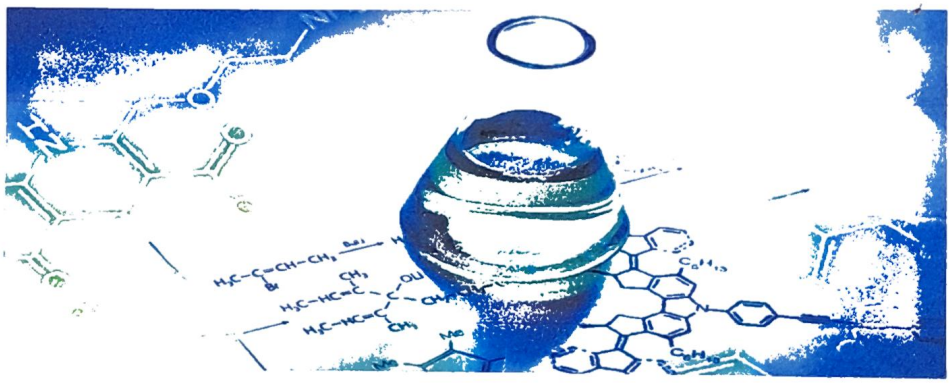
Dissertation

On

"In-situ generated palladium NHC catalyzed Suzuki-Miyaura reaction"

DEPARTMENT OF CHEMISTRY

A Project Submitted for the partial fulfillment of the requirement for the degree of Bachelor of Science in Chemistry Paper DSE-4 of Dibrugarh University.



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CERTIFICATE

It is my pleasure to forward the dissertation entitle

In-situ generated palladium NHC catalyzed Suzuki-Miyaura reaction.

Submitted by Manashjyoti Polong , student of semester VI of our college, bearing Roll No. 30820022 for the partial fulfillment of requirement for B.Sc degree in chemistry Core under Dibrugrah University, Assam. He carried out the investigation under my constant supervision and guidance. The results incorporated in this dissertation have not been submitted to any University or Institute for any purpose. The dissertation is in my opinion worthy of consideration for the paper DSE-4 of Chemistry Major accordance with regulation of Dibrugrah University.

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Declaration

I, Manashjyoti Polang , hereby declare that the project report entitled,

"In-situ generated palladium NHC catalyzed Suzuki-Miyaura reaction"

Submitted by me under the guidance of Dr. Dhrubajit Borah, Assistant Professor of Chemistry. Nanda Nath Saikia College, Titabar. The empirical finding results are based on original work done by me. I also declare that no material contained in this project has been published earlier in any manner.

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CONTENT

Abstract

The dissertation describes the synthesis of a new imidazolium salt and the salt was characterized by various spectroscopic methods such as ^{1}H, ^{13}C, ^{19}F NMR and high resolution mass spectrometry (HRMS). The imidazolium salt was applied for in-situ generation of active catalyst in the presence of inorganic base, and $Pd(OAc)_2$ for the Suzuki-Miyura reaction. The study suggests that presence of imidazolium salt enhances the catalytic efficiency of $Pd(OAc)_2$ in Suzuki-Miyaura reaction.

1. Introduction

In the last century, transition metal catalysis has emerged as one of the most powerful discipline in the domain of synthetic organic chemistry.[1-3] Development of new catalyst based on transition metal with various ligands systems and understanding of reaction mechanism provide enormous opportunities to synthesis a multitudes of organic compounds under mild reaction conditions.[4] Among these transition metal catalysts, palladium deserves a unique place in the realm of catalysis.[5] Owing to stability of palldium complexes with different ligands and facile inter-conversion of oxidation states of palladium, complexes of palladium serve as efficient catalyst in various organic transformation reactions.[6-8]

