SYNTHESIS, STRUCTURAL ANALYSES AND ANTIBACTERIAL ACTIVITIES OF NEW NON-FUNCTIONALIZED AND NITRILE-FUNCTIONALIZED SILVER(I) *N*-HETEROCYCLIC CARBENE COMPLEXES

by

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LIST OF ABBREVIATION AND SYMBOLS

^{o}	Degrees
^oC	Degrees Celcius
δ	Chemical shift in ppm
σ	Sigma
π	Pi
µg	Microgram
µL	Microliter
^1H NMR	Proton nuclear magnetic resonance
^{13}C NMR	Carbon-13 nuclear magnetic resonance
Å	Angstrom, 1×10^{-10} m
Anal.	Analysis
Ar	Arene
ATCC	American type culture collection
Benzimi	Benzimidazole
Benz/imidazole	Imidazole and Benzimidazole
Calc.	Calculated
cm	Centimetre
COD	1,5-Cyclooctadiene
d	Doublet
D_c	Density
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EtOH	Ethanol
FT-IR	Fourier transforms infrared
g	Gram

h	Hours
Hz	Hertz
J	Nuclear spin-spin oupling constant through bonds
K	Kelvin
kV	Kilovolt
m	Multiplet
M	Molecular mass
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz
mL	Millilitre
mmol	Millimoles
mm	millimeter
mol	Moles
NHC	*N*-heterocylic carbene
OAc	Acetate
ppm	Part per millions
RT	Room temperature
s	Singlet
t	Triplet
T	Temperature
THF	Tetrahydrofuran
V	Volume
XRD	X-ray single crystal diffraction

SINTESIS, STRUKTUR HABLUR DAN AKTIVITI ANTIBAKTERIA KOMPLEKS BAHARU ARGENTUM(I) *N*-HETEROSIKLIK KARBENA YANG BUKAN DAN BERFUNGSIAN NITRIL

ABSTRAK

Dua siri baru garam benzimidazolium benzil bergantian iaitu bukan berfungsi (**1-3**·PF_6 and **7-9**·$2PF_6$) dan berfungsian nitril (**4-6**·PF_6 and **10-12**·$2PF_6$) telah berjaya di sintesis sebagai pelopor untuk *N*-heterosiklik karbena (NHC). Tindak balas antara garam benzimidazolium dan argentum(I) oksida dengan kadar bersesuaian telah memudahkan garam benzimidazolium untuk berdeprotonasi *in situ* yang mendapatkan dua siri kompleks argentum(I)-NHC, $[Ag_n(L)_2]\cdot nPF_6$ (**Ag1-Ag12**), masing-masing (di mana L = **1-6**: 1-(2'/3'/4'-metilbenzil/metilbenzonitril)-3-(2''-propil)benzimidazolium, n = 1 atau L = **7-12**: 3,3-(butana-1,4-diyl)-1,1-(2'/3'/4'-metilbenzil/metilbenzonitril)bisbenzimidazolium, n = 2). Kegunaan satu kompleks argentum(I)-NHC, **Ag1** sebagai ejen pemindahan telah berjaya dilihat di dalam pembentukan kompleks palladium(II)-NHC, **Pd1** yang telah berformula sebagai $[PdCl(L)_2(MeCN)]PF_6$ (di mana L = **1**: 1-(2'-metilbenzil)-3-(2''-propil)benzimidazolium). Kedua-dua garam benzimidazolium dan kompleks logam-NHC telah dicirikan menggunakan analisis tahap lebur, teknik analisis unsur, spektroskopi FT-IR dan spektroskopi ^1H dan ^{13}C NMR. Spektra ^1H NMR kompleks adalah lebih kurang serupa dengan sebatian garam masing-masing tetapi signal bagi proton H2’ benzimidazolium telah hilang sepenuhnya dan mencadangkan pengkompleksan yang berjaya. Dalam kes spektrum ^{13}C NMR kompleks, resonans karbon C2’ telah muncul di kawasan medan rendah (lebih kurang 185 ppm) mengesahkan pembentukan kompleks. Struktur molekul untuk sebahagian sebatian dan kompleks telah dikenalpasti melalui teknik pembelauan sinaran-X hablur tunggal. Analisis stuktur mendapati bahawa di dalam ketiadaan sebarang ikatan hidrogen yang berpotensi sebagai penderma dan penerima, pelbagai interaksi supramolekular memainkan peranan penting dalam menstabilkan seluruh struktur. Oleh itu, mengikut semua data-data yang didapati, semua garam benzimidazolium dan kompleks logam-NHC telah berjaya disintesis. Kajian antibakteria melawan bakteria Gram-negatif *Escherichia coli* (ATCC 25922) dan bakteria Gram-positif *Staphylococcus aureus* (ATCC 12600), telah dijalankan ke atas semua garam benzimidazolium dan kompleks logam-NHC yang telah disintesis menggunakan kaedah bersesuaian. Kesemua garam benzimidazolium menunjukkan keputusan negatif dalam kajian ini manakala aktiviti antibakteria untuk kesemua logam-NHC berbeza mengikut keadaan ligan. Semua kompleks mononuklear argentum(I)-NHC mempamerkan aktiviti antibakteria yang sederhana manakala kompleks dinuklear argentum(I)-NHC adalah rendah dalam aktiviti berbanding antibiotik standard, ampicillin. Kompleks palladium(II)-NHC, **Pd1** hanya menunjukkan aktiviti yang rendah melawan *S. aureus* berbanding **Ag1** dan ampicillin.

SYNTHESIS, STRUCTURAL ANALYSES AND ANTIBACTERIAL ACTIVITIES OF NEW NON-FUNCTIONALIZED AND NITRILE FUNCTIONALIZED SILVER(I) *N*-HETEROCYLIC CARBENE COMPLEXES

ABSTRACT

Two series of new benzyl substituted benzimidazolium salts, both non-functionalized, (**1-3**·PF_6 and **7-9**·$2PF_6$) and nitrile-functionalized, (**4-6**·PF_6 and **10-12**·$2PF_6$) were successfully synthesized as *N*-heterocyclic carbene (NHC) precursors. The reaction of an appropriate ratio of respective benzimidazolium salts with silver(I) oxide facilitated the *in situ* deprotonation of the benzimidazolium salts that afforded the formation of two series of silver(I)-NHC complexes, $[Ag_n(L)_2]\cdot nPF_6$ (**Ag1-Ag12**), (where L = **1-6**: 1-(2’/3’/4’-methylbenzyl/methylbenzonitrile)-3-(2’’-propyl)benzimidazolium, n = 1 or L = **7-12**: 3,3-(butane-1,4-diyl)-1,1-(2’/3’/4’-methylbenzyl/methylbenzonitrile)bisbenzimidazolium, n = 2). The uses of one of the silver(I)-NHC complex, **Ag1** as a transfer agent was successfully observed in the formation of a palladium(II)-NHC complex, **Pd1** formulated as $[PdCl(L)_2(MeCN)]PF_6$ (where L = **1**: 1-(2’-methylbenzyl)-3-(2’’-propyl)benzimidazolium). Both the benzimidazolium salts and metal-NHC complexes were characterized by melting point analysis, elemental analyses, FT-IR spectroscopy and ^1H and ^{13}C NMR spectroscopy. The ^1H spectra of complexes are rather similar to those of the respective salts with the signal for the benzimidazolium

