire reaction vessel via friction energy of rotating molecules caused by oscillating field.[36,37] Through this heating method, the temperature of reaction mixture can be rapidly raised and the induction time can be decreased.

I. 6. Research Objectives

γ-Alumina supported Pd-NHC complex was prepared, characterized, and tested as a catalyst for Suzuki-Miyaura reaction in water/DMF solution. The catalytic activity is expected to be high in aqueous solution due to the hydrophilicity of γ-alumina and high stability of Pd-NHC complex. Low palladium leaching and good reusability is also expected from the stability of Pd-NHC complex in aqueous environment.

II. Experimental Section

II. 1. General

II. 1. 1. Materials

Unless otherwise noted, all of the reagents and solvents were bought from commercial suppliers and used without further purification.

II. 1. 2. Instruments

The structure of silylating agents, 1-substituted imidazoles, and NHC precursors were confirmed by ^{1}H NMR (Bruker Avance-400). The morphology of γ-alumina and γ-alumina supported catalysts were characterized by field emission scanning electron microscopy (FE-SEM, Jeol Inc. JSM-7800F Prime). The elemental composition of the catalysts were roughly identified by energy-dispersive X-ray spectroscopy (EDS, Jeol Inc. JSM-7800F Prime) and Pd loading level was measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES, SHIMADZU, ICPS-8100). Binding energies of palladium species were investigated by electron spectroscopy for chemical analysis (ESCA, ThermoVG SIGMA PROBE). Most of the Suzuki reactions were performed in 10 mL glass vials with magnetic stirring, or microwave heating with CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). Product yields were measured and calculated by gas chromatography/mass spectroscopy (GC-MS, Agilent Technologies) based on limiting reactants.

II. 2. Preparation of γ-Alumina Supported Pd-NHC

II. 2. 1. Synthesis of 1-Substituted Imidazoles

2,4,6-Trimethylaniline (14.0 mL, 100 mmol) and 40% glyoxal solution (11.5 mL, 100 mmol) were added to MeOH (200 mL) in a 500 mL 3-neck RBF and stirred at room temperature for 20 h. After the reaction, bright yellow solid appeared. Formaldehyde (35 %, 17 mL, 210 mmol) and ammonium chloride (10.7 g, 200 mmol) were added to the reaction mixture. The mixture was heated in an oil bath at 70 °C in N_2 atmosphere for 1 h. Phosphoric acid (85 %, 14.4 mL, 210 mmol) was added to the reaction mixture via a dropping funnel (1 drop per second) and reacted further at 70 °C for 5 h in N_2 atmosphere. When the color turned dark, the solvent of the mixture was evaporated by rotary evaporator at 50 °C. After cooling to room temperature, the mixture was poured into 1L beaker in an icebath. 2M KOH aqueous solution (about 250 mL) was dropped into the mixture and stirred until the pH became 9. The mixture turned brown-black and lumpy.

To separate the desired product, the reaction mixture in 1L beaker was poured into 500 mL separatory funnel and extracted with ether (150 mL, 3 times). The collected organic layer (reddish brown) was washed with brine (150 mL) and deionized water (150 mL), and dried by magnesium sulfate. After drying, the solvent was evaporated through rotary evaporator. The remaining liquid was purified by silica column chromatography using hexane/ethyl acetate (1:1, v/v) as an eluent. The obtained product, 1-(2,4,6-trimethylphenyl)-1*H*-imidazole (bright ivory color), was dried under reduced pressure at room temperature.

1-(2,6-Diisopropylphenyl)-1*H*-imidazole was also prepared using 2,6-diisoproylaniline instead of using 2,4,6-trimethylaniline by the same procedure as above. Whole procedure of preparing 1-substituted imidazole was followed by the method of Liu et al.[38] The structures of products were confirmed by ^{1}H NMR using DMSO-d_6 as a solvent.

1-(2,4,6-Trimethylphenyl)-1*H*-imidazole. ^{1}H NMR (400 MHz, DMSO-d_6, TMS) : δ (ppm) = 7.6 (s, 1H), 7.2 (s, 1H), 7.1 (s, 1H), 7.0 (s, 2H), 2.3 (s, 1H), 1.9 (s, 1H) (see the appendix).

1-(2,6-Diisopropylphenyl)-1*H*-imidazole. ^{1}H NMR (400 MHz, DMSO-d_6, TMS) : δ (ppm) = 7.7 (s, 1H), 7.5 (t, 1H), 7.3 (d, 2H), 7.3 (d, 1H), 7.1 (d, 1H), 2.2 (quin, 2H), 1.1 (d, 12H) (see the appendix).

II. 2. 2. Preparation of 3-(Iodopropyl)triethoxysilane

3-(Iodopropyl)triethoxysilane was prepared by the same procedure of Melo et al.[39] Sodium iodide (14.0 g, 93.5 mmol) was dissolved in dry acetone (200 mL) in a 3-neck RBF (500 mL) at 70 °C under N_2 atmosphere. (3-Chloropropyl)triethoxysilane (15 mL, 62.4 mmol) was dropped into the solution via dropping funnel for 1 h. Then, the reaction mixture was stirred at 70 °C for 6 days. All the reagents were added during N_2 purging and all the apparatus were sealed by Teflon tape to exclude from moisture. Some salts were precipitated during the reaction. After the reaction, solvent was evaporated via rotary evaporator at 50 °C. The remaining solid mixture was filtered, dissolved in ether (100 mL), and evaporated. This procedure was repeated until salt precipitation did not occur. The yellow liquid product, 3-(iodopropyl)triethoxysilane, was dried under reduced pressure at room temperature, and the structure was confirmed by ^1H NMR using DMSO-d_6 as solvent.

^1H NMR (400 MHz, DMSO-d_6, TMS) : δ (ppm) = 3.75 (q, 6H), 3.3 (t, 2H), 1.8 (m, 2H), 1.1 (t, 9H), 0.7 (t, 2H) (see the appendix).

II. 2. 3. Preparation of NHC Precursors

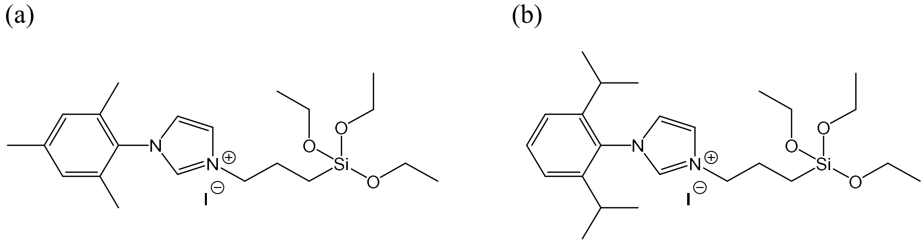
1-(2,4,6-Triemethylphenyl)-1*H*-imidazole (1 g, 5.37 mmol) was dissolved in dry MeCN (100 mL) in a 3-neck RBF (250 mL). The solution was heated at 80 °C under N_2 atmosphere. After sealing all the apparatus by Teflon tape, (3-iodopropyl)triethoxysilane (1.75 g, 5.26 mmol) was added via syringe, and stirred for 20 h at 80 °C. After the reaction, solvent was evaporated through rotary evaporator and caramel-like crude product was obtained. MeCN (1 mL) was added again to dissolve the crude product and the solution was washed with dry ether (100 mL X 3) to remove impurity. The obtained product **1** (Fig. 1 (a)) was dried under reduced pressure. The structure of the product **1** was confirmed by ^{1}H NMR.

NHC precursor **2** (Fig. 1 (b)) was also prepared by using 1-(2,6-diisopropylphenyl)-1*H*-imidazole instead of using 1-(2,4,6-triemethylphenyl)-1*H*-imidazole.

NHC precursor 1. ^{1}H NMR (400 MHz, DMSO-d_6, TMS) : δ (ppm) = 9.4 (s, 1H), 8.1 (s, 1H), 8.0 (s, 1H), 7.2 (s, 2H), 4.3 (t, 2H), 3.75 (q, 6H), 1.8 (m, 2H), 1.1 (t, 9H), 0.5 (quin, 2H) (see the appendix).