NHCs have become a very important class of ligands in organo-metalic chemistry and catalysis.[9-10] The strong sigma-donating but poor pi-accepting ability of these NHCs leads to the formation of many stable metal-carbene complexes.[11-15] For this reason, the metal-NHC complexes have been widely used as highly reactive and rather selective catalyst

for numerous chemical transformations.[16] Metal- NHCs have also been utilized extensively in medicinal application.[17-19] Now a days, many research groups around the world currently focusing on metal NHC complexes.[20] Palladium-catalyzed bond-forming reactions are one of the most common tools synthetic chemists employ, in industry .[21-25]The strong palladium-NHC bonds contribute to the high stability of the active species, even at low catalyst and high temperature.[26-27] With a number of available, stable, user friendly, and powerful palladium-NHC catalysts, the goal of a cross-coupling catalyst is within reach. Palladium-catalyzed cross-coupling reactions are now widely used to form C-C and C-N bond formation. [28]

The Suzuki-Miyaura cross-coupling is a metal catalyzed reaction[29] , generally Pd[30] , between an vinyl[31] , aryl[32] , or alkynyl organoborane (boronic acid or boronic ester,or special cases with aryl triflouroborane[33]) an halide under basic conditions . This reaction is used to create carbon–carbon bonds .The interest in the Suzuki-Miyaura cross-coupling reaction has increased exponentially, which shows the efficiency and effectiveness of this reaction.[34] The importance of the Suzuki-Miyaura reaction has been recognized by the award of the 2010 Nobel Prize in Chemistry to Akira Suzuki, along with Richard F. Heck and Ei-ichi Negishi.[34] This method is highly effective which provides a huge industrial use for the production of hypertensive drugs.[35] This is because of its mild reaction conditions, the broad functional group tolerance, availability, and high stabilities towards air and moisture. Both palladium and nickel are used in this coupling reaction, and success has been achieved mainly by the means of ligand design. [36-37]

In the last two decades, multitudes of catalytic systems have been developed to study their efficiency in various reactions.[38-39] Among these, pyridine bearing NHC-Pd

complexes, better known as palladium PEPPSI (Pyridine enhaced pre catalyst stabilization, initiation) has drawn considerable research interest due to their air-stability and high-catalytic potentials. [40-44]

Herein, we proposed to synthesize anew palladium PEPPSI complex and investigate its catalytic application in cross-coupling reactions.[45-47]

Proposed objectives:

1. Synthesis of a new imidazolim salt to use as ligand precrussors
2. Synthesis of a new Pd-PEPPSI complex.
3. Characterization of synthesized imidazolium salt and the complex will be performed by NMR, Mass spectra, etc.
4. The catalytic activities of homogenous catalytic systems will be evaluated for cross-coupling reactions.

2. Experimental

3. Materials and Methods

Chemicals and solvents were purchased from various chemical pharm such as Sigma-Aldrich, TCI etc. The solvents were used as they are found from commercial suppliers without further purification. ^{1}H, ^{13}C, and ^{19}F NMR spectra of the imidazolium salts and the complex was recorded at Bruker avance (500 MHZ) spectrometer. High resolution mass spectra were recorded with an Agilent 6550 iFunnel Q-TOF MS system.

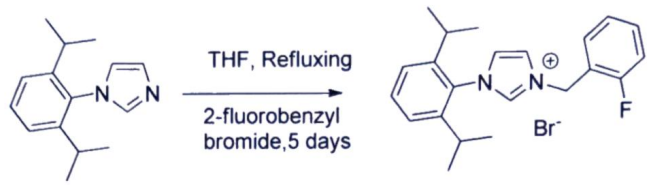
(a) Synthesis of ligands - 1-(2,6-diisopropylphenyl)imidazole (1 mmol), and2-flourobenzyl bromide (10 mmol) are taken in a round bottom flask and the mixture is allowed to dissolve in 5 ml THF and then the resulting mixture was heated at 60^0 C for 120 hours. The reaction mixture is allowed to cool and upon addition of hexane solid mass was precipitated. The solution was filtered and filtrate part was washed with hexane thrice .The solid mass was dried in vaccum

(b) Synthesis of Pd-PEEPSI complex : -Imidazolium salt (0.5mmol), Palladium chloride (0.7mmol) and potassium carbonate(K_2CO_3 ,2.5mmol) ,then added excess of KBr and are taken in a round bottom flask and the mixture is allowed to dissolve in 4 mL pyridine and the resultant mixture was heated at 85^0 C for 72 hours. The reaction mixture is allowed to cool, added silica gel mesh (100-200) and DCM to it and then evaporated with the help of rotary evaporator. And the final mixture was then worked up with column chromatography.