H2’ proton completely absent suggesting successful complexation. In the case of ^{13}C NMR spectra of the complex, C2’ carbon resonance appeared as doublets in the downfield region (ca. 185 ppm) confirming the complex formation. The molecular structures of some of the compounds and complexes were established by single crystal X-ray diffraction analyses. Structural analysis indicated that in the absence of any potential hydrogen bond donors or acceptors, various supramolecular interactions played an important role in stabilizing the entire structure. Hence, *via* all the data obtained, the benzimidazolium salts and metal-NHC complexes were successfully synthesized. Antibacterial studies against a Gram-negative bacteria *Escherichia coli* (ATCC 25922) and a Gram-positive bacteria *Staphylococcus aureus* (ATCC 12600), were carried out for all the synthesized benzimidazolium salts and metal-NHC complexes using established methods. All the benzimidazolium salts were inactive while the antibacterial activity of the metal-NHC complexes varied depending on the nature of the ligands. All the mononuclear silver(I)-NHC complexes exhibited medium antibacterial activities while dinuclear silver(I)-NHC complexes were low in the activities compared to the standard antibiotic, ampicillin. The palladium(II)-NHC complex, **Pd1** showed only low activities againts *S. aureus* compared to **Ag1** and ampicillin.

CHAPTER 1

INTRODUCTION

1.1 Carbene and *N*-heterocyclic carbene

Carbene is a type of carbon intermediate that contains a divalent carbon atom. Carbene carbon is bonded to two adjacent groups by covalent bonds, and the other two electrons are present as nonbonding electrons (Figure 1.1).[1] These three groups allow an *sp*^{2} hybridization for the carbene carbon, with a plane occupied by the C and two R groups and a vacant *p* orbital extending above and below the plane. The remaining one pair of electron occupies an *sp*^{2} hybrid orbital. These electrons may have antiparallel spins (singlet spin) or parallel spins (triplet state).

(a) (b)

Figure 1.1: (a) General structure of carbene. (b) Examples of carbenes.

The possibility of carbene being in the singlet state or triplet state depends on the difference in energy between its frontier orbitals. As the energy increases in difference, the singlet state becomes more likely because the higher the energy, the less the tendency of the frontier molecular orbital to be occupied. On the other hand, triplet state is favoured in ground state if the energy difference is low (Figure 1.2).[2]

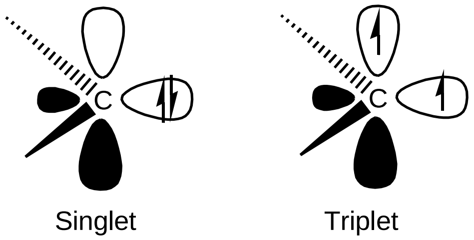


Figure 1.2: The ground state of carbene.

Carbenes are classified according to their reactivity towards metal ions. The first type of carbenes, namely Fischer carbenes appeared as singlet carbenes with electrophilic character. These carbenes having *σ* electrons will donate the electron pair from *sp*^{2} orbital and the empty *p*-orbital will accept back donations from the metal in *π* mode (Figure 1.3). The first stable Fischer carbene complex with tungsten(0) was successfully synthesized in 1964 (Scheme 1.1).[3]

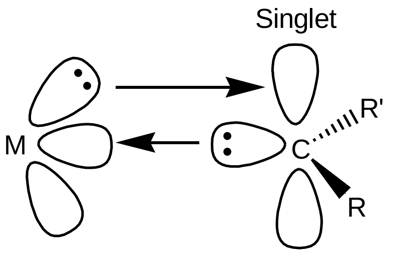
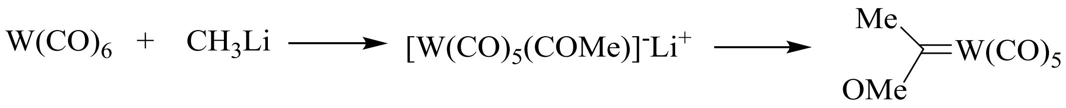


Figure 1.3: Bonding in Fischer carbene complexes.



$$W(CO)_6 + CH_3Li \longrightarrow [W(CO)_5(COMe)]^-Li^+ \longrightarrow (Me)(OMe)C{=}W(CO)_5$$

Scheme 1.1: Synthesis of first stable Fischer complex.[3]

The second type of carbene was reported one decade after the discovery of Fischer carbenes. Known as Schröck carbenes, these carbenes were considered as triplet carbenes with nucleophilic character. Schröck carbenes have two unpaired electrons and these electrons interacted with metal to form two covalent bonds

(Figure 1.4). The first stable Schröck carbene was discovered by Schröck in 1974 (Scheme 1.2).[4]

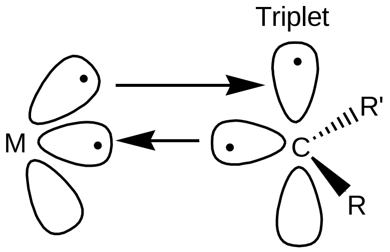
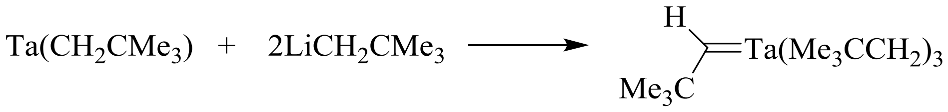


Figure 1.4: Bonding in Schröck carbene complexes.



$$Ta(CH_2CMe_3) + 2LiCH_2CMe_3 \longrightarrow (H)(Me_3C)C{=}Ta(Me_3CCH_2)_3$$

Scheme 1.2: Synthesis of first stable Schröck carbene.[4]

Different from Fischer and Shröck carbenes, *N*-heterocyclic carbenes (NHC) are singlet carbenes with neutral character. The contribution of the electronegativity of the nitrogen atoms make the NHC appear as a singlet state carbene. Also known as Arduengo's carbenes, these cyclic carbenes are usually derived from the deprotonation of azolium salts using strong base. The electron pair of the carbene occupies the σ-orbital and will be donated to the metal by forming a single dative bond with the metal. The resulting empty *p*-orbital of carbene carbon will receive electron density from the lone pair electrons of both adjacent nitrogen atoms (Figure 1.5).

