DINUCLEAR SILVER(I)-*N*- HETEROCYCLIC CARBENE COMPLEXES BASED ON IMIDAZOLIUM DERIVATIVES: SYNTHESIS AND BIOLOGICAL ACTIVITIES

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2018

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by

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Thesis submitted in fulfilment of the requirements

For the degree of

Master of Science

July 2018

ACKNOWLEDGEMENT

First of foremost, I would like to thank my God for helping those who need you. So I have deep faith that you will not abandon me.

I would like to thank my supervisors: Dr. Mohd Rizal Razali for his support and expert leadership and for giving me this opportunity to study under his supervision. Without his timely guidance I could not have achieved my goals. Assoc Prof. Dr Rosenani for the assistance, encouragement and valuable suggestions you have provided to aid me in overcoming the difficulties that I've faced during the course of this work.

I would like to thank Dean of School of Chemical Sciences for providing such a good research environment and necessary research facilities. I am deeply thankful to IPS staff who helped me throughout.

A huge thank you to the academic staff in the School of Chemical Science, particularly Mr. Mohd Nizam, Mr. Azizo and Mdm. Nur Asma for their helps and supports in completing NMR, FT-IR and CHN analysis studies, respectively. Thank you to Mr. Mohd Mustaqim from School of Physics for crystal structures determination. My gratitude goes to Silas Avicor from School of Biological Sciences for his assistance during larvicidal activities.

A great thank you has to go to everyone past and present who have been in the inorganic section. Dr Muhammad Adnan Iqbal, Dr Patrick, Dr Tabinda, Umie Fatihah, Sunusi Yahya and Yeap Choon Wan, making my time during my master so enjoyable and their sincere support.

I wish to thank my family for their love, kindness and unlimited support, my brother and sisters for their unconditional encouragement during my study. Without you all I would not have been able to complete my goals. I would like to give special thanks to my friends: Ruzaina, Thilaga, Hintumathi, Yamuna, Ghajendran, Kevin Jason, Ramesh, Ramendirran, Shanmugam, Shanti, Nhivashini, Mohana, and Sarasvathy.

Puvana Devi a/p Selvarajoo, 2017

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LIST OF ABBREVIATION AND SYMBOLS

Δ	Chemical shift in ppm
°	Degrees
°C	Degrees Celcius
µg	Microgram
µL	Microliter
Π	Pi
Σ	Sigma
Å	Angstrom, 1 x 10^{-10} m
Anal.	Analysis
Ar	Aromatic Ring
Calc.	Calculated
^{13}C NMR	Carbon-13 nuclear magnetic resonance
D	Doublet
D_c	Density
DMSO	Dimethylsulfoxide
EtOH	Ethanol
FT-IR	Fourier transforms infrared
G	Gram
^{1}H NMR	Proton nuclear magnetic resonance
Hz	Hertz

J	Coupling constant
K	Kelvin
Kv	Kilovolt
LC_{50}	Lethal concentration required to kill 50%
M	Molecular mass
M	Multiplet
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz
mL	Millilitre
Mm	Millimeter
Mmol	Milimoles
Mol	Moles
NHC	N-heterocyclic carbenes
OAc	Acetate
Ppm	Part per millions
RT	Room temperature
S	Singlet
T	Temperature
T	Triplet
Tert-BuOK	Potassium tertiary butoxide
THF	Tetrahydrofuran
V	Volume
XRD	X-ray single crystal diffraction

KOMPLEKS DINUKLEAR ARGENTUM(I)-*N*-HETEROSIKLIK KARBENA BERDASARKAN DERIVATIF IMIDAZOLIUM: SINTESIS DAN AKTIVITI BIOLOGI

ABSTRAK

Kajian ini menerangkan sintesis dua siri baru, empat garam pelopor baru dalam siri bukan berfungsi, dinamakan, 3,3' [(1,2 fenilinbis(metilin)] bis(1-siklopentanaimidazolium bis-heksaflorofosfat (**1**), 3,3' [(1,3 fenilinbis(metilin)] bis(1-siklopentanaimidazolium bis-heksaflorofosfat (**2**), 3,3' [(1,4 fenilinbis(metilin)] bis(1-siklopentanaimidazolium bis-heksaflorofosfat (**3**), 3,3' [(etana-1,2-diyl)] bis(siklopentanaimidazolium) bis heksaflorofosfat (**4**) dan empat garam sepadan dalam siri berfungsian nitril**,** dinamakan, 3,3' [(1,2 fenilinbis(metilin)] bis(4'-benzonitrilimidazolium) bis-heksaflorofosfat (**9**), 3,3' [(1,3 fenilinbis(metilin)] bis(4'-benzonitrilimidazolium) bis-heksaflorofosfat (**10**), 3,3' [(1,4 fenilinbis(metilin)] bis(4'-benzonitrilimidazolium) bis-heksaflorofosfat (**11**) and 3,3' [(etana-1,2-diyl)] bis(4'-benzonitrilimidazolium) bis-heksaflorofosfat (**12**). Tindak balas garam imidazolium dengan argentum(I) oksida menghasilkan pembentukan dua siri baru kompleks argentum(I)-NHC, masing-masing, (**5-8)** dan **(13-16)**. Struktur untuk semua sebatian disahkan dengan spektral (spektroskopi Fourier Transform Inframerah, spektroskopi ^{1}H dan ^{13}C NMR dan analisis CHN). Struktur molekular untuk sebatian **3, 5, 7,** dan **10** dicapai menggunakan analisis sinaran-X hablur tunggal. Kajian antibakteria melawan bakteria Gram-positif *Staphyococcus aureus (S. aureus)* (ATCC 12600) dan Gram-negatif *Escherichia coli (E. coli)* (ATCC

25922) untuk kesemua 16 sebatian dijalankan. Kesemua garam imidazolium menunjukkan tiada perencatan manakala kesemua kompleks yang menunjukkan aktiviti antimikrob menunjukkan tiada perbezaan besar dalam diameter zon perencatan.. Kesemua garam imidazolium menunjukkan tiada perencatan manakala aktiviti larvisidal untuk kompleks argentum(I)-NHC.

DINUCLEAR SILVER(I)-*N*- HETEROCYCLIC CARBENE COMPLEXES BASED ON IMIDAZOLIUM DERIVATIVES: SYNTHESIS AND BIOLOGICAL ACTIVITIES

ABSTRACT

This research describes the syntheses of two new series, non-functionalized series of four new precursor salts **,** namely 3,3' [(1,2 phenylenebis(methylene)] bis(1-cyclopentylimidazolium bis-hexaflourophosphate (**1**), 3,3' [(1,3 phenylenebis(methylene)] bis(1-cyclopentylimidazolium) bis-hexaflourophosphate (**2**), 3,3' [(1,4 phenylenebis(methylene)] bis(1-cyclopentylimidazolium) bis-hexaflourophosphate (**3**), 3,3' [(ethane-1,2-diyl)] bis(1-cyclopentylimidazolium) bis-hexaflourophosphate (**4**) and nitrile functionalized series of four new correspondence salt**,** namely 3,3' [(1,2 phenylenebis(methylene)] bis(4'-benzonitrilelimidazolium) bis-hexaflourophosphate (**9**), 3,3' [(1,3 phenylenebis(methylene)] bis(4'-benzonitrilelimidazolium) bis-hexaflourophosphate (**10**), 3,3' [(1,4 phenylenebis(methylene)] bis(4'-benzonitrilelimidazolium) bis-hexaflourophosphate (**11**) and 3,3' [(ethane-1,2-diyl)] bis(4'-benzonitrilelimidazolium) bis-hexaflourophosphate (**12**). Reaction of respective imidazolium salts with silver(I) oxide afforded the formation of two new series of silver(I)-NHC complexes, **(5-8)** and **(13-16)**, respectively. The structures of all the compounds were confirmed by the elemental analysis data, (Fourier Transform Infrared spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and CHN analysis). Selected molecular structure of compounds **3**, **5**, **7**, and **10** were established by single crystal X-ray diffraction analysis. The antibacterial studies against the Gram-positive *Staphyococcus aureus (S. aureus)* (ATCC 12600)

and Gram-negative *Escherichia coli (E. coli)* (ATCC 25922) of all sixteen compounds were carried out. All the imidazolium salts show no inhibition while all complexes displayed antimicrobial activity shows no huge difference in the diameter of the zone of inhibition. On the other hand, larvicidal activities against *Ae. aegypti and Cx. Quinquefasciatus* showed no inhibition for imidazolium salts but their silver(I)-NHC complexes showed larvicidal activity. Therefore, this study quantified the larvicidal property of silver(I)-NHC complexes, providing information on lethal concentration that have potential for the control of mosquitoes.