4. Result and Discussion

Initially, for preparing the imidazolium salts, we have adopted the standard literature procedure and the reaction of imidazole precursor with 2-florobenzyl bromide was carried out in refluxing CH_3CN for three days. However, after completion of required time, it was observed that the yield of the resulting compound is discernibly low. Therefore, the reaction was carried out in DMF at 82^0C and the 56% yield of corresponding imidazolium salt was obtained. Gratifyingly, when the same reaction was carried out in refluxing THF for 3 days,

the yield of imidazolim salt was improved to 79%. The schematic representation of preparation of imidazolium salt is given below- (Scheme1).

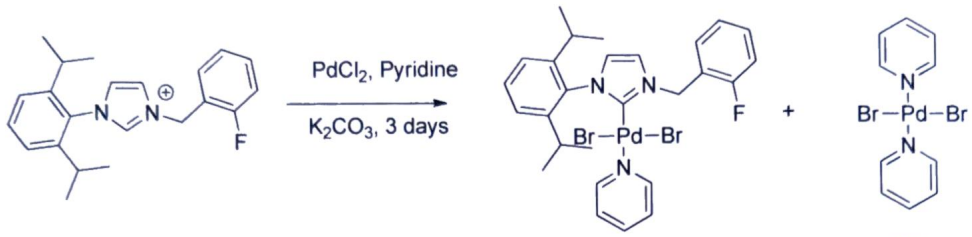


Scheme 1: Preparation of imidazolium salts

It is worthwhile to mention that the pure imidazolim salt can be obtained by precipitating it from the cool reaction mixture by addition of hexane. The successful formation of the salt was confirmed by observing downfield shift of imidazolium proton to 9.83ppm . Moreover, additional signal appeared at 5.64 ppm (singlet) for two benzylic protons. Further ^{13}C NMR spectrum of the ligand also indicates the successful formation of salts. In ^{13}C NMR spectrum of the ligand, a peak was observed at about 145 ppm which was assigned for NCHN C atom of the salt. Moreover, the peak for benzylic C was observed at 47 ppm. Finally, the formation of imidazolium salts was further confirmed by observing peak at mass spectrometry at m/z value 337.23 which is corresponds to [M-Br] peak.

Pd-PEPPSI complex is synthesized when imidazolium salt react with $PdCl_2$ in refluxing Pyridine in the presence of K_2CO_3 as a base and a large excess of KBr for 72 hour . The resulting reaction mixture was diluted with DCM and silica gel . Then the DCM was removed by rotary evapourator and the Pd-PEPPSI complexes present in the reaction mixture are absorbed by the silica gel. After that isolated the required Pd-PEPPSI complex with the help of column chromatrogrphy . But unfortunately we failed to isolate the Pd-PEPPSI complex. Instead of it, bis-pyridine Pd(II) complex is recovered from the reaction

mixture. The schematic representation that adopted for the preparation of Pd-PEPPSI complex is given below – (Scheme2)