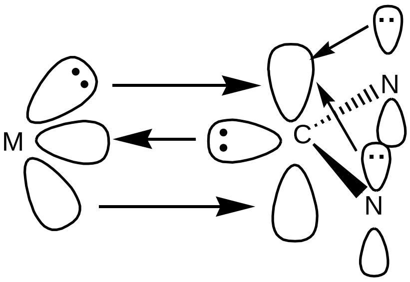
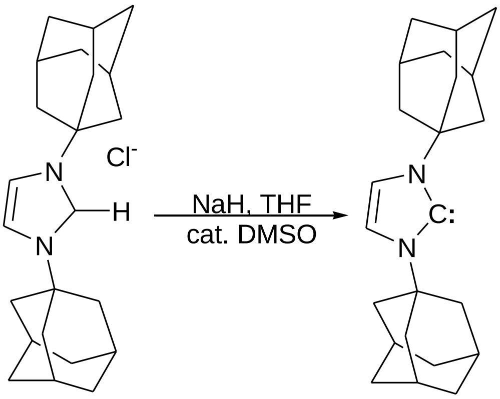


Figure 1.5: Bonding in NHC complexes.

The history of the NHCs chemistry began with research done by Wanzlick around 1960s,[5] but in 1991, the first stable crystalline free NHC, 1,3-di-(1-adamantyl)imidazol-2-ylidene (**1.1**) was isolated by Arduengo and co-workers.[6] This isolation was done via deprotonation of 1,3-di(adamantyl)imidazolium chloride with sodium hydride (Scheme 1.3). In the absence of oxygen and moisture, this carbene was found to have a unique stability at room temperature.



(**1.1**)

Scheme 1.3: The synthesis of 1, 3-di-(1-adamantyl)imidazol-2-ylidene (**1.1**).[6]

NHCs owed their powerful stability due to the adjacent nitrogen atoms that afford a unique electronic structure.[7] This interaction was called pull and push stabilization. The “pull” stabilization (Figure 1.6(a)) due to the σ-bonding between the carbene carbon with the two electronegativity of nitrogen atoms while the "push" stabilization (Figure 1.6(b)) is because of the two $\pi_N \rightarrow \pi_C$ donor interactions from the electron pairs on the nitrogen into the empty *p*-orbital of the carbene carbon.[8] However, this electronic structure made NHC good σ-donor but poor π-acceptor ligands.[9]

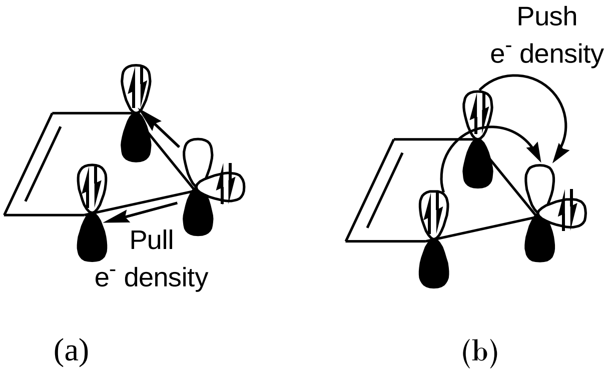


Figure 1.6: (a) pull interaction and (b) push interaction in NHCs.

1.2 Benzimidazole and benzimidazolium salts

With the formula $C_6H_4N_2HCH$, benzimidazole is one of the heterocyclic cores of NHC other than imidazole, pyrazole, triazole and tetrazole.[10] Benzimidazoles are heterocyclic compounds in which benzene is fused with five membered ring containing two heteroatoms. Both heteroatoms are nitrogen (N), which are present at non-adjacent position.[11] The position of hydrogen atom can be either at nitrogen position 3 or 1 (Figure 1.7), and this allows benzimidazole exist in two equivalent tautomeric forms 1*H*- and 3*H*-benzimidazole.

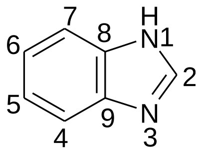
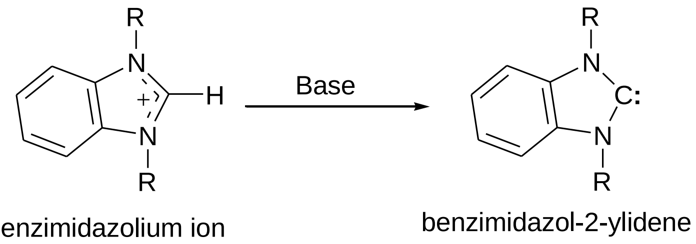


Figure 1.7: The numbering in benzimidazole.

Benzimidazolium salts are formed easily from the protonation or by the attachment of a wide variety of groups onto positions 1- and 3- of the ring.[12] When a benzimidazolium salt has substitutions on both of its nitrogen atoms, this salt behaves like quaternary ammonium salts and organic base hydrochlorides.[8,13] When an acidic proton from a benzimidazolium ion is removed by a strong base, the NHC can be formed (Scheme 1.4)



Scheme 1.4: The base deprotonation resulting in a singlet state NHC.

For more than five decades, imidazole and benzimidazole derived NHC precursors have been known in the area of organometallic chemistry and imidazole-based derivatives may have been the first NHC precursors ever used by the organometallic chemists.[14] With the abundance of transition/inner transition metal ions in different oxidation states, the organometallic chemistry of NHCs especially imidazole and benzimidazole, varies widely.[15]

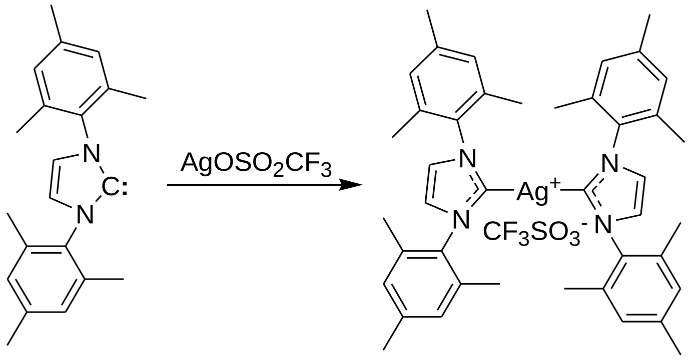
Benzimidazolium salts also have been reported to poses antithrombotic, herbicidal, anthelmintic and catalytic properties since the past few years.[16] Recently, the synthesis of benzimidazole derivatives have been found to have pharmacological activities such as antitumour, anti-ulcer, antibacterial, and antifungal properties.[17] There are many antibacterial and antifungal drugs used in the treatment of bacterial and fungal infections but some of them have desirable side effect.[18] Hence, this type of NHC is easy to synthesis in a few steps, the substituent can be easily changed and their reactivity in biological medium can be easily be manipulated.[19]

1.3 Synthetic method of metal-NHC complexes

An NHC complex is where the free electrons pair of carbene carbon is donated to the metal atom and this electron deficiency is stabilized by electron from nitrogen atom next to carbene carbon.[20] There are many methods that can be used to synthesise metal complexes of NHC. The three major routes are:

1.3.1 Free carbene method

The free carbene method is one of the method that been used to synthesis the metal NHC complexes, especially containing silver(I)- and mercury(II)-NHC complexes.[23] These reactions can be done by leaving the azolium salts to react with a strong base such as potassium tert-butoxide, sodium hydride and lithium bis(trimethyl)amide[6] to prepare a free NHCs, in which later the metal sources are then added. These free carbenes can be isolated or used without isolation by this method. The first silver(I)-NHC complex was reported by Arduengo and co-workers in 1993 using free carbene method after their success in obtaining the aforementioned free carbene (**1.1**) and carbene (**1.2**).[7] The formed silver(I)-NHC complex (**1.3**) was obtained by the reaction of silver(I) triflate with two equivalents of the NHC ligand (**1.2**), in THF under a dry nitrogen atmosphere (Scheme 1.5).



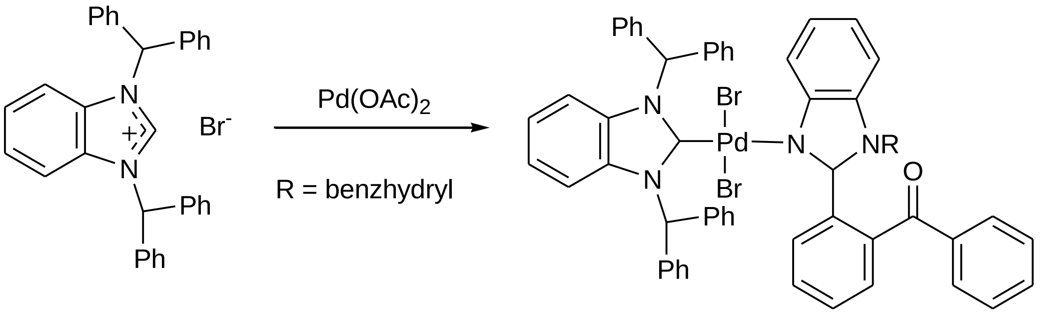
(1.2) **(1.3)**

Scheme 1.5: Synthesis of first silver(I)-NHC complex (**1.3**) by Arduengo and co-workers.[7]

Using this method, there are large variety of metal-NHC without special requirement can be synthesized, however, the free NHC can face some problems as the NHC ligands may decompose as this type of ligand are known to be sensitive to air and moisture as well as thermally sensitive.[24] Sometimes dimerization of the free NHC ligands (Wanzlick equilibrium) may occur before they react with a metal source (Scheme 1.8).[25]

1.3.2 In-situ deprotonation

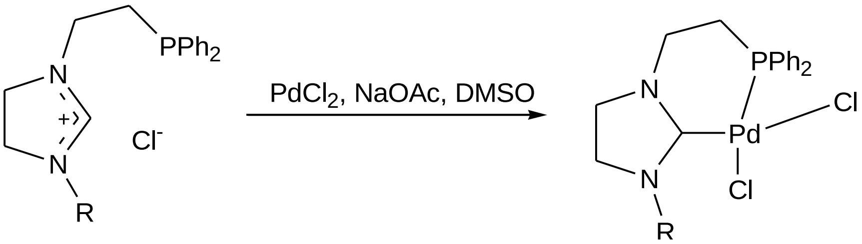
With many apparent limitations of the free carbene method, alternative synthetic methods for the synthesis of the metal-NHC complexes have been developed. The most popular method is the *in-situ* deprotonation method introduced by Öfele in 1968.[22] In this method, there are two kinds of *in-situ* reactions. First method is by using basic metal complexes reagent such as silver(I) oxide,[26] mercury(II) acetate[21] and palladium(II) acetate.[27,28] For example, in Scheme 1.9, the acetate from the palladium(II) acetate was used to attract an acidic proton from the carbene precursor, and the resulting carbene is trapped by palladium from the same metal source to form the desired palladium(II)-NHC complex (**1.4**) (Scheme 1.6).



(1.4)

Scheme 1.6: $Pd(OAc)_2$ as a base and metal source.[28]

The second type of *in-situ* deprotonation in the formation of NHC complexes is by using the external base to deprotonate NHC salts. The strong bases in this reaction including potassium tert-butoxide, lithium tert-butoxide,[29] and sodium acetate[30] will deprotonate the NHC salts before the metalation occur using metal from other metal source by choice. For example, palladium(II)-NHC complexes (**1.5**) was obtained by the extraction of acidic proton by external base, sodium acetate then the carbenes were trapped by palladium from palladium(II) chloride (Scheme 1.7).[30]

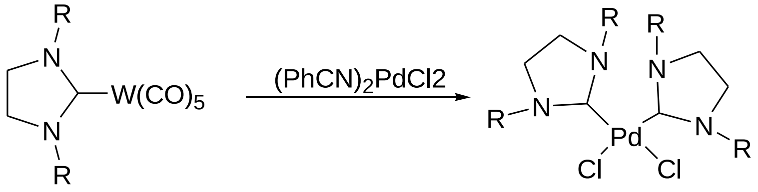


(1.5)

Scheme 1.7: The example of *in-situ* deprotonation using external base, NaOAc before treating with metal source, $PdCl_2$.[3]

1.3.3 Transmetallation (NHC Transfer)

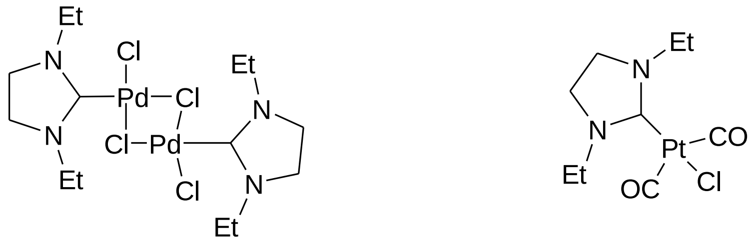
Transmetallation or carbene transfer method is where a NHC is transferred from one metal centre to another. Carbene transfer reaction between metal ions was first investigated by Fischer and Bech.[31] Later in 1998, Liu and co-workers introduces the transfer of NHC reaction from tungsten(0) to palladium(II)-NHC and platinum(II)-NHC. In their reaction, palladium(II)-NHC complex (**1.7**) was yielded when the tungsten(0)-NHC complex (**1.6a**) was treated with 0.5 mole equivalent of $(PhCN)_2PdCl_2$ (Scheme 1.8) while (**1.8**) and (**1.9**) was obtained when (**1.6b**) was left to react with 1 equivalent of same palladium source, $(PhCN)_2PdCl_2$ and platinum source, $(PhCN)_2PtCl_2$ (Figure 1.8).[32] This method was then extended to produce rhodium(I)- and gold(I)- NHC complexes from tungsten(0)- and molybdenum(0)-NHC complexes as the transfer agents.[33]



(**1.6a**) R= $-CH_2CHCH_2$ (**1.7**)

