2.I.1 Introduction

This section deals with the objectives, synthesis and characterization of a palladium N-heterocyclic carbene \([\text{Pd(NHC)Cl}_2]\) complex of thiamine hydrochloride, Vitamin B\(_1\) (VB\(_1\)).

Since the discovery of the first stable N-heterocyclic carbene (NHC) by Arduengo\(^1\), NHC-transition metal complexes have attracted considerable attention in the fields of organometallic chemistry and catalysis.\(^2\), \(^3\) Due to the strong σ-donating and little π-back bonding abilities to stabilize the complexes, NHCs can generally be seen as alternatives to the widely used phosphine ligands.\(^4\), \(^5\) Various complexes of palladium with NHC ligands have been prepared for coupling reactions.\(^6\), \(^7\)

Some of the examples are as below.

Biffis and co-workers developed a chelated bis-benzimidazolium based Pd-NHC complex \([\text{Pd(Blm-NHC)Br}_2]\) for Fujiwara hydroarylation of alkynes with substituted arenes. 0.1 mol% catalyst loading was found to be highly effective for the selective hydroarylation with excellent yields (Scheme 2.I.1).\(^8\)

**Scheme 2.I.1** \([\text{Pd(Blm-NHC)Br}_2]\) catalyzed Fujiwara hydroarylation of alkynes

\[
\begin{align*}
\text{Pd(Blm-NHC)Br}_2 & = \quad \begin{tikzpicture}
\draw[thick] (0,0) -- (1.5,0);
\draw[thick] (1.5,0) -- (3,0);
\draw[thick] (3,0) -- (1.5,1.5);
\draw[thick] (3,0) -- (1.5,-1.5);
\draw[thick] (1.5,0) -- (0,1.5);
\draw[thick] (1.5,0) -- (0,-1.5);
\draw[thick] (1.5,0) -- (3,1.5);
\draw[thick] (1.5,0) -- (3,-1.5);
\filldraw[fill=black] (1.5,0) circle (0.1);
\filldraw[fill=white] (1.5,0) circle (0.1);
\filldraw[fill=black] (1.5,0) circle (0.1);
\filldraw[fill=white] (1.5,0) circle (0.1);
\end{tikzpicture}
\end{align*}
\]

\[
\begin{align*}
\text{R}^+ \quad + \quad \text{H} \equiv \text{COOEt} & \xrightarrow{\text{Pd(Blm-NHC)Br}_2 (0.1 \text{ mol\%})} \quad \text{R}^+ \quad \text{COOEt}
\end{align*}
\]

Shao and co-workers reported the regioselective C–H bond arylation of benzo[b]furans with aryl chlorides catalyzed by a well-defined NHC-Pd(II)-Im complex (Scheme 2.I.2).\(^9\)
Scheme 2.I.2 NHC-Pd(II)-Im Complex catalyzed reactions of benzo[b]furan with aryl chlorides

Allolio et al. developed a series of palladium complexes by chelating aryl- and alkyl-substituted bis-NHC ligands, including [(H₃C-Im)₂CH₂]PdBr₂, [(C₆H₅-Im)₂CH₂]PdBr₂ and [(H₃CO-C₆H₄-Im)₂CH₂]PdBr₂. These were employed as catalysts for the Mizoroki–Heck reaction of styrene with p-bromoacetophenone (Scheme 2.I.3).

Scheme 2.I.3 Pd-bis-NHC catalyzed Mizoroki–Heck reaction

Ghosh and co-workers reported a series of new PEPPSI (Pyridine Enhanced Precatalyst Preparation Stabilization and Initiation) themed (NHC)PdI₂(pyridine) type precatalysts (Pd₁₄) of abnormal NHCs for the highly desirable Cu-free and amine-free Sonogashira coupling in air in a mixed-aqueous medium (Scheme 2.I.4).
Khramov et al. developed a synthetic pathway leading to palladium complexes bearing NHC ligands featuring functional groups with different electronic properties for the Mizoroki-Heck reaction of aryl halides with tert-butyl acrylates (Scheme 2.I.5).\(^\text{12}\)

**Scheme 2.I.4** Sonogashira coupling reactions with catalysts (NHC)PdI\(_2\)(pyridine) 1-4

\[
\begin{align*}
\text{ArBr} + \text{ArCH}=CH_2 & \xrightarrow{(2.0 \text{ mol} \%) \text{DMF} : \text{H}_2\text{O} 7:3 \text{ v/v} \quad \text{Cs}_2\text{CO}_3, 90^\circ \text{C}, 1 \text{ h}} \quad \text{ArCH}2=CH_2,
\end{align*}
\]