Scheme 2: Preparation of Pd-PEPPSI complex

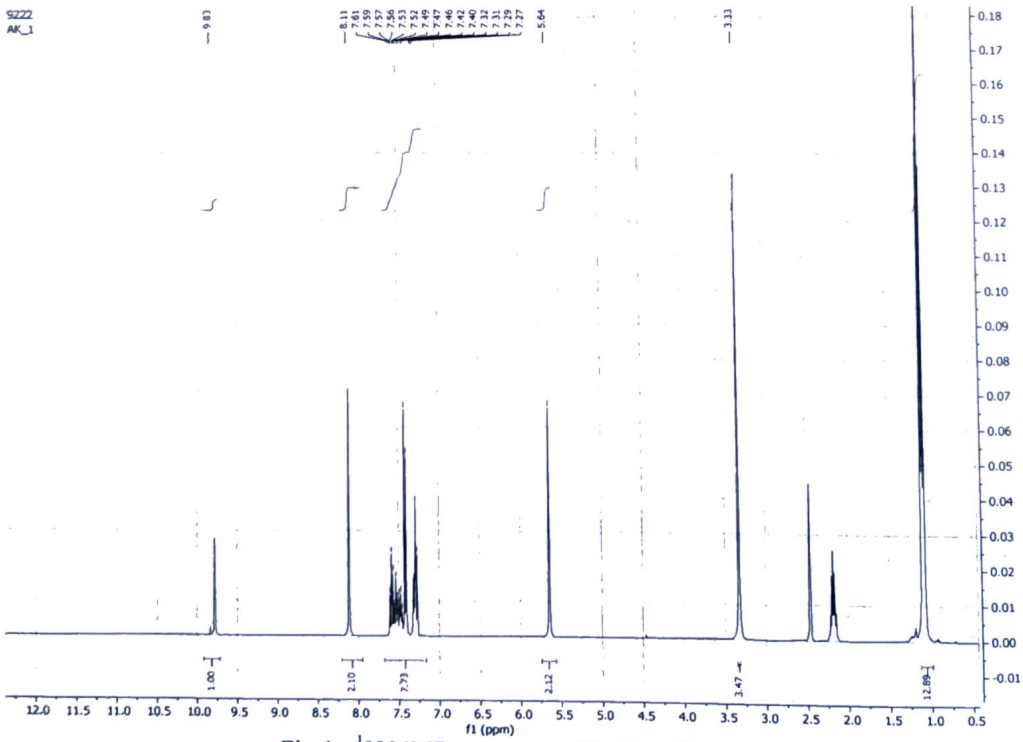


Fig 1 : ^{1}H NMR spectrum of imidazolium salt

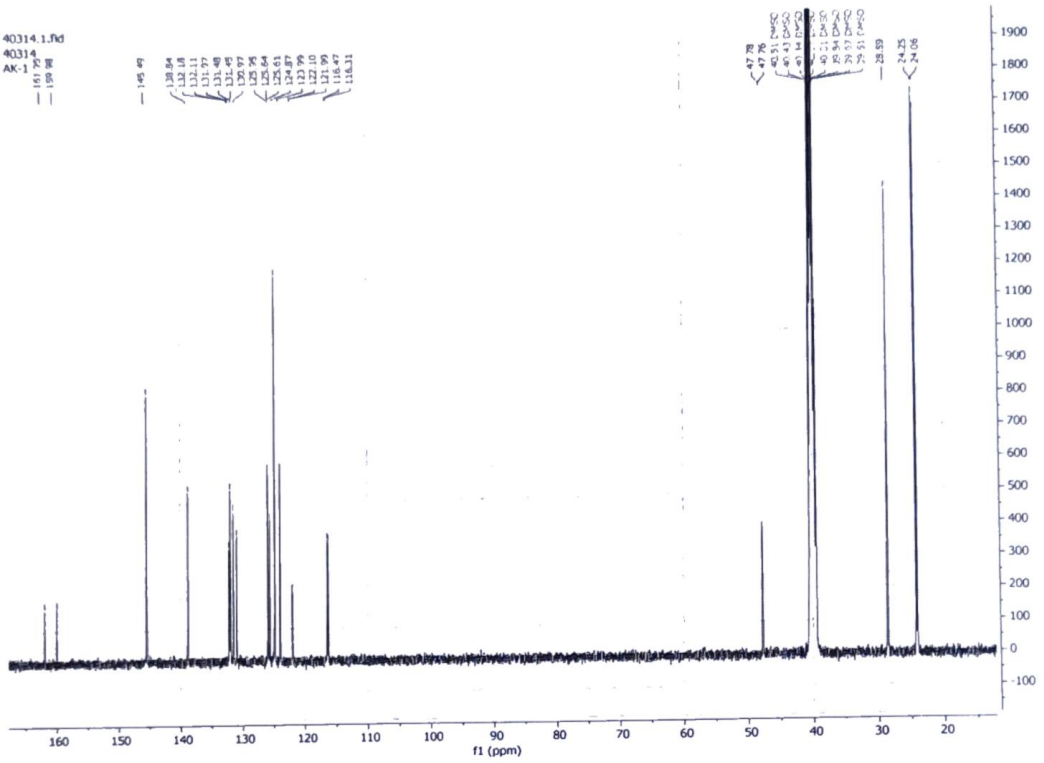


Fig 2 : ^{13}C NMR spectrum of imidazolium salt

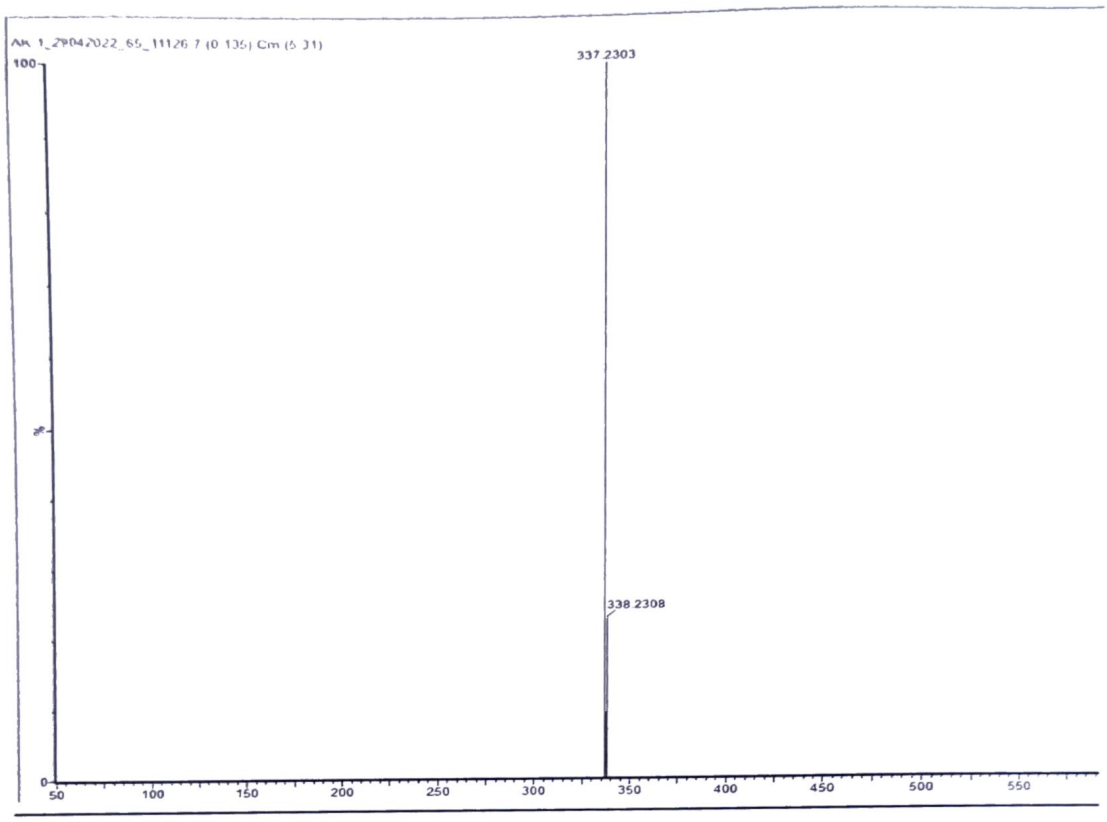
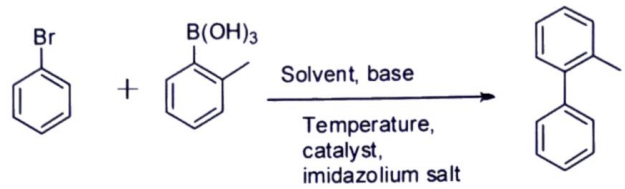


