

**BIS-, TRIS-, AND TETRAKIS-  
BENZIMIDAZOLIUM SALTS AND THEIR  
SILVER(I) COMPLEXES: SYNTHESIS,  
CHARACTERIZATION AND BIOLOGICAL  
APPLICATIONS**

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**UNIVERSITI SAINS MALAYSIA**

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APPLICATIONS**

by

**NURADDEEN ABDURRAHMAN**

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## **DEDICATION**

This thesis is dedicated to:

My lovely father late Malam Abdurrahman Muhammad Dikko Shagumba.

My lovely mother, Rabi'atu Mu'az Mai'unguwa Makaurachi.

All members of my family.

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## LIST OF SYMBOLS

$\delta$	Chemical shift in ppm
o	Degree
°C	Degree Celsius
d	Doublet
D <sub>c</sub>	Density
dd	doublet of doublet
cm <sup>-1</sup>	per centimeter
g	gram
Hz	Hertz
h	Hours
IS	Insoluble
J	Nuclear spin-spin coupling through bonds
K	Kelvin
M	Metal
MHz	Megahertz
MP	Melting point
MTT	Methylthialyldipheny
μg	Microgram
μL	Microliter
μM	Micromolar
mL	milliliter
mmol	Millimoles
mol	moles
MW	Molecular weight
<i>m</i>	Multiplet

nm	nanometer
OD	Optical density
ppm	parts per million
%	Percent
$\pi$	pi
$\sigma$	Sigma
s	Singlet
S	Soluble
T	Temperature
<i>t</i>	Triplet

## LIST OF ABBREVIATIONS

Å	Angstroms, $1 \times 10^{-10}$ m
Ac	Acetone
ACN	Acetonitrile
NH <sub>4</sub> BF <sub>4</sub>	Ammonium tetrafluoroborate
Alipha.	Aliphatic
Anal.	Analysis
Ar	Arene
Arom.	Aromatic
AuCl(SMe <sub>2</sub> )	Chloro(dimethylsulfide)gold(I)
Benzimidazolium	Benzimidazolium and imidazolium
Benzimi.	Benzimidazole
BF <sub>4</sub>	Boron tetrafluoride
Br <sup>-</sup>	Bromide anion
<sup>13</sup> C NMR	Carbon-13 nuclear magnetic resonance
Calc.	Calculated
CHN	Carbon hydrogen and nitrogen
<i>d</i> <sub>6</sub> -DMSO	Deuterated dimethyl sulfoxide
DCM	Dichloromethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
PdCl <sub>2</sub> (MeCN) <sub>2</sub>	Dichlorobis(acetonitrile)palladium(II)
Et <sub>2</sub> O	Diethyl ether
FC	Ferrocenyl
FTIR	Fourier transform infrared
IC <sub>50</sub>	Half maximal inhibitory concentration

PF <sub>6</sub> <sup>-</sup>	Hexafluorophosphate(VI) anion
LDA	Lithium diisopropylamide tetrazoliumbromide
MeOTf	Methyl trifluoromethanesulphonate
CF <sub>3</sub> SO <sub>2</sub> OCH <sub>3</sub>	Methyl trifluoromethanesulphonate
NA	No activity
NHC	<i>N</i> -heterocyclic carbene
KPF <sub>6</sub>	Potassium Hexafluorophosphate
PBS	Phosphate buffer saline
KO <sup>t</sup> Bu	Potassium tertiary butoxide
pPh <sub>3</sub>	Triphenyl phosphine
RT	Room temperature
Ag(I)	Silver(I) ions
tertButOLi	Lithium tertiary butoxide
THF	Tetrahydrofuran
TMS	tetramethyl saline
OTf	Trifluoromethanesulfonate
UV	Ultraviolet radiation
V	Volume
XRD	X-ray single crystal diffraction

**GARAM BIS-, TRIS-, DAN TETRAKIS-BENZIMIDAZOLIUM SERTA  
KOMPLEKS ARGENTUM(I): SINTESSIS, PENCIRIAN DAN  
APLIKASI BIOLOGI**

**ABSTRAK**

Penyelidikan ini menerangkan sintesis, pencirian, struktur kristal dan aktiviti sitotoksiti beberapa garam bis-, tris- dan tetrakis-benzimidazolium baharu, (**1-24**) dan kompleks argentum(I)-benzimidazol-2-ylidene masing-masing, (**Ag1-Ag24**). Semua sebatian yang disintesis adalah baru berdasarkan literatur yang dikaji, ia dicapai dengan menukar sama ada alkil atau substituen aril pada sistem benzimidazolium dan atau ligan penghubung yang berkaitan dengan sebatian yang dilaporkan sebelum ini. Garam telah disintesis melalui tindak balas penggantian nukleofilik dan dikategorikan kepada lima siri. Garam adalah **1-5, 6-9, 10-14, 15-19, 20-24** masing-masing sebagai siri pertama, kedua, ketiga, keempat dan kelima. Garam yang disintesis telah digunakan untuk sintesis kompleks argentum(I)-benzimidazol-2-ylidene masing-masing, melalui kaedah deprotonasi in-situ dengan kehadiran argentum(I)oksida. Potensi sitotoksiti sebatian yang disintesis telah dijalankan dengan kaedah ujian MTT, di mana saluran sel kanser payudara dan serviks digunakan. Garam **1-5, 6-9, 15-19**, dan kompleks argentum(I)-benzimidazol-2-ylidene, (**Ag1-Ag5, Ag6-Ag9, Ag15-Ag19**) telah diuji terhadap garis sel kanser payudara, manakala garam, **10-14, 20-24**, dan kompleks argentum(I)-benzimidazol-2-ylidene mereka, (**Ag10-Ag14, Ag20-Ag24**) telah diuji terhadap garis sel kanser serviks. Kawalan positif yang digunakan untuk sel kanser payudara ialah tamoxifen dan etoposide untuk sel kanser serviks. Semua garam dan kompleks argentum(I)-benzimidazol-2-ylidene masing-masing yang disintesis telah dicirikan menggunakan

pelbagai teknik pencirian termasuk FTIR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, analisis unsur, dan kaedah pembelauan sinar-X kristal tunggal. Sifat fizikal telah dicapai dengan analisis takat lebur, dan ujian keterlarutan dalam pelbagai pelarut organik. Daripada penjelasan struktur, telah disahkan bahawa **Ag2** adalah kompleks argentum(I)-benzimidazol-2-ylidene dinuklear, dengan dua anion  $\text{PF}_6$  sebagai pembilang mengimbangi cas keseluruhan molekul. Kompleks **Ag13** disahkan sebagai kompleks trinuklear argentum(I)-benzimidazol-2-ylidene seperti silinder yang mengandungi tiga ion argentum(I) yang dirapatkan oleh dua ligan seperti cakera. Struktur **Ag24** ialah struktur seperti pinset sebagai kompleks argentum(I)-benzimidazol-2-ylidene binuklear yang mengandungi dua ion argentum(I) yang dirapatkan oleh hanya satu ligan tetrakis-benzimidazolium yang mengandungi dua  $\text{PF}_6$  sebagai pembilang. Keputusan untuk sitotoksiti dalam semua garam didapati tidak aktif terhadap garisan sel kanser yang diuji kecuali garam **20**, dengan sedikit aktiviti terhadap garisan sel HeLa. Semua kompleks mempamerkan aktiviti sitotoksiti yang munasabah dengan mengambil kira nilai  $\text{IC}_{50}$  mereka dan menunjukkan potensi sitotoksiti pergantungan dos yang serupa. Dalam siri tersebut,  $\text{IC}_{50}$  bagi kompleks adalah dalam susunan: **Ag2** > **Ag3** > **Ag1** > **Ag5** > **Ag4**, **Ag8** > **Ag9** > **Ag7** > **Ag6**, **Ag12** > **Ag10** > **Ag11** > **Ag13** > **Ag14**, **Ag19** > **Ag17** > **Ag18** > **Ag15** dan **Ag23** > **Ag22** > **Ag21** > **Ag20** > **Ag24**. Antara siri tersebut, didapati kompleks **Ag2**, **Ag8**, dan **Ag18** yang mengandungi substituen rantai heksil adalah paling aktif dengan nilai  $\text{IC}_{50}$  masing-masing  $2.87 \pm 0.78$ ,  $2.56 \pm 0.44$  dan  $3.9 \pm 0.5$   $\mu\text{M}$ . Kompleks **Ag9** (oktil), **Ag16** (butil) dan **Ag17** (pentil) adalah serupa dalam aktiviti dengan  $\text{IC}_{50}$ ,  $5.00 \pm 0.5$ ,  $5.20 \pm 0.2$ ,  $4.6 \pm 0.4$   $\mu\text{M}$  masing-masing. mereka adalah yang kedua paling aktif antara tiga siri. Yang ketiga aktif antara siri ini ialah **Ag1** ( $6.36 \pm 0.8$ ), **Ag3** ( $6.32 \pm 0.95$   $\mu\text{M}$ ), **Ag6** ( $6.35 \pm 0.22$   $\mu\text{M}$ ), **Ag7** ( $6.00 \pm 0.22$   $\mu\text{M}$ ), dan **Ag15** ( $6.10 \pm 0.6$

$\mu\text{M}$ ), mengandungi metil, heptil, propil, pentil, rantai propil masing-masing. Kompleks **Ag4** dan **Ag5** yang mengandungi substituen oktil dan 4-metil benzil dengan nilai  $\text{IC}_{50}$  masing-masing  $13.23 \pm 0.4$  dan  $9.47 \pm 0.77 \mu\text{M}$  boleh dianggap sebagai senarai kompleks aktif dalam siri ini. Semua kompleks lebih aktif daripada ubat antikanser standard yang digunakan.

