Transition Metal Complexes with Protic-NHC Ligands

M.Sc. Research Thesis

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Transition Metal Complexes with Protic-NHC Ligands

A THESIS

Submitted in partial fulfillment of the requirements

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of

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by

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled "**Transition Metal Complexes with protic-NHC Ligands**," in the partial fulfilment of the requirements for the award of the degree of **MASTER of SCIENCE** and submitted to the **DEPARTMENT of CHEMISTRY**, Indian Institute of Technology Indore, is an authentic record of my work carried out during the period July 2025 to May 2026 under the supervision of **Dr. Amrendra K. Singh**, Department of Chemistry, Indian Institute of Technology Indore. The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute



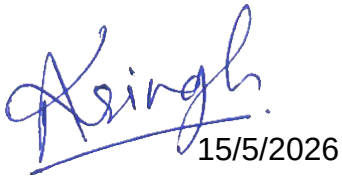
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15/5/2026

Signature of the supervisor of M. Sc Thesis with Date

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ABSTRACT

In this work, we investigated the design and synthesis of a palladium-based N-heterocyclic carbene (Pd-NHC) PEPPSI-type protic palladium complex that features an unsymmetrical NNC pincer ligand framework. We used a previously synthesized ligand system in our laboratory for this study. The synthesis included key C-N bond-forming reactions, followed by *N*-methylation to create the carbene precursor. We obtained the desired Pd-NHC protic palladium complex by combining the precursor with palladium under inert conditions. We confirmed the formation of the protic palladium complex using spectroscopic and analytical techniques, mainly LC-MS and UV-visible spectroscopy. Mass spectrometry showed molecular ion peaks that matched the proposed Pd-NHC species. UV-Vis studies revealed charge-transfer transitions, indicating effective coordination between the metal center and the ligand. Although we could not perform NMR characterization due to the limited solubility of the isolated complex, analysis of the reaction filtrate provided strong evidence for its formation. The ligand design includes a pyridine group that mimics PEPPSI-type systems, where the pyridine acts as a labile "throw-away" ligand, helping generate the catalytically active species. The hemilabile nature of the ligand framework is expected to improve catalytic performance by allowing flexible coordination during the catalytic cycle. Overall, this study presents a tailored Pd-NHC protic palladium complex with potential applications in cross-coupling catalysis, particularly for challenging substrates such as aryl chlorides. This work contributes to the development of stable, efficient, and phosphine-free catalytic systems in modern organometallic chemistry.

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ACRONYMS

DMSO-d_6	Deuterated dimethyl sulphoxide
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
THF	Tetrahydrofuran
Dppf	1,1′-Bis(diphenylphosphino)ferrocene
EA	Ethyl acetate
NaO^tBu	Sodium tert-butoxide
KO^tBu	Potassium tert-butoxide
HRMS	High-resolution mass spectra
LC-MS	Liquid chromatography-mass spectrometry
NMR	Nuclear magnetic resonance

NOMENCLATURE

h	hour
Hz	Hertz
M	Molar
mL	milliliter
mg	milligrams
MHz	megahertz
mmol	millimole
nm	nanometer
ppm	parts per million

CHAPTER 1

INTRODUCTION

1.1 Aim of the project:

Thus, the general purpose of this work is to design a new Pd-NHC PEPPSI-type catalyst containing pyridine ligands and evaluate its catalytic activity in cross-couplings. It should be noted that aryl iodides and bromides are generally preferred substrates for the commonly used Suzuki and Heck cross-coupling reactions due to their high reactivity. However, aryl chlorides are used much more rarely than iodide and bromide analogs due to the poor reactivity of aryl chlorides resulting from the stronger C-Cl bond and, therefore, difficult oxidative addition reaction.[1] Thus, another goal of this study is to develop a catalyst that activates aryl chlorides, thereby expanding the range of possible substrates. In particular, for this purpose, the ligand system was selected to contain a pyridine ligand, as in PEPPSI-type catalysts, which acts as a "throw-away" ligand to help produce the catalytically active form.[2] In addition, the ligand's hemilability is expected to enhance catalytic activity by facilitating coordination. The main purpose of the present research is to aid the development of a powerful, inexpensive, and effective Pd-NHC catalyst system capable of activating less reactive aryl chlorides for subsequent reactions.

1.2 General Introduction:

Pincer ligands have become a crucial type of ligand in transition metal catalysis because of their strong tridentate coordination and ability to improve the stability and reactivity of metal complexes.[3] These ligands are commonly used in various catalytic reactions, including cross-coupling, C-H activation, hydrogenation, and dehydrogenation. The firm coordination framework provided by pincer ligands ensures strong metal binding, which boosts catalytic efficiency and selectivity. Unsymmetrical pincer systems, in particular, offer additional advantages by introducing different donor atoms, thereby allowing changes in the electronic properties of the metal center.[4] Among the various ligand systems, N-heterocyclic carbenes (NHCs) have

attracted considerable attention in organometallic chemistry due to their strong σ-donating ability, excellent thermal stability, and adjustable steric and electronic properties.[5] NHC ligands form strong metal-carbon bonds, enhancing the overall stability of the complex and preventing catalyst breakdown during reactions. These features make NHC-based complexes highly effective in facilitating key catalytic steps such as oxidative addition and reductive elimination.

Palladium complexes with NHC ligands (Pd-NHC) have become particularly significant in cross-coupling catalysis. Compared to traditional phosphine-based systems, Pd-NHC complexes exhibit greater stability and superior catalytic performance, particularly for challenging transformations involving less reactive substrates such as aryl chlorides.[6] The strong metal-ligand interaction in Pd-NHC systems increases electron density at the palladium center, thereby aiding challenging bond activation processes.[7] Additionally, the development of PEPPSI-type Pd-NHC complexes has greatly advanced this field. These complexes incorporate a pyridine ligand as a labile "throw-away" ligand. They are easy to synthesize, stable in air and moisture, and highly active in many C-C and C-N bond-forming reactions.[2] The presence of hemilabile coordination in these systems enables flexible ligand behavior, thereby improving catalytic turnover and efficiency.[8]

Overall, the combination of pincer ligand frameworks with NHC donors in palladium complexes offers a strong platform for designing reliable and effective catalysts. These systems not only improve catalytic performance but also broaden the range of cross-coupling reactions, making them highly valuable in modern synthetic chemistry.

1.3 N-Heterocyclic carbene (NHC):

N-Heterocyclic carbene (NHC) chemistry began in 1968 with the pioneering work of Ofel[9] and Wanzlick[10], who focused on metal coordination compounds derived from azolium salts. The successful isolation and characterization of an N-heterocyclic carbene in 1991 opened up a new class

of organic compounds for investigation. N-Heterocyclic carbenes (NHCs) are neutral, cyclic molecules that have a divalent carbene carbon atom bonded to at least one nitrogen atom in the ring. Carbenes are usually very reactive intermediates. NHCs achieve stability through both electronic and steric factors.[2]

Electronic Stabilization:

σ-Donation: NHCs are strong sigma donors, which means they donate substantial electron density to a metal center or nearby atoms. This makes strong, stable bonds.

π-Back-Donation: In complexes, stability is further improved by π-back-donation from the metal to the empty π-orbital of the carbon atom in the carbene. In the ring, the nitrogen atoms give π-donation to this empty π-orbital. This increases the electron density on the carbene carbon and stabilizes the singlet state.[11,12]

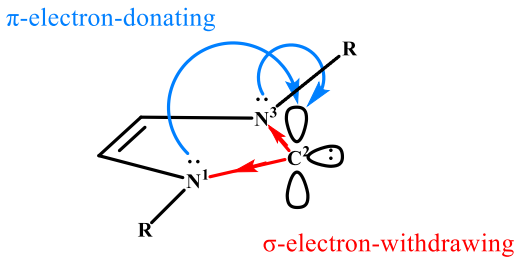


Figure 1: Ground-state electronic structure of imidazol-2-ylidenes.

Steric Stabilization: Big groups on the nitrogen atoms create "steric shielding" around the carbene center. This physical barrier stops the highly reactive carbene carbon from dimerizing or having unwanted side reactions. Benzimidazol-2-ylidenes are a specific type of NHC in which a benzene ring is fused to a five-membered imidazole ring.[2,13]

Structural Benefits: The fusion of the benzene ring makes the ligand more rigid and stable at high temperatures than simple imidazole-based NHCs.[14]

Adjustable Properties: The benzimidazole core is very flexible. You can change its electronic and steric properties by adding different substituents to

the nitrogen atoms or the aromatic backbone. Adding bulky groups to the aromatic ring, for instance, has been shown to improve biological activity and structural stability.[15]

Catalytic[16] and Biological Utility[17]: Benzimidazol-2-ylidene complexes, including those with silver or palladium, are highly active in many settings. They are widely used in PEPPSI-type palladium catalysts for C-H arylation reactions because they stabilize the catalyst and improve its steric profile, thereby increasing catalytic turnover and selectivity. They also show great promise as anticancer and antimicrobial agents[18] in medicinal chemistry.[19] N-Heterocyclic carbenes (NHCs) have become one of the most important ligand systems in organometallic chemistry over the past few decades. Their growing popularity stems mainly from their ability to form very strong, stable bonds with transition metals, which directly affects the performance of metal complexes in catalysis.[2]

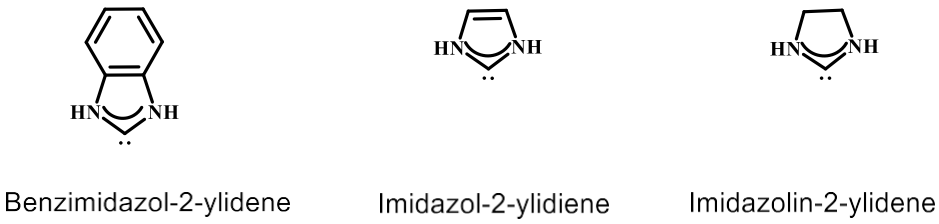


Figure 2: N-heterocyclic Carbenes.

Another major advantage of NHCs is their robustness.[20] These ligands are highly stable under thermal and chemical conditions that many traditional ligands cannot withstand. Because of this, NHC-based complexes can be used under demanding reaction conditions without rapid decomposition, a significant advantage in practical catalysis.[21]

What makes NHCs even more interesting is their design flexibility. By changing substituents on the nitrogen atoms or modifying the backbone, their steric and electronic properties can be easily tuned. Recent studies have also shown that NHCs are not limited to classical neutral forms but can also exist as protic NHCs, which introduce additional interactions, such as hydrogen

bonding.[22] These features can influence reactivity and, in some cases, improve catalytic behavior.

In addition, NHC ligands are known to adopt various coordination modes, including normal and abnormal binding modes.[23] This flexibility allows better control over the metal center and can lead to unique reactivity patterns. Because of these properties, NHC-based complexes have shown excellent performance in various catalytic transformations, particularly in cross-coupling reactions, where both stability and reactivity are crucial. Overall, NHCs provide a powerful and versatile platform for designing efficient metal catalysts, and their continued development is advancing modern synthetic chemistry.[24]

1.4 NHC-Palladium Complexes

Palladium-NHC complexes have emerged as highly efficient catalytic systems, particularly in cross-coupling reactions.[25] The strong σ-donating nature of NHC ligands makes the metal center electron-rich, which significantly facilitates key steps such as oxidative addition. This effect becomes especially important for less reactive substrates, such as aryl chlorides, where activating the C-Cl bond is inherently challenging.[18,26,27]

In addition to promoting oxidative addition, the steric bulk of NHC ligands also plays a crucial role in enhancing reductive elimination, thereby improving the overall catalytic cycle.[28] Furthermore, the strong metal-ligand interaction helps stabilize low-valent palladium species and prevents catalyst decomposition into inactive forms, such as palladium black, a common issue in cross-coupling reactions.

A major advancement in this area was the development of PEPPSI-type palladium complexes (Pyridine Enhanced Pre-catalyst Preparation, Stabilization, and Initiation), first reported by Steven P. Nolan and co-workers.[29] These complexes were later extensively developed and applied by

Organ and other research groups, establishing them as practical and versatile catalytic systems.[2]

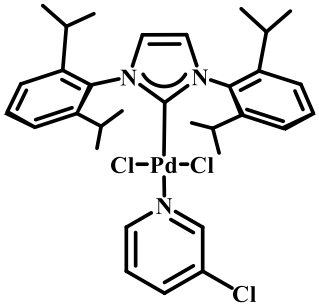


Figure 3: First reported PEPPSI Complex

The resulting NHC-stabilized palladium species exhibit high catalytic activity across a wide range of cross-coupling reactions, including Suzuki-Miyaura, Negishi, Kumada, and Buchwald-Hartwig reactions. Their operational simplicity, stability under ambient conditions, and versatility make Pd-NHC PEPPSI complexes highly attractive for practical applications in organic synthesis.