NHC precursor 2. ^{1}H NMR (400 MHz, DMSO-d_6, TMS) : δ (ppm)

= 9.6 (s, 1H) 8.2 (d, 1H), 8.1 (d, 1H), 7.6 (t, 1H), 7.4 (d, 2H), 4.3 (t, 2H), 3.75 (q, 6H), 2.2 (quin, 2H), 1.9 (quin, 2H), 1.1 (m, (12+9)H) 0.5 (quin, 2H) (see the appendix).



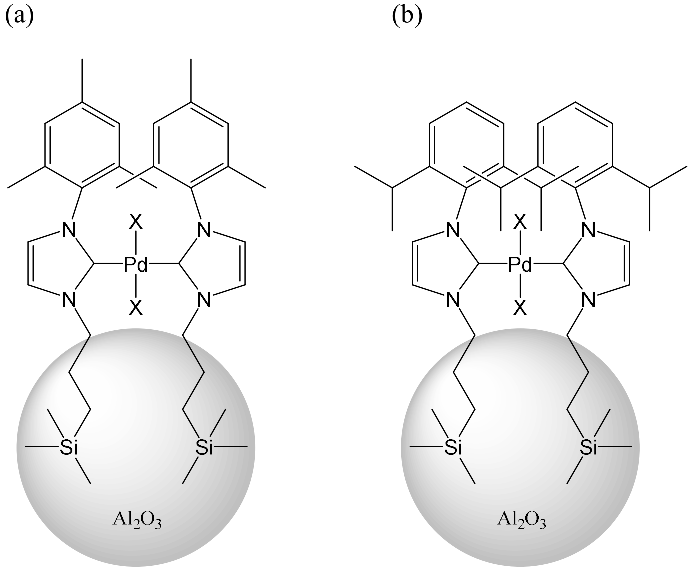
1

2

Fig. 1. Structures of NHC precursor **1** (a) and **2** (b).

II. 2. 4. Immobilization of Pd-NHC Complex on γ-Alumina

Pd-NHC complex was prepared as follows. $Pd(OAc)_2$ (135 mg, 0.60 mmol) was dissolved in dry THF (50 mL) and NHC precursor **1** (0.933 g, 1.80 mmol) was added to the solution. The mixture (dark red) was stirred by overhead stirrer for 1.5 h at room temperature and heated to 60 °C for 4.5 h under N_2 atmosphere. After preparing Pd-NHC complex, γ-alumina (3.00 g) was added to the mixture and stirred at 60 °C for 18 h under N_2 atmosphere. The color of the added γ-alumina changed from white to orange-brown. The reaction mixture was filtered by thimble filter and washed with THF. Simply adsorbed Pd species and unreacted NHC precursors were removed via soxhlet extraction using THF as a solvent. The prepared catalyst **3** (Fig. 2 (a)) was washed with MC (10 mL x 3) and MeOH (10 mL x 3), and dried under reduced pressure. The Pd loading was measured by ICP-AES. Catalyst **4** (Fig. 2 (b)) was prepared by the same procedure using NHC precursor **2** (1.009 g, 1.80 mmol) instead of NHC precursor **1.**



3

4

Fig. 2. Structures of catalyst **3** (a) and catalyst **4** (b).

For ICP-AES analysis, catalyst **3** and **4** were treated by HCl (35 %, 3 mL) and HNO_3 (1 mL) for 18 h at room temperature. After filtration of the mixture, filtrate was diluted to 25 mL with deionized water and analyzed by ICP-AES.

II. 3. Suzuki-Miyaura Reaction Catalyzed by γ-Alumina Supported Pd-NHC

II. 3. 1. General Experimental Procedure for Suzuki-Miyaura Reaction

Aryl halide (0.1 mmol), phenylboronic acid (0.12 mmol), and base (0.15 mmol) were dissolved in deionized water and DMF (several ratio of water/DMF, v/v, 3 mL), followed by addition of the Pd catalyst (0.1 μmol Pd) in a sealed vial (10 mL). The mixture was heated at several temperatures (50 ~ 100 ℃) in an oil bath for various time (2.5 min ~ 2 h). After filtration of the catalyst, extraction was performed by diethyl ether (3 mL), and the crude product was identified by GC-MS. If needed, the filtered catalyst was washed with MC (3 mL X 3) and MeOH (3 mL X 3) and dried under reduced pressure for reusability test.

II. 3. 2. Optimization of Suzuki-Miyaura Reaction in Various Solvents and Bases

4-Bromoanisole (12.5 µL, 0.10 mmol), phenylboronic acid (14.6 mg, 0.12 mmol), Cs_2CO_3 (48.9 mg, 0.15 mmol), and the Pd catalysts (0.1 µmol Pd) were added in various solvent, and heated at 50 ℃ for 2 h in a sealed vial (10 mL). Various ratios of deionized water and DMF (total volume of 3 mL) were tested as a solvent; H_2O, H_2O/DMF (3:1), H_2O/DMF (2:1), H_2O/DMF (3:2), H_2O/DMF (1:1), H_2O/DMF (2:3), H_2O/DMF (1:2), H_2O/DMF (1:3), and DMF. To examine the effect of bases, the following bases were tested instead of Cs_2CO_3; $LiOH \cdot H_2O$ (3.6 mg, 0.15 mmol), NaOH (6.0 mg, 0.15 mmol), KOH (8.4 mg, 0.15 mmol), $CsOH \cdot H_2O$ (25.2 mg, 0.15 mmol), $Ba(OH)_2 \cdot 6H_2O$ (25.7 mg, 0.15 mmol), Na_2CO_3 (15.9 mg, 0.15 mmol), K_2CO_3 (20.7 mg, 0.15 mmol), $Na_3PO_4 \cdot 12H_2O$ (50.0 mg, 0.15 mmol), K_3PO_4 (31.8 mg, 0.15 mmol), and Et_3N (20.9 µL, 0.15 mmol). Finally, KOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4, which showed the best results were retested in 3 kinds of solvent systems (3 mL); H_2O/DMF (3:1), H_2O/DMF (2:1), and H_2O/DMF (3:2).

II. 3. 3. Determination of Reaction Kinetics

4-Bromoanisole (12.5 μL, 0.1 mmol), phenylboronic acid (14.6 mg, 0.12 mmol) and K_3PO_4 (31.8 mg, 0.15 mmol) were dissolved in water and DMF (2:1, v/v, 3mL) followed by addition of catalyst **4** (0.1 μmol Pd) in a sealed vial (10 mL). The reaction mixtures were heated at 50 °C for 2.5 min, 5 min, 10 min, 20 min, 30 min, 45 min, 1 h, and 2 h. After filtration of the catalyst, extraction was performd by diethyl ether (3 mL). The crude product in diethyl ether was identified by GC-MS.

II. 3. 4. Reaction Profiles at Various Temperature by using Microwave as Heating Method

4-Bromoanisole (12.5 μL, 0.1 mmol), phenylboronic acid (14.6 mg, 0.12 mmol) and K_3PO_4 (31.8 mg, 0.15 mmol) were dissolved in water and DMF (2:1, v/v, 3mL), followed by addition of catalyst **4** (0.1 μmol Pd) in a sealed vial (10 mL). The reaction mixtures were heated at 50, 60, 70, 80, 90, and 100 °C for 15 min by microwave (40 W, 20 bar). After filtration of the catalyst, extraction was performd by diethyl ether (3 mL). The crude product in diethyl ether was identified by GC-MS.