(**1.6b**) R= $-CH_2CH_3$

Scheme 1.8: Transmetallation reaction to produce palladium(II)-NHC (**1.7**) using tungsten(0)-NHC (**1.6a**) as transfer agent.[32]



(**1.8**) (**1.9**)

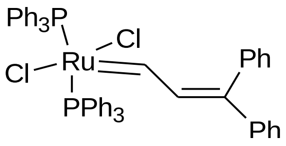
(a) (b)

Figure 1.8: (a) Palladium(II)-NHC complex (**1.8**) and (b) platinum(II)-NHC complex (**1.9**) from reaction of (**1.6b**) with respective metal sources.[32]

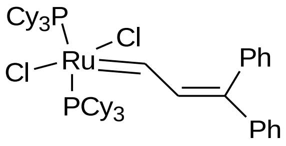
1.4 Application of metal-NHC complexes

1.4.1 Catalysis studies

NHC become crucial ligands in homogenous catalysis since the isolation of free carbene in 1991.[6] In 1996, Grubbs and co-worker conducted a research on olefin methathesis reaction using ruthenium alkylidene diphosphine complexes, (**1.10**) and (**1.11**), which were known as the first generation Grubbs catalysts (Figure 1.9).[34-36] Later, the second generation Grubbs catalyst, for example (**1.12**) where phosphine was replaced by an NHC ligand for alkene metathesis were developed (Figure 1.10).[37,38] Later, more ruthenium(II)-NHC complexes were isolated, showing more activity with selectivity in the reactions. Other than that, the uses of palladium(II)-NHC complexes in C-C bond forming reactions such as Heck and Suzuki couplings,[20,39-45] iridium(III)-NHC catalysed hydrogenation and hydrogen transfer,[46-48] platinum(II)-NHC catalysed hydrosilation,[49] mercury(II)-NHC in Hofmann elimination reaction,[50] nickel(II)-NHC catalysed polymerisation reactions,[51-56] and rhodium(I)-NHC catalysed hydroboration[57] proved the powerful uses of NHC metal complexes in catalysis activity.

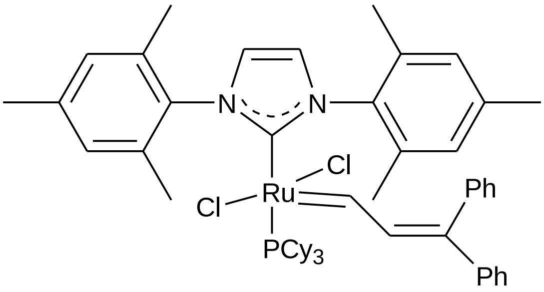


(1.10)



(1.11)

Figure 1.9: The first generation of Grubbs catalyst.

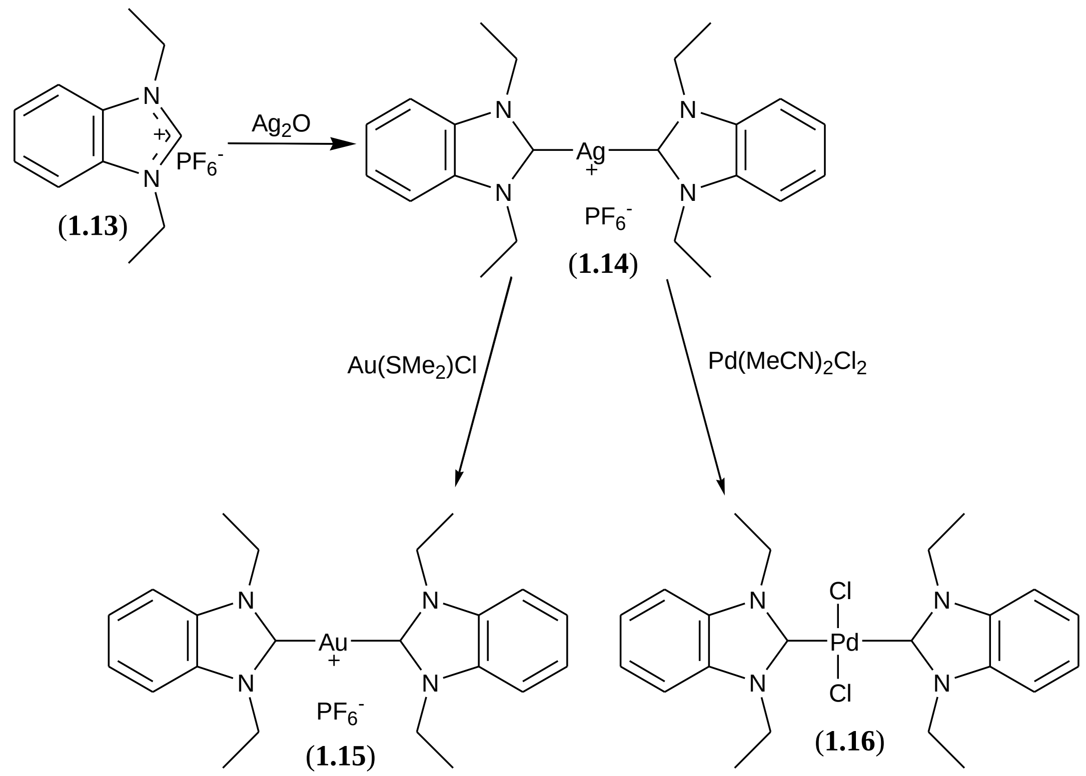


(1.12)

Figure 1.10 The example of second generation of Grubbs catalyst.

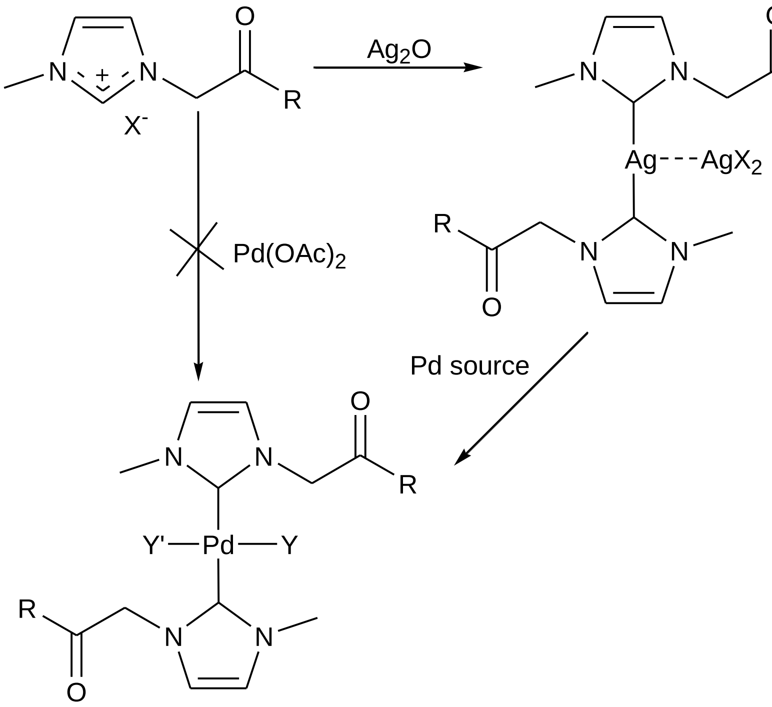
1.4.2 Carbene transfer chemistry

In 1998, Wang and Lin have reported their gold(I)- and palladium(II)-NHC complexes, (**1.15** and **1.16**) respectively, obtained from the respective silver(I)-NHC (**1.15**) as a transfer agent (Scheme 1.9).[26] After the discovery, many complexes such as palladium(II)-, platinum(II)- ruthenium(II)- and rhodium(I)-NHC complexes have been synthesized using transmetallation from silver(I) complex.