Overall, the combination of strong electronic donation, steric control, and the unique role of pyridine as a labile ligand makes Pd-NHC PEPPSI complexes powerful tools for developing efficient catalytic systems, particularly for challenging transformations such as the activation of less reactive aryl halides.[2]

CHAPTER 2

EXPERIMENTAL SECTION

2.1 General information:

All reagents utilized in this study were procured from the commercial suppliers and utilized without additional purification, unless specified otherwise. But before use, toluene, dichloromethane (DCM), acetonitrile, and methanol were distilled. We did all of the reactions in a nitrogen atmosphere with a Schlenk line. We used TLC (thin-layer chromatography) on Merck 60F254 precoated silica gel plates to monitor the reaction. We used column chromatography with silica gel (100–200 mesh) to clean the products.

2.2 Chemicals and Reagents:

All solvents and reagents used in this study were obtained from commercial suppliers, and solvents were used with further purification. These were benzimidazole (SRL, 99%), 2,6-dibromopyridine (Alfa Aesar, 98%), 2-bromopyridine (Spectrochem, 99%), potassium carbonate (SRL, 99.5%), sodium bicarbonate (SRL, 99.5%), sodium tetrachloropalladate (Aldrich, 98%), and methyl iodide (Spectrochem, 99%).

2.3 Instrumentation

NMR spectra were collected at 25 ℃ with Bruker Avance III 400 and 500 MHz spectrometers. Mass spectrometry measurements were done on a Bruker Daltonics microTOF-Q II instrument.

2.4 SYNTHESIS OF LIGANDS

Experiment procedure

2.4.1 Synthesis of Ligand L1:

A round-bottom flask was charged with 2,6-dibromopyridine (2.0 g, 0.008 mol), Benzimidazole (1.5 g, 0.012 mol), K_2CO_3 (1.75 g, 0.012 mol), and dry DMSO (15 ml). The flask was then placed in the Microwave for 30 minutes at 65 ℃. Once the reaction was completed, the reaction mixture was extracted

with DCM and brine, passed through sodium sulfate, and the crude residue was purified by using column chromatography on silica gel (60–120 mesh) using hexane/ethyl acetate (70:30) as the eluent to obtain the product. We obtained the crude product (72%, 0.656 g) and determined it to be the ligand by analyzing its ^{1}H and ^{13}C NMR data. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C δ 8.55(s,1H), 8.13–8.00(m,1H), 7.91–7.82(m, 1H), 7.73(t, J=7.8Hz,1H), 7.52(d, J=8.0Hz, 1H), 7.46(d, J=7.8Hz, 1H), 7.39(m, J=19.6,7.4, 1.3Hz,2H).$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 25 °C) δ149.61, 144.66, 141.16, 140.95, 140.89, 131.80, 125.79, 124.67, 123.76, 120.79, 112.93, 112.18.

2.4.2 Synthesis of Ligand L2:

p-Toluidine (2.14 g, 0.020 mol) and 2-bromopyridine (2.0 mL, 0.020 mol) were placed into a pressure tube and heated at 160 °C for 24 hours. After the completion of the reaction, the mixture was treated with a saturated Na_2CO_3 solution and extracted. A greenish solid formed, which was separated by filtration and washed with dichloromethane (DCM). Next, the residue was treated with hexane to encourage precipitation. The mixture was allowed to sit undisturbed for two days to ensure complete crystallization. The resulting solid (2.5 g, 68.3%) was collected by filtration and checked by thin-layer chromatography (TLC) to confirm its purity and identity. The structure was verified by ^{1}H and ^{13}C NMR analysis.^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 8.17 (d, *J* = 4.8 Hz, 1H), 7.46 (q, *J* = 6.3, 5.4 Hz, 1H), 7.24 – 7.09 (m, 4H), 6.82 (d, *J* = 7.7 Hz, 2H), 6.69 (q, *J* = 5.6, 5.0 Hz, 1H), 2.33 (s, 3H).$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 25 °C) δ 156.63, 148.38, 137.79, 137.69, 132.82, 129.87, 121.29, 114.59, 107.70, 20.85.

2.4.3 Synthesis of Ligand L3

A 100 mL two-neck round-bottom flask was taken and equipped with a reflux condenser, was filled in an inert atmosphere with **L1** (1.0 g, 0.003 mol), **L2** (0.874 g, 0.004 mol), $Pd(dba)_2$ (0.103 g, 0.00018 mol), dppf (0.099 g,

0.00018 mol), NaO^{t}Bu (0.449 g, 0.00468 mol), and dry toluene (15 mL). The reaction mixture was refluxed at 110 °C for 24 hours. After completion of the reaction, the reaction mixture was cooled at room temperature, followed by the addition of Ethyl acetate (20 mL). The mixture was stirred for 30 minutes. The reaction mixture was then filtered through a Celite pad to remove any insoluble residues. Next, the excess solvent was removed using a Rotavapor, yielding a brown crude product. Further purification was done by column chromatography on silica gel (60–120 mesh) using a mixture of ethyl acetate and hexane (70:30) as the eluent, yielding the desired compound as a light brown solid (0.88 g, 65% yield). HRMS (ESI)$^+$ *m/z* calculated for $C_{24}H_{19}N_5$ 378.1715, found 378.1713 and ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 8.44 (s, 1H), 8.43 (d, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.71 (t, J = 8.2 Hz, 1H), 7.62 (dd, J = 19.7,8.3Hz,2H),7.29 (d, J = 7.7 Hz, 3H), 7.23 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.9 Hz, 1H), 7.08 (t, J = 9.3 Hz, 3H), 7.04 (d, J = 5.9Hz, 1H), 2.44(s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C) δ 158.07, 157.85, 148.83, 144.74, 142.11, 141.37, 140.29, 138.27, 136.94, 132.47, 131.11, 128.65, 124.19, 123.46, 120.54, 119.40, 118.56, 114.32, 112.37, 105.90, 21.57

2.4.4 Synthesis of Ligand L4·HI

A well-dried pressure tube was taken and charged with **L3** (200 mg, 0.530 mmol). Then, methyl iodide (33 µL, 0.530 mmol) was added. Anhydrous toluene was included to ensure complete dissolution of the reactants. The tube was sealed, and the reaction mixture was heated at reflux temperature with continuous stirring for 24 hours. After completion of the reaction, the mixture was cooled to room temperature before work-up, and the crude product was collected (154.2 mg, 75.26% yield). LCMS (ESI)$^+$ *m/z* calculated for $C_{17}H_{14}N_5Br^+$ 392.1870, found 392.1872 ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 11.46 (s, 1H), 8.40 (dd, *J* = 4.9, 2.0 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.69 (dd, *J* = 8.5, 4.2 Hz, 2H), 7.62 (td, *J* = 7.8, 2.1 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.33 – 7.21 (m, 5H), 7.20 – 7.12 (m, 2H), 7.05 (dd, *J* = 7.3, 4.9 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 4.38

(s, 3H), 2.41 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 156.87, 148.15, 145.73, 141.00, 140.85, 139.81, 138.05, 136.78, 131.97, 130.66, 129.27, 128.22, 127.29, 127.25, 119.33, 117.96, 114.36, 112.10, 107.53, 34.31, 20.92.

2.4.5 Synthesis of Ligand L5

A 50 mL two-neck RB flask was taken and fitted with a reflux condenser under an inert atmosphere. Into this flask, 6-bromo-2-benzimidazole (1.370 g, 5 mmol), 2-aminopyridine (0.611 g, 6.5 mmol), $Pd(dba)_2$ (0.109 g, 0.19 mmol), dppf (0.105 g, 0.19 mmol), and NaO^tBu (0.5765 g, 6 mmol) were added, followed by 10 mL of dry toluene. The reaction mixture was heated under reflux conditions for 24 hours. Once the reaction was complete, it cooled to room temperature, and 20 mL of ethyl acetate was added. After that, the reaction mixture was stirred again for an additional 30 minutes, during which a red solid formed. The reaction mixture was then filtered through a Celite pad to remove any insoluble residues. yielding a light brown residue.

After that, the crude product was purified using column chromatography over silica gel with an ethyl acetate/hexane (70:30) mixture as the eluent, yielding the desired compound as a brown solid (0.95 g, 66% yield). LCMS $(ESI)^+$ *m/z* calculated for $C_{17}H_{13}N_5$ 288.1249, found 288.1256. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 8.49 (s, 1H), 8.23 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.93 – 7.84 (m, 1H), 7.78 (dt, *J* = 7.4, 3.6 Hz, 1H), 7.71 – 7.58 (m, 2H), 7.58 – 7.50 (m, 1H), 7.33 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.26 (dh, *J* = 7.9, 3.0 Hz, 2H), 6.97 (dd, *J* = 7.7, 2.7 Hz, 1H), 6.83 (dd, *J* = 7.2, 5.0 Hz, 1H).

2.4.6 Synthesis of Ligand L6

An oven-dried RB flask was filled with **L3** (25 mg, 0.066 mmol). Next, N-bromosuccinimide (NBS) was added (11.79 mg, 0.066 mmol). After that, the mixture was stirred at 0 °C for 30 minutes. Thin-layer chromatography (TLC) monitored the reaction's progress. It showed two distinct spots, suggesting multiple products were formed. Next, LC-MS was performed on the crude

reaction mixture to confirm the bromination. To separate the components, the mixture was subjected to column chromatography, yielding two individual products. Further structural characterization using ^{1}H NMR spectroscopy showed that bromination did not happen at the C2 position of the benzimidazole ring. This was clear from the unchanged characteristic proton signal at this position, which was the same as the parent ligand. This indicated that substitution occurred at a different site.

2.4.7 Synthesis of Ligand L7

An oven-dried round-bottom flask was filled with **L5** (25 mg, 0.066 mmol). Then, N-bromosuccinimide (NBS) was added (11.79 mg, 0.066 mmol). The reaction mixture was kept at 0 ℃ and stirred for 30 minutes. Thin-layer chromatography (TLC) monitored the reaction's progress, showing two distinct spots. This indicated the formation of multiple products. Next, the crude mixture was analyzed by LC-MS, which confirmed that bromination had taken place. To separate the components, the mixture was purified by column chromatography, resulting in two distinct fractions. Further characterization through ^{1}H NMR spectroscopy showed that bromination did not occur at the C2 position of the benzimidazole ring. This was confirmed by the characteristic proton signal at that position, which remained unchanged compared to the parent ligand. This indicates that substitution happened at a different site.

2.5 SYNTHESIS OF COMPLEXES:

2.5.1 Synthesis of Precursor P1:

Sodium tetrachloropalladate (100 mg, 0.34 mmol) was taken and dissolved in HCl (1 mL) and stirred for 20 minutes. After that, the reaction mixture was cooled to room temperature. After that, ethanol was added, and stirring continued for another 10 minutes. A white precipitate of NaCl formed during this time and was removed by filtration. Next, the clear liquid was treated with cyclooctadiene (COD) and stirred until precipitation occurred. The final resulting solid was isolated by decantation and washed multiple times with diethyl ether, yielding the palladium precursor as a yellow fluffy solid (70 mg, 72% yield).

2.5.2 Synthesis of Precursor P2:

Sodium tetrachloropalladate (200 mg, 0.68 mmol) was added to a well-dried Schlenk tube. It was dissolved in 10 mL of distilled acetonitrile to create a clear solution. It was performed under nitrogen and heated to reflux for 18 hours. Once finished, a wine-red solution appeared along with a white precipitate. We ran the reaction mixture through a Celite pad while it was still hot to get rid of any impurities that couldn't be dissolved. The filtrate was then concentrated on a rotary evaporator under lower pressure, which gave the crude product. The palladium precursor, $PdCl_2(MeCN)_2$, was collected as a yellow solid (120 mg, 62% yield).

2.5.3 Synthesis of Complex Pd1

Method-a: A well-dried Schlenk tube was taken with a magnetic stir bar, and the ligand **L3** (12.85 mg, 0.034 mmol) was added. We dissolved it in distilled methanol and degassed it under nitrogen for 30 minutes. Next, we added sodium tetrachloropalladate (10.0 mg, 0.04 mmol) under inert conditions. We refluxed the mixture for 12 hours while stirring. LC-MS of the mixture did not show the expected peak at m/z 520.0363. This initial

trial established the standard reaction conditions but did not yield successful complex formation.

Method-b: In a modified attempt, **L3** (13.12 mg, 0.034 mmol) was dissolved in distilled methanol and degassed for 30 minutes under a nitrogen atmosphere. $Pd(dba)_2$ (10.0 mg, 0.034 mmol) was then added. The reaction mixture was heated at reflux for 12 hours. LC-MS analysis still did not show the desired molecular ion peak. Compared to method-a, changing the palladium precursor alone did not improve the reaction outcome.

Method-c: L3 (50 mg, 0.0965 mmol) was taken and dissolved in DCM, and degassed for 15 minutes under a nitrogen atmosphere. The solution was then cooled at room temperature, and Ag_2O (22.36 mg, 0.0965 mmol) was added. The reaction mixture was stirred in the dark for 1 hour to facilitate carbene formation. After that, precursor P1 (0.115 mmol) was added under a nitrogen atmosphere, and the reaction mixture was refluxed for 24 hours. After filtering through Celite, LC-MS analysis did not detect any desired product. In contrast to earlier attempts, creating the carbene intermediate in advance did not produce the desired complex.

Method-d: L3 (10 mg, 0.02 mmol) was dissolved in THF and degassed under a nitrogen atmosphere for 15 min. Sodium tetrachloropalladate (7.79 mg, 0.02 mmol) was added, and the reaction mixture was refluxed for 24 hours. LC-MS analysis did not detect any desired product. Changing the solvent system to THF did not significantly affect the reaction efficiency.

Method-e: When method-d was shown to be unavailing, a substitute method was applied. Again, a Schlenk tube was taken, equipped with a magnetic stir bar, charged with **L3** (20 mg, 0.05 mmol) dissolved in distilled methanol, and degassed under nitrogen for 15 min. To this solution, the metal precursor, **P1** (15.13 mg, 0.05 mmol) and triethylamine were also added under inert conditions. The mixture was then refluxed for 24 h. The reaction was evidenced by LC-MS and a calculated m/z value of 520.0363 for $C_{24}H_{20}N_5ClPd$ $[M]^+$, which was not observed.

Method-f: The compound **L3** (20 mg, 0.05 mmol) was dissolved in methanol and degassed for 15 min. After adding $PdCl_2(PPh_3)_2$ (36.02 mg, 0.05 mmol) under nitrogen, the reaction mixture was heated to reflux for 12 h. No desired product was detected through LC-MS measurements. Use of a phosphine-supported Pd precursor was also ineffective under these conditions.

Method-g: The Compound **L3** (20 mg, 0.05 mmol) was dissolved in distilled dichloromethane, and the reaction mixture was then degassed for 15 minutes under a nitrogen atmosphere. The mixture was refluxed for 12 hours following the addition of $PdCl_2(PPh_3)_2$ (36.02 mg, 0.05 mmol). Again, the LC-MS analysis did not reveal the anticipated chemical ion peak. The reaction results did not improve when the solvent was switched from methanol to dichloromethane.

Method-h: Again, a Schlenk tube was taken, with a magnetic stirring bar, and charged with **L3** (20 mg, 0.05 mmol) in methanol. The mixture was degassed for 15 minutes. After cooling the reaction mixture at room temperature, Ag_2O (11.58 mg, 0.05 mmol) was added. For one hour, the reaction mixture was agitated in the dark. After adding $Pd(PPh_3)_2Cl_2$ (36.02 mg, 0.05 mmol), the reaction mixture was then refluxed in the dark for 24 hours. The product was not formed, as confirmed by LC-MS analysis. This Pd source did not yield the desired complex, even with carbene preformation.

Method i: After obtaining fruitless results, a Schlenk tube was taken with a magnetic stirring bar, and charged with **L3** (20 mg, 0.05 mmol), which was dissolved in distilled dichloromethane and degassed for 15 minutes. The reaction mixture was stirred in the dark for 1 hour after the addition of Ag_2O (11.58 mg, 0.05 mmol). $Pd(PPh_3)_2Cl_2$ (36.02 mg, 0.05 mmol) was then added, and the reaction mixture was refluxed for 24 hours. LC-MS analysis again failed to show the desired product. This further confirmed that carbene formation alone was not enough under these conditions.

Method-j: When the outcome of method-i was not in our favor, a new method was pursued. Again, a Schlenk tube was taken, equipped with a magnetic stirring bar, charged with **L3** (35 mg, 0.09 mmol) dissolved in acetonitrile, and degassed for 15 minutes. Sodium tetrachloropalladate (23.85 mg, 0.11 mmol) was added under inert conditions. The reaction mixture was refluxed for 12 hours. LC-MS analysis did not show the expected peak. Even in a coordinating solvent like acetonitrile, the reaction did not work.

Method-k: After many failed attempts, a new approach was needed. Ligand **L3** (18 mg, 0.04 mmol) was taken in a well-dried Schlenk tube, mixed with distilled methanol, and left to degas for 30 minutes. In an inert atmosphere, the metal precursor **P2** (13.75 mg, 0.04 mmol) was added to this solution. The reaction mixture was then stirred and refluxed for 18 hours. A yellow solid formed when it was done. We used filtration to separate the precipitate, and LC-MS analysis of the filtrate showed that the desired complex had formed. The LC-MS $(ESI)^+$ m/z for $C_{24}H_{20}N_5ClPd$ $[M]^+$ 520.0363 was found to be 520.0403.

The systematic investigation of the synthesis of the Pd(II)-NHC complex from ligand **L3** was conducted under diverse reaction conditions (Methods a-k). Even though there were many tries, some reactions didn't make the product we wanted. This shows how sensitive carbene generation and metal coordination are to changes in reaction conditions. In the preliminary methodologies (Methods a and b), the direct interaction of the ligand **L3** with palladium precursors, including $Na_2PdCl_4$and $Pd(dba)_2$ in methanol, did not yield complex formation. This failure is due to the lack of an efficient method for making carbenes in situ. Since **L3** exists in its neutral form, it is not possible to make a free carbene without a suitable base or activating agent. To solve this, we attempted to generate a carbene using Ag_2O (Methods c, h, and i), which is often used to generate Ag-NHC intermediates. However, even in these circumstances, no desired product

was seen. This could be because the carbene formation isn't complete or effective, or because the intermediate species aren't stable under the reaction conditions. Also, the possible breakdown of silver intermediates or competing side reactions may have made it harder to transfer metals to palladium effectively. The effect of the solvent was also studied using methanol, dichloromethane, and THF as solvents (Methods d, g, and j). The non-reactivity of THF (Method d) could be due to its comparatively weak coordinating capacity, which may fail to adequately stabilize reactive intermediates. Methanol, on the other hand, is a polar solvent that can also make carbene less stable by forming hydrogen bonds or protonation. This makes it harder for carbene to form. Dichloromethane, which is also non-polar and weakly coordinating, may not be able to help create a stable metal-ligand complex. Using bases like triethylamine (Method e) didn't work either, and the desired complex didn't form. This indicates that straightforward base-mediated deprotonation is insufficient to produce a stable carbene from **L3**, probably because the carbene-forming energy barrier is comparatively high in the absence of an appropriate precursor, such as an imidazolium salt. The application of phosphine-supported palladium precursors (Methods f-i) was likewise ineffective. This might be because phosphine ligands bind very tightly to palladium, preventing ligand exchange and preventing the NHC ligand from binding to the metal center. Method-k made a significant step forward by using **P2** as the palladium source. The effectiveness of this method is due to the presence of labile acetonitrile ligands, which are weakly bound and can be readily replaced by the new NHC ligand. This makes it easier to coordinate and form the Pd-NHC complex. **P1**, on the other hand, has cyclooctadiene ligands that are more tightly bound and less mobile, making it less effective at forming complexes. Also, acetonitrile, as a coordinating solvent, may help stabilize intermediate species and accelerate ligand-exchange processes. The successful formation of a complex was made possible by the combined effects of a labile precursor and a suitable reaction environment.

In general, these observations show how important it is to choose the right precursor, solvent environment, and method for making carbenes when preparing Pd-NHC complexes. The research demonstrates that effective complex formation requires both appropriate ligand design and meticulous optimization of reaction conditions.

2.5.4 Synthesis of Complex Pd2

We put 27 mg (0.057 mmol) of **L4·HI** into a well-dried Schlenk tube. This was dissolved in distilled methanol and left to degas for 20 minutes at reflux temperature under nitrogen. We added Ag_2O (13.16 mg, 0.057 mmol) after the reaction mixture had cooled to room temperature. The reaction mixture was stirred for an hour in the dark to promote the formation of carbenes. Then, in an inert environment, the metal precursor **P2** (0.015 mmol) was added. After adding the metal precursor, the mixture was stirred at reflux temperature for 24 hours. The reaction mixture was passed through a celite pad, yielding a clear, yellow liquid. After that, the extra solvent was evaporated from the rotary evaporator. The resulting product was analyzed by LCMS, confirming the formation of the desired complex. LC-MS (ESI) m/z calculated for $C_{25}H_{21}N_5ClPd^+$ $[M]^+$ 534.0519, found: 534.0563.

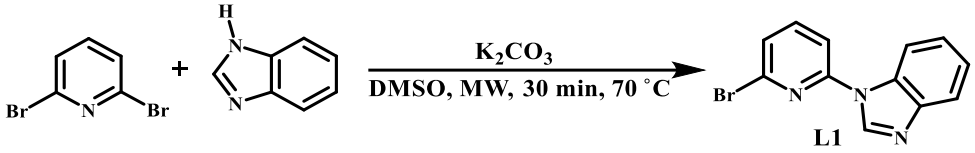
CHAPTER 3

Results And Discussion

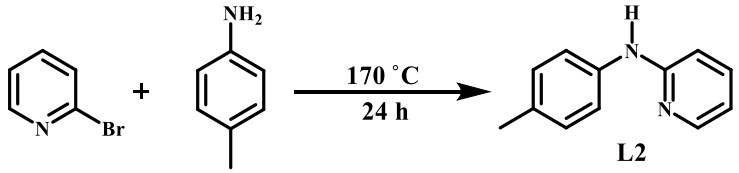
3.1 Synthesis of Ligand Precursor:

The unsymmetrical NNC pincer ligands **L3** and **L4·HI** were prepared via a multistep process. First, the intermediate compounds **L1**(1-(6-bromopyridin-2-yl)-1*H*-benzo[*d*]imidazole) and **L2** (*N*-(*p*-tolyl)pyridin-2-amine) were prepared according to methods reported in the literature.[30] Next, these intermediates were combined via a palladium-catalyzed Buchwald-Hartwig amination reaction[31], yielding the target ligand **L3** (6-(1*H*-benzo[*d*]imidazol-1-yl)-*N*-(pyridin-2-yl)-*N*-(*p*-tolyl)pyridin-2-amine) with a 65% yield. To synthesize **L1**, 2,6-dibromopyridine was reacted with benzimidazole in the presence of K_2CO_3 as a base in dry DMSO. This reaction follows a Ullmann-type C-N coupling mechanism. The synthesis of ligand L1 was confirmed by its ^{1}H NMR spectrum, which showed a distinct singlet at δ 8.55, corresponding to the proton on the carbon atom between the two nitrogen atoms of the benzimidazole ring. For **L2**, *p*-toluidine was reacted with 2-bromopyridine. NMR analysis confirmed the successful formation of this ligand. In the ^{1}H NMR spectrum, a singlet at δ 8.17 matched the secondary amine proton, and the methyl group appeared as a singlet at δ 2.33 (3H). The ligand, **L3**, was characterized by LC-MS and NMR. The LC-MS (ESI) spectrum showed a molecular ion peak at m/z 378.1713, which aligns with the protonated species (calculated 378.1715 for $C_{24}H_{19}N_5$). In the ^{1}H NMR spectrum, the benzimidazole proton related to the carbene framework showed a singlet at δ 8.44, while the ortho-pyridyl proton resonated as a doublet at δ 8.41. The methyl substituent produced a singlet at δ 2.44. The ^{13}C NMR spectrum further confirmed the structure, showing signals at δ 158.07 and 157.85 for the pyridine carbons at the 2nd and 6th positions, along with a peak at δ 21.57 for the methyl carbon. The final ligand **L4·HI** (Scheme 4) was obtained by *N*-methylation of the benzimidazole nitrogen using methyl iodide. The NMR and LC-MS analyses confirm the synthesis of the ligand **L4·HI**. The LC-MS (ESI) spectrum showed a molecular ion peak at m/z

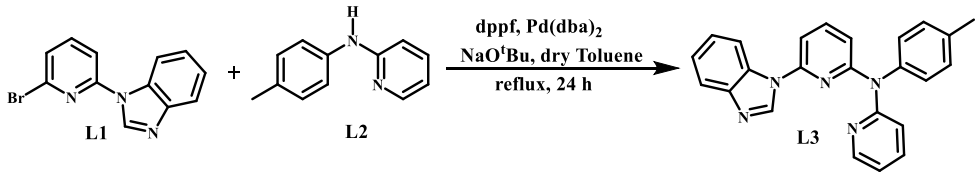
392.1908, which matched the expected mass of the methylated ligand. In the ^{1}H NMR spectrum, the *N*-methyl protons appeared as a distinct singlet at δ 4.38, confirming that methylation was successful. Additionally, the ^{13}C NMR spectrum displayed a characteristic signal at δ 34.31, corresponding to the methyl carbon attached to the nitrogen atom. This data supports the successful synthesis and structural assignment of the final ligand L4·HI. Additionally, to access ligand **L7**, we explored an alternative synthetic route. We prepared ligand **L5** from **L1** by reacting it with 2-aminopyridine under conditions similar to those of the Buchwald-Hartwig reaction. The formation of **L5** was confirmed by ^{1}H NMR analysis. We used this intermediate for further synthetic transformations toward **L7**.



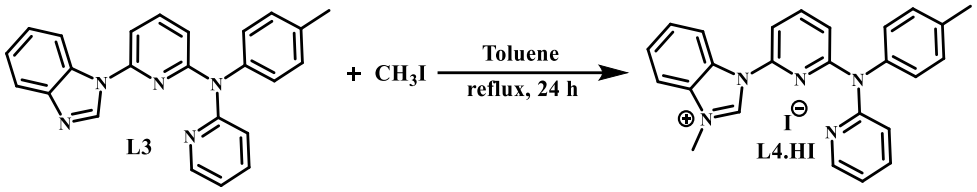
Scheme 1: Synthesis of Ligand **L1**



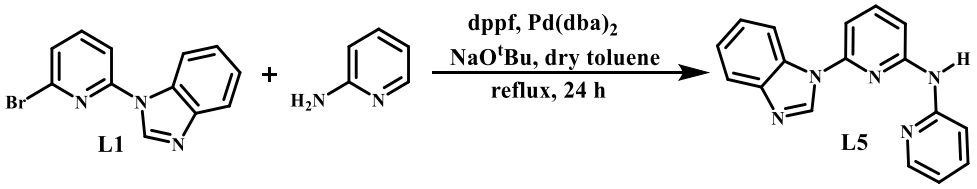
Scheme 2: Synthesis of Ligand **L2**



Scheme 3: Synthesis of Ligand **L3**



Scheme 4: Synthesis of Ligand **L4·HI**



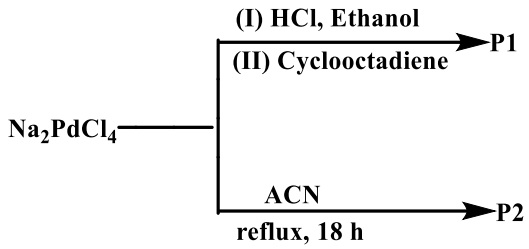
Scheme 5: Synthesis of Ligand **L5**

3.2 Synthesis of Precursor

3.2.1 Synthesis of Precursor P1 and P2:

To access suitable palladium precursors for further complexation studies, $PdCl_2(COD)$ **(P1)** was synthesized from sodium tetrachloropalladate using an acid-assisted method. First, Na_2PdCl_4 was treated with HCl and then with ethanol. This process caused NaCl to precipitate, which was removed by filtration. The resulting solution reacted with cyclooctadiene (COD), yielding the desired precursor **P1** as a yellow, fluffy solid with 72% yield. LC-MS analysis will confirm the formation of **P1**, and IR data will support this. Next, a second palladium precursor, $PdCl_2(MeCN)_2$ **(P2),** was prepared by refluxing sodium tetrachloropalladate in acetonitrile under an inert nitrogen atmosphere for 18 hours. This reaction created a wine-red solution and a white precipitate, which was removed by hot filtration through a Celite pad. Concentrating the filtrate under reduced pressure yielded the desired precursor **P2** as a yellow solid with 62% yield. The formation of **P2** was mainly confirmed by IR spectroscopy. A strong absorption band at 2329 cm^{-1} corresponds to the -CN stretching vibration of acetonitrile, indicating successful coordination of MeCN to the palladium center. Additional vibrational features in the IR spectrum further support the formation of the desired Pd(II) precursor. These findings match

well with previously reported palladium-acetonitrile complexes. The ν(-CN) stretching frequency reported in the range of ~2300–2350 cm^{-1} supports the successful formation of the desired precursor.



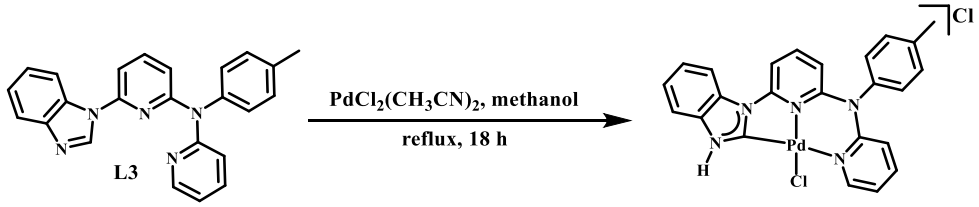
Scheme 6: Synthesis of Metal Precursor **P1** & **P2**

3.3 Synthesis of complexes:

3.3.1 Synthesis of Metal Complex Pd1

The synthesis of the Pd(II)-NHC complex used the pincer ligand precursor **L3** and palladium precursor **P2** under inert conditions. The reaction was performed in methanol at reflux, yielding a yellow precipitate. This indicated the formation of a new palladium species. The complex's formation was further indicated by its unique solubility behavior. The precipitate did not dissolve in common deuterated solvents, which made direct NMR characterization impossible. To investigate the formation of the desired complex, we analyzed the filtrate obtained after precipitate removal by LC-MS. The mass spectrum showed a strong peak at m/z 520.0403, which matched the $[M]^+$ species (calculated 520.0363), confirming that the Pd-NHC complex had formed. Alongside the main peak, there were some minor signals, possibly related to intermediate or partially coordinated species in the solution. We also gathered more evidence for complex formation through UV-visible spectroscopy. The spectrum showed a weak absorption band around 380 nm, likely linked to either a ligand-to-metal charge-transfer (LMCT) or a metal-to-ligand charge-transfer (MLCT) transition. This feature is often found in Pd(II)-NHC systems. Although we could not isolate a fully soluble form of the complex suitable for NMR

analysis due to its low solubility, the LC-MS and UV-Visible data strongly indicate that the Pd(II)-NHC complex has successfully formed.

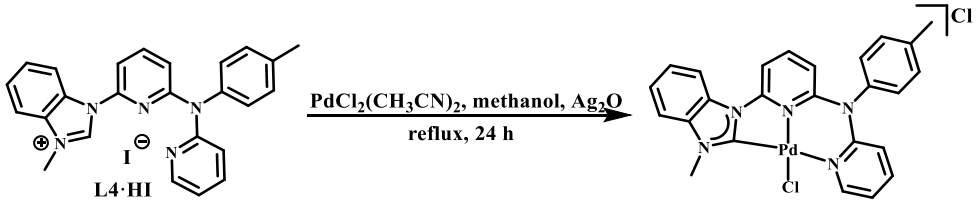


Scheme 7: Synthesis of Metal Complex Pd1

3.3.2 Synthesis of Metal Complex Pd2

The Pd(II)-NHC complex **Pd2** was synthesized via a carbene-generation method using Ag_2O and the ligand precursor **L4·HI**. We generated the carbene in in-situ by treating **L4·HI** with Ag_2O in methanol while maintaining an inert atmosphere. This process produced a reactive Ag-NHC intermediate. We then added the palladium precursor **P2** and refluxed the mixture for 24 hours to obtain the desired Pd-NHC complex. We could observe the reaction progress by noting changes in the mixture and the formation of insoluble residues, which we filtered out using a Celite pad. We confirmed the formation of the Pd2 complex through LC-MS analysis. The LC-MS (ESI) spectrum showed a peak at m/z 534.0563, which corresponds to the $[M]^+$ species. This indicates that the NHC ligand successfully coordinated to the Pd(II) center. We also observed minor peaks in the spectrum that likely correspond to intermediate or partially coordinated species present during the reaction. Initially, we had synthesized this complex in our lab using precursor **P1** in earlier studies. However, to improve the synthetic efficiency and product quality, we used the precursor **P2** in this work. The use of **P2** resulted in a higher yield, better purity, and a cleaner LC-MS spectrum. It also increased the stability of the resulting complex. These findings suggest that **P2** is a better palladium source for forming the Pd-NHC complex under the tested conditions. In summary, the successful formation of **Pd2** via the Ag_2O-mediated pathway,

along with the enhanced results obtained with precursor **P2**, demonstrate the effectiveness of this method for preparing stable Pd(II)-NHC complexes



Scheme 8: Synthesis of Metal Complex **Pd2**

3.4.1 Characterization of Ligand L1

3.4.1.1 LCMS of Ligand L1

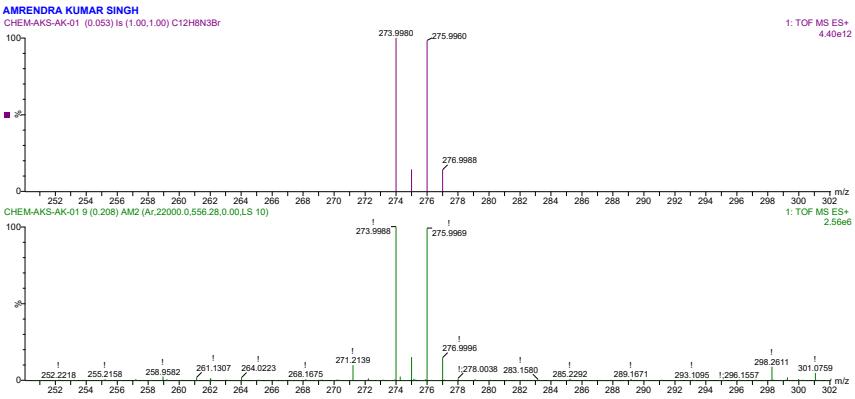


Figure 4: LCMS of Ligand **L1**

3.4.1.2 NMR spectra of Ligand L1

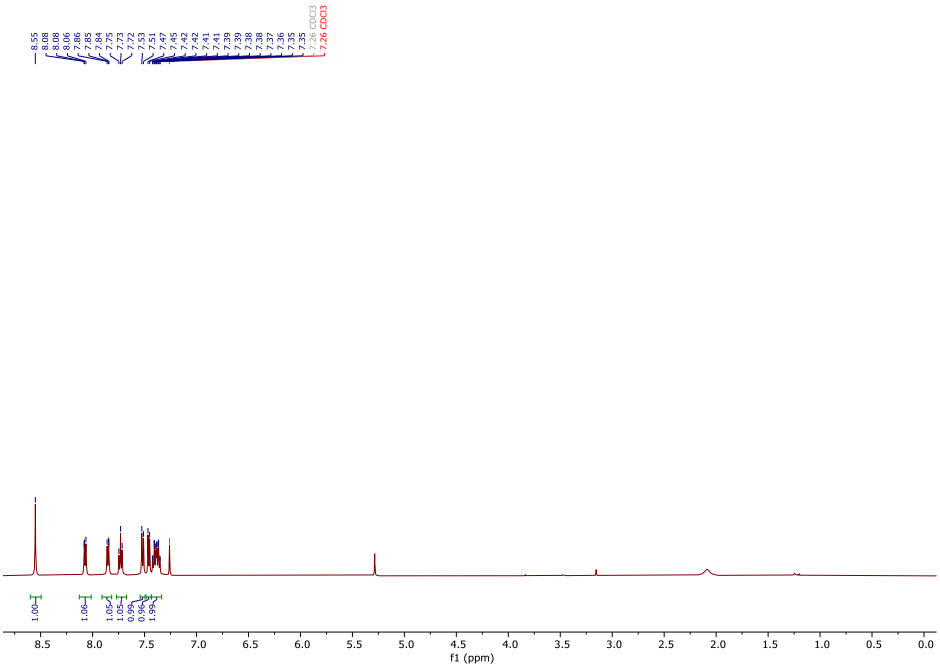


Figure 5: ^{1}H NMR of Ligand **L1** in $CDCl_3$

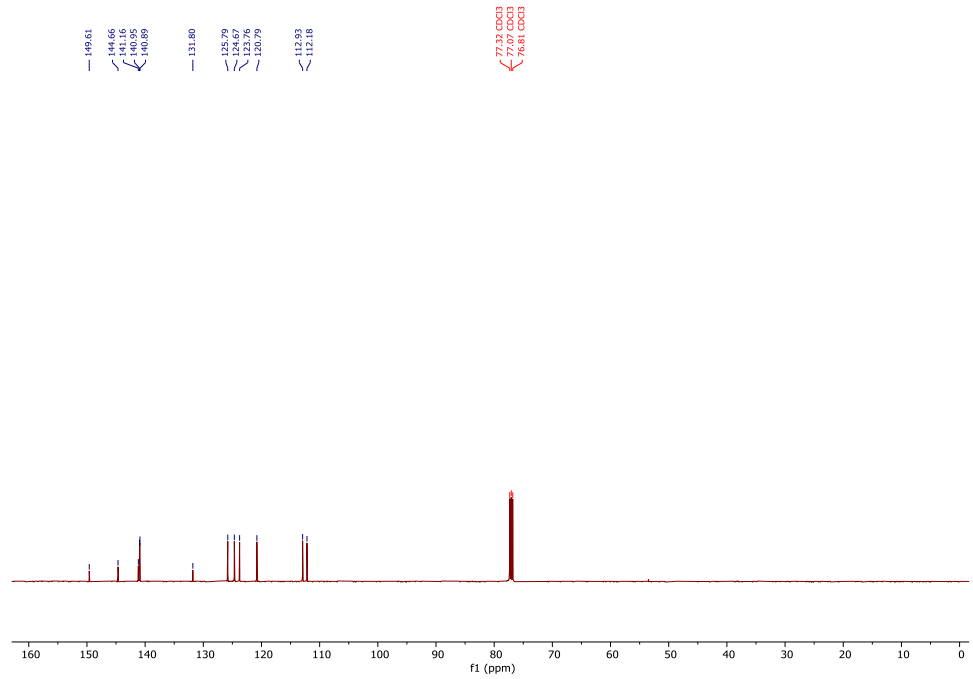


Figure 6: $^{13}C\{^{1}H\}$ NMR of Ligand **L1** in $CDCl_3$

3.4.2 Characterization of Ligand L2

3.4.2.1 LCMS of Ligand L2

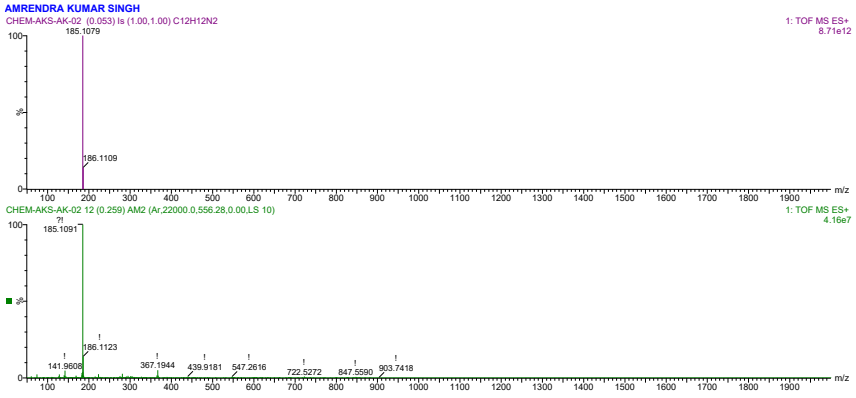


Figure 7: LCMS of Ligand **L2**

3.4.2.2 NMR spectra of Ligand L2

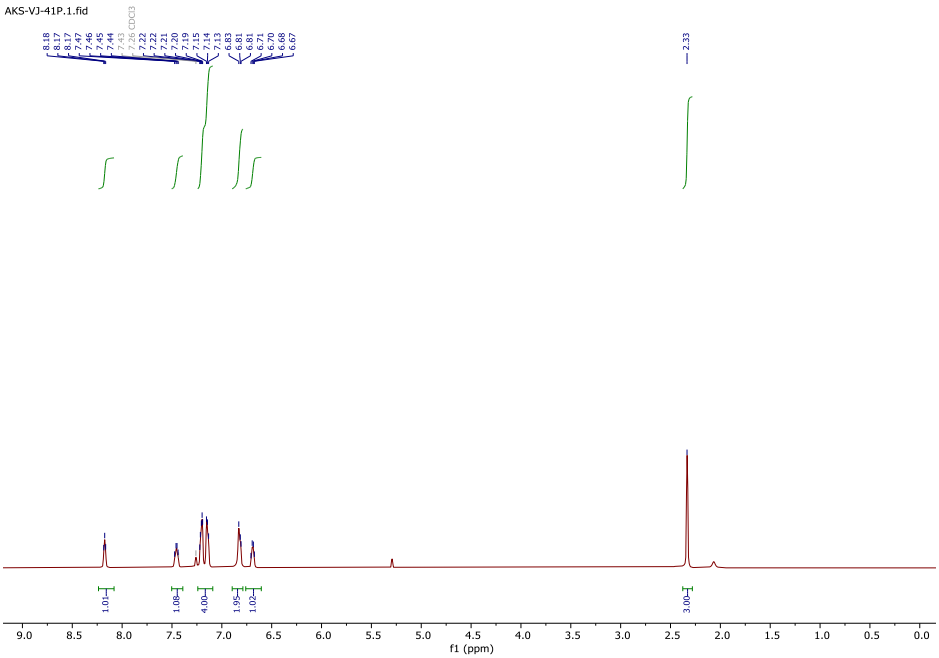


Figure 8: ^{1}H NMR of Ligand **L2** in $CDCl_3$

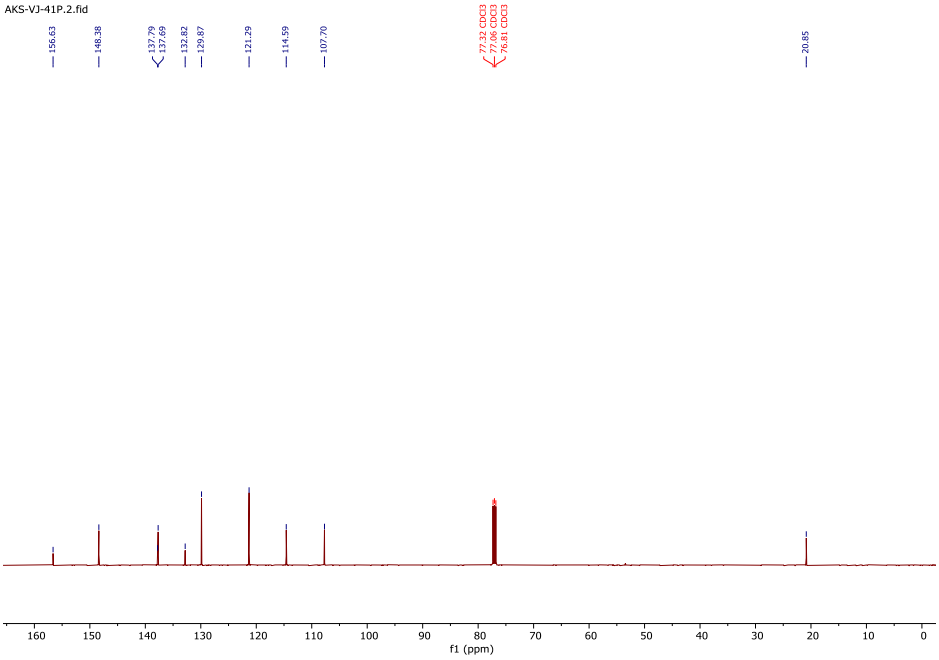


Figure 9: $^{13}C\{^{1}H\}$ NMR of Ligand **L2** in $CDCl_3$

3.4.3 Characterization of Ligand L3

3.4.3.1 LCMS of Ligand L3

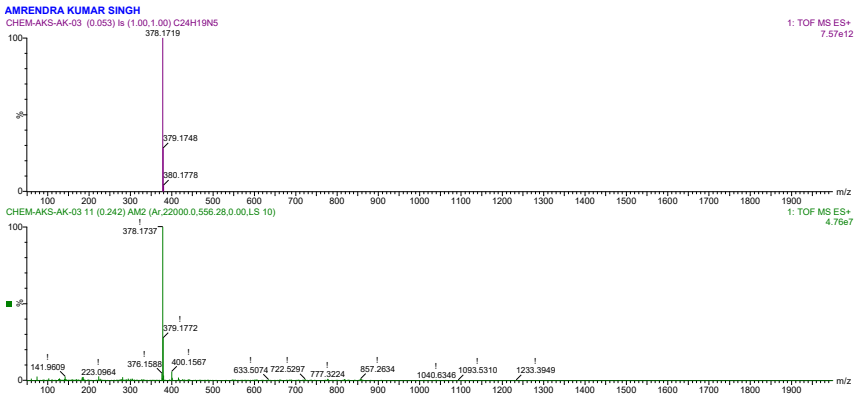


Figure 10: LCMS of Ligand **L3**

3.4.3.2 NMR spectra of Ligand L3

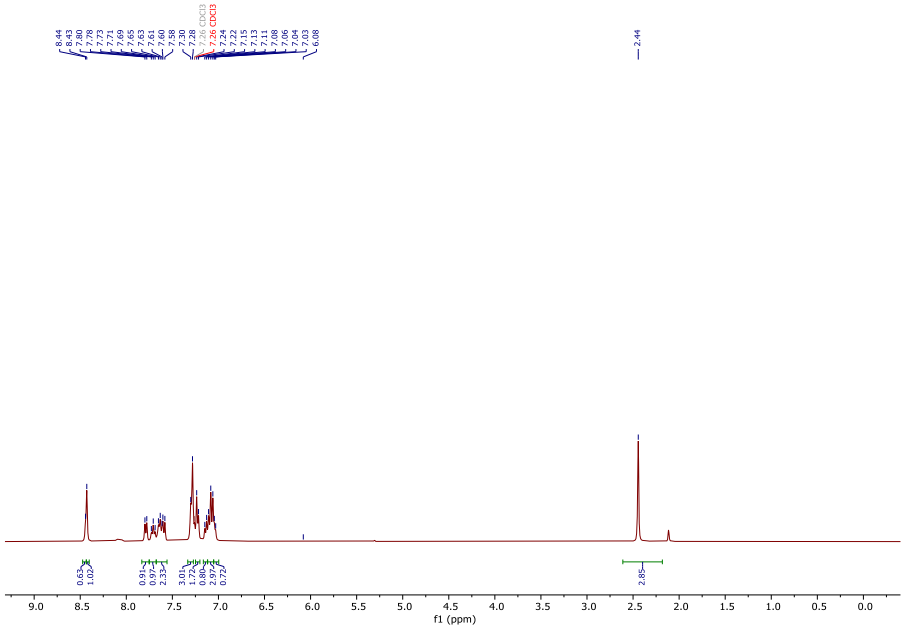


Figure 11: ^{1}H NMR of Ligand **L3** in $CDCl_3$

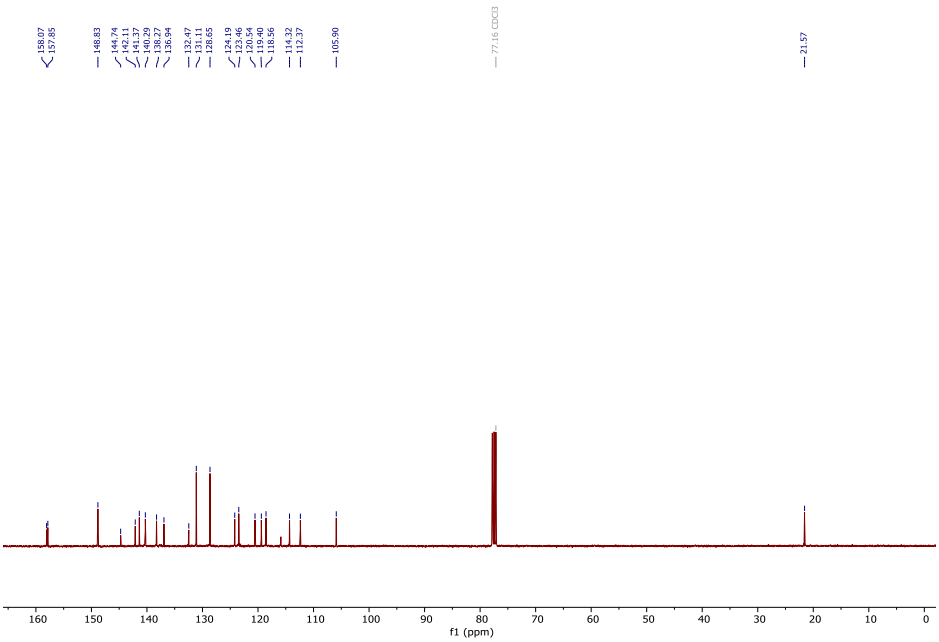


Figure 12: $^{13}C\{^{1}H\}$ NMR of Ligand **L3** in $CDCl_3$

3.4.4 Characterization of Ligand L4·HI

3.4.4.1 LCMS of Ligand L4·HI

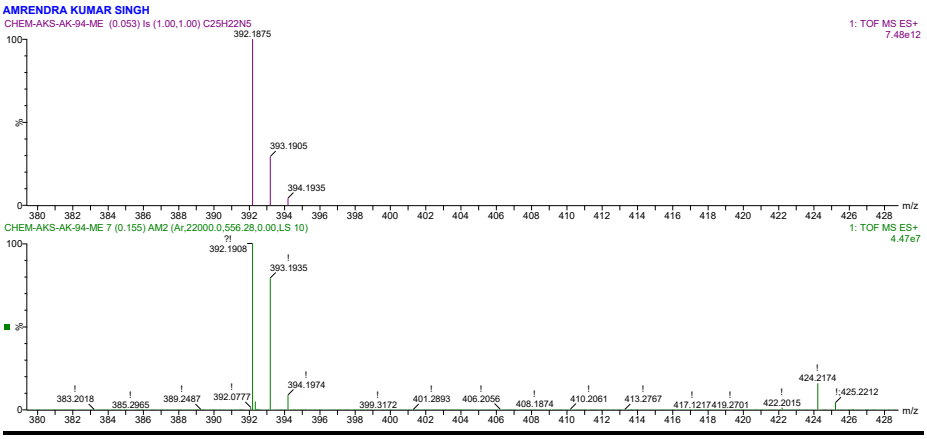


Figure 13: LCMS of Ligand **L4·HI**

3.4.4.2 NMR spectra of Ligand L4·HI

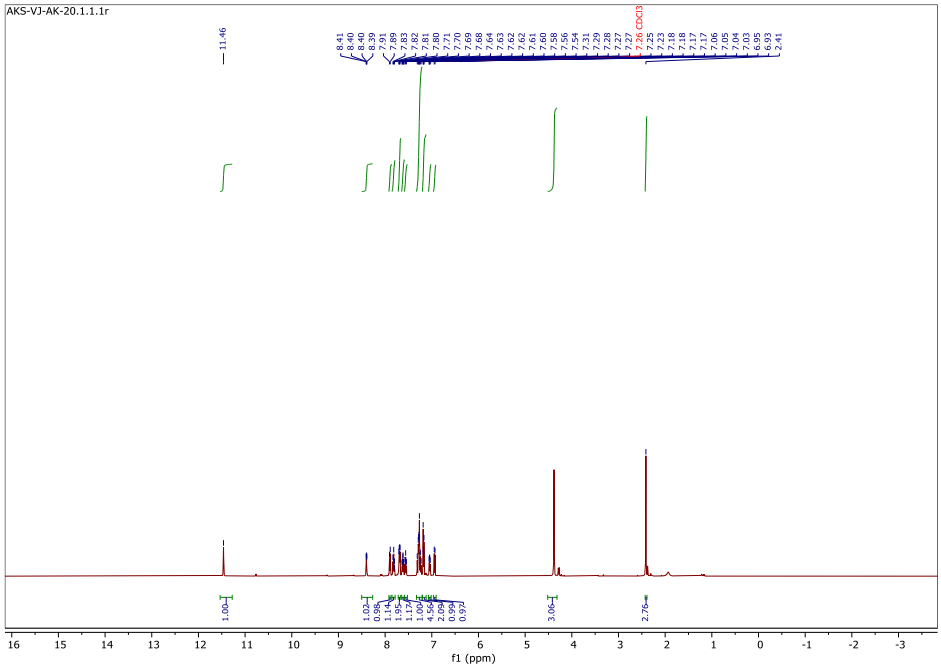


Figure 14: ^{1}H NMR of Ligand **L4·HI** in $CDCl_3$

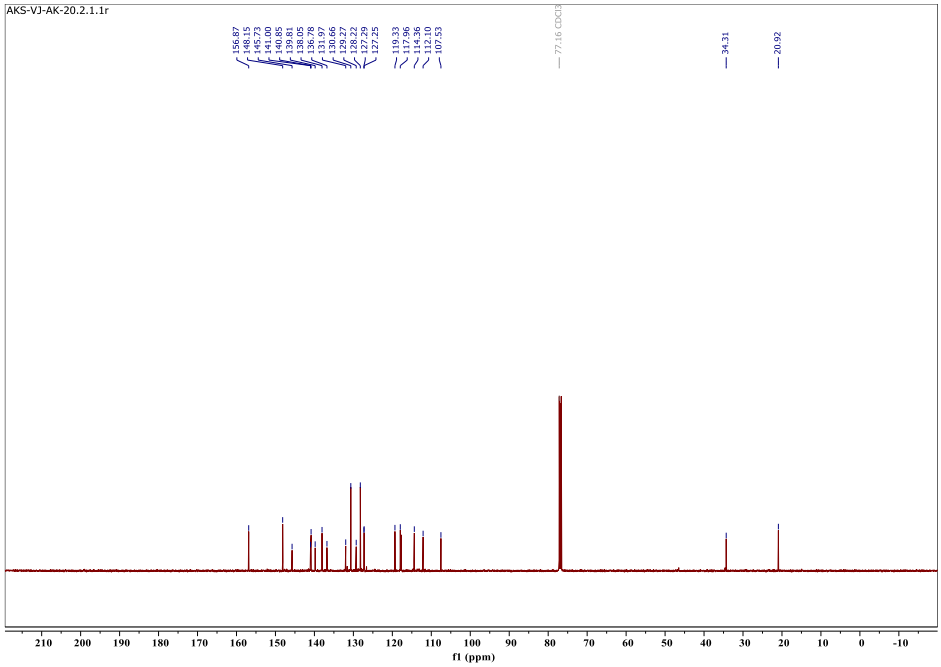


Figure 15: $^{13}C\{^{1}H\}$ NMR of Ligand **L4·HI** in $CDCl_3$

3.4.5 Characterization of Ligand L5

3.4.5.1 LCMS of Ligand L5

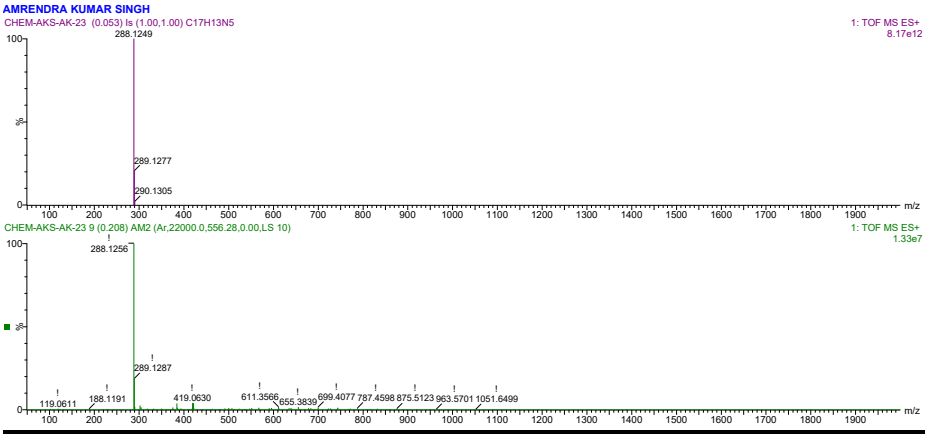


Figure 16: LCMS of Ligand **L5**

3.4.5.2 NMR spectra of Ligand **L5**

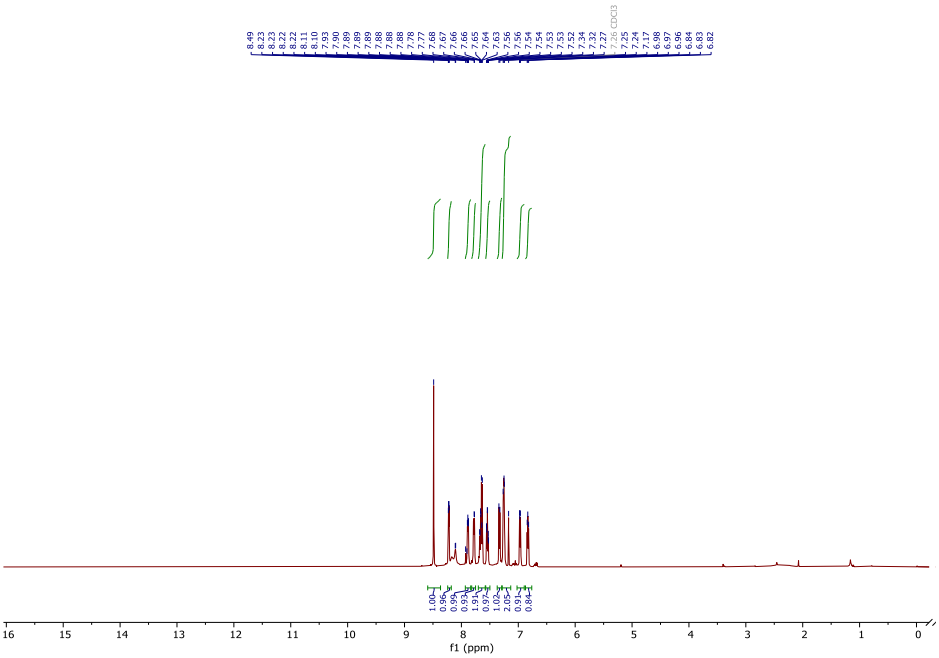


Figure 17: ^{1}H NMR of Ligand **L5** in $CDCl_3$

3.4.6 Characterization of Ligand L6

3.4.6.1 NMR spectra of Ligand L6

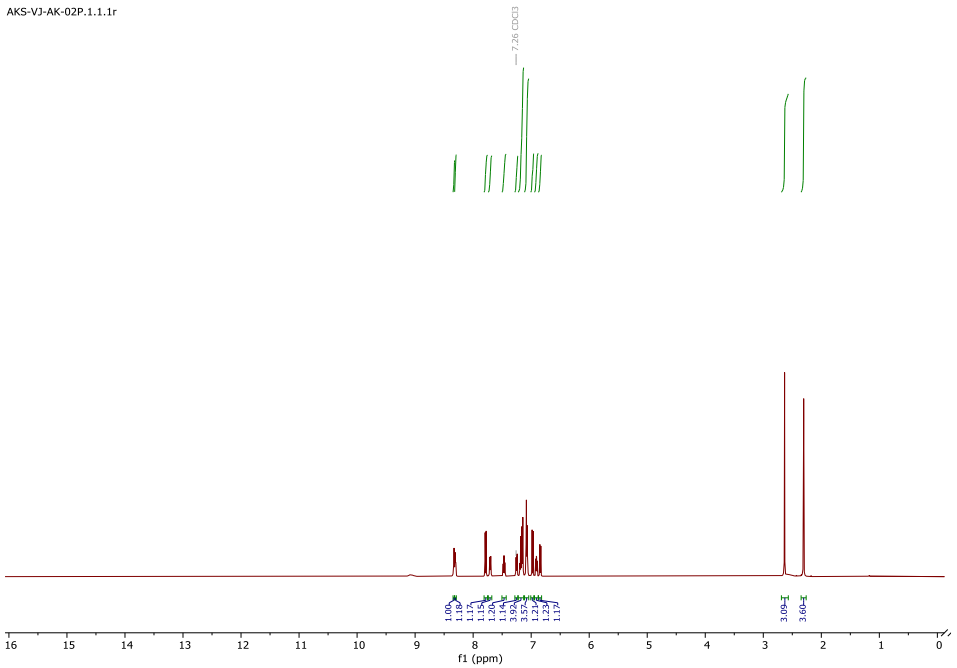


Figure 18: The expected product is not obtained, as confirmed by ^{1}H NMR of Ligand **L6** in $CDCl_3$

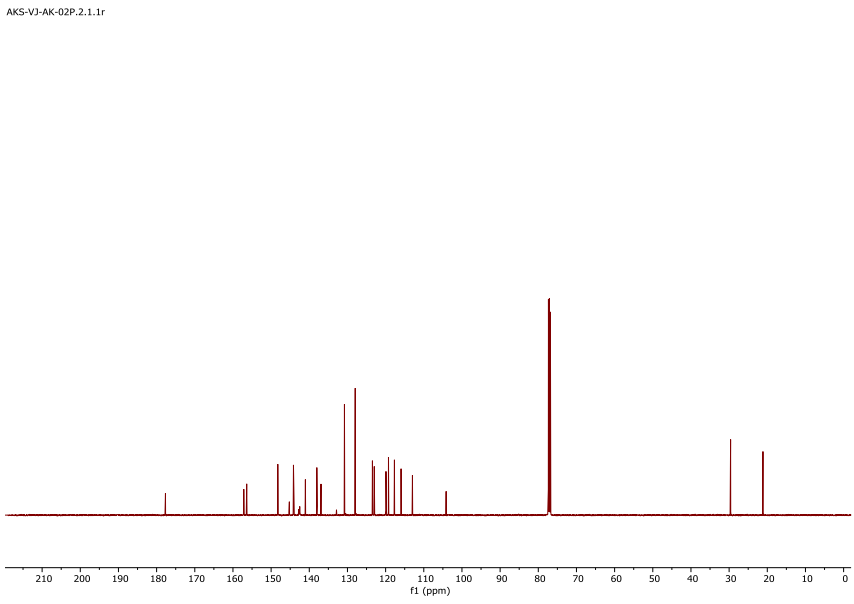


Figure 19: The expected product is not obtained, as confirmed by $^{13}C\{^{1}H\}$ NMR of Ligand **L6** in $CDCl_3$

3.4.7 Characterization of Ligand L7

3.4.7.1 LCMS of Ligand L7

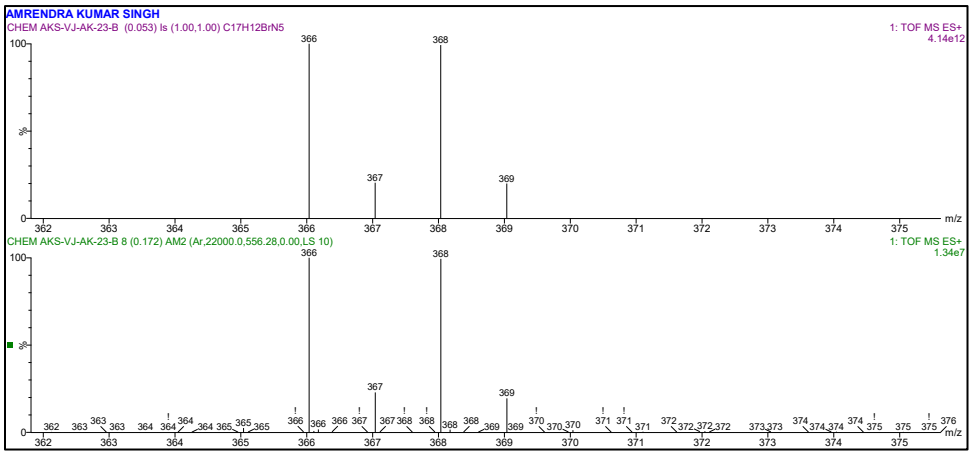


Figure 20: LCMS of Ligand **L7**

3.4.7.2 NMR spectra of Ligand L6

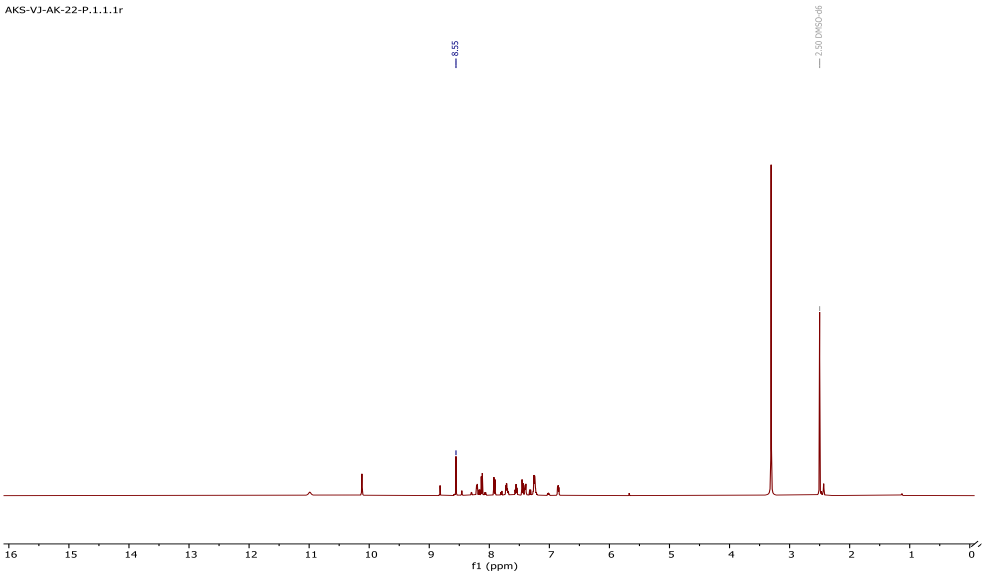


Figure 21: The expected product is not obtained, as confirmed by ^{1}H NMR of Ligand **L7** in $CDCl_3$

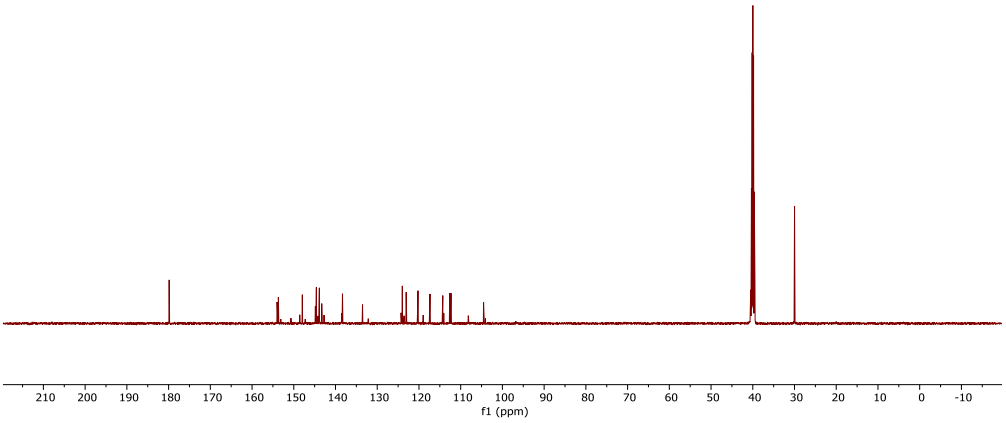


Figure 22: The expected product is not obtained, as confirmed by $^{13}C\{^{1}H$ NMR of Ligand **L7** in $CDCl_3$

3.4.8 Characterization of Metal Precursor P2

3.4.8.1 FT-IR Spectra of Metal Precursor P2

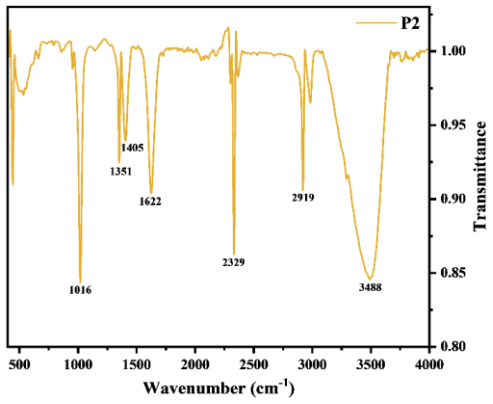


Figure 23: FT-IR Spectrum of Metal Precursor **P2**

3.4.9 Characterization of complex Pd1

3.4.9.1 LCMS of Complex Pd1

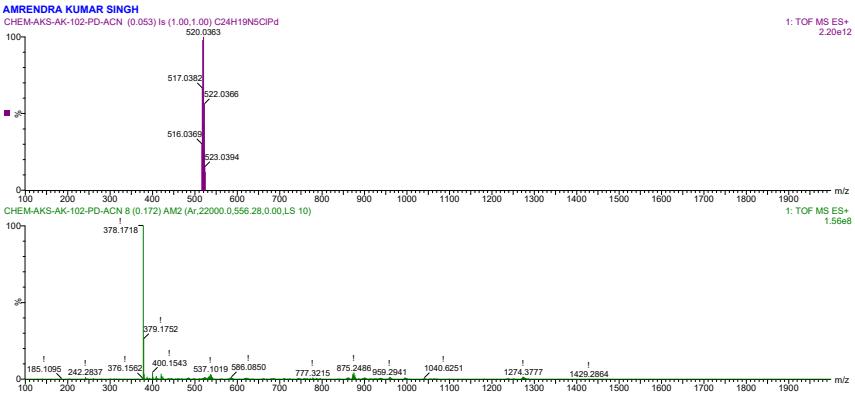


Figure 24a: The expected product is not obtained, as confirmed by LCMS

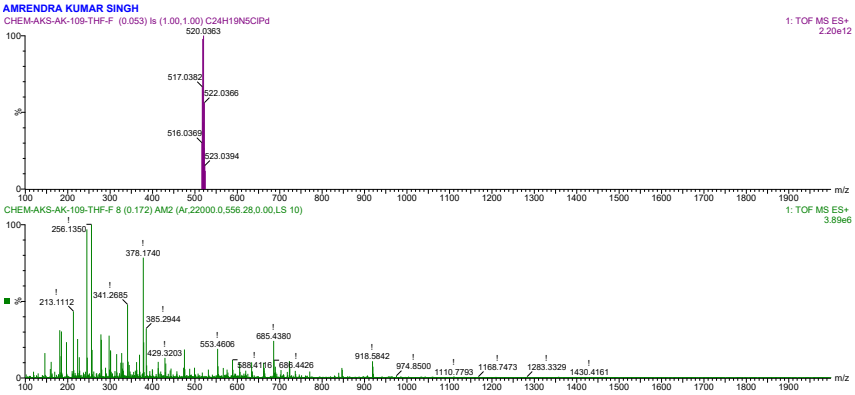


Figure 24b: The expected product is not obtained, as confirmed by LCMS

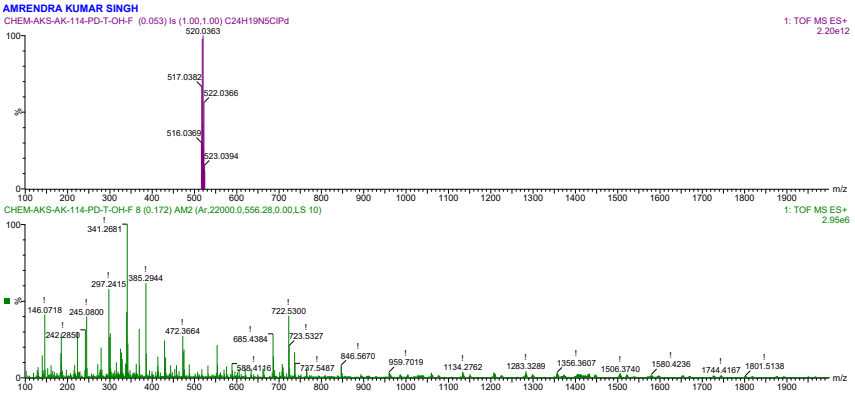


Figure 24c: The expected product is not obtained, as confirmed by LCMS

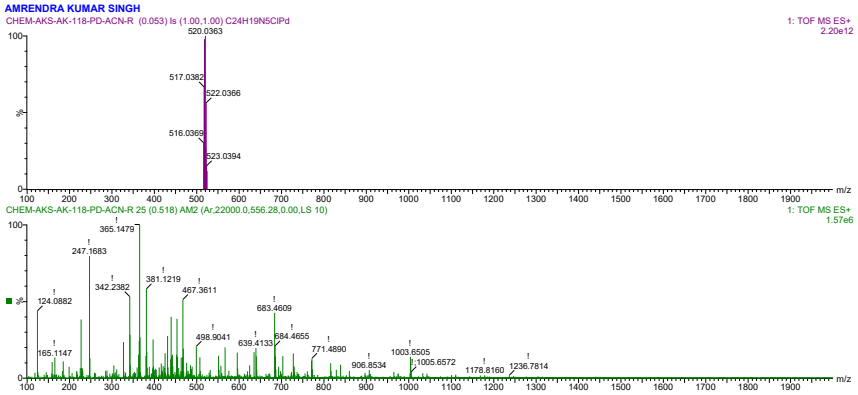


Figure 24d: The expected product is not obtained, as confirmed by LCMS

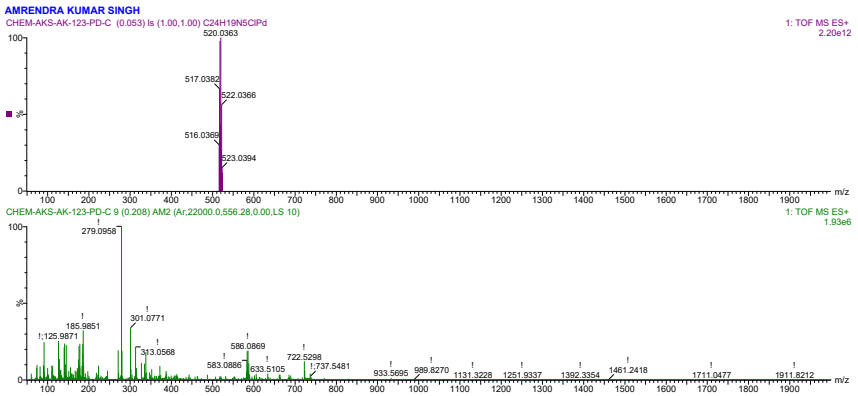


Figure 24e: The expected product is not obtained, as confirmed by LCMS

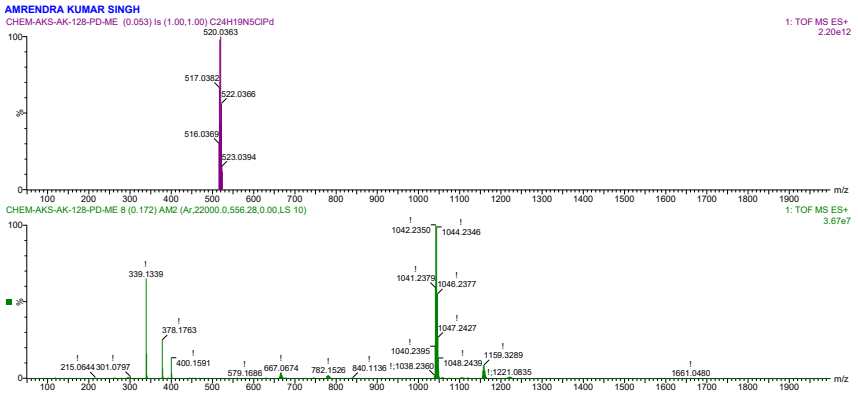


Figure 24f: The expected product is not obtained, as confirmed by LCMS

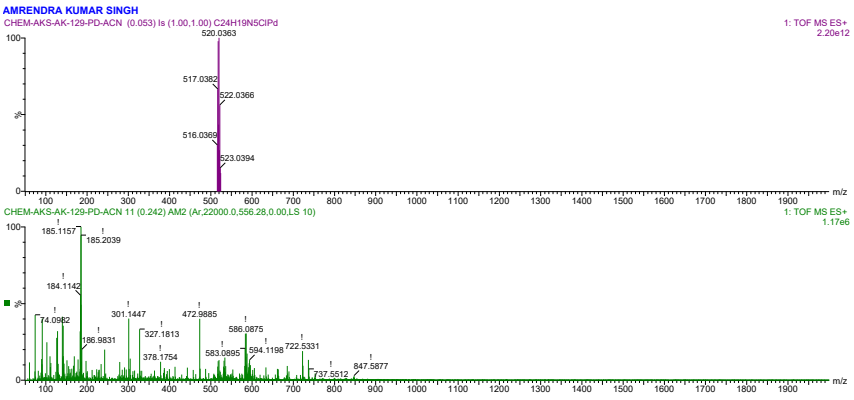


Figure 24g: The expected product is not obtained, as confirmed by LCMS

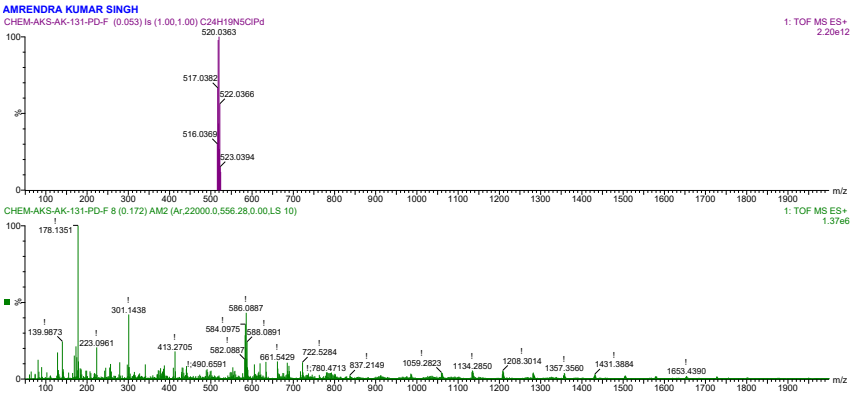


Figure 24h: The expected product is not obtained, as confirmed by LCMS

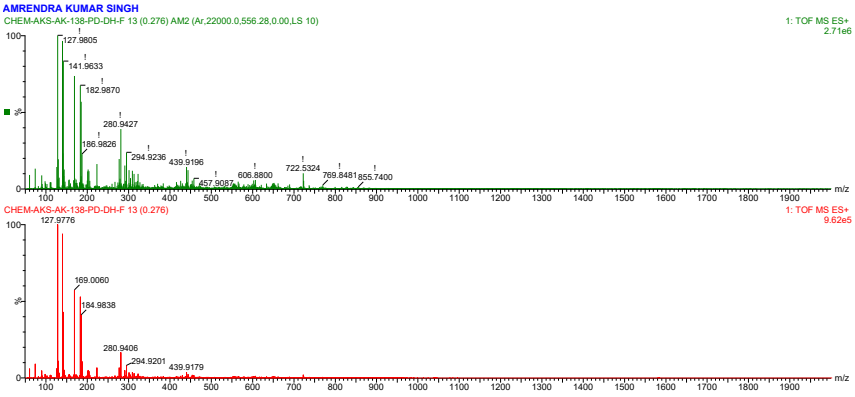


Figure 24i: The expected product is not obtained, as confirmed by LCMS

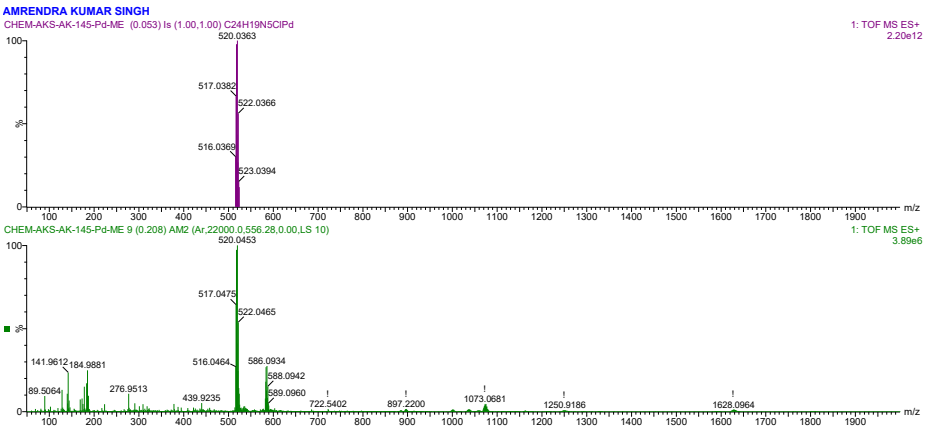


Figure 24k: LCMS of Metal Complex **Pd1**

3.4.9.2 HRMS of Complex Pd1

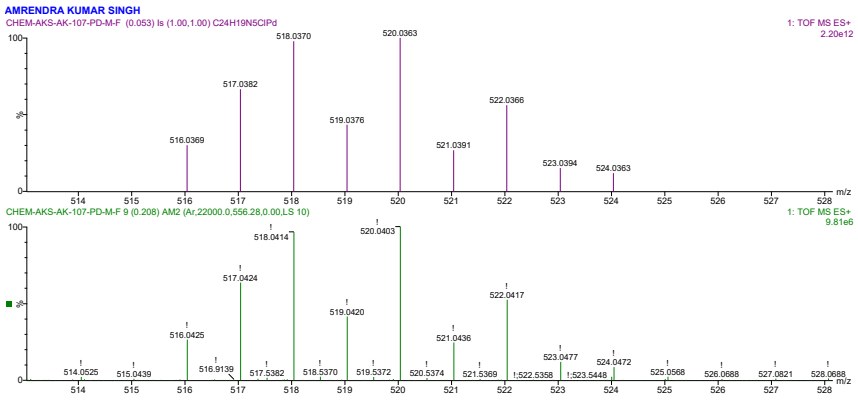


Figure 25: HRMS of Metal Complex **Pd1**

3.4.9.3 UV-Visible spectra of Complex Pd1

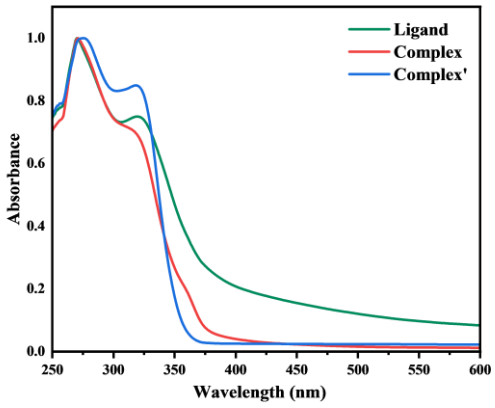


Figure 26: UV-Visible spectra of Metal Complex **Pd1**

3.4.10 Characterization of complex Pd2

3.4.10.1 LCMS of Complex Pd2

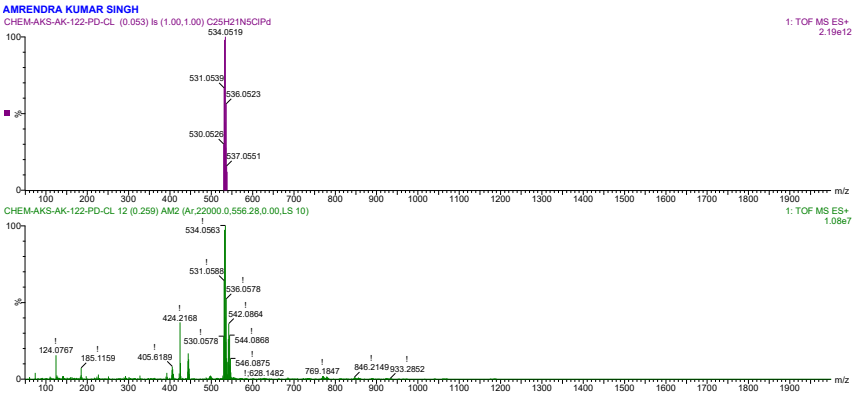


Figure 27: LCMS of Metal Complex **P2**

3.4.10.2 HRMS of Complex Pd2

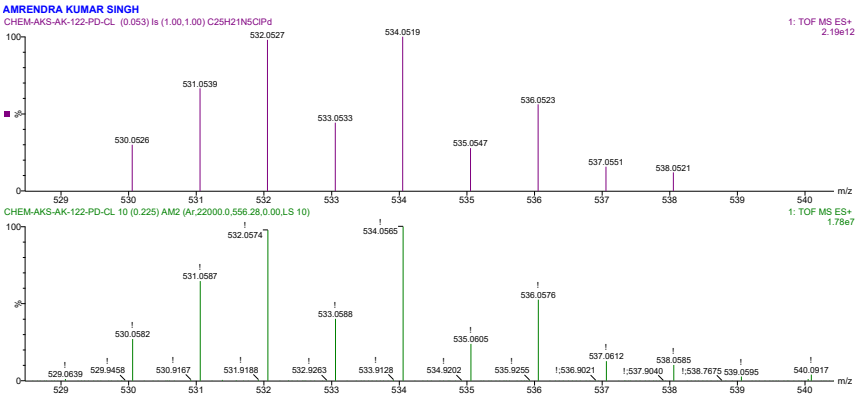


Figure 28: HRMS of Metal Complex **Pd2**

CHAPTER-4

4.1 CONCLUSION:

In this work, we investigated unsymmetrical NNC pincer-type ligands with protic-NHC frameworks. We synthesized the ligand precursors **L1** and **L2** through efficient processes. Then, we coupled them using a Buchwald-Hartwig amination strategy to produce the target ligand **L3**. Additionally, we did *N*-methylation of ligand **L3** and yielded the imidazolium salt precursor **L4·HI**, enabling carbene generation. We characterized the synthesized ligands using NMR and LC-MS techniques, confirming their structural integrity. We also prepared and validated the palladium precursors $PdCl_2(COD)$ **(P1)** and $PdCl_2(MeCN)_2$ **(P2)** using various spectroscopic methods, including FT-IR. We systematically investigated the synthesis of Pd-NHC complexes using the **L3** ligand. We explored multiple reaction conditions involving different solvents, bases, and palladium sources. While several approaches did not yield the desired product, these studies provided valuable insights into the limitations of carbene generation and coordination under different conditions. Notably, we successfully formed the Pd(II)-NHC complex Pd1 using precursor **P2** under optimized conditions, as confirmed by LC-MS and UV-Visible analysis. Additionally, we synthesized the **Pd2** complex via an Ag_2O-mediated carbene-generation route with **L4·HI**, demonstrating an effective route to Pd-NHC complexes. We found that using $PdCl_2(MeCN)_2$ **(P2)** yielded higher purity, greater reproducibility, and better overall performance than other palladium sources.

Overall, this study emphasizes the importance of ligand design, precursor selection, and reaction conditions in the synthesis of Pd-NHC complexes. Although we faced challenges in achieving complete structural characterization due to solubility issues, the successful formation of the desired complexes suggests the potential of these systems.

Future research may aim to improve solubility for detailed spectroscopic analysis and to assess the catalytic activity of these complexes in cross-

coupling reactions, especially with less reactive substrates such as aryl chlorides. This will further establish their usefulness in modern catalytic transformations.

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