**BIS-, TRIS-, AND TETRAKIS-BENZIMIDAZOLIUM SALTS AND THEIR  
SILVER(I) COMPLEXES: SYNTHESIS, CHARACTERIZATION,  
AND BIOLOGICAL APPLICATIONS**

**ABSTRACT**

This research describes the synthesis, characterization, crystal structure and cytotoxicity activity of several new bis-, tris- and tetrakis-benzimidazolium salts, (**1-24**) and their respective silver(I)-benzimidazol-2-ylidene complexes, (**Ag1-Ag24**). All the compounds synthesized were new based on literature reviewed, it was achieved by changing the either the alkyl or aryl substituents on the benzimidazolium systems and or the bridging ligands related to the previously reported compounds. The salts were synthesized by nucleophilic substitution reaction and were categorized into five series. The salts were **1-5**, **6-9**, **10-14**, **15-19**, **20-24** as first, second, third, fourth and fifth series respectively. The synthesized salts were utilized for the synthesis of their respective silver(I)-benzimidazol-2-ylidene complexes, by *in-situ* deprotonation method in the presence of silver(I)oxide. The cytotoxicity potential of the synthesized compounds was carried out by MTT assay method, in which the breast and cervical cancer cell lines were used. Salt **1-5**, **6-9**, **15-19**, and their silver(I)-benzimidazol-2-ylidene complexes, (**Ag1-Ag5**, **Ag6 -Ag9**, **Ag15-Ag19**) were tested against breast cancer cell lines, while salts, **10-14**, **20-24**, and their silver(I)-benzimidazol-2-ylidene complexes, (**Ag10-Ag14**, **Ag20-Ag24**) were tested against cervical cancer cell lines. The positive control used for the breast cancer cell was tamoxifen and etoposide for the cervical cancer cell. All the salts and their respective silver(I)-benzimidazol-2-ylidene complexes synthesized were characterized using various characterization techniques including FTIR, <sup>1</sup>H, <sup>13</sup>C

NMR, elemental analysis, and single crystal X-ray diffraction method. Physical properties were accessed by melting point analysis, and solubility tests in various organic solvents. From structural elucidation, it was confirmed that **Ag2** was dinuclear silver(I)-benzimidazol-2-ylidene complex, with two PF<sub>6</sub> anions as counterions balancing the charges of the entire molecule. Complex **Ag13** confirmed to be a cylinder-like trinuclear silver(I)-benzimidazol-2-ylidene complex containing three silver(I) ions bridged by two disc-like ligands. The structure of **Ag24** was a tweezer-like structure as a binuclear silver(I)-benzimidazol-2-ylidene complex containing two silver(I) ions bridged by only one tetrakis-benzimidazolium ligand bearing two PF<sub>6</sub> as counterions. The results for cytotoxicity in all the salts were found inactive against tested cancer cell lines except salt **20**, with little activity against HeLa cell lines. All complexes exhibited reasonable cytotoxicity activity considering their IC<sub>50</sub> values and indicated similar dose-dependence cytotoxicity potential. Within the series, the IC<sub>50</sub> of the complexes were in the order: **Ag2** > **Ag3** > **Ag1** > **Ag5** > **Ag4**, **Ag8** > **Ag9** > **Ag7** > **Ag6**, **Ag12** > **Ag10** > **Ag11** > **Ag13** > **Ag14**, **Ag19** > **Ag18** > **Ag17** > **Ag16** > **Ag15** and **Ag23** > **Ag22** > **Ag21** > **Ag20** > **Ag24**. Among the series, it was found that complexes **Ag2**, **Ag8**, and **Ag18** bearing the hexyl chain substituents been most active with IC<sub>50</sub> values 2.87±0.78, 2.56±0.44 and 3.9±0.5 μM respectively. Complexes **Ag9** (octyl), **Ag16** (butyl) and **Ag17** (pentyl) were similar in their activity with IC<sub>50</sub>, 5.00±0.5, 5.20±0.2, 4.6±0.4 μM respectively. they were the second most active among the three series. The third active among these series were **Ag1** (6.36±0.8), **Ag3** (6.32±0.95 μM) , **Ag6** (6.35±0.22 μM) , **Ag7** (6.00±0.22 μM) , and **Ag15** (6.10±0.6 μM), containing methyl, heptyl, propyl, pentyl, propyl chain respectively. Complexes **Ag4** and **Ag5** bearing octyl and 4-methyl benzyl substituents with IC<sub>50</sub> values of 13.23±0.4 and 9.47±0.77

$\mu\text{M}$  respectively can be considered as the list active complexes in these series. All complexes were more active than the standard anticancer drugs used.

# CHAPTER 1

## INTRODUCTION

### 1.1 Carbenes

Carbenes are neutral organic compounds acquiring divalent carbon atoms with two unshared electrons and only six electrons in their outermost shell; in different ways, the two unshared electrons can be assigned to two nonbonding orbitals [1–3]. They are considered too reactive to be isolated [4,5]. This might be true for a more significant number of them, and later, it was confirmed to be an incorrect evaluation regarding them (1.1) (Figure 1.1) [5].

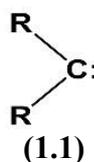


Figure 1.1 General structure of carbene, 1.1 (R= alkyl/aryl group) [2].

### 1.2 Electronic structure of carbenes

Because of their incomplete octet electrons, carbenes are mostly a more reactive group. The carbene carbon atom can be either straight or twisted (linear or bend) and each shape is characterizable by a certain amount of hybridization. The  $sp$ -hybridized carbene carbon atom maintains linear geometry with two nonbonding degenerate orbitals ( $P_x$  and  $P_y$ ); in  $sp^2$  type of hybridization in which the carbon maintains bent geometry, the degeneracy is broken in this case, the  $p_x$  is stabilized by acquiring some  $s$  character, which is called  $\sigma$  while  $p_y$  is called  $\pi$  usually remain unaffected. It is noted that carbenes are mostly  $sp^2$  hybridized (bent) [6]. Due to the break in degeneracy, carbene can exist in singlet and triplet states. The singlet state carbenes have both nonbonding electrons pair in the same orbitals, either  $\sigma$  or  $p\pi$

orbital. In the triplet state, the two nonbonding electrons occupy two orbitals with a parallel spin (Figure 1.2) [7].

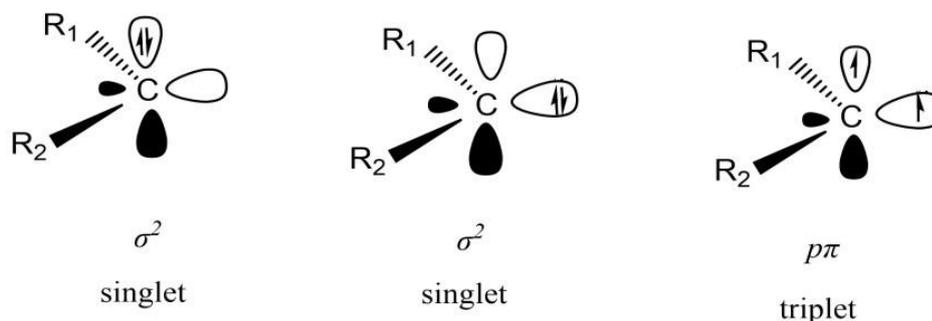
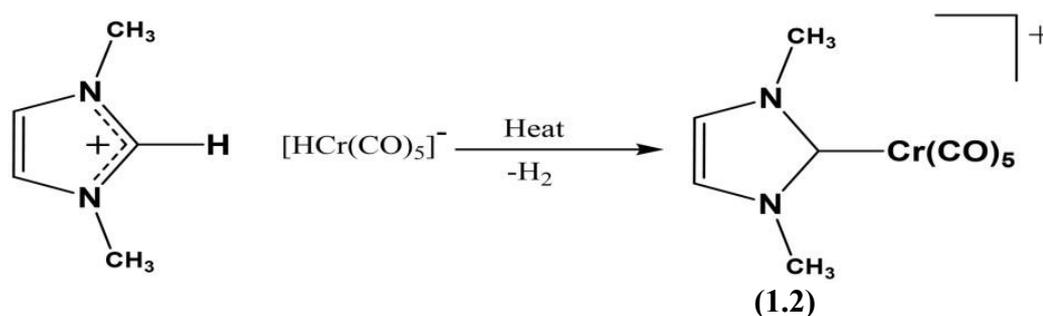


Figure 1.2 Electronic structure of singlet and triplet carbene [8].

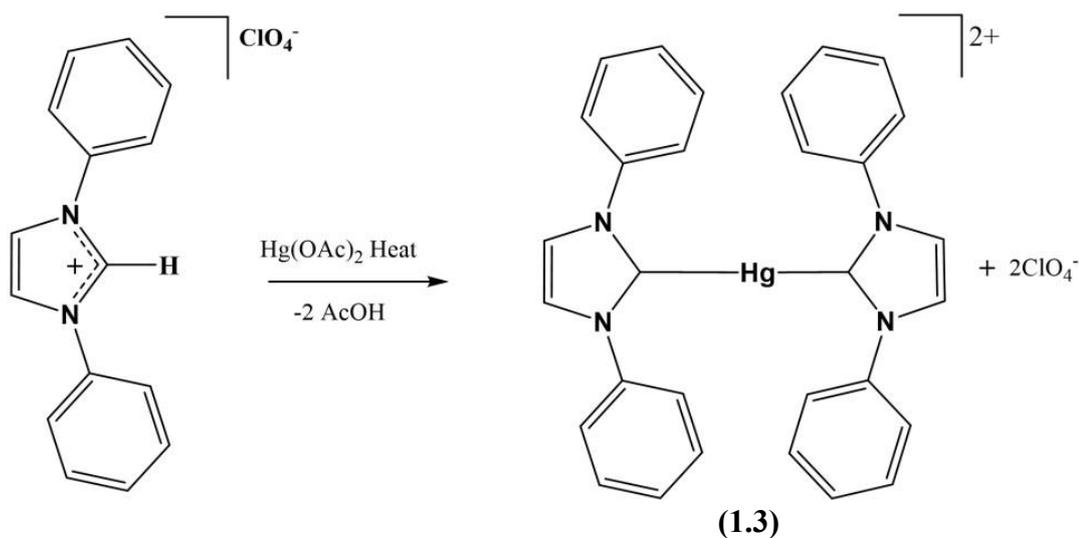
### 1.3 Brief history of carbenes

Since the first evidence of their existence, carbenes have substantially impacted organic chemistry. For the time being, many of the earliest synthesis in the laboratory was vested in the 1950s by Skell and later by Fischer *et al.*, who pioneered carbenes in inorganic and organometallic chemistry in 1964 [1].

Moreover, in 1968, the first examples of complex compounds containing *N*-heterocyclic carbene (imidazole-2-ylidene) were reported by Ofele (1.2) and Wanzlick (1.3) (Scheme 1.1 and 1.2). This research area from that time maintained enormous progress, and a massive amount of imidazol-2-ylidene complex compounds with main group elements and transition metals have been synthesized and characterized [9].

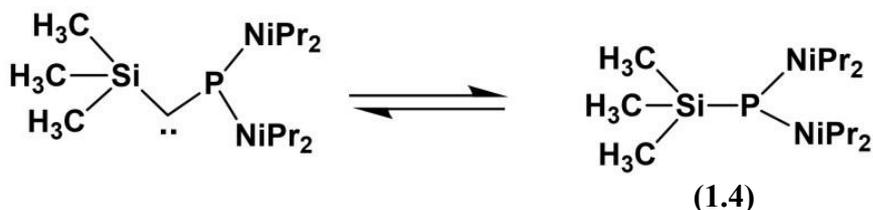


Scheme 1.1 Synthesis of Ofele's complex of imidazolium salts, **1.2** [10].



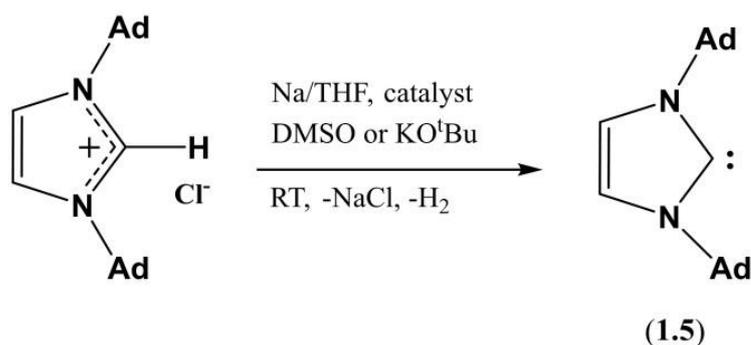
Scheme 1.2 Synthesis of Wanzlick's complex, **1.3** [11].

Furthermore, after two decades of Ofele and Wanzlick's work, Bertrand, and his team in 1988 isolated free and stable phosphinocarbene, “[bis-(diisopropylamino)phosphino](trimethylsilyl)” carbene balanced by phosphorus and silicon substituents next to the carbene centre (**1.4**) (Scheme 1.3) [9]. This was possible through favourable interactions with adjacent phosphorus and silicon-substituted compounds [9,12].



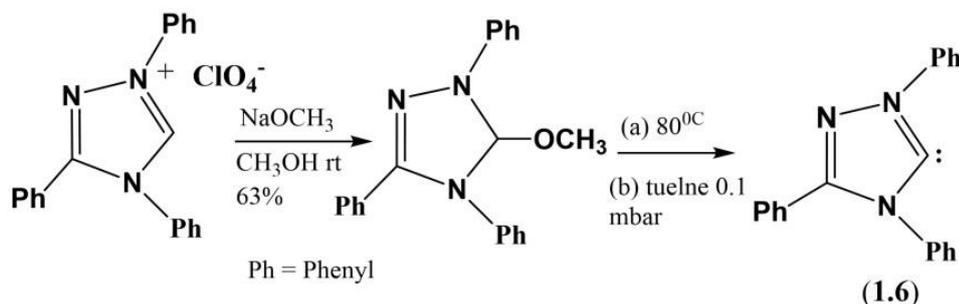
Scheme 1.3 Phosphinocarbene reported by Bertrand 1988, **1.4** [12].

After three years of Ofele and Wanzlick attempts, the isolation and characterization of 1,3-bis(adamantyl)imidazolin-2-ylidene (**1.5**) by Arduengo and his team brought the first free and stable imidazole (Scheme 1.4) [9,12].



Scheme 1.4 Arduengo carbene, **1.5** (where Ad = Adamantine) [13].

In 1995, triazole precursor was used by Enders and coworkers in which they presented the synthesis of the crystalline triazolin-5-ylidene carbene. Notably, compound 1,3,4-triazolin-5-ylidene (**1.6**) was the first free carbene to be commercialized (Scheme 1.5) [14].



Scheme 1.5 First commercialized stable carbene, **1.6** [15].

#### 1.4 Classification of carbenes

An essential factor in the classification of carbenes is the polarity variation of the electron density linking the metal and carbene centre. The variation exists from differentiation in energy among the  $p\pi$ -orbital of the carbene carbon and the  $d\pi$ -orbital of the metal. Carbenes are classified to three types, namely, (i) Fischer carbene, (ii) Schrock carbene, and (iii) Benzimidazolium salts [8].

- i. Fischer carbenes are classified as singlet carbenes. These carbenes are usually bonded to the transition metals with lower oxidation states coordinatively [16]. Additionally, carbene-to-metal bonds occur through the  $\sigma$ -donation of the lone pair of electrons from carbene to an empty  $d\pi$ -orbital of the metal atom. Thus, the energy interaction mainly indicated the  $d\pi$ -orbital of metal is in a lower energy position than of  $p\pi$ -orbital in the carbene atom. The metal-carbon bond polarized  $\sigma^-$  on metal and  $\sigma^+$  on carbon to generate electrophilic carbene (Figure 1.3) [8,17].

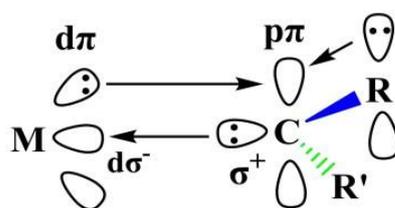


Figure 1.3 Fischer carbenes nature of the bond with metals [17].

- ii. Schrock carbenes are triplet carbenes and usually coordinate with the metal atom with a high oxidation number (Figure 1.4) [16,17]. In this instance, the carbenes and metal atom reaction occurs in a covalent condition where the  $d\pi$ -orbital of metal is higher in energy than  $p\pi$ - for the carbene carbon atom. In this case, the nucleophilic carbene is formed by the metal-carbon bond, with usual polarization as positive ( $\sigma^+$ ) on metal and negative ( $\sigma^-$ ) on carbene carbon [8].

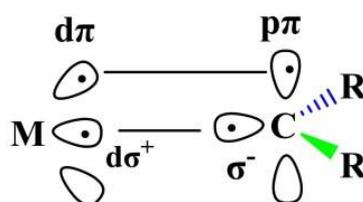


Figure 1.4 Schrock carbenes nature of the bond with metals [17].

iii. The benzimidazolium are characterized as the Fischer carbene because of their singlet state nature [2]. The  $p\pi$ -orbital of benzimidazolium has excessive energy because of the existence of multiple bonds between the carbene carbon and nitrogen atoms; this brought weak interaction with the  $d\pi$ -orbital of the metal atom by nearly stopping  $\pi$ -back donation to the carbene by the metal; thus, only one bond occurred in between the carbene centre and metal (Figure 1.5) [8].

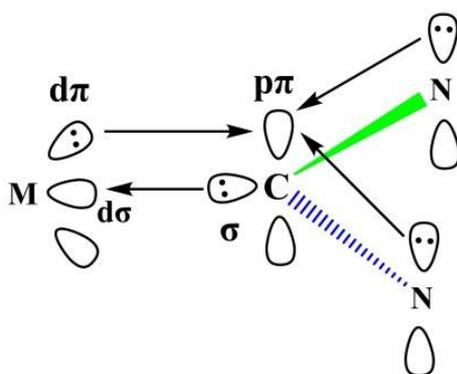


Figure 1.5 benzimidazolium salts nature of bonds with metals [17].

### 1.5 Structure and electronic properties of *N*-heterocyclic carbene (benzimidazole)

The benzimidazole, also known as Arduengo's carbene, is one of the types of carbenes that contains at least one nitrogen atom and the carbene centre within the structure [2]. Within the last 20 years, a thorough assessment of benzimidazolium as ligands for transition metals revealed a rich coordination chemistry with improving applications [18]. The benzimidazolium salts are described as perfectly-recognized, highly relevant, and promising types of ligands in organometallic chemistry [19–21]. This is because of their ability to form stable compounds in both higher and lower oxidation states transition metals [22]. The formation of such metal complexes is

attributed to their stronger bonding to transition metals due to their strong  $\sigma$ -donating and weak  $\pi$ -accepting capacity when interacting with metals [23–26].

The presence of nitrogen atoms in benzimidazole influence the stability of carbene's singlet conformation because of their  $\sigma$ -electron-withdrawing and  $\pi$ -electron-donation ability [27]. Aside from this, the carbene centre (C2) in a singlet state arrangement, leaving the  $p\pi$ -orbital of the carbene centre (C2) vacant. This permits the two nitrogen atoms to balance the carbene centre (C2) by contributing  $\pi$ -electrons to the empty  $p\pi$ -orbital while minimizing the energy of the occupied  $\sigma$ -orbital (C2) concurrently by applying  $\sigma$ -electron withdrawing consequences on the carbene centre [27].

The aromatic group attached to carbene ligands improve their stability, which influences their properties electronically. Furthermore, the various substituted groups bound to the nitrogen atom beside the carbene centres (C2) provide extra stability. However, this result is less than the stability the nitrogen atoms gave electronically. The voluminous substituted groups on the benzimidazolium salts similarly help to initiate a chirality (Figure 1.6) [14].

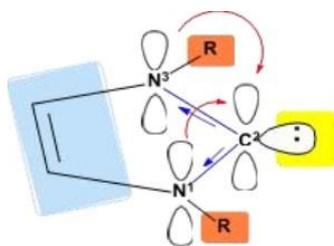


Figure 1.6 Electronic stabilization of benzimidazolium salts [14].

## 1.6 Metal complexes of *N*-heterocyclic carbene (benzimidazole-2-ylidene)

Fischer and coworkers pioneered the chemistry of carbene metal complexes in 1964 for successfully synthesizing the tungsten carbonyl carbene complex [28].

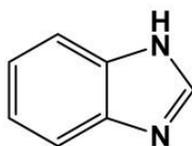
Moreover, the discovery of benzimidazolium as ligands in metal complexes by Ofele [10] (Scheme 1.1) and Wanzlick [11] (Scheme 1.2), followed by the successful isolation of free benzimidazolium by Arduengo in 1991 (Scheme 1.3), [29] has led to their complexation with a variety of transition and main group metal elements.

The formation of such metal complexes by benzimidazolium is attributed to their stronger bonding with transition metal elements owing to their strong  $\sigma$ -donating to an empty metal's orbital and the weak  $\pi$ -accepting capacity when interacting with metals [24–26,30]. Typically, when benzimidazolium ligands interact with the metals, they contribute their lone pair of electrons, and subsequently, they weakly attract the  $\pi$ -electrons from the metal into their  $p$ -orbital; this is known as back donation, while the  $\pi$ -donation from carbene is minor. Thus, the contribution of the  $\pi$ -electrons is constricted to only delocalization within the benzimidazolium system; therefore, the bonds between the metal and carbene centre remain single, not double. The bond between carbene and the metal form remains very strong. This is due to the fact that free carbenes are generally thermodynamically unstable [8]. Thus, they are essential spectator ligands that are difficult to participate in reductive elimination or insertion reaction [8]. Structural modifications were usually achieved with the changes in adjacent chains annexed to the nitrogen atoms; this shed more light on minor changes in the ligand's electronic and steric ownership, which affect the comparative complexes' solubility, stability, and lipophilicity [31].

## 1.7 Synthesis of azolium salts

Apart from imidazole, triazole, tetrazole, and pyrazole, benzimidazole (1.7) makes up most of azole compounds. Benzimidazolium is a neutral chemical that serves as two electron donor ligands with a heterocyclic core [32]. Benzimidazoles

are organic heterocyclic aromatic compounds comprising a benzene ring fused with five-membered rings with two nitrogen atoms occurring at an isolated site (**1.7**) (Figure 1.7) [33].

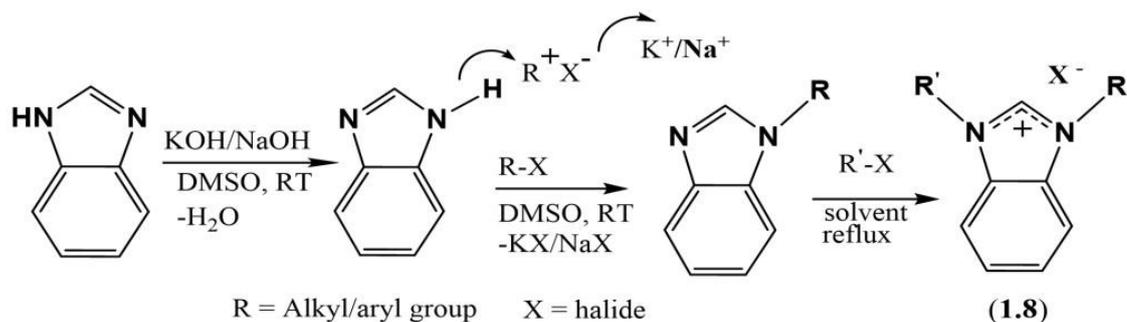


(1.7)

Figure 1.7 Structure of benzimidazole, **1.7** [33].

Since the successful synthesis and separation of free imidazole by Arduengo in 1991 [13], numerous procedures have been evolved and adopted to synthesize and isolate many benzimidazolium [34,35]. The two most frequent methods are the alkylation of the nitrogen atoms of imidazole/benzimidazole and the multi-component reactions of primary amines, glyoxal, and formaldehyde, giving symmetrical *N, N'*-substituted azolium salts [12].

The first method is otherwise called nucleophilic substitution or *N,N*-substitution of the benzimidazole with convenient alkyl/aryl halide, which resulted in the generation of a high yield *N,N*-substituted benzimidazolium salts. The reaction occurs in three steps: benzimidazole is deprotonated using a strong base (NaOH, KOH) to produce sodium or potassium benzimidazolate. In the second stage, the sodium or potassium benzimidazolate reacted with the same molar equivalent alkyl/aryl halide to produce the desired *N*-substituted benzimidazole. Thirdly, *N*-substituted benzimidazole finally reacts with desired alkyl/aryl halide to give *N, N*-substituted benzimidazolium salts (**1.8**) (Scheme 1.6) [36].



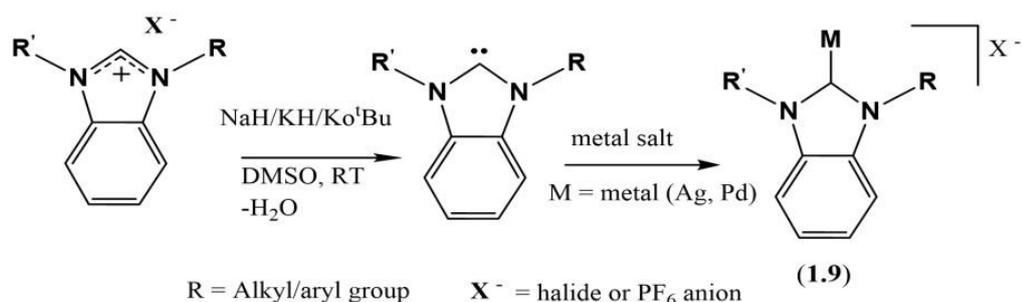
Scheme 1.6 General synthesis of benzimidazolium salt by nucleophilic substitution reaction, **1.8** [36].

## 1.8 Synthesis of metal complexes of *N*-heterocyclic carbene

The discovery of benzimidazolium as ligands in metal complexes by Ofele [10] and Wanzlick [11] has provided more opportunities in organometallic chemistry. This opened a new chapter in their history as more methods were developed for their synthesis.

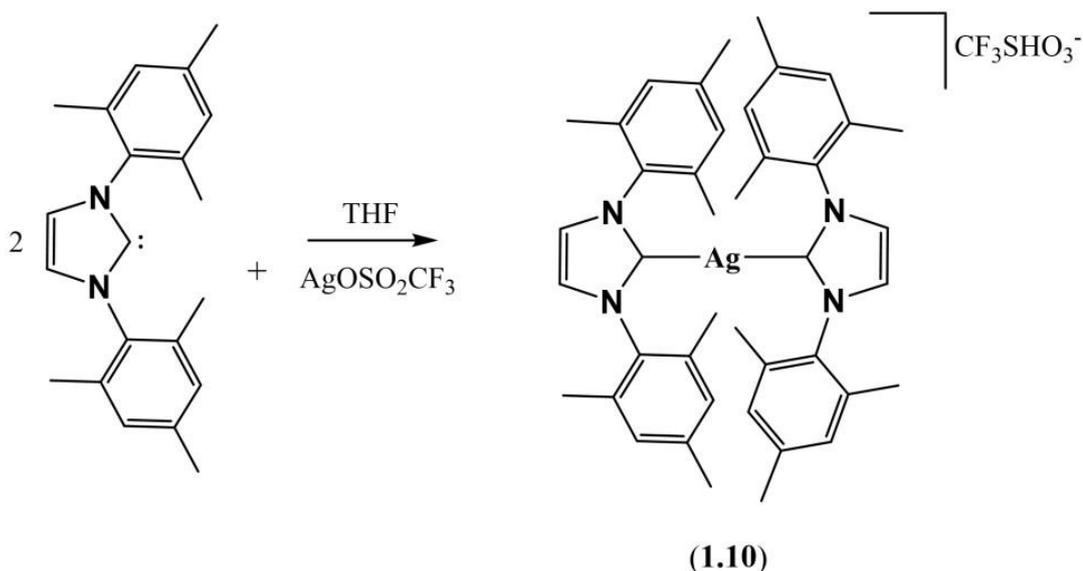
### 1.8.1 Metal complexes of *N*-heterocyclic carbene via free carbene

The free carbene synthesis is achieved by reacting benzimidazolium salts with strong bases like NaH, KH, or Ko<sup>t</sup>Bu, which leads to the deprotonation of acidic proton to generate the free carbene. The isolated free carbene is then further reacted with a suitable metal salt to enable the emergence of benzimidazoli-2-ylidene metal complex (**1.9**) (Scheme 1.7). [37].



Scheme 1.7 Benzimidazol-2-ylidene metal complex synthesis via free carbene method, **1.9** [37].

After the successful isolation of free carbene by Arduengo in 1991 (Scheme 1.4) [13]. He later prepared the first silver(I)-imidazol-2-ylidene complex in 1993 where 1,3-dimesitylimidazol-2-ylidene (**1.10**) in tetrahydrofuran (Scheme 1.8) [38].



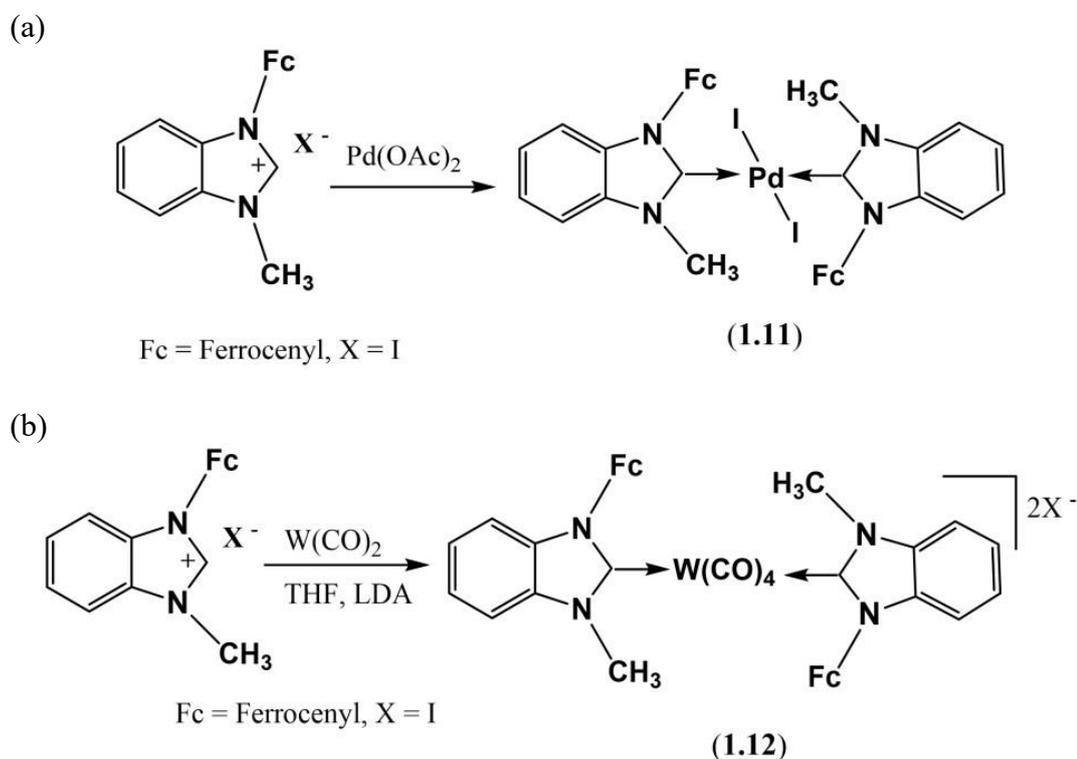
Scheme 1.8 Synthesis of first silver imidazol-2-ylidene complex via free carbene method, **1.10** [38].

### 1.8.2 Metal complexes of N-heterocyclic carbene via in-situ-deprotonation of benzimidazolium salts

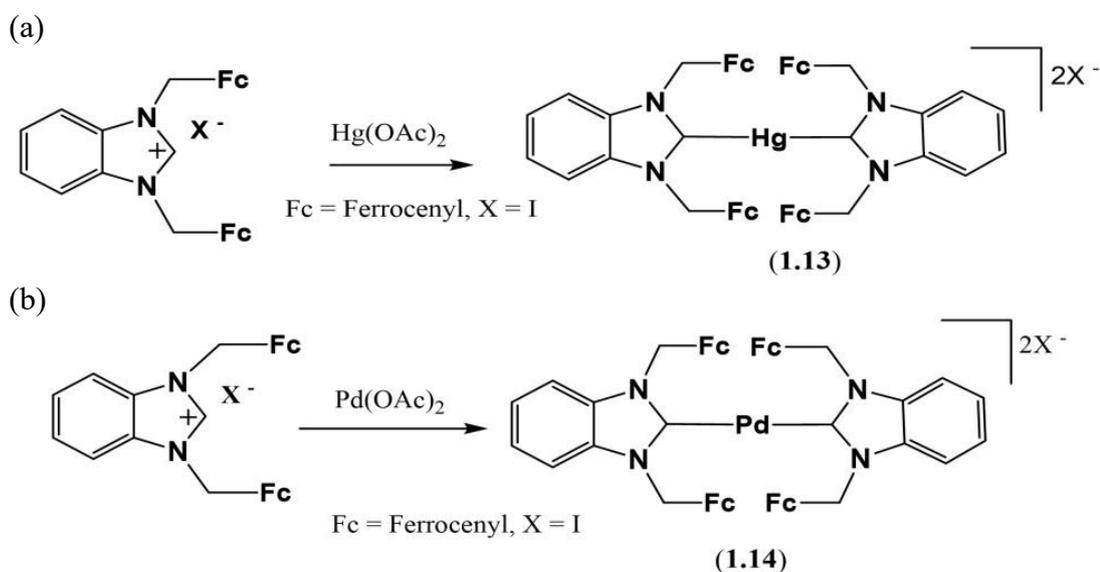
This method has been used by Ofele [10] and Wanzlick [11] before the isolation of free carbene by Arduengo [13]. Their effort became the first *in-situ* deprotonation of benzimidazolium salts with mercury and chromium salts as the metal sources and bases to yield their benzimidazolium complexes. The advantage of this method is the ease of isolation of the complexes that are sensitive to moisture and air [8]. Thus, the preparation for free benzimidazolium is not required [39]. This method is the only way to prepare the necessary complex when the carbene is unstable or difficult to manage. The literature reported it in two pathways [39].

i. Using basic anion for deprotonation

Basic anions from the Bronsted bases on the metal precursor or the benzimidazolium salts are used. The deprotonation and complexation processes in the same reaction media occur concurrently to yield the desired benzimidazol-2-ylidene complexes [8]. The metal salts are available commercially, such as oxides, acetates, alkoxides, and acetylacetonate, are used because of their simplicity in preparation [40]. More complexes were synthesized using this method; for examples, palladium(II)- benzimidazol-2-ylidene (**1.11**), W(IV)- benzimidazol-2-ylidene (**1.12**), and Hg(II)- benzimidazol-2-ylidene (**1.13**), palladium(II)- benzimidazol-2-ylidene (**1.14**) complexes (Scheme 1.9 and 1.10).



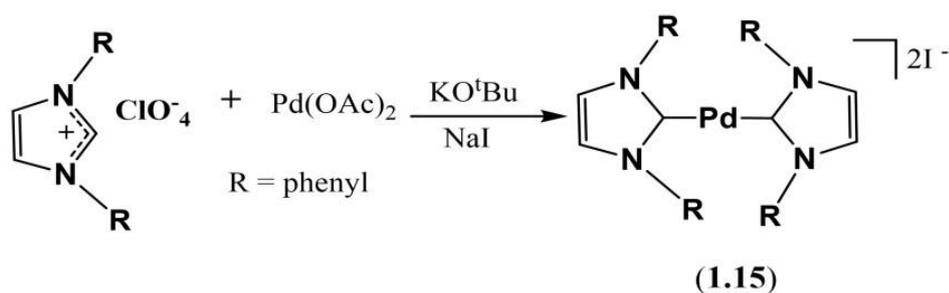
Scheme 1.9 Synthesis of benzimidazol-2-ylidene complex via in-situ deprotonation by basic anions. (a) Reaction of benzimidazolium salt with Pd(II) acetate; and (b) with W(II) dicarbonyl. The acetate ion acted as a base in the formation of **1.11** and **1.12** [41].



Scheme 1.10 Synthesis of benzimidazol-2-ylidene complex via in-situ deprotonation by basic anions. (a) Reaction of benzimidazolium salt with Hg(II); and (b) with Pd(II) acetate. The acetate ion acted as a base for the formation of **1.13** and **1.14** [42].

ii. *Application of external base for deprotonation*

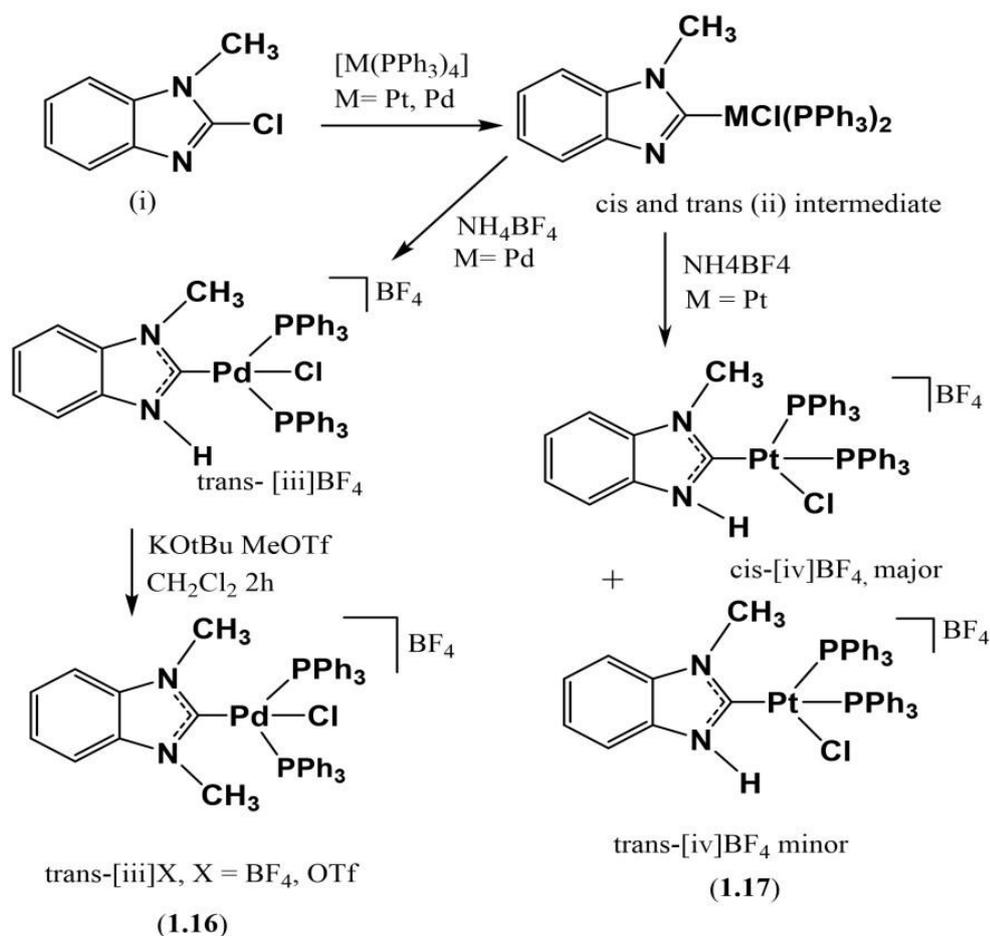
Using external base KO<sup>t</sup>Bu to deprotonate imidazolium or benzimidazolium salts can give rise to the formation of various imidazol-2-ylidene complexes in comparison to applying metal salts with basic anions. In this, for instance, a dimeric mono-imidazol-2-ylidene complex was formed by the reaction of imidazolium perchlorate in the presence KO<sup>t</sup>Bu and NaI, as reported by Enders *et al.* in 1996 for the formation of palladium(II)-imidazol-2-ylidene complex, **1.15** (Scheme 1.11) [40,43].



Scheme 1.11 Synthesis of Pd(II) of dimeric imidazolin-2-ylidene complexes by in-situ deprotonation using external base reported, **1.15** by Enders et al.; 1996 [43].

### 1.8.3 Metal complexes of N-heterocyclic carbene via oxidative addition reaction of benzimidazolium salts

This method involved the oxidative addition reaction between benzimidazolium carbon-bearing halogen, hydrogen, or alkyl group at the C2 position (C2-X, X = hydrogen, halogen, alkyl) with transition metals in a lower oxidation state [44–47]. It was reported that 2-chloro-*N*-methylbenzimidazole (i) was added oxidatively to tetrakis(triphenylphosphine) platinum(0) and palladium(0), which gave C2-metallated intermediate (ii) and on successive protonation with  $\text{NH}_4\text{BF}_4$  as weak acid yields the complex with an NH, NR-substituted benzimidazolium ligand. Pd(0) gave trans-isomer (iii) as the most stable thermodynamically, and it undergoes methylation reaction to produce NCH<sub>3</sub>, NCH<sub>3</sub> substituted benzimidazol-2-ylidene Pd(0) complex in the presence of strong base  $\text{K}^t\text{Bu}$  and  $\text{CF}_3\text{SO}_2\text{OCH}_3$  as methylating agent. Pt(0) gave cis and trans-isomers (iv) as major and minor products, respectively (**1.16** and **1.17**) (Scheme 1.12) [44]. The process hindrance related to the order of this arrangement is C-methyl > C-hydrogen > C-halogen, thus, haloimidazoliums proved to lead to more exothermic processes. It has been reported that there is a restriction using this method to generate benzimidazol-2-ylidene complexes with other metals [48].



Scheme 1.12 Synthesis of benzimidazol-2-ylidene metal complexes of Pd(0), (1.16) and Pt(0), (1.17) via oxidative addition of benzimidazolium salt [44].

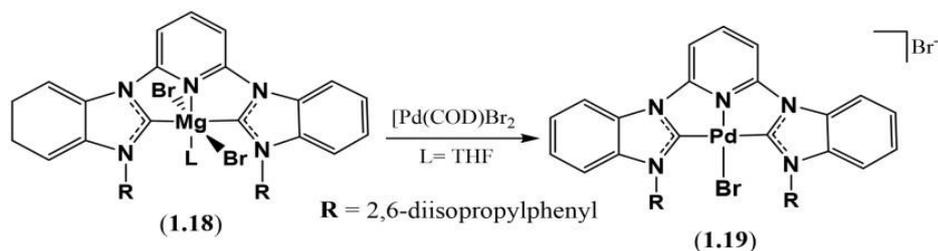
#### 1.8.4 Transmetalation reaction

The study of organometallic chemistry includes many elucidative reactions that form the bedrock of this area as part of inorganic chemistry [49]. An additional vital reaction of organometallic compounds is transmetalation, a common term which trendy meaning expresses the transfer of carbon ligands, for example, aryl, alkyl, and allyl, from one metal to another [49,50]. Additionally, transmetalation has been used to transfer metal from one organic part to another, exchanging one metal for another in a compound containing several metal species. This is not limited to transition metals; main group metals can be exchanged for transition metals as well.

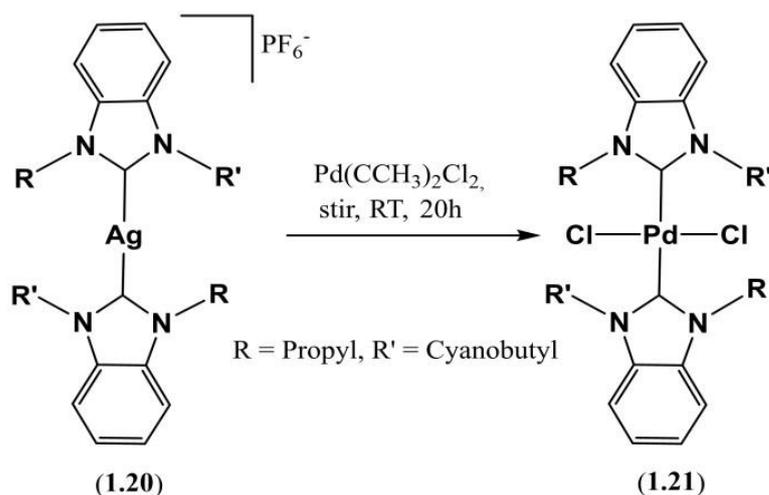
For example, in 2019, Messelberger *et al.* reported the synthesis of Pd(II) benzimidazol-2-ylidene complex (**1.19**) by transmetallation reaction from magnesium bis-benzimidazol-2-ylidene complex (**1.18**) in the presence of dibromo(1,5-cyclooctadiene)palladium(II) THF and the product was up to 85% (Scheme 1.13) [49,50].

Transmetallation has a prolonged record, and the reaction dates to the initial origination of organometallic chemistry due to the effort of Edward Frankland, an English chemist (1825–1899). In 1849, Frankland reported the preparation of ethyl zinc species, diethyl zinc, ethyl zinc iodide and zinc iodide from zinc metal and ethyl iodide [49]. Moreover, in 1970, Fischer and Beck prepared metal complexes of benzimidazolium salts from methoxyphenyl carbene carbonyl cyclopentadienyl nitrosyl molybdenum(I), which reacted with pentacarbonyl iron(0) in benzene which was subjected to UV irradiation [51]. Similarly, the first palladium(II)-benzimidazol-2-ylidene and gold(I)-benzimidazol-2-ylidene complexes reported in 1998 by Wang and Lin from Silver benzimidazol-2-ylidene bonds made silver(I)-benzimidazol-2-ylidene complexes effective carbene transfer mediums. Their work described the application of two benzimidazolylidene complexes of silver(I) as a carbene source by the reaction of  $\text{PdCl}_2(\text{MeCN})_2$  and  $\text{AuCl}(\text{SMe}_2)$ , correspondingly [48]. The process was replicated in 1998 by Liu and his team, in which palladium(II) and Platinum(II) were obtained by benzimidazolium salts transfer from the W(0) benzimidazol-2-ylidene complex [52]. Since then, many benzimidazol-2-ylidene of gold(III), platinum(II) and palladium(II) have been synthesized and characterized [53–56]. In more detail for example, Sanusi *et al.* 2018 reported the synthesis of Pd(II) complexes by transmetallation reaction of mono nuclear silver(I)-

benzimidazol-2-ylidene in the presence of Pd(CCH<sub>3</sub>)Cl<sub>2</sub> in 20-hour stirring at RT (1.20 and 1.21) (Scheme 1.14) [53]



Scheme 1.13 Synthesis of palladium(II)- benzimidazol-2-ylidene complex, (1.19) by transmetalation reaction with main group metal benzimidazol-2-ylidene complex, Mg(II)- benzimidazol-2-ylidene, (1.18) [50].



Scheme 1.14 Synthesis of palladium(II) benzimidazol-2-ylidene, (1.21) by transmetalation reaction of silver(I)- benzimidazol-2-ylidene (1.20) [53].

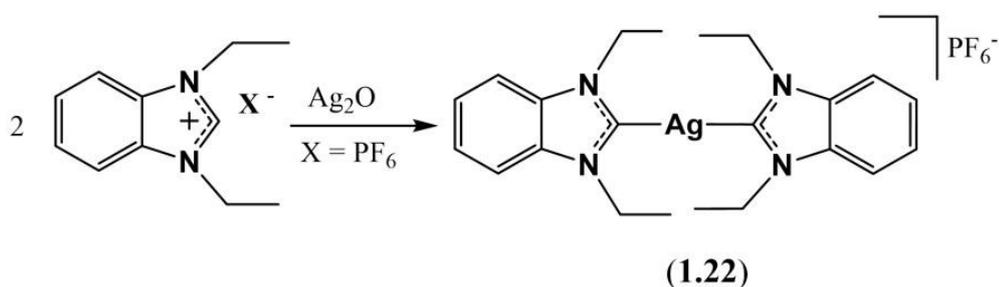
## 1.9 Silver(I)- benzimidazol-2-ylidene complexes

### 1.9.1 In-situ deprotonation as the preferred synthetic method

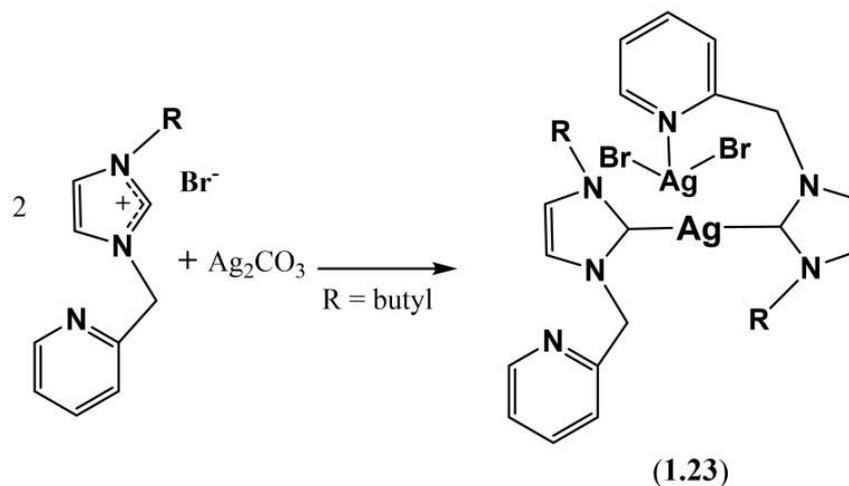
Since the synthesis of the first benzimidazol-2-ylidene silver(I) complex from free carbene ligand by Arduengo and coworkers in 1993 (Scheme 1.8), many compounds were synthesized in accordance with this method. However, due to easiest way of *in-situ* deprotonation, it was mainly adopted for the preparation of silver(I)- benzimidazol-2-ylidene compounds as this reaction requires no external

base and can be conducted at room temperature [57,58]. The source of silver(I) ions is also significant; hence, the first application of silver(I) acetate as a silver (I) ion source was reported in 1997 [59]. Similarly, the first application of silver(I) oxide as a silver(I) ion source in the synthesis of the silver(I) imidazol-2-ylidene complex compound was pioneered by Wang and Lin a year later (**1.22**) (Scheme 1.15) [60]. Moreover, silver(I) carbonate was reportedly used as a silver(I) ion source in silver(I)- benzimidazol-2-ylidene complex synthesis (**1.23**), even though the reaction time is longer compared to the use of silver(I) oxide (Scheme 1.16) [61].

However, the frequently used of silver(I) ion source for the metalation of benzimidazolium salts into their silver(I) complexes is silver(I) oxide. This is due to its commercial availability and stability. Similarly, the compounds are stable, high-yield, and good transmetallation agents [62]. Separation and purification of the complexes can be achieved upon completion of the reaction time simply by removing the remaining uncoordinated silver(I) oxide and AgBr and by separation using a pad of celite and subsequent metathesis reaction using potassium hexafluorophosphate, (**1.22**) [63,64].



Scheme 1.15 First application of Ag<sub>2</sub>O to synthesize silver(I)- benzimidazol-2-ylidene complex via in-situ deprotonation, (**1.22**) [60].



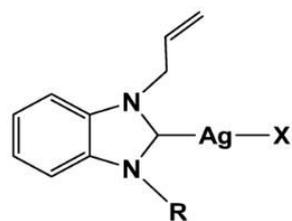
Scheme 1.16 First application of  $\text{Ag}_2\text{CO}_3$  to synthesize silver(I)-imidazol-2-ylidene complex via in-situ deprotonation, (1.23) [61].

### 1.9.2 Classification of benzimidazol-2-ylidene silver(I) complexes

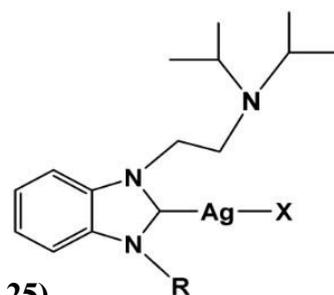
Generally, benzimidazol-2-ylidene complexes can be categorized based on the number of metals attached to the benzimidazolium ligands. They are mono-, bis-, tris- and poly benzimidazolium salts metal complexes. This research described bis-benzimidazol-2-ylidene silver(I) obtained from bisbenzimidazolium salts, tris-benzimidazol-2-ylidene from tris-benzimidazolium salts and binuclear-benzimidazol-2-ylidene silver(I) from tetrakis-benzimidazolium salts series.

#### 1.9.2(a) Mono- benzimidazol-2-ylidene silver(I) complexes

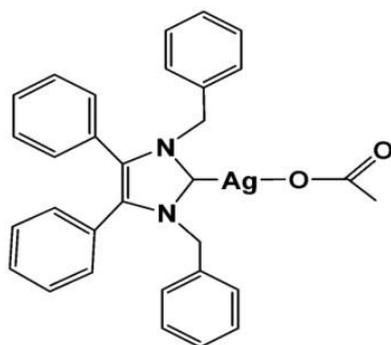
In this class, the benzimidazol-2-ylidene complex contains only one silver and one benzimidazolium ligand, and it is a neutral complex as the metal coordinates with another type of non- benzimidazolium ligand. Thus, it has the general formula of [benzimidazol-2-ylidene-Ag-X], where X = halides, benzoate, acetate, and many of them were reported for instance, (1.24-1.27) (Figure 1.8) [17,64–67].



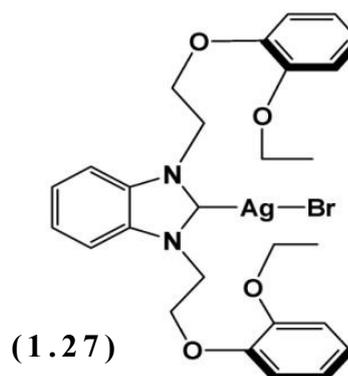
(1.24)



(1.25)



(1.26)



(1.27)

Figure 1.8 Examples of mononuclear silver(I)-benzimidazol-2-ylidene complexes with the general formula of [benzimidazolium-Ag-X] (where X = halide), by in-situ deprotonation of benzimidazolium salts, (1.24 - 1.27) [64–67].

The silver(I)- benzimidazol-2-ylidene complexes also exist with the general formula of [benzimidazol-2-ylidene-Ag-benzimidazol-2-ylidene]PF<sub>6</sub>. These complexes are also known as bis-benzimidazol-2-ylidene mononuclear silver(I), as represented by structures, **1.28-1.31** [17]. The presence of the non-coordinated counterion in the lattice will balance the charge for entire molecule (Figure 1.9) [68–70].

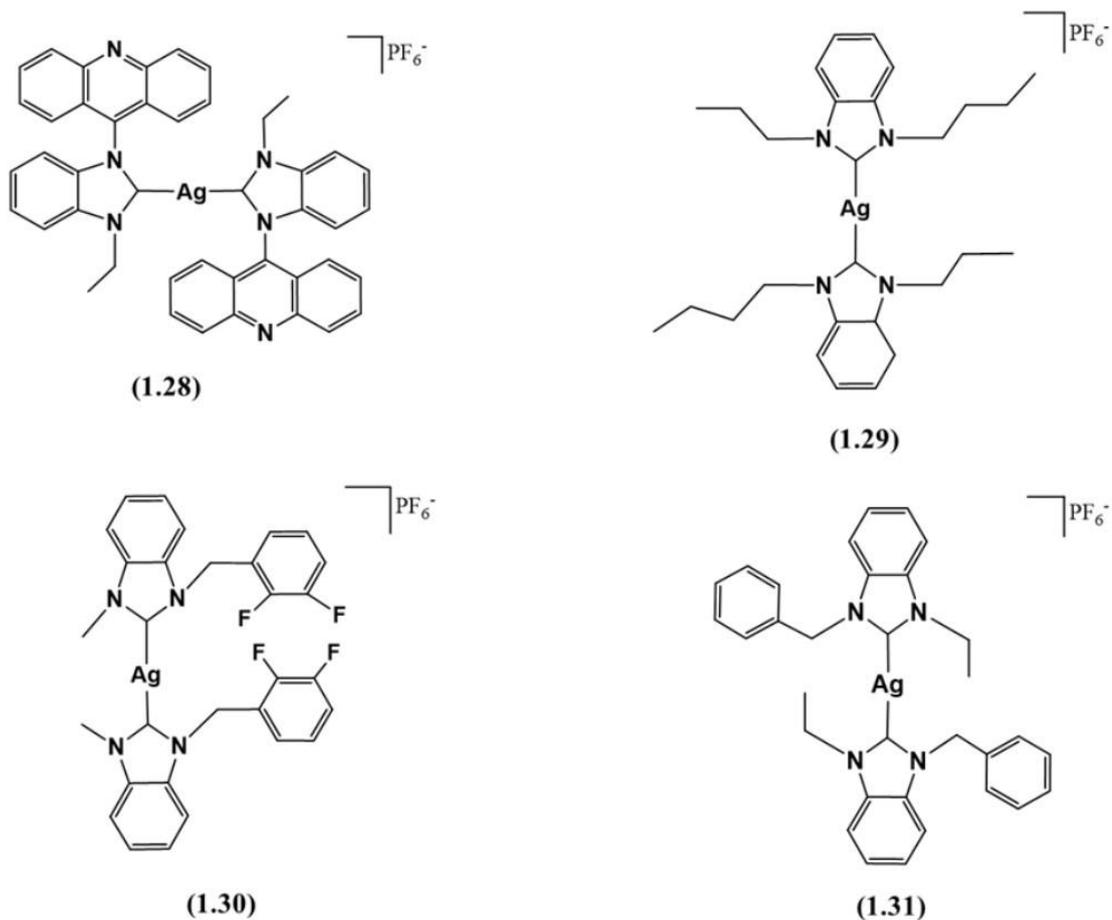


Figure 1.9 Examples of mononuclear benzimidazol-2-ylidene silver(I) with the general formula [benzimidazol-2-ylidene-Ag-benzimidazol-2-ylidene]PF<sub>6</sub>, (**1.28**–**1.31**), prepared by in-situ deprotonation of benzimidazolium salts [55,68–70].

### 1.9.2(b) Bis-benzimidazol-2-ylidene silver(I) complexes

Bis-benzimidazolium salts are the essential starting materials for the synthesis of various mononuclear or binuclear silver(I) bis-benzimidazol-2-ylidene complexes. It's interesting to note that the benzimidazolium moieties in these complexes are bridged by alkyl or aryl groups, introducing different structural variations. For instance, in complex **1.32**, the bridging ligand used was para-xylyl, whereas in complex **1.33**, trimethylene was utilized as the bridging ligand. Likewise, dimethylene served as a bridge between the two benzimidazolium ligands in complex **1.34**. These variations in bridging ligands can significantly impact the properties and

potential applications of these complexes. A few years back, much research was carried out on their synthesis and characterization (**1.32–1.36**) (Figure 1.10) [71–73].

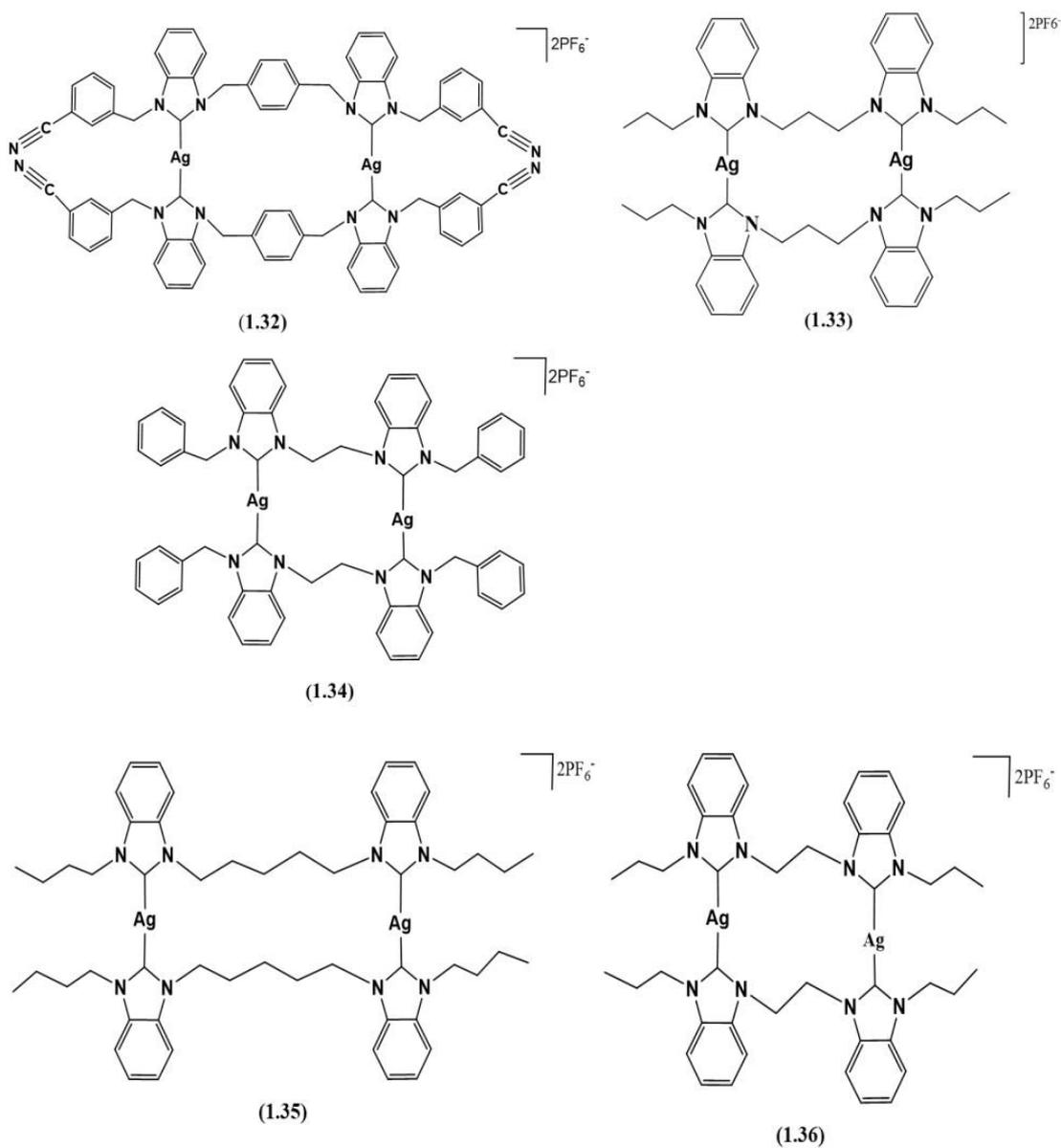


Figure 1.10 Examples of binuclear silver(I)- benzimidazol-2-ylidene complexes prepared by in-situ deprotonation of benzimidazolium salts, (**1.33-1.36**) [71–73].

### 1.9.2(c) Tris- benzimidazol-2-ylidene silver(I) complexes

Tris-HNC and their respective silver(I) compounds are proportionately smaller in numbers compared to mono-, bis-, and tetra-benzimidazolium salts and their complexes. The pioneered work is by Hu and his group nearly two decades ago whereby they synthesized a new benzimidazolium-tridentate poly-carbene ligand and subsequently converted it to trinuclear silver(I) complex, (**1.37**) by *in-situ* deprotonation of the salt (Figure 1.11) [74].

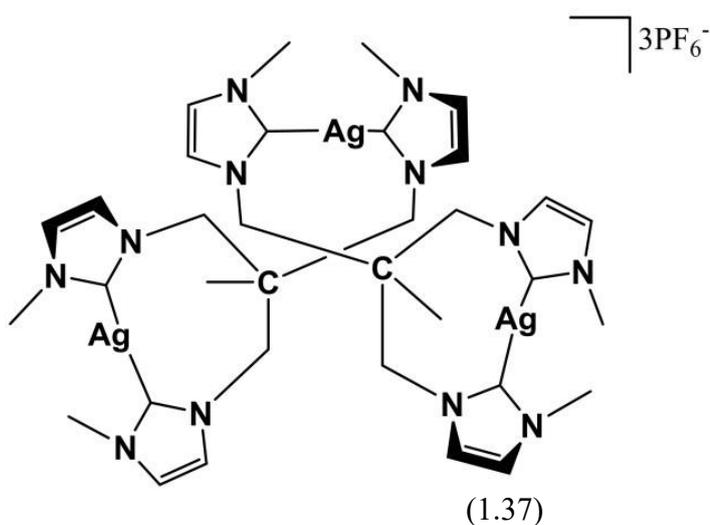


Figure 1.11 Example of first tris-imidazol-2-ylidene trinuclear silver(I) complex by *in-situ* deprotonation of tris-imidazolium salt, (**1.38**) [74].

From that time, much more research was carried out involving tris-benzimidazolium salts and their respective silver(I) complexes. Recent studies on tris-benzimidazolium salts and related silver(I) complexes with phenyl bridges have been published by Rit and colleagues. As the co-starting material, 1,3,5-tris(bromo)benzene was used to prepare tris-imidazolium salts through a reaction with three equimolar *N*-substituted imidazole. The trinuclear silver(I) complex of the same salt was obtained by *in-situ* deprotonation in the presence of silver(I) oxide in dimethylsulfoxide, (**1.38**) (Figure 1.12) [75,76].

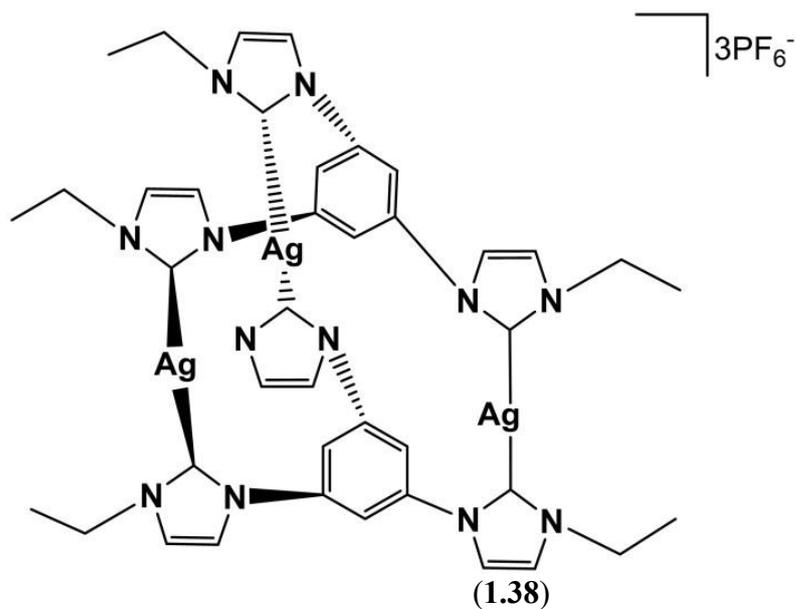


Figure 1.12 Example of tris-imidazol-2-ylidene trinuclear silver(I) complex by in-situ deprotonation of tris-HNC salt, **(1.38)** [75,76].

Similarly, in 2017, Fatima *et al.* reported on a new strategy for tri-benzimidazolium carbene salts obtained from the reaction between benzimidazole and 3-(2-bromoethyl)-1-benzylbenzimidazolium bromide as precursors in one to two molar equivalents. The subsequent metalation of the obtained salts with silver(I) oxide resulted in trinuclear silver(I) complexes, **(1.39)** and **(1.40)** (Figure 1.13) [62].