II. 3. 5. Reusability of γ-Alumina Supported Pd-NHC

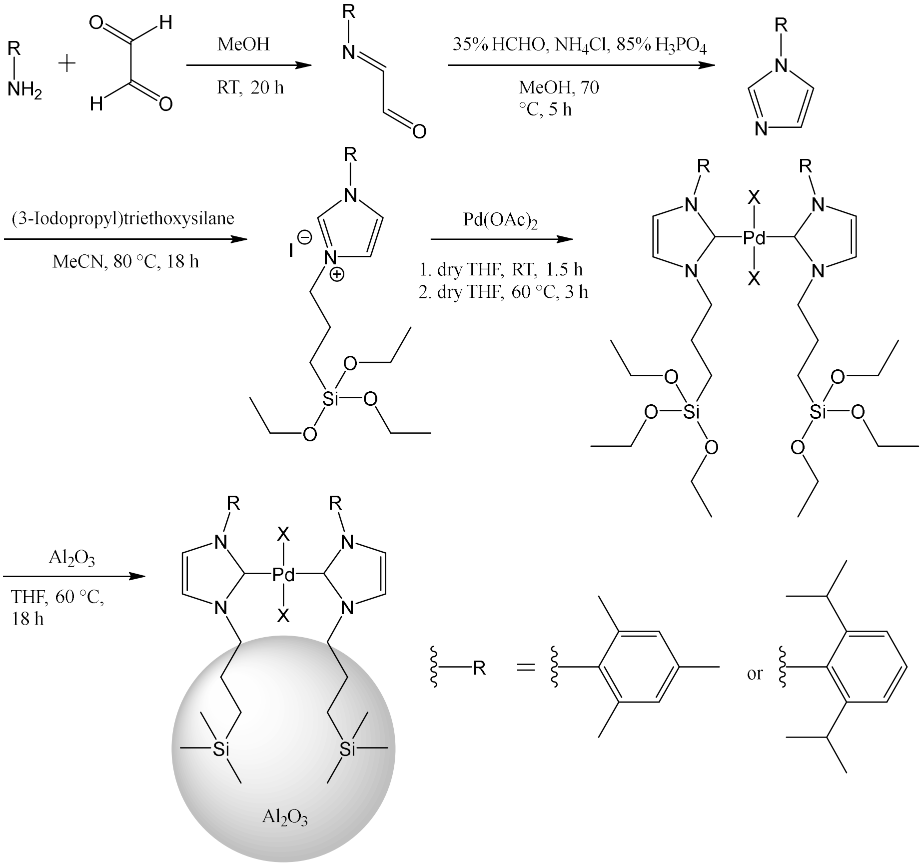
4-Bromoanisole (12.5 μL, 0.1 mmol), phenylboronic acid (14.6 mg, 0.12 mmol) and K_3PO_4 (31.8 mg, 0.15 mmol) were dissolved in water and DMF (2:1, v/v, 3mL) followed by addition of catalyst **4** (0.3 μmol Pd) in a sealed vial (10 mL). The reaction mixture was heated at 50 ℃ for 2 h. After filtration of the catalyst, extraction was performd by diethyl ether (3 mL). The crude product in diethyl ether was identified by GC-MS. The filtered catalyst was washed with MC (3 mL X 3) and MeOH (3 mL X 3) and dried under reduced pressure. Dried catalyst **4** was reused 4 times for the same reaction.

III. Results and Discussion

III. 1. Preparation and Characterization of γ-Alumina Supported Pd-NHC

III. 1. 1. Preparation of γ-Alumina Supported Pd-NHC

To prepare NHC precursors, 2,4,6-trimethylphenyl and 2,6-diisopropylphenyl groups were chosen as the substitution groups of imidazole. Those two compounds, 1-(2,4,6-trimethylphenyl) -1*H*-imidazole and 1-(2,6-diisopropylphenyl)-1*H*-imidazole, have been the most studied NHC precursor and also known to afford good performance as a catalytic ligand. As mentioned earlier, synthetic method of 1-substitued imidazole was previously reported by Liu et al.[38] The yields of 1-(2,4,6-trimethylphenyl)-1*H*-imidazole and 1-(2,6-diisopropyl-phenyl)-1*H*-imidazole were about 60, and 50 % respectively. (3-Chloropropyl)triethoxysilane was used as a source of silylating agent to immobilize the NHC structure on γ-alumina. The chlorine of the silylating agent was substituted to iodine by NaI. The resulting (3-iodopropyl)triethoxy-silane is better silylating agent than (3-chloroproyl)triethoxysilane. Sodium iodide was dissolved in dry acetone under N_2 atmosphere and (3-chloropropyl)triethoxysilane was dropped into the solution. After the reaction for 6 days, the structure of final product was confirmed by ^{1}H NHR (Fig. A. 1-6). The reaction was proceeded well and the yield was almost 100 %. As previously demonstrated, Pd-NHC complexes are stable in air and moisture due to the strong bonding between Pd(II) and NHC, and each NHC is relatively reactive toward Pd(II) in forming the complex. Therefore, after attaching the silylating agent to the 1-substituted imidazole, the NHC precursors were reacted with $Pd(OAc)_2$ in dry THF to form the bidentate Pd-NHC complexe before immobilizing the complex on γ-alumina. (Scheme 2)



Scheme 2. Preparation of Pd-NHC@γ-alumina.

III. 1. 2. Characterization of γ-Alumina Supported Pd-NHC

The morphologies of the prepared Pd-NHC@γ-alumina catalysts were visualized by FE-SEM (Fig. 3) to check the morphology changes of the catalyst. After preparation, the catalysts gave the same physical appearance which means that the support did not suffer from mechanical damage during the immobilization of Pd-NHC complex. Simultaneously, Pd, C, Si, and I were identified by EDS analysis (Fig. 4). The presence of C, and Si in the spectra indicates that the NHCs were successfully immobilized on γ-alumina. The presence of Pd also indicates that Pd-NHC complexes were formed. But N could not be detected because of its small quantity. Additionally, to identify the exact ratio of Pd species, the catalysts were analyzed by XPS. The binding energy of Pd(0) $3d_{5/2}$ is known as 335.0 eV, and the binding energy of palladium(II) oxide $3d_{5/2}$ is 336.3 eV.[40] The observed binding energies of catalyst **3** and catalyst **4** were 336.2 and 335.7 eV (Fig. 5 and Table 1). These results suggests that most of the Pd species in the catalysts were Pd(II). The small shifts to a lower energy (0.1 and 0.6 eV) means that electron density of Pd in the Pd-NHC is higher than that of Pd in palladium(II) oxide because electronegativity of carbene carbon in the NHC becomes lower. Finally, to quantify the amounts of Pd, the catalysts were analyzed by ICP-AES. The contents of Pd in catalyst **3** (Entry 1 in Table 2) was 7.5 μmol/g and catalyst **4** (Entry 2 in Table 2) was 14.2 μmol/g.

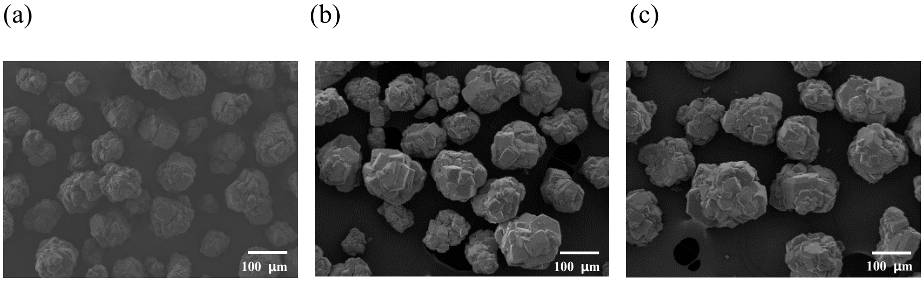


Fig. 3. SEM images of γ-alumina(a), catalyst **3** (b), and catalyst **4** (c).

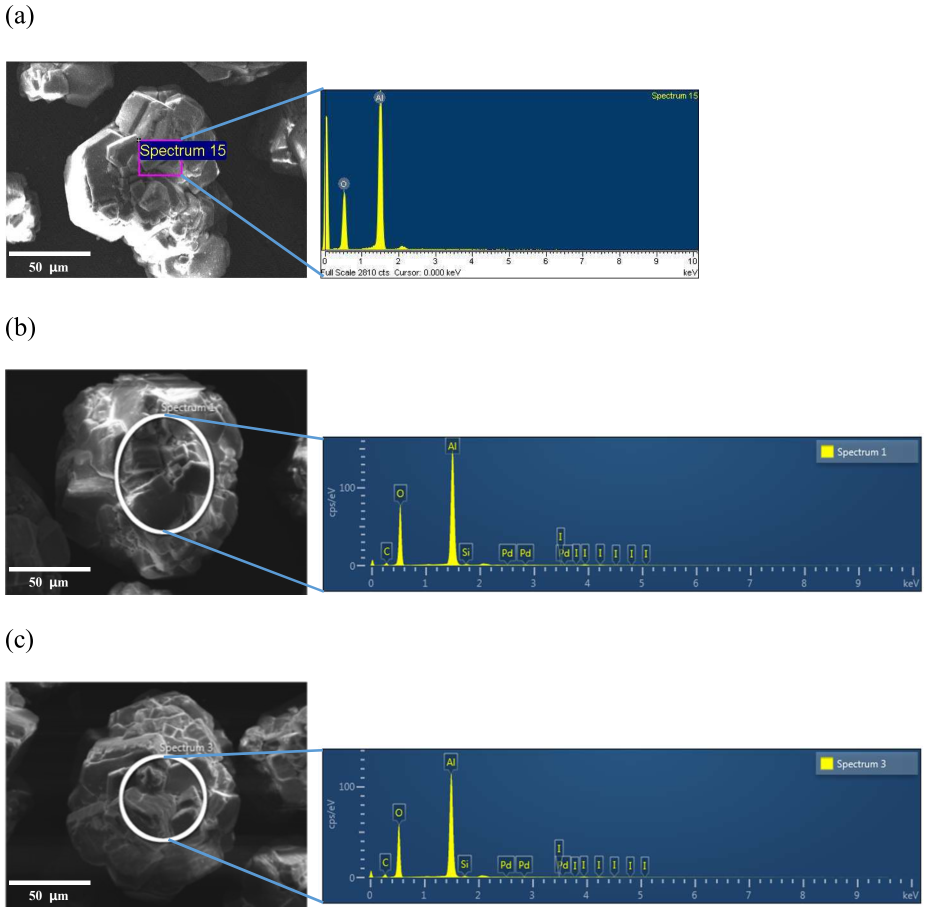


Fig. 4. EDS analysis of γ-alumina (a), catalyst **3** (b), and catalyst **4** (c).

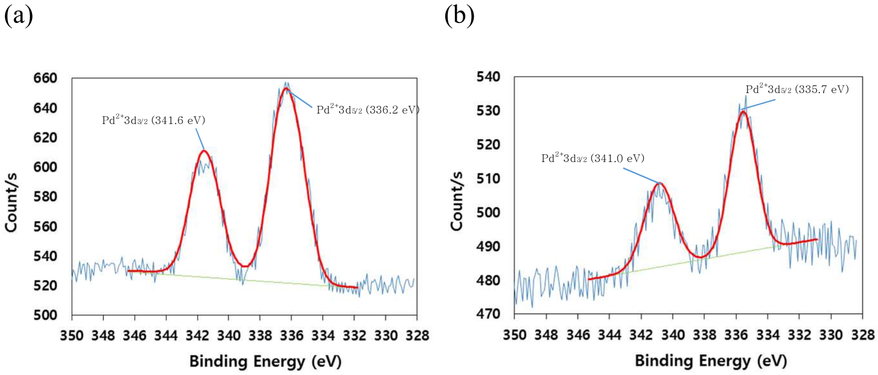


Fig. 5. XPS analysis of catalyst **3** (a) and catalyst **4** (b).

Table 1. Binding Energies of Pd Species

Species	Catalyst	Peak Binding Energy (eV)	
		Pd3d5/2	Pd3d3/2
Pd(II)	**3**	336.2	341.6
	4	335.7	341.0

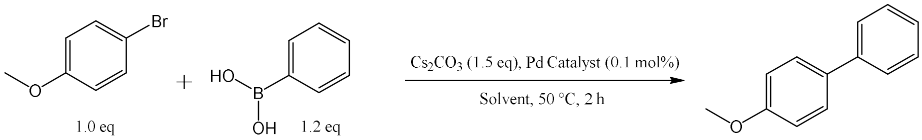
Table 2. Pd Contents of Catalysts

Entry	Catalyst	Pd loading (μmol/g)
1	**3**	7.5
2	**4**	18.3

III. 2. Suzuki-Miyaura Reaction Catalyzed by γ-Alumina Supported Pd-NHC

III. 2. 1. Effects of Solvents and Bases in Suzuki-Miyaura Reaction

4-Bromoanisole and phenylboronic acid were chosen as model reactants to find out the optimized C-C coupling reaction condition. The reaction was carried out using water as a base solvent and DMF as a co-solvent to solubilize water-insoluble 4-bromoanisole. Lastly, Cs_2CO_3 was chosen as a base because Pd-NHC Suzuki-Miyaura catalyst usually shows good activity in the presence of carbonate series.[41] The tested solvent systems were H_2O, H_2O/DMF (3:1), H_2O/DMF (2:1), H_2O/DMF (3:2), H_2O/DMF (1:1), H_2O/DMF (2:3), H_2O/DMF (1:2), H_2O/DMF (1:3), and DMF, and the amount of Pd was 0.1 mol% (Scheme 3). As shown in Table 3 and 4, H_2O/DMF (2:1) gave the highest yield in the series of tests (Entry 3 in Table 3 and Entry 3 in Table 4). However, slightly decreased yield was observed in the H_2O/DMF (3:1) condition (Entry 2 in Table 3 and Entry 2 in Table 4) and much lower yield was obtained in pure H_2O (Entry 1 in Table 3 and Entry 1 in Table 4). This means that the catalysts promote Suzuki-Miyaura reaction in water dominant solvent and the water insoluble aryl halides are not reactive as the water ratio increases.



Scheme 3. Suzuki-Miyaura reaction of 4-bromoanisole with phenylboronic acid in various solvent systems.

Table 3. Effect of Solvents on Suzuki-Miyaura Reaction of 4-Bromoanisole with Phenylboronic Acid by Catalyst **3**[a]

Entry	Solvent	Yield (%)[b]
1	H_2O	20
2	H_2O/DMF (3:1)	80
3	H_2O/DMF (2:1)	91
4	H_2O/DMF (3:2)	89
5	H_2O/DMF (1:1)	65
6	H_2O/DMF (2:3)	28
7	H_2O/DMF (1:2)	15
8	H_2O/DMF (1:3)	5
9	DMF	2

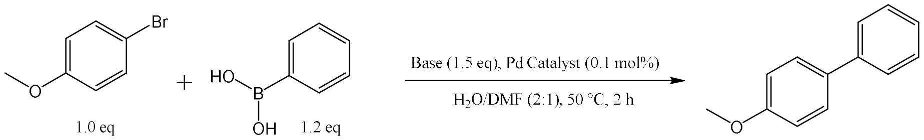
[a] 4-Bromoanisole (0.1 mmol), phenylboronic acid (0.12 mmol), catalyst **3** (0.1 mol%), Cs_2CO_3 (0.15 mmol), solvent (3 mL) at 50 ℃ for 2 h. [b] GC yields.

Table 4. Effect of Solvents on Suzuki-Miyaura Reaction of 4-Bromoanisole with Phenylboronic Acid by Catalyst **4**[a]

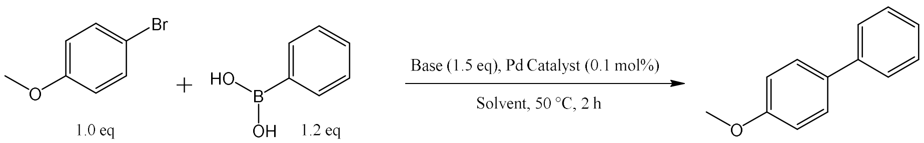
Entry	Solvent	Yield (%)[b]
1	H_2O	31
2	H_2O/DMF (3:1)	89
3	H_2O/DMF (2:1)	94
4	H_2O/DMF (3:2)	85
5	H_2O/DMF (1:1)	62
6	H_2O/DMF (2:3)	27
7	H_2O/DMF (1:2)	16
8	H_2O/DMF (1:3)	6
9	DMF	<1

[a] 4-Bromoanisole (0.1 mmol), phenylboronic acid (0.12 mmol), catalyst **4** (0.1 mol%), Cs_2CO_3 (0.15 mmol), solvent (3 mL) at 50 ℃ for 2 h. [b] GC yields.

From the solvent screening test results, H_2O/DMF (2:1) was selected as the solvent condition for the following base performance tests (Scheme 4). Potassium salts (Entry 3, 7 and 9 in Table 5 and Entry 3, 7 and 9 in Table 6), carbonates (Entry 6-8 in Table 5 and Entry 6-8 in Table 6) and phosphates series (Entry 9 and 10 in Table 5 and Entry 9 and 10 in Table 6) generally showed good performance whereas $Ba(OH)_2$ (Entry 5 in Table 5 and Entry 5 in Table 6) gave poor yields probably because of poor solubility of $Ba(OH)_2$ in water. TEA (Entry 11 in Table 5 and Entry 11 in Table 6), which is an organic base, presented lower yields then the others. Being different from TEA, there were some noticeable tendency in the yields with inoranic bases. First, most of inorganic bases presented higher yields than that of TEA. It might be due to the weak basicity of TEA because transmetalation step of Suzuki-Miyaura reaction are retarded under low pH.[42] Next, cations might affect the yields when it came to hydroxides (Entry 1-4 in Table 5 and Entry 1-4 in Table 6). The higher the periodic number of cations, the higher yield was obtained because they can affect Pd leaching[41]. Also, most of potassium bases (Entry 3, 7 and 9 in Table 5 and Entry 3, 7 and 9 in Table 6) exhibited better yields than the corresponding sodium bases (Entry 2, 6 and 10 in Table 5 and Entry 2, 6 and 10 in Table 6). From these screening test results, several potassium salts, carbonates, and a phosphate (KOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4) was chosen, and tested further in the following solvent systems H_2O/DMF (3:1), H_2O/DMF (2:1), and H_2O/DMF (3:2) for final optimizations (Scheme 5). Most of the reactions showed maximum performance in H_2O/DMF (2:1) and K_3PO_4, which appeared to be the best base in the same solvent system (Entry 14 in Table 7 and Entry 14 in Table 8). Therefore, K_3PO_4 and H_2O/DMF (2:1) were chosen in the following experiments.



Scheme 4. Suzuki-Miyaura reaction of 4-bromoanisole with phenylboronic acid using various bases.



Scheme 5. Suzuki-Miyaura reaction of 4-bromoanisole with phenylboronic acid using various bases in several solvent conditions.

Table 5. Effect of Bases on Suzuki-Miyaura Reaction of 4-Bromoanisole with Phenylboronic Acid by Catalyst **3**[a]

Entry	Base	Temp (℃)	Yield (%)[b]
1	LiOH	50	79
2	NaOH	50	81
3	KOH	50	84
4	CsOH	50	90
5	$Ba(OH)_2$	50	63
6	Na_2CO_3	50	91
7	K_2CO_3	50	89
8	Cs_2CO_3	50	91
9	K_3PO_4	50	94
10	Na_3PO_4	50	94
11	Et_3N	50	65

[a] 4-Bromoanisole (0.1 mmol), phenylboronic acid (0.12 mmol), catalyst **3** (0.1 mol%), base (0.15 mmol), H_2O/DMF (v/v, 2:1, 3 mL) for 2 h. [b] GC yields.

Table 6. Effect of Bases on Suzuki-Miyaura Reaction of 4-Bromoanisole with Phenylboronic Acid by Catalyst **4**[a]

Entry	Base	Temp (℃)	Yield (%)[b]
1	LiOH	50	90
2	NaOH	50	86
3	KOH	50	93
4	CsOH	50	86
5	$Ba(OH)_2$	50	57
6	Na_2CO_3	50	93
7	K_2CO_3	50	95
8	Cs_2CO_3	50	94
9	K_3PO_4	50	95
10	Na_3PO_4	50	85
11	Et_3N	50	75

[a] 4-Bromoanisole (0.1 mmol), phenylboronic acid (0.12 mmol), catalyst **4** (0.1 mol%), base (0.15 mmol), H_2O/DMF (v/v, 2:1, 3 mL) for 2 h. [b] GC yields.

Table 7. Optimization of Solvent and Base Conditions in Suzuki-Miyaura Reaction of 4-Bromoanisole with Phenylboronic Acid by Catalyst **3**[a]

Entry	Base	Solvent	Temp (℃)	Yield (%)[b]
1	KOH	H_2O/DMF (3:1)	50	83
2	KOH	H_2O/DMF (2:1)	50	84
3	KOH	H_2O/DMF (3:2)	50	85
4	Na_2CO_3	H_2O/DMF (3:1)	50	83
5	Na_2CO_3	H_2O/DMF (2:1)	50	91
6	Na_2CO_3	H_2O/DMF (3:2)	50	81
7	K_2CO_3	H_2O/DMF (3:1)	50	80
8	K_2CO_3	H_2O/DMF (2:1)	50	89
9	K_2CO_3	H_2O/DMF (3:2)	50	84
10	Cs_2CO_3	H_2O/DMF (3:1)	50	80
11	Cs_2CO_3	H_2O/DMF (2:1)	50	91
12	Cs_2CO_3	H_2O/DMF (3:2)	50	89
13	K_3PO_4	H_2O/DMF (3:1)	50	84
14	K_3PO_4	H_2O/DMF (2:1)	50	94
15	K_3PO_4	H_2O/DMF (3:2)	50	80

[a] 4-Bromoanisole (0.1 mmol), phenylboronic acid (0.12 mmol), catalyst **3** (0.1 mol%), base (0.15 mmol), solvent (3 mL) for 2 h. [b] GC yields.

Table 8. Optimization of Solvent and Base Conditions in Suzuki-Miyaura Reaction of 4-Bromoanisole with Phenylboronic Acid by Catalyst **4**[a]

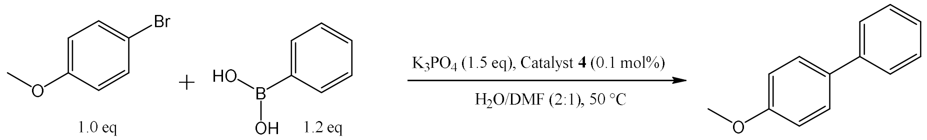
Entry	Base	Solvent	Temp (℃)	Yield (%)[b]
1	KOH	H_2O/DMF (3:1)	50	90
2	KOH	H_2O/DMF (2:1)	50	93
3	KOH	H_2O/DMF (3:2)	50	94
4	Na_2CO_3	H_2O/DMF (3:1)	50	91
5	Na_2CO_3	H_2O/DMF (2:1)	50	93
6	Na_2CO_3	H_2O/DMF (3:2)	50	89
7	K_2CO_3	H_2O/DMF (3:1)	50	90
8	K_2CO_3	H_2O/DMF (2:1)	50	95
9	K_2CO_3	H_2O/DMF (3:2)	50	84
10	Cs_2CO_3	H_2O/DMF (3:1)	50	89
11	Cs_2CO_3	H_2O/DMF (2:1)	50	94
12	Cs_2CO_3	H_2O/DMF (3:2)	50	85
13	K_3PO_4	H_2O/DMF (3:1)	50	86
14	K_3PO_4	H_2O/DMF (2:1)	50	95
15	K_3PO_4	H_2O/DMF (3:2)	50	83

[a] 4-Bromoanisole (0.1 mmol), phenylboronic acid (0.12 mmol), catalyst **4** (0.1 mol%), base (0.15 mmol), solvent (3 mL) for 2 h. [b] GC yields.

III. 2. 2. Reaction Profiles of Suzuki-Miyaura Reaction

To identify the reaction kinetics, Suzuki-Miyaura reactions with 4-bromoanisole, and phenylboronic acid using **4** as a catalyst were carried out for 2.5, 5, 10, 20, 30, 45, and 60 min in an oil bath or microwave reactor (Scheme 6) (Fig. 6).

As expected, microwave heating accelerated the initial reaction but both oil bath and microwave heating showed similar reaction time for reaching the reaction plateau between 0.5-1 h, and also exhibited similar yields. This indicates that microwave heating promotes faster initial reaction by allowing fast temperature increase. However, microwave heating did not change the maximum yield. Microwave heating in Suzuki-Miyaura reaction using **4** as a catalyst had an effect on the yield only when the reaction time is less than 20 min.



Scheme 6. Suzuki-Miyaura reaction of 4-bromoanisole with phenylboronic acid by oil bath heating or microwave (100W) heating using K_3PO_4 as a base.

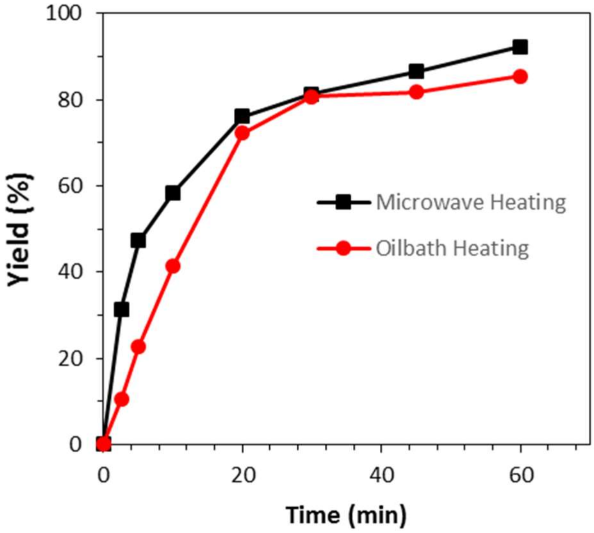


Fig. 6. Reaction kinectics of Suzuki-Miyaura reaction with 4-bromoanisole (0.1 mmol), phenylboronic acid (0.12 mmol), with catalyst **4** (0.1 mol%), and base (0.15 mmol) in H_2O/DMF (v/v, 2:1, 3 mL) for 2 h at 50 ℃ by oil bath heating and microwave heating.

The reaction profiles at various temperature (50, 60, 70, 80, 90, and 100 °C) were obtained for 15 min by microwave heating instead of oil bath heating because the initial reaction kinetics by oil bath heating method is not accurate at eartly stage of the reaction (Fig. 7). As expected, the higher the temperature, the higher yields were obtained. However, the improvements of initial kinetics became small by the microwave heating method.

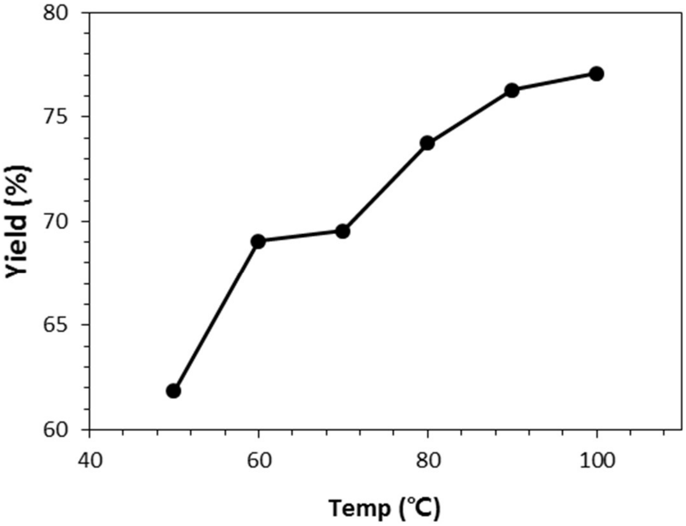
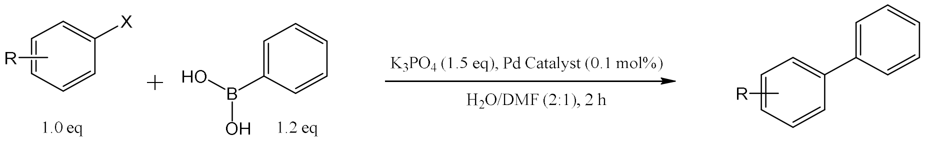


Fig. 7. Temperature dependancy of Suzuki-Miyaura reaction with 4-bromoanisole (0.1 mmol), phenylboronic acid (0.12 mmol), with catalyst **4** (0.1 mol%), and base (0.15 mmol) in H2O/DMF (v/v, 2:1, 3 mL) for 2 h at 50 ℃ by microwave heating.

III. 2. 3. Suzuki-Miyaura Reaction of Various Aryl Halides with Phenylboronic acid

Suzuki-Miyaura reactions were performed by oil bath heating with phenylboronic acid and several aryl halides (Scheme 7). The result with catalyst **3** (Table 9) and **4** (Table 10) showed that the reaction proceeded in moderate or excellent yields with most of aryl bromides under mild conditions. However, Suzuki-Miyaura reaction with aryl chlorides (Entry 11-16 in Table 9 and Entry 11-16 in Table 10) gave relatively lower yields even under harsher conditions than those of aryl bromides (Entry 1-10 in Table 9 and Entry 1-10 in Table 10). Catalyst **3** and **4** showed moderate catalytic activity with aryl bromides and aryl chlorides that contain a heteroatom in the aromatic ring. Generally, the reaction with aryl halides with electon withdrawing substituents gave higher yields than the ones with electron donating substituents.



Scheme 7. Suzuki-Miyaura reaction of various aryl halides with phenylboronic acid using K_3PO_4 as a base.

Table 9. Suzuki-Miyaura Reaction of Various Aryl halides with Phenylboronic Acid by Catalyst **3**[a]

Entry	Substrate	Temp (℃)	Yield (%)[b]
1	2-Bromoanisole	50	78
2	4-Bromoanisole	50	92
3	4-Bromobenzonitrile	50	90
4	2-Bromotoluene	50	78
5	4-Bromotoluene	50	90
6	4-Bromobenzaldehyde	50	>99
7	4'-Bromoacetophenone	50	>99
8	2-Bromonaphthalene	50	94
9	2-Bromothiophene	80	82
10	2-Bromopyridine	80	83
11	2-Chloroanisole	80	4
12	4-Chloroanisole	80	7
13	4-Chlorobenzonitrile	80	45
14	4-Chlorotoluene	80	5
15	4'-Chloroacetophenone	80	43
16	2-Chloropyridine	80	41

[a] Aryl halide (0.1 mmol), phenylboronic acid (0.12 mmol), catalyst **3** (0.1 mol%), K_3PO_4 (0.15 mmol), H_2O/DMF (v/v, 2:1, 3 mL) for 2 h. [b] GC yields.

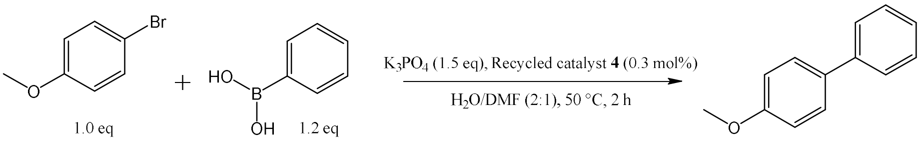
Table 10. Suzuki-Miyaura Reaction of Various Aryl halides with Phenylboronic Acid by Catalyst **4**[a]

Entry	Substrate	Temp (℃)	Yield (%)[b]
1	2-Bromoanisole	50	81
2	4-Bromoanisole	50	95
3	4-Bromobenzonitrile	50	>99
4	2-Bromotoluene	50	74
5	4-Bromotoluene	50	83
6	4-Bromobenzaldehyde	50	>99
7	4'-Bromoacetophenone	50	76
8	2-Bromonaphthalene	50	92
9	2-Bromothiophene	80	62
10	2-Bromopyridine	80	74
11	2-Chloroanisole	80	3
12	4-Chloroanisole	80	6
13	4-Chlorobenzonitrile	80	37
14	4-Chlorotoluene	80	11
15	4'-Chloroacetophenone	80	39
16	2-Chloropyridine	80	36

[a] Aryl halide (0.1 mmol), phenylboronic acid (0.12 mmol), catalyst **4** (0.1 mol%), K_3PO_4 (0.15 mmol), H_2O/DMF (v/v, 2:1, 3 mL) for 2 h. [b] GC yields.

III. 2. 4. Reusability of γ-Alumina Supported Pd-NHC for Suzuki-Miyaura Reaction

The recyclability of catalyst **4** (0.3 mol%) was examined in Suzuki-Miyaura reaction of 4-bromoanisole with phenylboronic acid (Scheme 8). The catalyst was recovered by filtration after 2 h of reaction. The catalyst was filtered, washed, and reused until the fourth cycle. Unexpectedly, the yield were dropped after each cycle (Table 11). The yield drop was about 10 % per cycle. To evaluate the amount of palladium leaching after the reaction, the recovered catalyst **4** after the each cycle was analyzed by ICP-AES. The Pd loading levels of the used catalysts after the first, second, third and fourth cycle were 17.6, 16.0, 15.0, and 13.4 μmol/g respectively. The original loading level was 18.3 μmol. Therefore, the amount of palladium leaching appeared to be about 4~10 % after each cycle. This proves that Pd leaching lowers the activity and reusability of the catalysts.



Scheme 8. Recycling of catalyst in Suzuki-Miyaura reaction.

Table 11. The Results of Recycling Test with Catalyst **4**[a]

Yield (%)[b]			
1st	2nd	3rd	4th
93	83	74	62

[a]4-Bromoanisole (0.1 mmol), phenylboronic acid (0.12 mmol), catalyst **4** (0.3 mol%), K_3PO_4 (0.15 mmol), H_2O/DMF (v/v, 2:1, 3 mL) for 2 h. [b]GC yields.

To identify why the Pd leaching happened, each recycled catalyst and catalyst **4** was analyzed by SEM-EDS (Figure 8). The amount of carbon which is correlated to the amount of NHC ligand in the catalysts was not seriously changed during the recycling test (Element C in Table 12). Thus, the detachment of NHC ligand from γ-alumina was not responsible to the Pd leaching. It might be due to some bond breaking between Pd and carbene carbon during the coupling reaction.

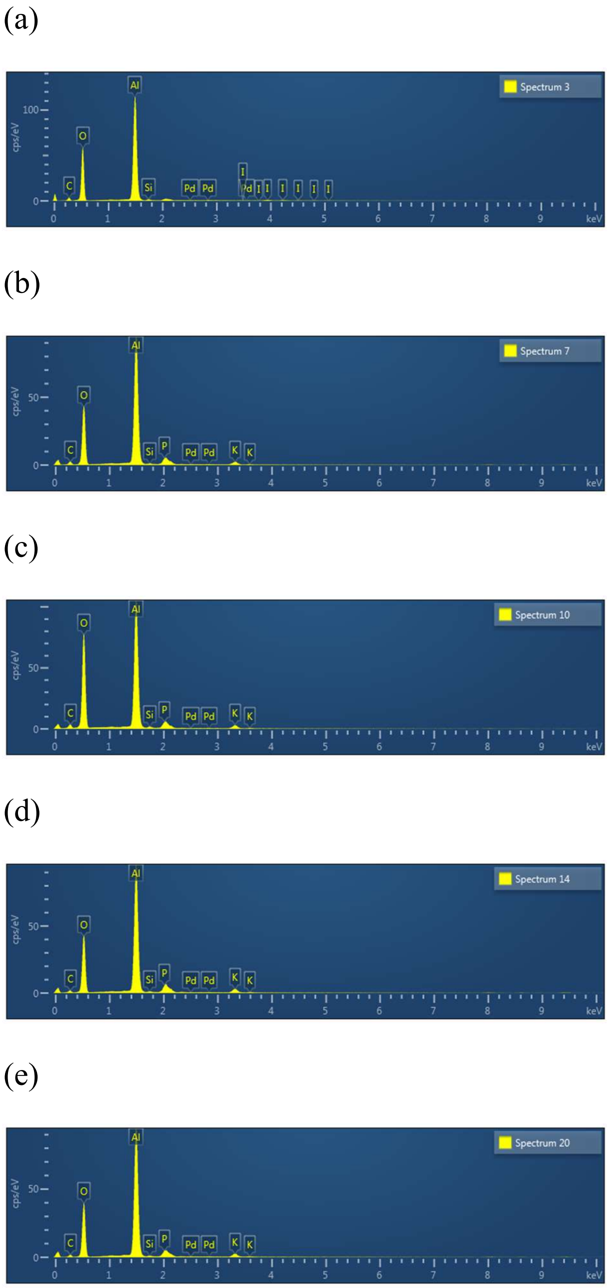


Fig. 8. EDS analysis of catalyst **4** (a) and recycled catalysts after 1st (b), 2nd (c), 3rd (d), and 4th cycle (e).

Table 12. The Amount of Atomic Elements Observed by EDS Analysis

Element	Wt%				
	Catalyst **4**	Cycle number			
		1st	2nd	3rd	4th
C	10.73	10.72	9.40	10.70	9.49
O	44.04	44.36	52.31	44.05	42.90
Al	42.40	40.23	33.80	39.69	42.50
Si	0.52	0.28	0.44	0.30	0.29
Pd	0.31	0.17	0.23	0.11	0.19
P	-	2.33	2.00	2.64	2.37
K	-	1.92	1.83	2.51	2.25
I	2.00	-	-	-	-
Total	100	100	100	100	100

IV. Conclusion

Pd-NHC@γ-alumina catalysts were prepared for Suzuki-Miyaura reaction through immobilization of Pd-NHC on γ-alumina using silylating coupling agent. The reaction between aryl bromides and phenylboronic acid proceeded well using Pd-NHC@γ-alumina (0.1 mol%) as catalysts in water dominant solvent. The catalysts showed moderate to low activities in the reaction of aryl chlorides with phenylboronic acid. Microwave reactor enhanced the initial reaction kinetics through effective heating which reduced the time to reach the steady state temperature. The initial kinetics (15 min) was improved by microwave heating with faster temperature increase. Finally, during recycling test using 4-bromoanisole and phenylboronic acid as substrates, the catalyst maintained moderate activities with 10 % of yield drops per cycle because of the Pd leaching probably due to the bond breaking between Pd and carbene carbon in the NHC.

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국문 초록

감마-알루미나에 담지된 팔라듐-질소헤테로고리카벤촉매는 물이 함유된 용매내에서 스즈키-미야우라 교차결합반응에 우수한 활성을 보였다. 질소헤테로고리카벤은 물에서 안정한 배위결합을 하기 때문에 스즈키-미야우라 교차결합반응에서 관망자 배위기로 사용되어 왔다. 고체상 지지체인 감마-알루미나는 친수성이며 넓은 표면적을 가진 것으로 알려져 있지만, 스즈키-미야우라 반응의 촉매 지지체로서는 그 동안 연구가 이루어지지 않았다. 본 연구에서는 두 종류의 1-치환된 이미다졸을 질소헤테로고리카벤의 전구체로 합성하였으며, 이 질소헤테로고리카벤으로부터 팔라듐-질소헤테로고리카벤 복합체를 합성한 다음, 감마-알루미나에 팔라듐-질소헤테로고리카벤 복합체를 고정시켜 스즈키-미야우라 교차결합반응 촉매를 합성하였고, 그 물리적 특성을 광전자 분광기, 주사전자현미경, 유도결합플라즈마 원자방출분광기로 분석하였다. 또한 물이 함유된 다양한 용매와 염기조건에서 기름 중탕 및 초단파 가열법을 사용하여 섭씨 50도에서 촉매의 성능시험을 한 결과 페닐 붕산과 아릴 브로민화물간의 2시간 반응에서 최고 99%의 수율까지 얻을 수 있었다.

Appendix

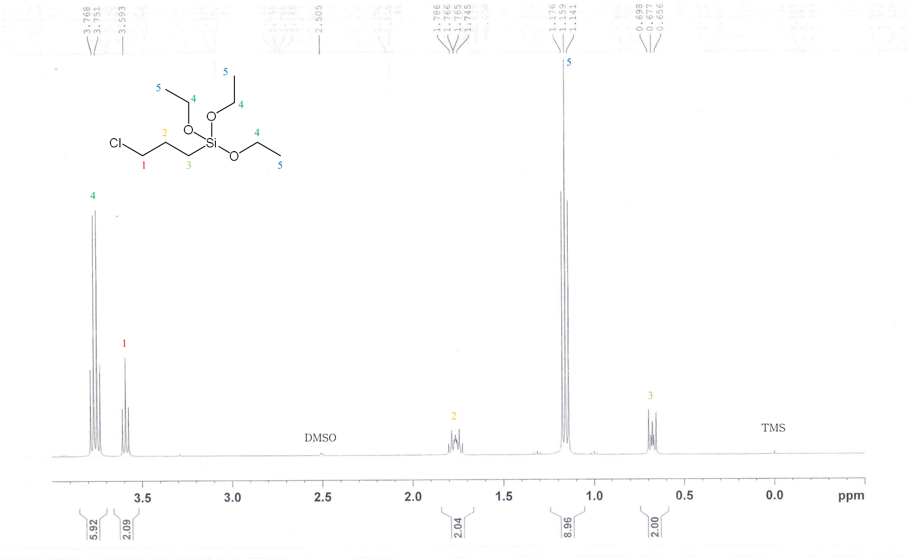

Fig. A.1. ^{1}H NMR spectra of (3-chloropropyl)triethoxysilane.

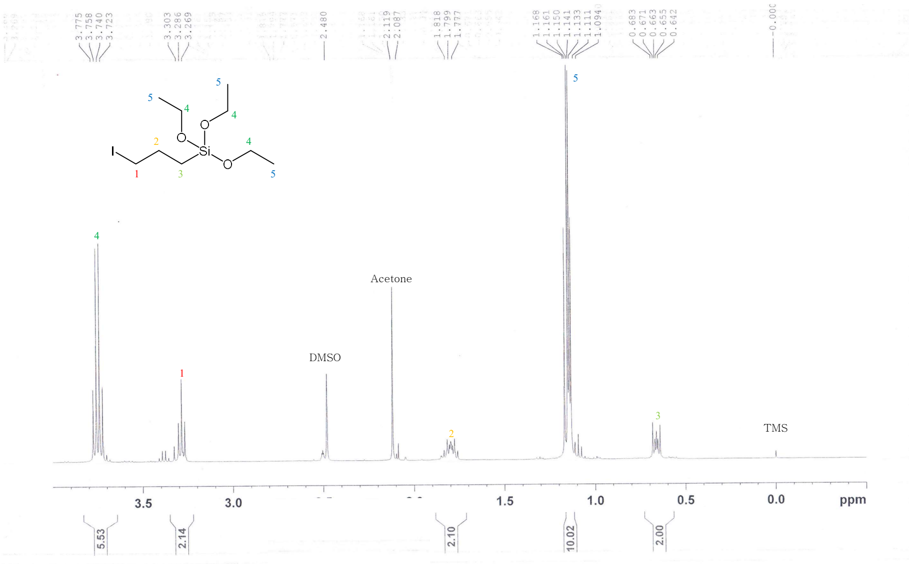

Fig. A.2. ^{1}H NMR spectra of (3-iodopropyl)triethoxysilane.

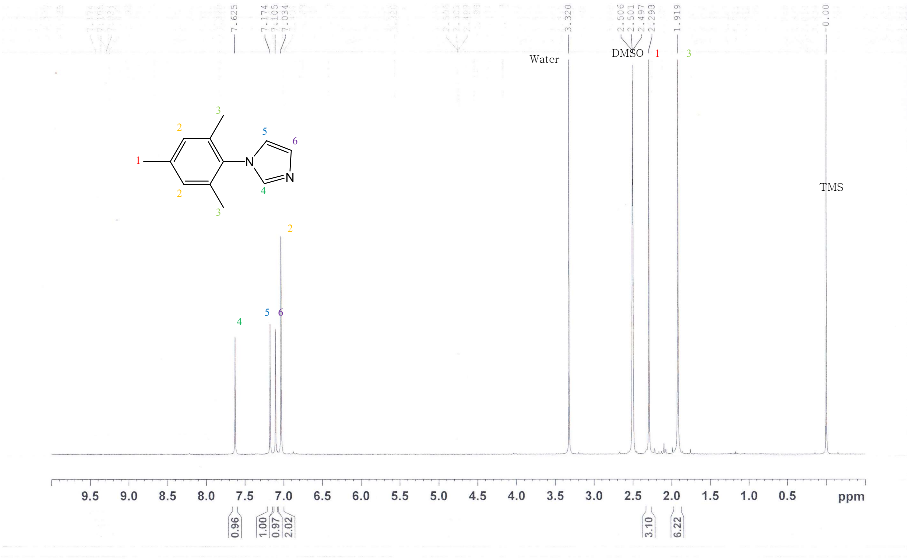

Fig. A.3. ^{1}H NMR spectra of 1-(2,4,6-trimethylphenyl)-1*H*-imidazole.

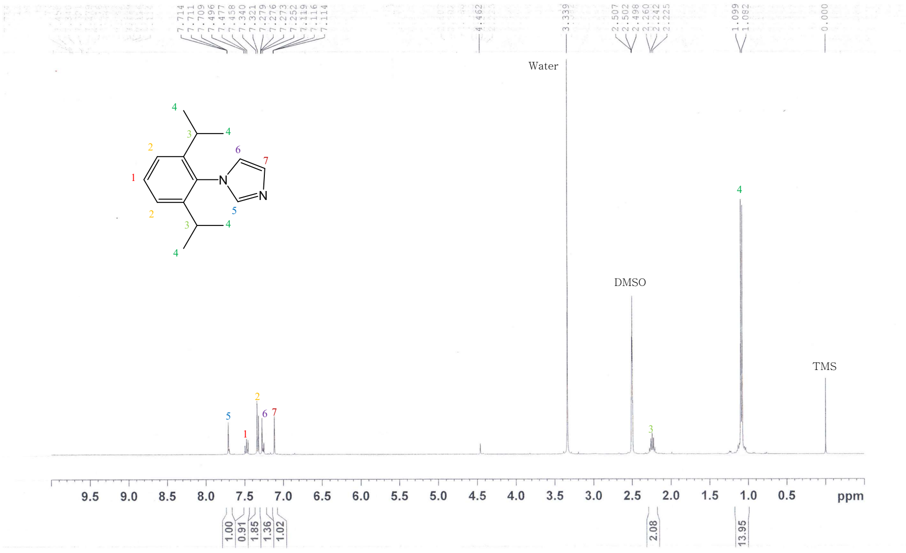

Fig. A.4. ^{1}H NMR spectra of 1-(2,6-diisopropylphenyl)-1*H*-imidazole.

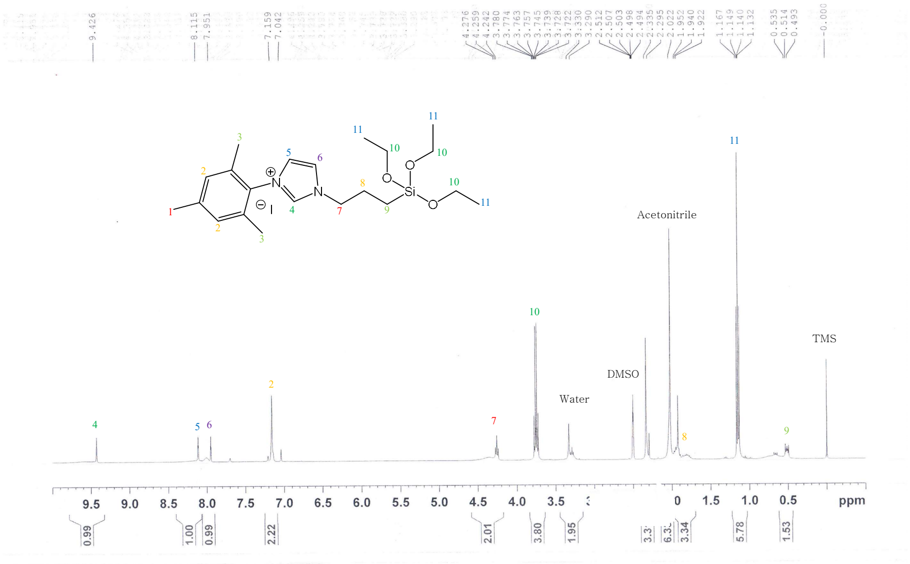

Fig. A.5. ^{1}H NMR spectra of NHC precursor **1**.

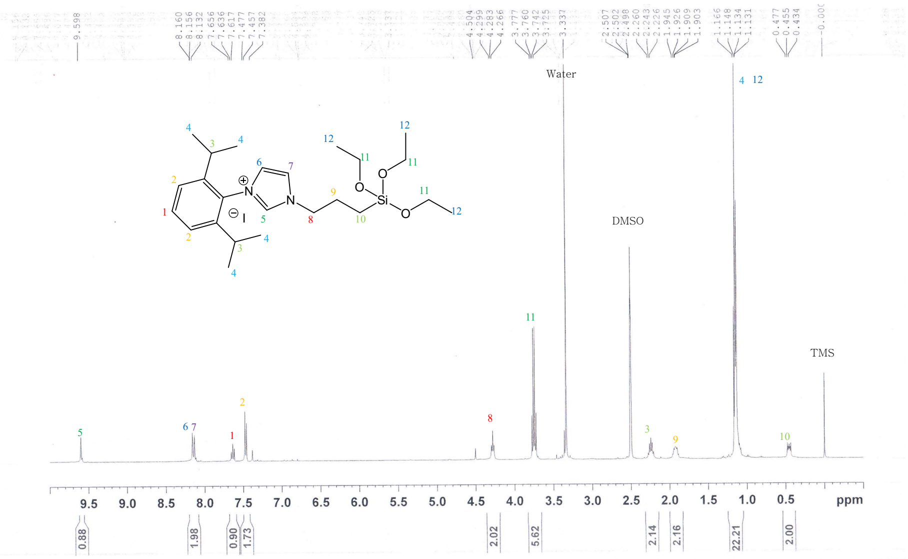

Fig. A.6. ^{1}H NMR spectra of NHC precursor **2**.