Scheme 1.9: Reaction by Wang and Lin to produce silver(I)-, gold(I)- and palladium(II)-NHC complexes.[26]

Carbene transfer method from silver complexes becomes an alternative route when dealing with NHC precursors that have acidic functional groups. This groups can interfere when preparing the desired complexes via conventional methods. For example, McGuiness and Cavell used this method to prepare a series of palladium(II)-NHC complexes because their attempts in preparing same complexes failed using *in situ* deprotonation (Scheme 1.10). This is due to the presence of acidic methylene protons in the substituent attached to their imidazolium salts that caused the interferences in the extracting the carbene proton by palladium(II) acetate.[58]



Scheme 1.10: General schematic diagram of preparation of palladium(II)-NHC complexes from silver(I)-NHC complexes by Guiness and Cavell.[58]

This method also avoids the formation of free NHC and the possibility of the NHC to decompose is low. However, there is some drawback in this method where there will be formation of product with low yield and sometimes the transmetalate unsuccessful. The NHC with saturated backbones have been shown to be relatively poor transmetalation reagents when compared to NHC with unsaturated backbones. Despite, the succesful transmetalation of saturated silver(I)-NHC complexes is also dependent upon the other metal source used.[59] Other than silver(I)-NHC, mercury(II)-NHC can also be used as a ligand transfer agent. Transfer of NHC ligands from mercury(II)-NHC to transition metals and main group element such as sulphur, selenium and tellurium have been achieved by this method.[60]

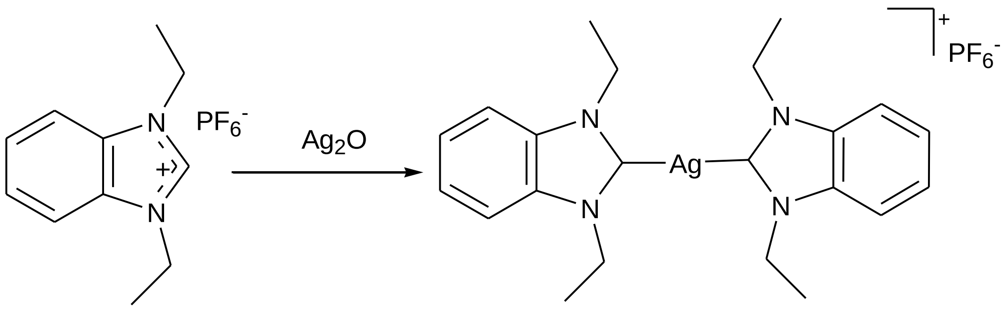
1.4.3 Biological activities and medicinal chemistry

Metal-NHC complexes have been widely studied for their catalytic properties, but their potential as biologically active agents still remain unexplored. In the past few years, biological studies such as antimicrobial and anticancer studies remain as an active research area because many silver(I)-,[61-65] gold(I)-,[16,66] copper(I)-,[67] ruthenium(II)-[68] and rhodium(I)-[67,69] NHC complexes have shown very excellent potential in these applications. Recently, palladium(II)-[70] and selenium-[71] NHC complexes also showed their potential as a good anticancer agents.

1.5 Silver(I)-NHC complexes

Silver(I)-NHC is interested to researchers due to the simpler synthetic strategies, structural diversity, stability, and their wide range of applications. Silver(I)-NHC complexes have been observed to be very stable in air and moisture, and can be prepared efficiently.[72] There are three common ways to synthesize silver(I)-NHC complexes. First method to produce the desired complexes is by the treatment of free NHCs with appropriate silver source, normally at liquid nitrogen temperature. As mentioned in Section 1.3(i), this free NHC method was used to synthesise the first silver(I)-NHC complex by Arduengo in 1993.[7]

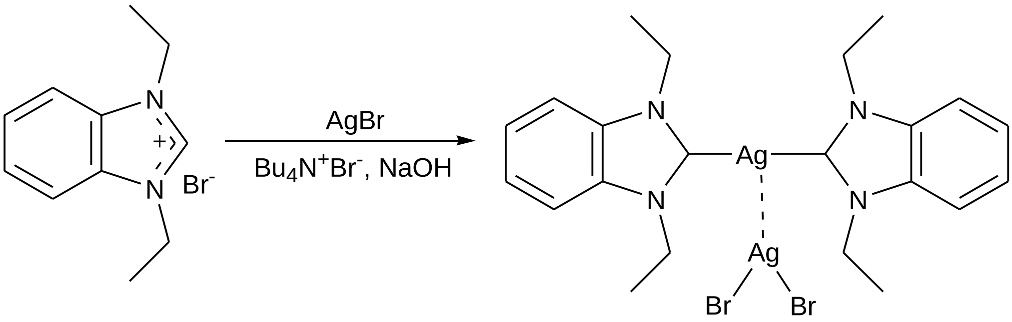
Although the desired silver(I)-NHC complexes can be prepared using free NHC method, but some inconveniences may be faced by these free NHCs.[25] Hence, several research groups discovered the second method in which the silver(I)-NHC complexes could be synthesized from the reaction of imidazolium salts and silver bases by *in-situ* method. The uses of silver bases start in 1997, in which the silver acetate was used in the synthesis of a silver(I)-NHC complexes from triazolium salts.[73] A year after, in 1998, Wang and Lin reported the used the silver oxide (Scheme 1.11)[26] while in 2000, silver carbonate was introduced to produce silver(I)-NHC complexes.[74] Among all the silver sources, silver(I) oxide are the most commonly used because it is relatively stable, commercially accessible, the reaction can be carried out in one-pot reaction at room temperature, solvent pretreatment, strong bases are not required and chirality can be retained.[75]



(**1.13**) (**1.14**)

Scheme 1.11: The silver(I)-NHC complex synthesized by Wang and Lin.[26]

The third way is by the treatment of silver salts with azolium salts under basic phase-transfer conditions introduced by Wang and Lin in 1998.[26] In this reaction, the complex (**1.18**) was synthesized by the reaction of benzimidazolium bromide (**1.17**) with AgBr with the present of strong base (Scheme 1.12).



(**1.17**) (**1.18**)

Scheme 1.12: Reaction of silver salts and azolium salts in presence of base.[26]

1.6 Silver(I)-NHC complexes as carbene transfer agent

Nowadays, silver(I)-NHC complexes are famously known because of their biological activities and as the carbene transfer agents in transmetallation studies. It is common to know about several methods to synthesis silver(I)-NHC complexes by conventional methods [25,26,73,74] as mentioned before but for preparing other carbene metals, the most popular approach is by transmetallation of NHCs from silver(I)-NHC complexes.[15] In this method, the synthesized silver(I)-NHC complex was reacted with other metal sources by choice. The first uses of silver(I)-NHC as a transfer agent was by Wang and Lin 1998 who prepared palladium(II)- and gold(I)-NHC.[26] In this reaction, the reported azolium salts was treated with Ag_2O to get the silver(I)-NHC complexes which then act as NHC transfer agents. Furthermore, the resulted silver(I)-NHC complex was let to react with other metal source to transfer the NHC ligand and the targeted metal-NHC complex was produced (Scheme 1.9).

1.7 Biological activities of silver(I)-NHC complexes

Other than their ability as NHC transfer agent, silver(I)-NHC complexes have also received many attention from researchers because of their biomedical applications such as anticancer as well as antimicrobial agents against numerous pathogens. Silver is not a natural metal in human body, but previous studies proved that they are relatively low toxic to human[76] but highly toxic to most microorganisms[77,78] and it showing strong biocidal effects on as many as 16 species of bacteria including *E. coli.*[79] The slow release of silver ions from the silver NHC complexes into the infected site could obtain better prevention of infection and promote healing. The inability of some of the current silver antimicrobial agents to kill the pathogens in a suistained period of time being a basic challenge and the slow release ability of the silver NHC complexes can be used to solve this problem.[80,81] Other than that, silver is also known for its potential in anticancer studies.[16,62,71,82,83] For example in 2008, Youngs and co-workers have synthesized several silver(I)-NHC complexes and later, this complexes were tested and proved their potential againtst the human derived ovarian (OVCAR-3), breast (MB157), and cervical (HeLa).[84]

1.8 Silver(I) complexes with functionalized benzimidazole-derived NHC

In recent years, many researchers have been interested in the chemistry of silver complexes with functionalized NHC ligands due to their extra stability which could led to diverse applications. These functionalized NHCs possessed a versatile class of carbene ligands with donor strengths and steric and electronic properties that could easily be manipulated by varying the sustituents. In general, the functionality of benzimidazole can be take place in two ways: on the benzimidazole ring (4-, 5-, 6- or /and 7- positions) or on the N atoms (1- or/and 3-positions) of the heterocycle (Figure 1.11). The former type doed not coordinate to the silver center but in contrast, the latter, does so in different modes, depending on the nature of the heteroatoms. [72]

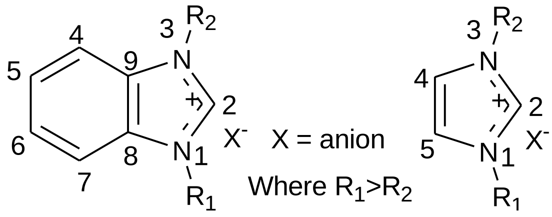
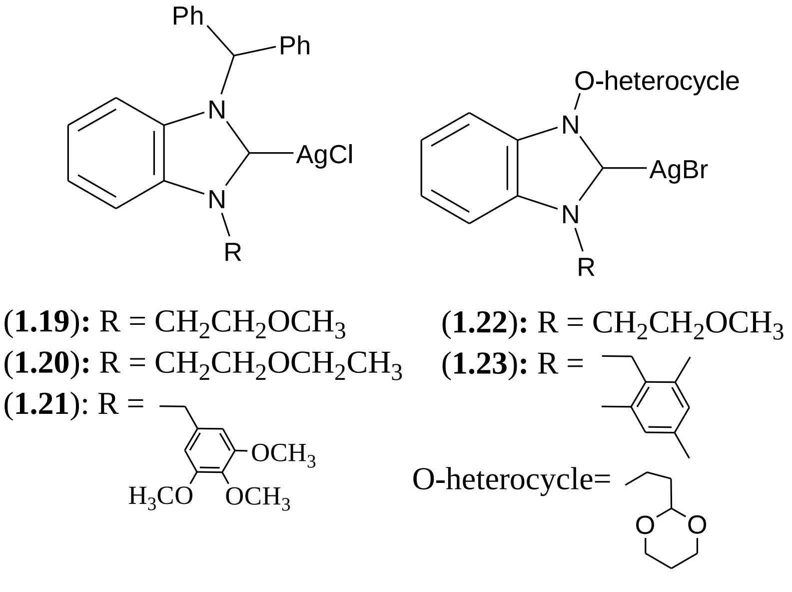


Figure 1.11: The possibilities to place the functionalities in benzimidazole and imidazole groups.

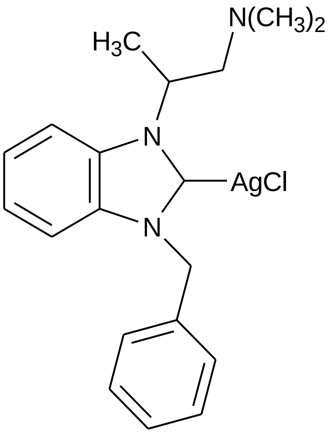
Oxygen-functionalized benzimidazolium salts and their corresponding silver(I)-NHC complexes (**1.19-1.23**) have been investigated by Özdemir and co-worker since recent years (Figure 1.12). These ether- and O-heterocycle-functionalized benzimidazolium halides and their silver(I)-NHC complexes were then tested for their antimicrobial studies and it showed good result for this group research. The antimicrobial activities result for their silver complexes also varied according to the etherel, alkoxy, or O-heterocycle substituent because of their different lipophilicities. Although the mechanism was not well developed, it is believed that the functionalized substituent on the nitrogen atoms of the benzimidazole ring might disturb the intermolecular interaction of the bacteria and causing the breakage of bilayered bacterial cellular membranes.[85]



(a) (b)

Figure 1.12: Silver(I)-NHC complexes bearing (a) Ether-functionalized (**1.19-1.21**); (b) O-heterocycle-functionalized (**1.22, 1.23**) benzimidazolium ligand by Özdemir and co-worker.[85]

Nitrogen-functionalized benzimidazolium salts and their silver(I)-NHC complexes also exhibited a good antibacterial and anticancer entities. Yiğit and co-workers reported a series of amine-functionalized substituted benzimidazolium chlorides and their silver(I)-NHC complexes, for example (**1.24**) (Figure 1.14). All the salts and complexes were evaluated againts several bacteria and fungi. The silver(I)-NHC complexes proved to have potent antimicrobial activities.[86]

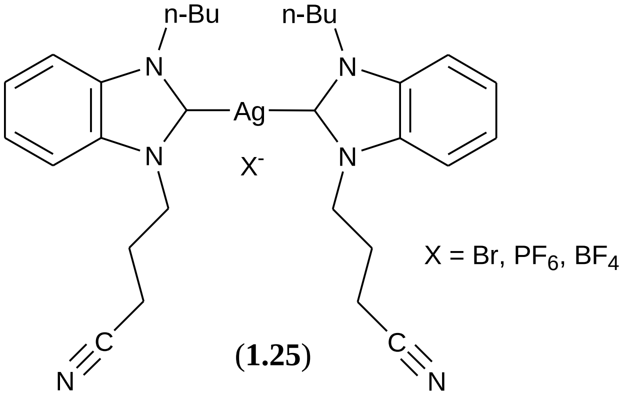


(**1.24**)

Figure 1.13: Example of amine-functionalized silver(I)-NHC complex, (**1.24**) by Yiğit and co-workers.[86]

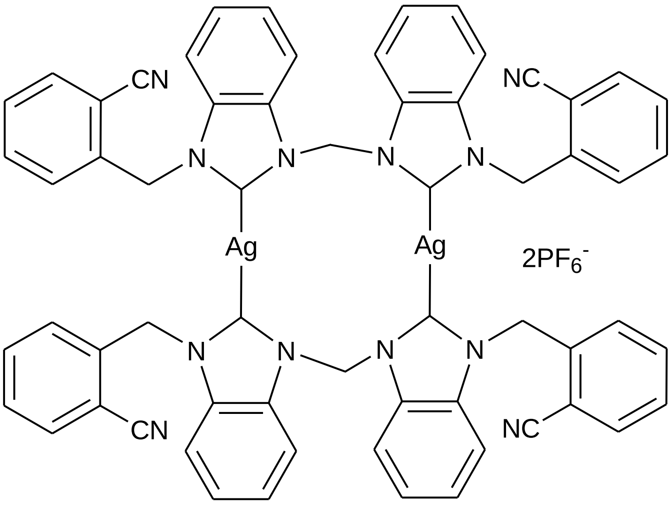
Haque and co-workers were synthesized nitrile-functionalized class of imidazole and benzimidazole with their metal-NHC complexes. A number of mono- (eg. **1.23**) and dinuclear silver(I)-NHC complexes (eg. **1.24**) of this class of compounds have been synthesized and furthermore, their DNA-binding studies,[87,88] antibacterial,[89] anticancer[63,90,91] and catalytic studies[50] were successfully investigated (Figure 1.14). The nitrile functionality on these ligands provided an extra space for bonding or bridging to silver(I) centre and this unique ability gave benefit either in coordination or in the formation of supramolecular architecture.[63]

Other than that, the binding effect due to interaction or coordination between the nitrile functionality and the silver(I) centre can result in more stable silver(I)-NHC complexes that can slowly release silver ions at the wound site, thus preserving the antibacterial effect over a longer time.[92]



(**1.25**)

(a)



(**1.26**)

(b)

Figure 1.14: Examples of nitrile-functionalized of (a) mono[88] (**1.25**) and (b) dinuclear[90] (**1.26**) benzimidazolium silver(I)-NHC complexes by Haque and co-workers

1.9 Conclusions

N-heterocyclic carbenes (NHC) were receiving more attention these few years due to their abilities in many fields such as catalysis and biological activities. Silver(I)-NHC complexes, unlike other metal-NHC, can be synthesized and isolated easily. Hence, NHC ligand salts with variety substituents were synthesized widely and their structural study has led to a diverse field of bonding motifs in solid state. Silver(I)-NHC displayed an excellent ability in biological activities and also in the transmetalation to other metal NHC.

1.10 Objectives of the studies

The objectives of this project are:

i. To synthesise *N*-heterocyclic carbenes (NHC) ligands based on benzimidazolium with different substituents to produce whether non-functionalized or nitrile-functionalized compound.

ii. To synthesise novel silver(I)-NHC complexes containing the NHC ligands.

iii. To synthesise novel palladium(II)-NHC complexes using silver(I)-NHC complexes as transfer agents.

iv. To characterize all the synthesized ligand salts and complexes using different spectral and analytical methods.

v. To prove the proposed structures for the synthesised compounds using single crystal X-ray diffraction analysis/crystallography.

vi. To evaluate the antibacterial activities of benzimidazolium salts and metal-NHC complexes.

1.10.1 Targeted benzimidazolium salts

For this project, benzimidazole was used instead of imidazole because of its medicinal importance. The targeted ligand salts are monodentate and bidentate benzimidazolium salts bearing one substituent of benzyl with different substituent at different positions as their PF_6^- salts. All the prepared salts were characterized using spectral and analytical methods. The structural properties were confirmed by using single crystal X-ray diffraction techniques. These will be discussed briefly in Chapter 3 and 4.

1.10.2 Targeted metal

The synthesised benzimidazolium salts were used as the NHC ligand precursors to produce mononuclear and dinuclear silver(I)-NHC complexes. The silver(I)-NHC complexes were then used to produce palladium(II)-NHC complexes.

Silver(I)-NHC complexes became the primary interest for this project because easy to prepare starting from silver(I) oxide and their potential biological activities. Silver(I)-NHC complexes are known to be useful carbene transfer reagents and the silver(I)-NHC complexes may serve as synthetic precursors for palladium(II) complexes through their reaction with any palladium metal source especially $Pd(COD)Cl_2$ (where COD= 1,5-cyclooctadiene) in this project. The detailed information about silver(I)-NHC and palladium(II)-NHC complexes will be discussed in Chapter 3 and 4 respectively.

CHAPTER 2

EXPERIMENTAL

2.1 Materials

Benzimidazole (Merck, for synthesis), 2-bromopropane (Merck, for synthesis), 1,4-dibromobutane (Sigma Aldrich, 99%), 2-methylbenzyl bromide (Sigma Aldrich), 3-methylbenzyl bromide (Sigma Aldrich, 96.0%), 4-methylbenzyl bromide (Sigma Aldrich, 97.0%), 2-(bromomethyl) benzonitrile (Merck, for synthesis), 3-(bromomethyl) benzonitrile (Merck, for synthesis), 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%), dichloro(1,5-cyclooctadiene)palladium(II) (Sigma Aldrich), Celite (Merck, size: 0.02-0.1 mm), dimethyl sulphoxide (DMSO) (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 without any further purification. The reagents, *N*-(2'-propyl)benzimidazole and *N,N'*-(1,4-diyl-butane)bisbenzimidazole were synthesized according to the literature procedure[94,113] with slight modifications.

2.2 Instruments

The melting point was tested using a Stuart Scientific SMP-1 (UK) instrument. Elemental analysis was carried out on a Perkin Elmer Series II, 2400 microanalyzer. The fourier transforms infrared (FT-IR) spectra were recorded 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