Gao and co-workers prepared magnetic maghemite (\(\gamma\)-Fe\(_2\)O\(_3\))-silica nanoparticles [Fe\(_2\)O\(_3\)-Si-Pd(NHC) catalyst] where Pd was complexed via a tethered NHC. The application of this catalyst gave good results in Suzuki coupling reactions of aryl iodides or aryl bromides (Scheme 2.I.6).\(^\text{13}\)

**Scheme 2.I.5** Mizoroki-Heck coupling with functionalized NHC-containing precatalysts

\[
\begin{align*}
\text{O-C}6H_4\text{Br} + \text{CH}_2=\text{CHCO}_2\text{Bu} & \xrightarrow{[\text{Cat.1-5]} (1.0 \text{ mol} \%) \quad \text{K}_2\text{CO}_3, \text{DMF} \quad 120^\circ \text{C}, 18 \text{ h}} \quad \text{O-C}6H_4\text{CH}=\text{CHCO}_2\text{Bu},
\end{align*}
\]
Bagal et al. developed environmentally benign and highly efficient polystyrene supported PS-Pd-NHC catalytic system for chemoselective conjugate reduction of α,β-unsaturated carbonyl compounds providing good to excellent conversion with remarkable chemoselectivity (Scheme 2.1.7).\(^1\)

**Scheme 2.1.7** PS-Pd-NHC catalyzed chemoselective transfer hydrogenation of α,β-unsaturated carboxyls

Zhang et al. disclosed the use of a chelating \(k^2\)-NHC-Pd complex in Hiyama cross-coupling of aryl halides with phenyltrimethoxysilane. The coupling was found to be successful using aryl bromides and activated aryl chlorides in the presence of tetra-n-butylammonium fluoride (TBAF) and Cs\(_2\)CO\(_3\) (Scheme 2.1.8).\(^2\)

**Scheme 2.1.8** Chelating \(k^2\)-NHC-Pd complex catalyzed Hiyama cross-coupling of aryl halides with phenyltrimethoxysilane
Scheme 2.I.9 Bth-NHC-PdI₂ catalyzed Heck coupling reaction

2.1.2 Hypothesis

After careful literature perusal, it was noted that most of the pioneering work to synthesize the complexes of Pd(II) with NHC ligands were limited to imidazolium-based NHC ligands which were toxic, poorly biodegradable and complicated to synthesize through multiple steps. After careful literature perusal, it was noted that most of the pioneering work to synthesize the complexes of Pd(II) with NHC ligands were limited to imidazolium-based NHC ligands which were toxic, poorly biodegradable and complicated to synthesize through multiple steps.²¹⁻²³

The present attempt is to explore new biodegradable and nontoxic NHC ligands from natural sources to assemble one of the main principles of green chemistry.²⁴ It is well known that thiamine hydrochloride (VB₁) is a nonflammable, cheap, stable, biodegradable and non-toxic compound. The structure of VB₁ contains a pyrimidine ring and thiazolium ring linked together by methylene bridge. In current study, the actual carbene was formed by deprotonation at position-2 of thiazole ring which is most acidic and was mostly applied in organocatalytic reactions.²⁵⁻²⁸

2.1.3 Objectives

The objectives were thoughtfully designed as follows.

- To synthesize a novel palladium N-heterocyclic carbene [Pd(NHC)Cl₂] complex of thiamine hydrochloride, Vitamin B₁ (VB₁).
- To characterize Pd(NHC)Cl₂ by elemental analysis, ¹H NMR, FTIR, EDX and UV–visible spectroscopy.
- To employ the prepared Pd(NHC)Cl₂ complex as a catalyst for regioselective ortho-C–H chlorination/bromination, thiolation and other C–C and C–N coupling reactions of 1-aryl-3-methyl-1H-pyrazol-5(4H)-ones via C–H bond
activation which are included in the subsequent chapters 3, 4 and 5 respectively.