Fig 3 – HRMS spectrum of imidazolium salt

5. Catalysis optimization

For obtaining the optimized reaction conditions for Suzuki-Miyaura reaction, a model reaction was performed using 2-methylphenyl boronic acid(1.5 mmol) and, bromobenzene (1.5 mmol) in the presents of $Pd(OAc)_2$ (1 mol%), the imidazolium salt (L1, 1 mol%), K_2CO_3(2 mmol) at 65°C for 24 h under aerobic conditions.

Table 1 : Screening of Precatalysts and Reaction Conditions for the Suzuki- Miayura Reaction in air



Entry	Base (mmol)	Solvent	Yield (%)
1	K_2CO_3	THF	85
2	K_2CO_3	Toluene	60
3	K_2CO_3	DMF	58
4	K_2CO_3	EtOH	55
5	K_2CO_3	H_2O	35
6	Na_2CO_3	THF	83
7	KotBu	THF	63
8	KOH	THF	32
9	NaOH	THF	34
10[a]	K_2CO_3	THF	56
11[b]	K_2CO_3	THF	86
12[c]	--	THF	00

13[d]	K_2CO_3	THF	00
14[e]	K_2CO_3	THF	57

(Unless otherwise specified , all reaction were carried out using same amount of 2-methylphenyl boronic acid and bromobenzene , base(2 m mol) , $Pd(OAc)_2$(2 mg) in solvent (4 mL) at 65°C for 24 h. [a] at room temperature, [b] 1.5 equiv of K_2CO_3, [c] in absence of base [d] in absence of $Pd(OAc)_2$ [e]

Initially, focused has been given to obtain a suitable solvent for the catalytic system. For this purpose, the model reaction was carried out in various solvents such as THF, toluene, DMF, ethanol, and water (Table 1, entries 1-5). Investigation of effect of solvents in the catalytic outcome shows that THF is the best solvent (Table 1, entry 1) for our catalytic system while the reaction delivered a low yield of corresponding cross-coupling product in water and ethanol (Table 1, entries 4 &5). Next, various bases such as K_2CO_3, Na_2CO_3, KotBu, KOH, and NaOH are screened to understand the effects of nature of bases on the reaction yield (Table 1, entries 1, 6-9). It has been found that K_2CO_3 is the best base for our catalytic system while Na_2CO_3 renders comparable result (Table 1, entries 1 & 6). Hydroxide bases such as KOH and NaOH furnished a low yield of corresponding cross-coupling product (Table 1, entries 8 & 9). Next, when the model reaction was carried out at room temperature, the yield of the reaction was declined to 56%. To investigate the effect of base load, the reaction was performed at 60°C and it has provided 86 % yield of corresponding cross-coupling product (Table 1, entry 11). In the absence of either base or $Pd(OAc)_2$, the reaction does not proceed at all to give the expected product. In absence of imidazolium salt, the reaction gave only 57% yield of corresponding cross-coupling products (Table 1, entry 14).

Conclusion - In conclusion, we have successfully prepared a pure imidazolium salt which was confirmed by ^{13}C NMR,^{1}H NMR and HRMS. The imidazolium salt along with $Pd(OAc)_2$ shows efficient catalytic activities in Suzuki-Miyuara reaction.

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