CHAPTER 1

INTRODUCTION

1.1 Persistent Carbenes

Carbenes are compound containing a neutral divalent carbon atom with two non-bonding electrons and six valence electrons, which the two unshared electrons can be assigned to nonbonding orbitals in different ways [1] (Figure 1.1) .

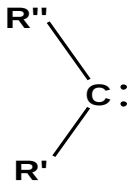


Figure 1.1: A general representation of carbene.

The existences of carbenes are depending on the electronic spins they possess (singlet or triplet states). Singlet state carbene has two unshared electrons paired spin adopts sp^2-hybridization in the same orbital (Figure 1.2). Triplet state carbene have unshared electrons arranged in two different orbitals with parallel spins and adopts the *sp*-hybridization (Figure 1.2) [2]. Triplet carbenes considered as diradicals because of their two unpaired electrons [3]. The ground state spin multiplicity can be determined by the relative energies of σ and $p\pi$ orbitals. According to Hoffmann, the energy differences greater than 2 eV is favored to be a singlet carbenes while the energy difference below 1.5 eV lead to a triplet ground state [4].

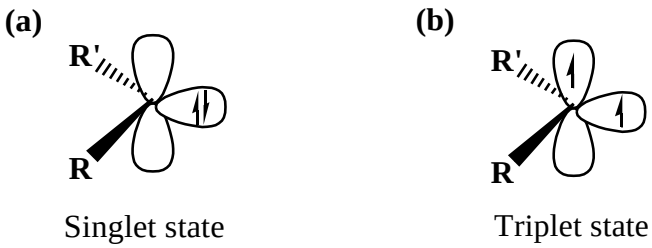
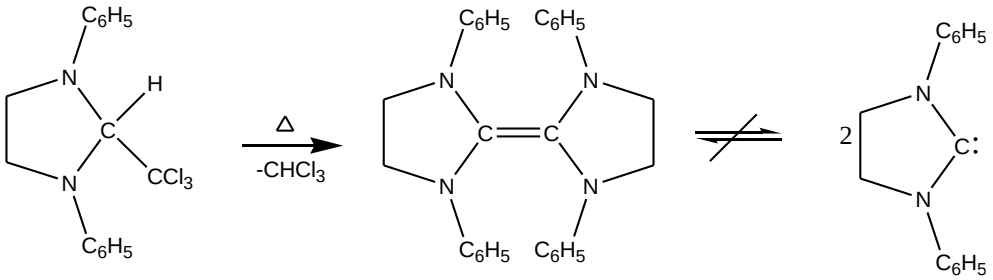


Figure 1.2: Electronic states of carbenes, (a) singlet state; (b) triplet state.

The energy difference gap can be increased by the existence of σ-electron withdrawing substituents adjacent to the divalent carbon atom. Thus, these groups will stabilize the σ-nonbonding orbital by increasing *s* orbital character, while leaving the *p*π orbital unchanged [5].

1.2 *N*-Heterocyclic carbene (NHC)

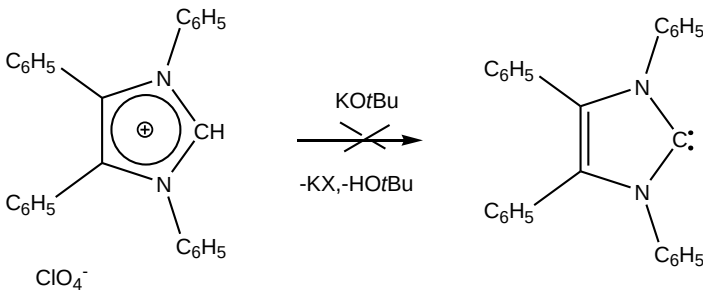
In early 1960, Wanzlick investigated saturated and unsaturated heterocyclic carbenes. The focus was first to synthesize C-C saturated molecules of type **3** (Scheme 1.1). However, Wanzlick could never isolate **3** and always obtained **2**, which acquired from the α-elimination reaction of chloroform from **1** [6].



1 **2** **3**

Scheme 1.1: Formation of dimeric entatraamine **2** instead of free NHC **3**.

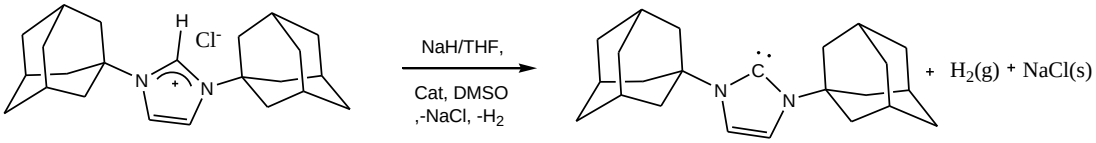
Later, Wanzlick tried to separate the dimeric entatramine, **2** using cross-metathesis method, however unsuccessful [7]. In 1970, Wanzlick changed the starting material to facilitate the formation of free NHC. In his intention to prepare carbene **5**, Wanzlick tried to deprotonate 1,2,3,4,5-tetraphenylimidazolium perchlorate, **4** with base catalysed medium, KO*t*Bu (Scheme 1.2), but the reaction could not be isolated as this method was detected as the intermediate product [8].



4 **5**

Scheme 1.2: Deprotonation of imidazolium salt from **4** to free carbene **5**.

Various efforts have been applied on synthesis and isolation of carbenes by researchers until pioneering studies in the late 1980s and early 1990s [9]. In 1991, Arduengo believed that the intermediate carbenes are unstable as being assumed by other researchers [10]. Arduengo and co-workers synthesized and isolated the first crystallogaphically explained NHC, **7** from an azolium salt, **6** in the presence of sodium hydroxide and DMSO using THF as reaction medium (Scheme 1.3) [11]. This carbene was found to be stable at room temperature in the absence of moisture and oxygen [12]. Further in 1998, Arduengo prepared, characterized and determine the single crystal structure of carbene, **5** which Wanzlick could not isolate in 1968 [13].

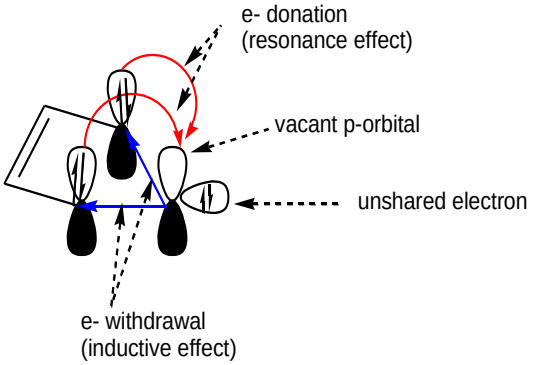


6 **7**

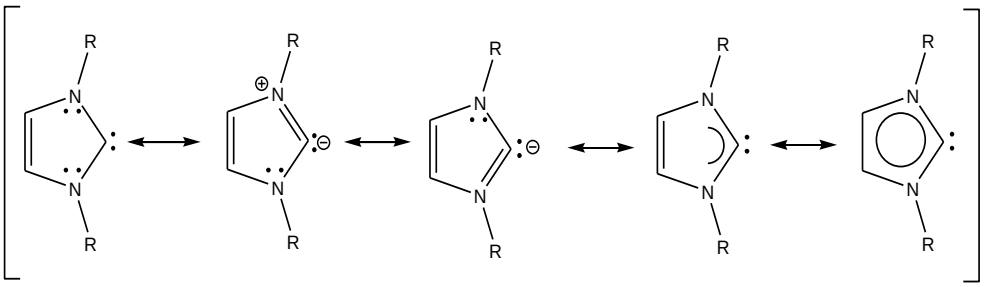
Scheme 1.3: First isolated carbene ion **7** from azolium salt **6**.

1.3 The stability of NHCs

Formerly, Arduengo stated that the stability of NHCs is due to the steric hindrance of the bulky *N*-adamantyl substituents which prevent the dimerization of the carbene. Nevertheless, Arduengo's syntheses of another stable carbene with *N*-methyl substituents proved this wrong [14]. Arduengo believed that the electronic contributions are the main factors in determining the stability of NHC and its complexes (Figure 1.3). Electronic contributions involve electron donation from the adjacent nitrogen atoms to the vacant *pπ* orbital of the carbene carbon. Moreover, due to higher electronegativity of nitrogen as compare to carbon atom, charge density is considered to be inductively withdrawn through the σ-framework, stabilizing the carbene lone pair [14].



(a)



(b)

Figure 1.3: **(a)** Electronic and **(b)** resonance stabilization in *N*-heterocyclic carbene.

Even NHCs are viewed mainly as σ–donor; recent theoretical and structural studies suggest the existence of some π–backbonding for certain metal centre (Figure 1.4). The electron donation makes NHC as nucleophilic character and gives them good σ-donors to transition metals in low and high oxidation states. In comparison to the Fischer and Schrock carbenes, NHCs are stable, capable of independent existence and can be readily prepared.

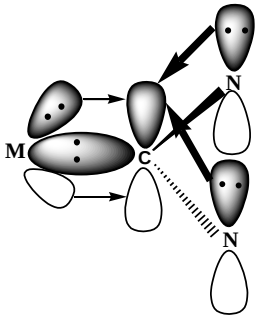


Figure 1.4: Metal bonding to *N*-heterocyclic carbene.

1.4 Types of NHC ligands

There are several variation of NHC based on their structures. Examples of NHC are imidazole-2-ylidine, imidazolidin-2-ylidenes, imidazole-5-ylidenes, 1,2,4-trazolodin-3,5-ylidenes, tetrahydropyramid-2-ylides and benzimidazol-2-ylidene. Among them, the five membered NHC are the most commonly studied (Figure 1.5).

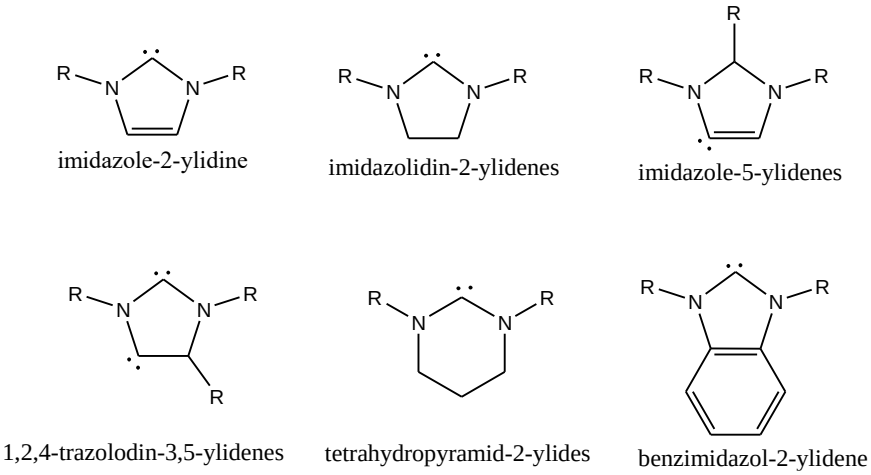


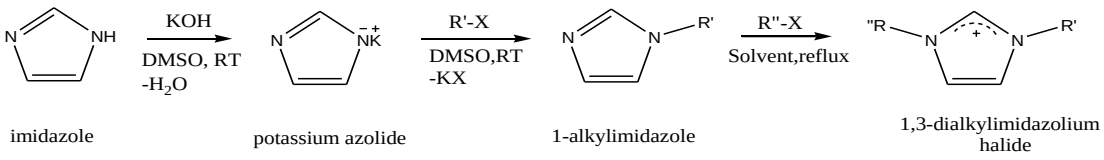
Figure 1.5: Type of *N*-heterocyclic carbene.

1.5 Synthesis of azolium salts: The NHC precursors

NHC precursors are prepared by two common routes [15]:

a) Nucleophilic substitution starting at the azole heterocycle

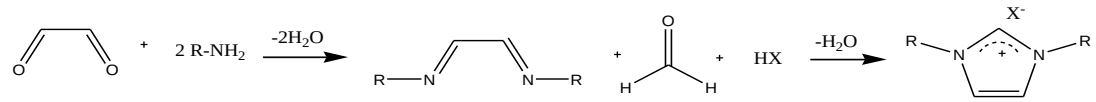
This route involves alkylation of azole (imidazole, benzimidazole, triazole etc) reacted with strong base such as KOH and NaOH. The potassium or sodium azolide formed is then treated with one equivalent of alkyl or aryl halide in a suitable solvent to obtain *N*-alkyl/aryl substituted azole [16]. The *N*-substituted azole is then reacted with one equivalent of alkyl or aryl halide to yield disubstituted of imidazolium salts (Scheme 1.4).



Scheme 1.4: General representation of syntheses of imidazolium salts by nucleophilic substitution.

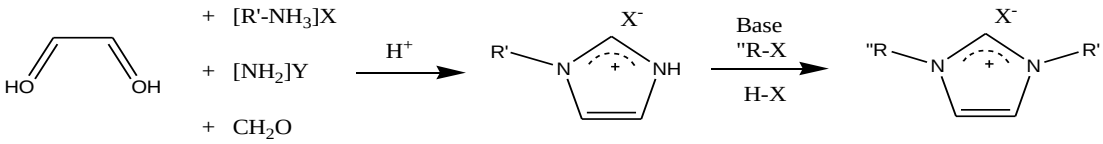
b) Multi-components reaction, building up the heterocycle with the appropriate substituents in one step

This route which involves one pot synthesis using primary amines, glyoxal, and formaldehyde are reacted in the presence of Brønsted acid [17, 18]. The reaction starts with coupling between amine and glyoxal to form Schiff base. Further, condensation with formaldeyde which facilitates the formation of imidazolium salt (Scheme 1.5).



Scheme 1.5: General representation of syntheses of imidazolium salts by multi-components reaction.

The flexible route is suitable for the syntheses of symmetrical 1,3- substituted azolium salts. Unsymmetrical substituted azolium salts can also be prepared by the combination of a multicomponent cyclization and follow with an *N*-alkylation reaction [19]. After the alkylation, alkyl group (R") attached at second nitrogen atom to obtain asymmetrically substituted derivative (Scheme 1.6).



Scheme 1.6: General representation of multicomponent cyclization and *N*-alkylation.

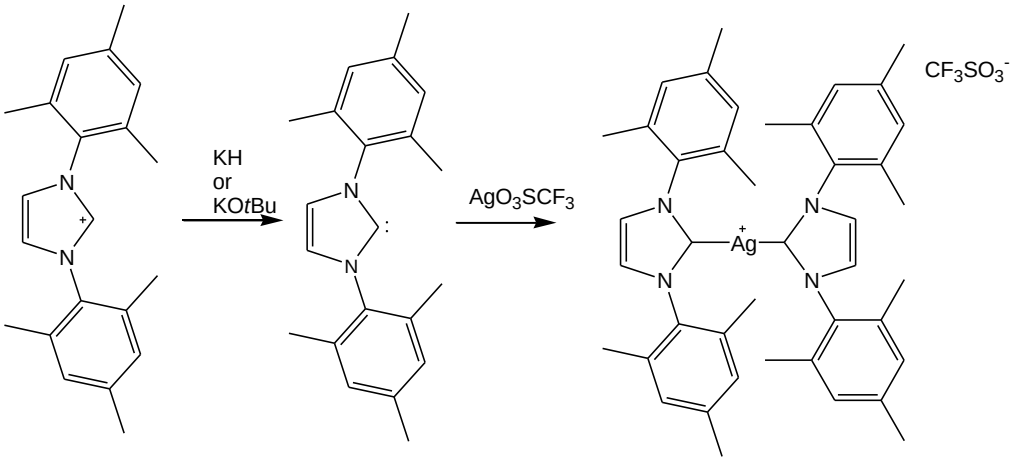
1.6 Synthesis of silver(I)-NHC complexes

NHCs have been extensively used in organometallic and inorganic chemistry for catalytic study [20] , transmetalation [21] and medicinal studies [22]. Three main synthetic methods are used to synthesis silver(I)-NHC complexes:

1.6.1 Preparation of the free carbene and reaction with silver salt

The first reported synthesis of silver(I) complex was achieved by this route in 1993. According to this route, deprotonation of imidazolium salt prepared with strong base and subsequently free carbon reacted with silver triflate to yield silver-

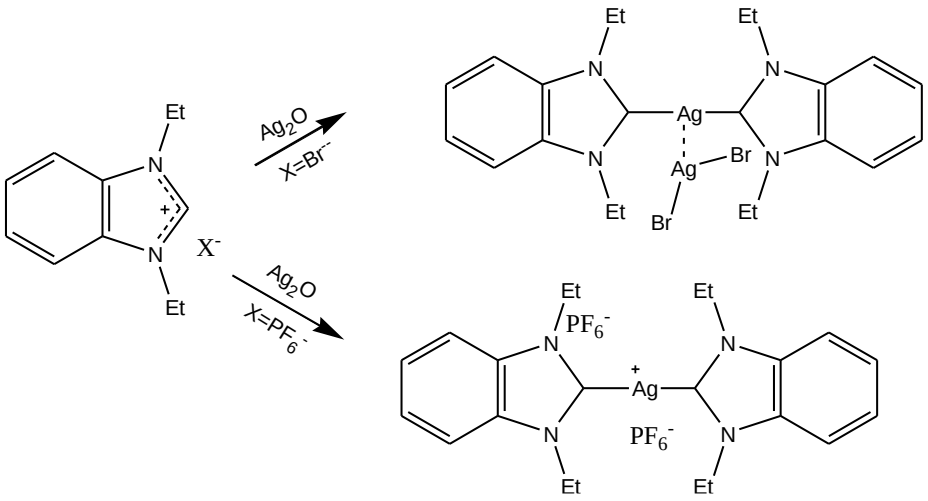
NHC complex (Scheme 1.7) [23]. Since then, various silver(I) complexes have been synthesized using this method [24-26]. A strong base suitable for deprotonation of imidazolium salts is either potassium hydride, KH or potassium *t*-butoxide, KO*t*Bu. As this route in the initial stage of free carbenes, it is limited to those imidazolium salts which can generate stable carbenes [24, 27-29].



Scheme 1.7: Preparation of silver(I)-NHC complexes by free carbene.

1.6.2 In-situ reaction of azolium salts

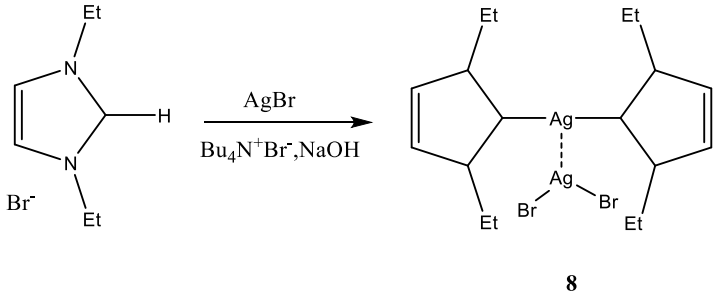
Deprotonation of azolium salt by the use of a silver(I) base such as Ag_2O, AgOAc, and Ag_2CO_3 [30, 31] has been the most widely used method in the syntheses of silver(I)-NHC complexes. Lin and co-workers investigated a procedure that using Ag_2O to form silver(I)-NHC complexes of 1, 3 diethylbenzimidazol– 2–ylidene (Scheme 1.8) [32, 33]. Silver oxide is the most frequently used of the metal bases as the reaction can easily controlled by removing insoluble silver oxide [34-38]. Different sorts of solvents have been used with Ag_2O in the synthesis of silver(I)-NHC complex such as dimethylformamide, dichloromethane, 1,2-dichloroethane, dimethyl sulfoxide, acetonitrile, methanol and acetone.



Scheme 1.8: *In-situ* reaction of benzimidazolium salts.

1.6.3 Silver salt in the basic medium

An alternative method to synthesize silver(I)-NHC complexes is through the deprotonation of imidazolium cations that was first employed by Wang and Lin [32]. These researchers used a basic phase transfer catalyst, tetrabutylammonium bromide ($Bu_4N^+Br^-$) to prepare **8** from imidazolium bromide in the presence of silver bromide (Scheme 1.9). The silver(I)-NHC complexes produced through this method are sensitive to moisture which leads to decomposition to imidazolium salt. Thus, this routes have been abandoned due to unsuccessful attempts and the aforementioned success of silver-based route using silver(I) oxide [39].



8

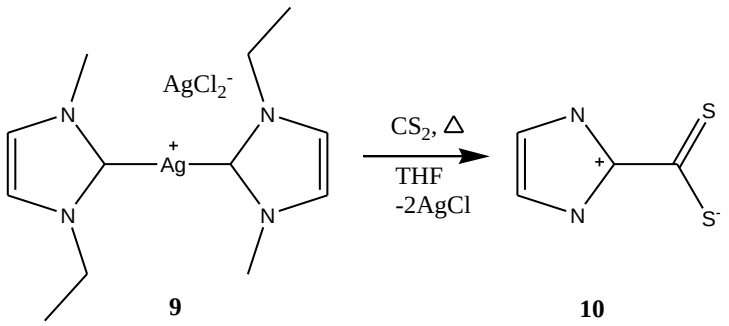
Scheme 1.9: Synthesis of silver(I)-NHC, **8** using basic phase transfer catalyst.

1.7 Applications of silver(I)-NHC complexes

1.7.1 Catalytic study

In 1996, Fernandez, Peris and co-workers were the first to study silver(I) NHC as donation from the substituents of the alkene by increasing the conversion rates of the diboration reaction. Later, they found that increasing the temperature of the diboration reaction, it slows the conversion of the alkene to the diborane. However, the active catalytic species of silver(I)-NHCs could not discover as the nature of silver(I)-NHC in solution.

Later, Waymouth and Hedrich have also studied silver(I)-NHCs for catalytic purposes [40]. They reported that silver(I)-NHCs, **9** undergoes thermolysis to produce free NHC (Scheme 1.10), which then used to catalyse the ring opening polymerization of L-lactide [41]. The thermal stability of **9** was studied by different scanning calorimetry and thermogravimetric analysis. They attempted to trap the free NHCs by heating complex **9** in the presence of a trapping reagent, carbon disulphide to produce zwitterion **10**.



9 **10**

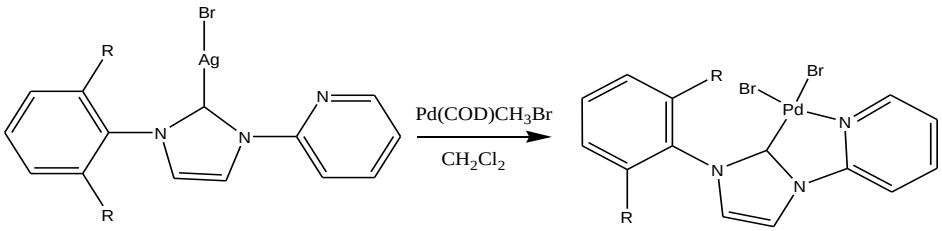
Scheme 1.10: Active catalytic species of silver(I)-NHC.

1.7.2 Carbene transfer chemistry

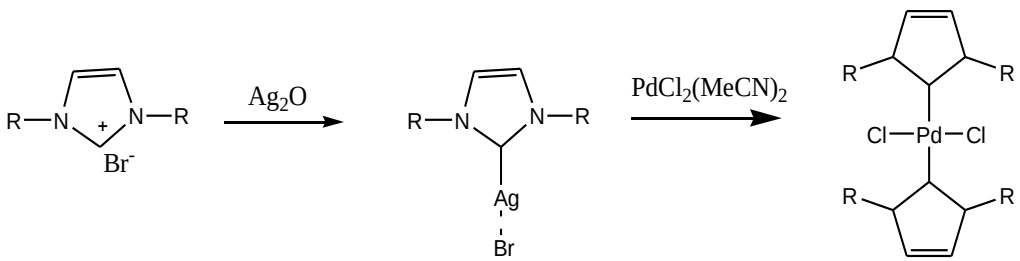
One of the most important application of silver(I)-NHC is transmetalation reaction. Many ligands are unsuccessfully metalate due to degradation under condition required. Silver(I)-NHC complexes have proven themselves as transfer agent to other metals such as Au(I), Cu(I), Cu(I), Pd(II), Pt(II), Ni(II), Ir(I), Ir(III), Rh(I), Rh(III), Ru(II), Ru(III), and Ru(IV). Transmetalation reaction can be carried out under aerobic conditions, inert atmosphere and presence of water [42]. Transmetallation become more important method in obtaining the NHC complexes of different metal with interesting biological applications [43].

Transmetalation from silver(I)-NHCs has become a general method for preparation of Pd(II)-NHCcomplexes where a variety of palladium reagents have been used for transmetalation including $Pd(COD)Cl_2$ [44-47], $Pd(COD)Br_2$ [48], $Pd(COD)CH_3Br$ [48], $Pd(COD)CH_3Cl$ [29, 44, 47-49], $PdCl_2$ [50-52], $[Pd(allyl)Cl]_2$ [53-55], $PdCl_2(CH_3CN)_2$ [50, 56-59], and $PdCl_2$-$(PhCN)_2$ [44, 60] (Scheme 1.11).

(a)



(b)



Scheme 1.11: Transmetalation of silver(I) complexes: (a) Using $Pd(COD)CH_3Br$ [48], (b) Using $PdCl_2(CH_3CN)_2$ [58].

1.7.3 Medicinal chemistry

a) The use of silver compounds as antimicrobials

Silver has been used as an antimicrobial in early years. The early civilizations used silver to store and purify drinking water [61-64]. Antimicrobial properties of silver nitrate were known in 1800s and it was recognized as an antiseptic in wound care for more than 200 years. In the late 19th century, it was reported that silver compounds can kill certain microorganisms at very low concentrations [65]. Créde began to use of 2% silver nitrate solution to prevent eye infections in new-borns, in 1881.

In 20th century, colloidal silver solutions were introduced to avoid the irritation associated with silver nitrate. Moyer found a treatment for large human burns using 0.5% silver nitrate solution [66]. In addition, Fox discovered the use of silver antibiotics using silver sulfadiazine [67] . Silver sulfadiazine (Figure 1.6) is designed to combine antibiotic sulphonamide, sulfadiazine, with silver to obtain wide spectrum antibiotics. It is in solid state, water insoluble complex and exists as polymer. Besides, it has been shown good biological activities against gram- positive and gram-negative bacteria [68]. Silver sulfadiazine remains one of most widely used antimicrobials for infections associated with burns [22].

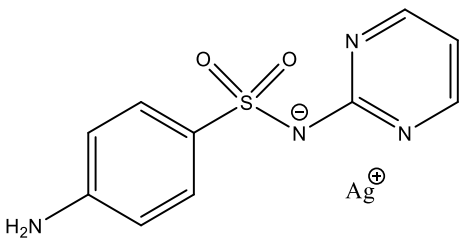


Figure 1.6: Structure of silver sulfadiazine [67].

Silver sulfadiazine have been observed to kill bacteria quickly, but loose their effect in a short time causing the wound site to be reinfected. The slow release of silver at the wound sites is essential for faster healing. The strong binding of NHCs to silver can result in more stable complexes that can slowly release silver ion, thus retaining the antimicrobial effect over a longer period of time.

b) The use of silver compounds as larvacides

Silver(I)-NHC complexes have been widely tested for their antimicrobial activities. However, they were rarely studied for their antilarvacidal activity.

At present, different types of metal nanoparticles are being produced including copper, zinc, titanium, magnesium, gold, alginate and silver [69].Among these, silver nanoparticles (AgNPs) have received considerable attention due to their attractive physico-chemical properties, surface plasmon resonance, surface-enhanced raman scattering (SERS) or biological applications. Biologically synthesised AgNPs have many applications, including for both in vivo and in vitro biomedical and industrial research. Addition to this, the AgNPs act as the very good insecticide for the control of mosquito vectors nowadays [70]. Thus, a novel attempt to test silver(I)-NHC against mosquito larvae have been reported.

1.8 Research Problem

1.8.1 This research problem of this project are to:

i. Evaluate angle and coordination of C-Ag-C geometry upon completion of silver(I)-NHC complexes using X ray diffraction analysis.
ii. Investigate coordination bond between nitrile groups after formation of silver(I)-NHC complexes.
iii. Examines the release rate of silver ion towards antimicrobial and larvicidal activities.

1.9 Proposed work

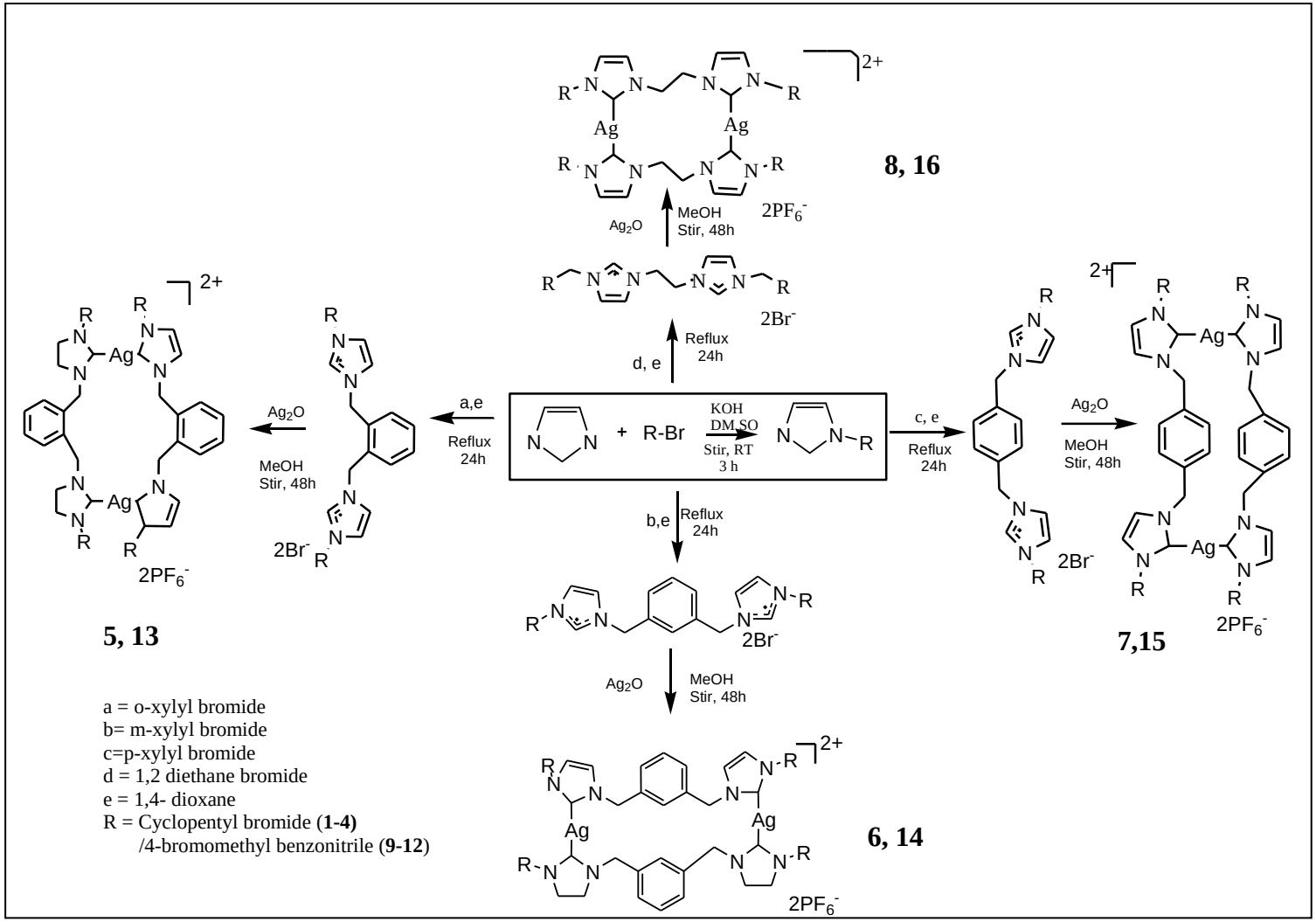
1.9.1 The objectives of this project are :-

i. To syntheses new *N*-heterocyclic carbenes (NHC) ligands of xylyl (ortho/meta/para) linked bis-imidazolium salt with cyclopentyl and 1,4-bromomethyl benzonitrile.
ii. To syntheses binuclear silver(I)-NHC complexes derives from xylyl (ortho/meta/para) linked bis-imidazolium salts.
iii. To characterize the ligands and complexes using elemental analysis and single crystal X ray diffraction analysis for selected compounds.
iv. To evaluate the antimicrobial and larvicidal activities of all synthesized imidazolium salts and silver(I)-NHC complexes.

1.9.2 Targeted imidazolium compounds

For this research, imidazole was used as a starting material. The targeted ligands are bidentate consist one substituent of either cyclopentyl or benzonitrile

bridged with different xylyl halide and dibromoethane as their halide salts. The prepared imidazolium salt were then used to produce dinuclear silver(I)-NHC complexes (Scheme 1.12). The synthesised compounds were characterised using spectral and analytical methods. Structure of compound **3**,**5**,**7** and **10** were confirmed using single crystal X-ray diffraction techniques. Then, all the compounds were evaluated for their antimicrobial studies and larvicidal activities.



Scheme 1.12: General scheme of bis- imidazolium salts (**1-4**, **9-12**) and their respective silver(I)-NHC complexes (**5-8**, **13-16**).

CHAPTER 2

EXPERIMENTAL

2.1 Materials

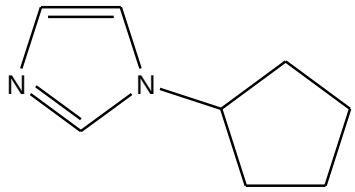
Imidazole (Merck, for synthesis), 1-bromocyclopentane (Merck, for synthesis), 1,2-dibromoethane (Sigma Aldrich, 99%), 4-(bromomethyl) benzonitrile (Sigma Aldrich, 99.0%), potassium hydroxide pellets (R&M chemicals,85%), potassium hexafluorophosphate (Across Organic, 99.0%), silver(I) oxide (Merck, 99.0%), Celite (Merck, size: 0.02-0.1 mm), dimethyl sulphoxide (QRëC), chloroform (QRëC), 1,4- dioxane (QRëC), methanol (QRëC), acetonitrile (QRëC), and diethyl ether (QRëC) were purchased from commercial sources and were used as received.

2.2 Instruments

The melting point was taken using a Stuart Scientific SMP-1 (UK) instrument. Elemental analysis was recorded on a Perkin Elmer Series II, 2400 microanalyzer. The Frontier Transforms Infrared (FT-IR) spectra were carried out in potassium bromide disks using a Perkin Elmer 2000 system spectrometer in the range of 4000 cm to 400 cm^{-1}. Nuclear Magnetic Resonance (NMR) spectra were recorded in d_6-DMSO d_3-acetonitrile using Bruker 500-MHz Ascend spectrometers at ambient temperature with TMS as an internal standard. The ^{1}H- and ^{13}C-NMR peaks are labelled as singlet (s), doublet (d), triplet (t), or multiplet (m). Chemical shifts are assigned with respect to NMR solvent signals.

2.3 Synthesis of non-functionalized compounds

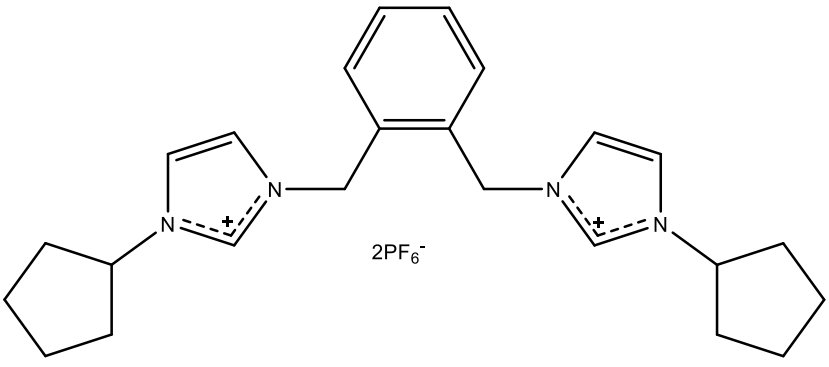
2.3.1 Synthesis of *N*-cyclopentyl imidazole



The *N*-cyclopentyl imidazole compound was synthesized according to the reported procedure [71]. The potassium azolide salt of imidazole was obtained by stirring imidazole with strong base potassium hydroxide in DMSO at room temperature. Cyclopentyl bromide subsequently was then added dropwise in the same reaction medium. The synthesized product yields in 84-92%.

2.3.2 Synthesis of non-functionalized bis-imidazolium salts (**1-4**)

*2.3.2(a) Synthesis of 3,3' [(1,2 phenylenebis(methylene)] bis(1-cyclopentylimidazolium) bis-hexaflourophosphate (**1**)*

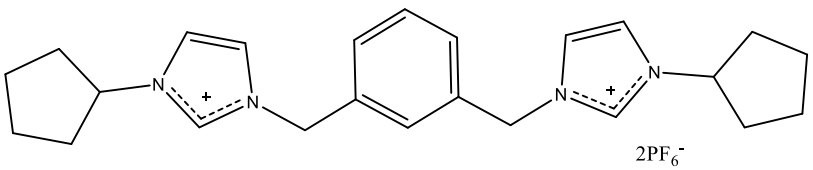


The obtained *N*-cyclopentyl imidazole (1.00 g, 7.30 mmol) was dissolved in 1,4-dioxane (40 mL). 1,2-dibromomethyl benzene (0.96 g, 3.64 mmol) was added to

the solution and refluxed at 100 °C for 24 h. The reaction was then cooled to room temperature. The white precipitates were filtered and washed with fresh 1,4-dioxane (3 x 5 mL) and diethyl ether (2 x 5 mL) to remove by-product. For further synthesis procedure, halide salt was used while for characterization purpose, the hexafluorphosphate salt of the compound was prepared. Bromide salt was directly converted into its hexafluorophosphate counterpart by metathesis reaction using two equivalent of KPF_6 in methanol (50 mL). The mixture was stirred for 3 h and filtered, washed with distilled water (3 x 5 mL) and then recrystallized from acetonitrile. Salt **1** was collected as white powder.

Yield: 2.10 g (86.7 %); **MP**: 181-183 °C**; Anal. Calcd. of** $C_{24}H_{32}F_{12}N_4P_2$: C, 43.12; H, 4.80; N, 8.40. **Found**: C, 43.52; H, 4.69; N, 8.27; **FT-IR** (KBr, cm^{-1}); 3177 (C-$H_{aromatic}$, 1567 (C=C), 1456 (C-N); **^{1}H NMR** (500 MHz, d_6-DMSO): δ 1.85 (16H, m, Cyclopentyl 8×CH_2), 4.78 (2H, m, Cyclopentyl 2×CHN), 5.56 (4H, d, 2×NCH_2, *J*=9.5 Hz), 7.44 (4H, m, 4×imid H), 7.81 (4H, m, 4×Ar H), 9.26 (2H, s, 2×NCHN); **^{13}C NMR** (125 MHz, d_6-DMSO): 23.1, 32.5 (Cyclopentyl 8×CH_2), 49.1 (Cyclopentyl 2×CHN), 60.8 (2×NCH_2), 121.6, 122.8 (4×imid C), 129.7, 132.7, (4×Ar C), 135.7 (2×NCHN).

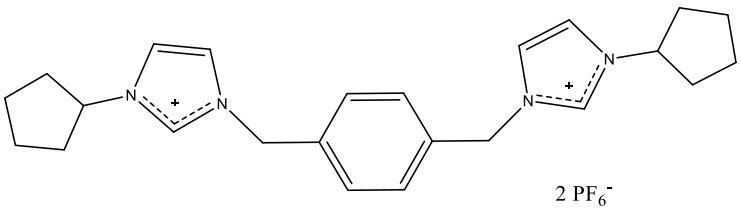
2.3.2.2 Synthesis of 3,3' [(1,3 phenylenebis(methylene)] bis(1-cyclopentylimidazolium) bis-hexaflourophosphate (**2**)



Compound **2** was prepared in a manner analogous to that resulting **1**, but using 1,3-dibromomethyl benzene (0.96 g, 3.64 mmol) instead of 1,2-dibromomethyl benzene. Salt **2** was collected as white powder.

Yield: 2.33 g (95.8 %); **MP**: 178-180 °C; **Anal. Calcd. of** $C_{24}H_{32}F_{12}N_4P_2$: C, 43.12; H, 4.80; N, 8.40. **Found**: C, 43.33; H, 4.72; N, 8.24; **FT-IR** (KBr, cm^{-1}); 3115 (C-$H_{aromatic}$, 1561 (C=C), 1456 (C-N); **^{1}H NMR** (500 MHz, *d_6*-DMSO): δ 1.97 (16H, m, Cyclopentyl 8×CH_2), 4.77 (2H, m, Cyclopentyl 2×CHN), 5.41 (4H, s, 2×NCH_2), 7.49 (4H, m, 4×imid H), 7.82 (4H, m, 4×Ar H), 9.33 (2H, s, 2×NCHN); **^{13}C NMR** (125 MHz, *d_6*-DMSO): 22.0, 31.6 (Cyclopentyl 8×CH_2), 50.7 (Cyclopentyl 2×CHN), 59.8 (2×NCH_2), 121.6 (4×imid C), 127.1, 127.6, 128.8 (4×Ar C), 134.3 (2×NCHN).

2.3.2.3 Synthesis of 3,3' [(1,4 phenylenebis(methylene)] bis(1-cyclopentylimidazolium) bis-hexaflourophosphate (**3**)

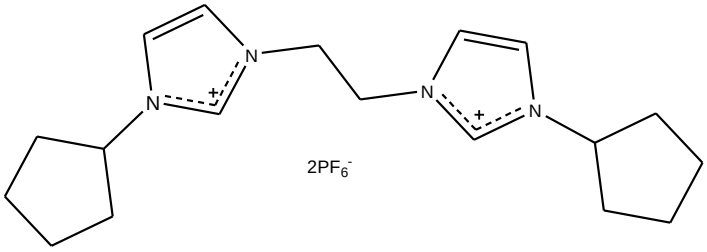


Compound **3** was prepared in a manner analogous to that resulting **1**, but using 1,4-dibromomethyl benzene (0.96 g, 3.64 mmol) instead of 1,2-dibromomethyl benzene. Salt **3** was collected as white powder. Colourless crystals of **3** were obtained by re-crystallization from acetonitrile.

Yield: 2.23 g (91.6 %); **MP**: 176–179 °C; **Anal. Calcd. of** $C_{24}H_{32}F_{12}N_4P_2$: C, 43.12; H, 4.80; N, 8.40. **Found**: C, 43.32; H, 4.90; N, 8.21; **FT-IR** (KBr, cm^{-1}); 3170 (C-$H_{aromatic}$, 1432 (C=C), 1356 (C-N); **^{1}H NMR** (500 MHz, *d_6*-DMSO,): δ 2.10 (16H,

m, Cyclopentyl 8×CH_2), 4.77 (2H, t, Cyclopentyl 2×CHN, *J*=7.0 Hz), 5.41 (4H, s, 2×NCH_2), 7.50 (4H, s, 4×imid H), 7.8 (2H, s, 2×Ar H), 7.86 (2H, s, 2×Ar H), 9.37 (2H, s, 2×NCHN); **^{13}C NMR** (125 MHz, d_6-DMSO): 23.1, 32.5 (Cyclopentyl 2×CH_2), 51.6 (Cyclopentyl 2×CHN), 60.8 (2×NCH_2), 121.7 (4×imid C), 122.6, 128.9, (4×Ar C), 135.3 (2×NCHN).

2.3.2.4 Synthesis of 3,3' [(ethane-1,2-diyl)] bis(1-cyclopentylimidazolium) bis-hexaflourophosphate (**4**)

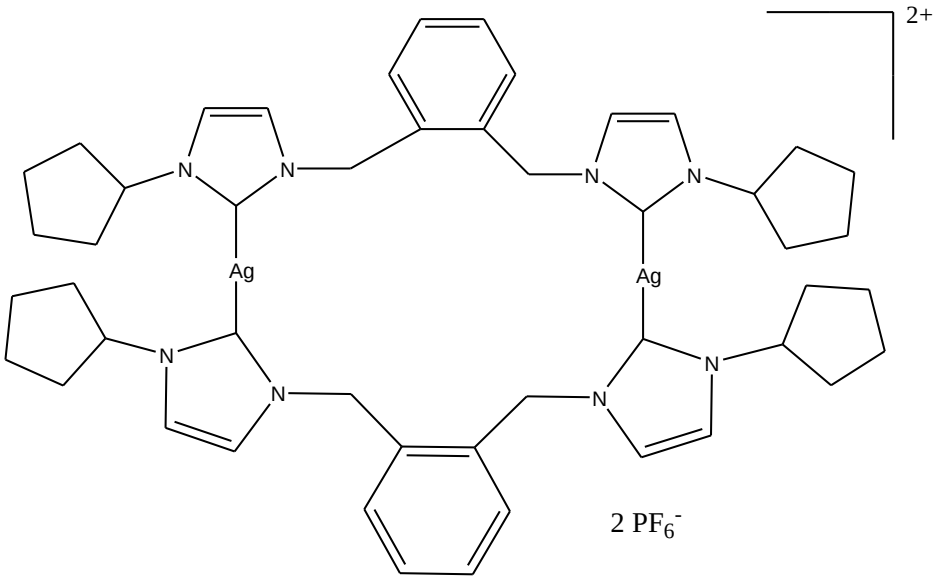


Compound **4** was prepared in a manner analogous to that resulting **1**, but using 1,2-dibromoethane (0.69 g, 3.64 mmol) instead of 1,2-dibromomethyl benzene. Salt **4** was collected as brown solid.

Yield: 1.96 g (90.6 %); **MP**: 190–193. °C; **Anal. Calcd. of** $C_{18}H_{30}F_{12}N_4P_2$: C, 36.21; H, 5.08; N, 9.49. **Found**: C, 36.55; H, 5.28; N, 9.22; **FT-IR** (KBr, cm^{-1}); 3166 (C-$H_{aromatic}$, 1565 (C=C), 1463 (C-N); **^{1}H NMR** (500 MHz, d_6-DMSO): δ 1.95 (16H, m, Cyclopentyl 8×CH_2), 4.65 (4H, s, NCH_2CH_2N), 4.73 (2H, m, Cyclopentyl 2×CH), 7.60 (2H, s, imid H), 7.85 (2H, s, imid H), 9.11 (2H, s, 2×NCHN); **^{13}C NMR** (125 MHz, d_6-DMSO): 32.4, 23.0 (Cyclopentyl 8×CH_2), 48.5 (Cyclopentyl 4×CHN), 60.9 (NCH_2CH_2N), 121.7, 122.6, (imid-C), 135.6 (2×NCHN).

2.3.3 Synthesis of non-functionalized silver (I)-NHC complexes **(5-8)**

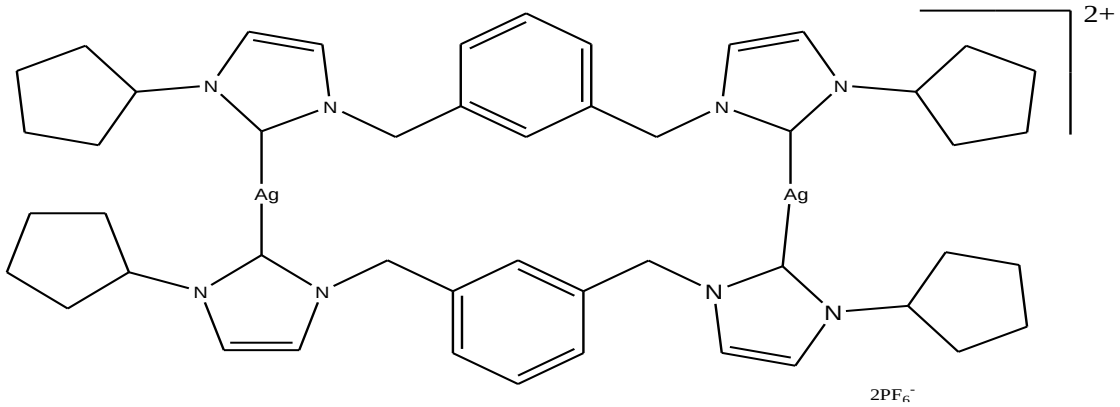
*2.3.3(a) Synthesis of 3,3'-[1,2-phenylenebis(methylene)] bis(1-cylopentylimidazolium) disilver(I) bis(hexaflourophosphate)(**5**)*



A mixture of bromide salt **1** (0.50 g, 0.93 mmol) and Ag_2O (0.50 g, 1.86 mmol) were dissolved in methanol (30 mL) and left to stir at room temperature for 48 h, covered from light. The reaction mixture was then filtered through Celite and the clear filtrate was collected. The filtrate was stirred with KPF_6 (0.30 g, 1.63 mmol) in methanol (20 mL), which then facilitated the formation of **5** as white powder. The product was filtered, washed with distilled water and dried under vacuum. Single crystals were obtained by recrystalization in a mixture of acetonitrile:1,4-dioxane at room temperature.

Yield: 0.76 g (65.7 %); **MP**: 179-181 °C; **Anal. Calcd. of** $C_{48}H_{60}Ag_2F_{12}N_8P_2$: C, 45.90; H, 4.78; N, 8.93. **Found**: C, 45.92; H, 4.70; N, 8.80; **FT-IR** (KBr, cm^{-1}); 3130 (C-$H_{aromatic}$), 1560 (C=C), 1424 (C-N); **^{1}H NMR** (500 MHz, d_6-DMSO): δ 1.82 (32H, m, Cyclopentyl 16×CH_2), 4.52 (4H, s, Cyclopentyl 4×CHN), 5.37 (8H, s, 4×NCH_2), 7.17 (4H, s, 4×Ar H), 7.42 (8H, s, 8×imid H), 7.62 (4H, s, 4×Ar H); **^{13}C NMR** (125 MHz, d_6-DMSO): 23.6, 30.6, 33.5 (Cyclopentyl 16×CH_2), 51.8 (Cyclopentyl 4×CHN), 62.4 (4×NCH_2), 120.0, 122.4 (8×imid C), 128.9, 129.1, 134.4, (8×Ar C), 179.6, 179.6, 178.2, 178.1 (4×NCHN).

*2.3.3(b) Synthesis of 3,3'-[1,3-phenylenebis(methylene)] bis(1-cylopentylimidazolium) disilver(I) bis(hexaflourophosphate) (**6**)*

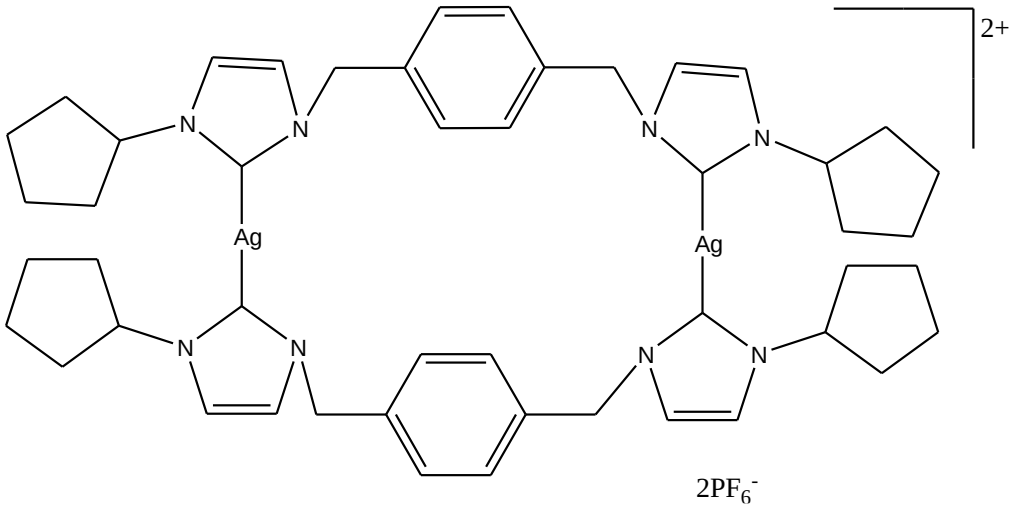


Complex **6** was prepared in a manner analogous to that resulting **5**, but using compound **2** (0.50 g, 0.93 mmol) instead of **1**. The product of **6** was collected as brown solid.

Yield: 0.85 g (72.8 %); **Anal. Calcd. of** $C_{48}H_{60}Ag_2F_{12}N_8P_2$: C, 45.90; H, 4.78; N, 8.93%. **Found**: C, 45.56; H, 4.60; N, 8.61%; **FT-IR** (KBr, cm^{-1}); 3144 (C-$H_{aromatic}$,

1452 (C=C), 1422 (C-N); **^{1}H NMR** (500 MHz, d_6-DMSO): δ 1.98 (32H, m, Cyclopentyl 16×CH_2), 4.77 (4H, s, Cyclopentyl 4×CHN), 5.13 (8H, d, 4×NCH_2), 7.08 (4H, s, 4×Ar H), 7.19 (8H, s, 8×imid H), 7.29 (4H, s, 4×Ar H); **^{13}C NMR** (125 MHz, d_6-DMSO): 33.5, 23.6 (Cyclopentyl 16×CH_2), 53.9 (Cyclopentyl 4×CHN), 62.5 (4×NCH_2), 119.7, 122.6 (8×imid C), 129.4, 134.6, (8×Ar C), 179.1 (4×NCHN).

*2.3.3(c) Synthesis of 3,3'-[1,4-phenylenebis(methylene)] bis(1-cylopentylimidazolium) disilver(I) bis(hexaflourophosphate) (**7**)*



Complex **7** was prepared in a manner analogous to that resulting **5**, but using compound **3** (0.50 g, 0.93 mmol) instead of **1**. The product of **7** was collected as a beige powder. The colorless crystals of **7** were obtained from re-crystallization in acetonitrile.

Yield: 0.80 g(68.4 %); **MP**: 171–173 °C; **Anal. Calcd. of** $C_{48}H_{60}Ag_2F_{12}N_8P_2$: C, 45.90; H, 4.78; N, 8.93%. **Found**: C, 45.90; H, 4.72; N, 8.90%; **FT-IR** (KBr, cm^{-1}); 3168 (C-$H_{aromatic}$), 1518 (C=C), 1452 (C-N); **^{1}H NMR** (500 MHz, d_6-DMSO): δ 2.01 (32H, m, Cyclopentyl 16×CH_2), 4.85 (4H, s, Cyclopentyl 4×CHN), 5.22 (8H, s, 4×NCH_2), 7.13 (8H, s, 8×imid H), 7.26 (4H, s, 4×Ar H), 7.31 (4H, s, 4×Ar H); **^{13}C**