2.I.4 Experimental

2.I.4.1 Synthesis of palladium N-heterocyclic carbene complex

A 50 mL round bottom flask was charged with Pd(OAc)$_2$ (0.5 mmol), thiamine hydrochloride (vitamin B$_1$) (1 mmol), NaOt-Bu (1 mmol) and THF (5 mL). The mixture was stirred at room temperature for 3 h and then refluxed for additional 2 h. After cooling to room temperature, the resulting orange residue was filtered, washed with acetonitrile (2 × 5 mL) and dried under vacuum to afford the title compound with 80% yield (Scheme 2.I.10).

![Scheme 2.I.10 Synthesis of palladium N-heterocyclic carbene [Pd(NHC)Cl$_2$] complex of Vitamin B$_1$](image)

2.I.5 Characterization of Pd(NHC)Cl$_2$ catalyst

The synthesized Pd(NHC)Cl$_2$ catalyst was thoroughly characterized by $^1$H NMR, FTIR, EDX and UV–visible spectroscopy.

2.I.5.1 FTIR analysis

FTIR spectrum of the catalyst (Figure 2.I.1) exhibited absorption bands at 1620 (C=N stretch) and 3630 cm$^{-1}$ (OH stretch). The characteristic amino stretching vibration bands were observed at 3340 and 3315 cm$^{-1}$. N-H bending absorption appeared at 1665 cm$^{-1}$. 
Figure 2.I.1 FTIR spectrum of Pd(NHC)Cl$_2$

![FTIR spectrum of Pd(NHC)Cl$_2$](image1)

Figure 2.I.2 $^1$H NMR spectrum of Pd(NHC)Cl$_2$

![$^1$H NMR spectrum of Pd(NHC)Cl$_2$](image2)

$^1$H NMR (400 MHz, DMSO-$d_6$): δ (ppm) 2.39 (s, 3H), 2.51 (s, 3H), 3.05 (t, 2H), 3.65 (t, 2H), 5.47 (s, 2H), 7.40 (s, 2H), 8.11 (s, 1H), 9.60 (s, 1H).
2.1.5.2 $^1$H NMR analysis

The assignment of $^1$H NMR spectrum of Pd(NHC)Cl$_2$ catalyst is shown in following table.

<table>
<thead>
<tr>
<th>$\delta$ (ppm)</th>
<th>Multiplicity</th>
<th>Number of protons</th>
<th>Assignment</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.39</td>
<td>singlet</td>
<td>3H</td>
<td>Methyl protons on thiazol ring</td>
<td></td>
</tr>
<tr>
<td>2.51</td>
<td>singlet</td>
<td>3H</td>
<td>Methyl protons on pyrimidine ring</td>
<td></td>
</tr>
<tr>
<td>3.05</td>
<td>triplet</td>
<td>2H</td>
<td>Methylene protons adjacent to thiazol ring</td>
<td></td>
</tr>
<tr>
<td>3.65</td>
<td>triplet</td>
<td>2H</td>
<td>Methylene protons adjacent to -OH</td>
<td></td>
</tr>
<tr>
<td>5.47</td>
<td>singlet</td>
<td>2H</td>
<td>Methylene protons bridged between thiazol and pyrimidine ring</td>
<td></td>
</tr>
<tr>
<td>7.40</td>
<td>singlet</td>
<td>2H</td>
<td>-NH$_2$ protons</td>
<td></td>
</tr>
<tr>
<td>8.11</td>
<td>singlet</td>
<td>1H</td>
<td>Pyrimidine ring proton</td>
<td></td>
</tr>
<tr>
<td>9.60</td>
<td>singlet</td>
<td>1H</td>
<td>-OH group</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2.1.3 EDX analysis of Pd(NHC)Cl$_2$
2.1.5.3 EDX analysis

The Energy dispersive spectroscopy analysis of X-rays (EDX) spectrum for the catalyst showed the existence of sulphur, chlorine and palladium elements (Figure 2.1.3) and confirmed the weight % of C, N, O, S, Pd and Cl respectively as 31.06, 13.06, 2.92, 8.31, 25.41 and 17.23 as expected with the calculated values of 32.56, 12.66, 3.61, 7.24, 24.04 and 16.02.

2.1.5.4 UV–visible spectra

The UV–visible spectra of free NHC ligand and the catalyst in distilled DMSO exhibited absorption bands at 268 and 275 nm respectively (Figure 2.1.4). The bathochromic shift in absorption spectrum may be assigned to complexation of NHC ligand with palladium.

Figure 2.1.4 UV–visible spectra of free NHC ligand and catalyst
References: