Silver (I) *N*-Heterocyclic Carbenes

**Abstract**

Silver(I) *N*-Heterocyclic Carbenes was first synthesized in 1968 by the reaction of silver compounds with imidazolium salts. The resulting complex is characterized using elemental analysis and various spectroscopic techniques. This complex finds useful medicinal and pharmaceutical as well as in the area of catalysis. They have been employed as catalysts in numerous syntheses where it further finds even more useful application in the area of transmetalation. This review explores the birth and growth of *N*-Heterocyclic Carbenes from laboratory curiosities to efficient synthetic tools.

**Introduction**

 *N*-heterocyclic carbenes (NHCs) commonly known as imidazol-2-ylidene carbenes can be synthesized by the deprotonation of *N, N*- disubstituted imidazolium salts. NHCs, just as the name implies are neutral strong Lewis bases with excellent nucleophilic properties.1,2 These compelling properties have made them a very attractive class of ligands that have been employed in the synthesis of transition metal complexes. NHCs have a characteristic sp or sp2 –hybridized carbon centre found between two heterogenic atoms. This determines the geometry of the carbene whether linear (sp) or bent (sp2). Within an sp- hybridized carbon, the two degenerate non-bonding p-orbitals has one electron in each orbital. This accounts for why the electron pair in sp hybridized carbene exist in a a triplet state as they have separate spin state. Bent (sp2) carbenes can exist as both singlet and triplet multiplicity depending on the energy difference between the pπ and the σ-orbitals. This is however influenced by the attached substituent located at the alpha carbon of the carbene (Durmus).

 

**Figure 1.** Orbital diagram of a linear carbene with filled Px and Py orbitals. The electron spins

are aligned in triplet state



**Figure 1.7** Orbital diagram of each possible electron and spin state arrangement within a bent
carbene. All are aligned in singlet states aside from the far right, which is in a triplet state

The first known synthesis of transition metal complexes of NHCs was investigated by Ofele and Wanzlick in 1968 who reported NHC complexes of chromium and mercury. This discovery paved way for series of other studies with the synthesis of several NHC metal complexes from electron rich olefins as the most notable.3,4 Despite this advancement in the world of NHCs, it was not until 1991 that the first stable NHC transition metal complex was successfully isolated. Arduengo et al5 reported the successful isolation of NHC, 1, 3-dadmantylmdazol-2-ylidene and since then, numerous products have been successfully isolated.



Figure 1. Formation of a free NHC radical from an imidazolium cation and some NHC complexes.

 NHCs are generally better sigma donors than most phosphines. They easily bind with most transition increasing their stability. Like other NHC complexes, Silver (I) *N*-Heterocyclic Carbenes finds useful roles as catalysts but have been used more as intermediates for the synthesis of other NHC metal complexes.6 Reactions such as Suzuki-Miyaura reaction, Heck reactions, olefin metathesis and hydrogenation all employ NHCs as catalysts in various capacities. In NHC transfer reactions, silver-NHC compounds are the most frequently used transfer agents following their straightforward synthesis which thwarts the need for the isolation of free NHCs as well as their relative stability in the presence of air and light.7

Silver as a metal have been used in the production of surgical needles, wound care and water purification among others. Since time antiquity, studies have reported that silver exhibits microbial properties and several derivatives have been employed in the treatment of lesions and infectious ailments. This has attracted interest and resulted in series of developments in the use of silver and its compounds to serve various medicinal purposes. Silver sulphadiazine was developed in 1967 and studies revealed that it exhibited more effective medicinal properties that silver nitrate especially in the treatment of wounds. Currently, silver sulphadiazine still finds useful applications globally.8



Figure 2: Structure of silver (I) N-heterocyclic carbene

Numerous derivatives of silver (I) *N*-Heterocyclic carbenes have been synthesized and examined to determine their antimicrobial properties. These complexes have been encapsulated into an electrospun polymer mat and its resulting microbial properties studied. It was revealed that the NCH complex decomposed slowly upon exposure to humid conditions resulting in the deposition of the silver particles into the polymer matrix. The encapsulated silver NHC fiber mats had better antimicrobial activity and faster kill rate than silver sulphadiazine and silver nitrate. This was attributed to the fact that the encapsulation of the silver NHC into the polymer mat increased the bioavailability of the active silver species.8 Several other silver NHC complexes have been synthesized with its applications still under investigation.

Silver (I) *N*-Heterocyclic carbenes have prompted several studies in medicine. In drug design and biotechnology, the synthesis of artificial chemical nucleases is paramount and pertinent for DNA manipulation.9 The presence and action of certain biological metalloenzymes have been confirmed to be a necessity for the observed nucleophilic displacement reactions on phosphate esters in living beings. This has prompted studies to develop metal ion-based hydrolytic catalysts and transition metal complexes that will be used in the synthesis of these proposed artificial nucleases.9,10 So far, silver (I) *N*-Heterocyclic carbenes are top contenders in various fields of research to achieve this foot following its proven compatibility with most biological systems.

Some of the biological properties assigned to silver (I) *N*-Heterocyclic carbenes are a sequel to the historical biological applications of elemental silver and some of its compounds. Some silver compounds have been reported to be used on newborns for the protection of their eyes from microorganisms as well as in the treatment of .chronic ulcers and excessive burns.9.11 The outstanding antimicrobial properties of most silver (I) *N*-Heterocyclic carbenes and its derivatives have been attributed to the rate of delivery of the silver cations across the cell membranes of these microbes. This process interferes with the electron transport system and interacts with the thiol groups of the vital enzymes of the microorganisms.12 The recent applications of silver NHCs in the treatment of cystic fibrosis and chronic lung infections13,14 further reiterates the significance of these complexes in medical and pharmaceutical applications.

Currently, Ag (I) *N*-Heterocyclic carbenes to some researchers serve only the purpose of transferring to other metal systems. Silver NHCs have been proven to be able to transfer to a variety of metals such as Au(I), Rh(I), Rh(III), Pd(II), Pt(II), Ni(II) among others. This is a process known as transmetallation and so far, palladium has been the most successful.2,15 Transmetallation into other metals have been reported but difficulty in isolation has also hindered further studies into the applications of the resulting complexes thus, very few applications have been reported for most. However, McGrandle and Saunders have reported a one-step transfer from silver to rhodium(III) and iridium(III) centers. The resulting complexes particular the rhodium complex finds potential application in radiopharmaceuticals.8

**Methods**

Several methods have been devised for the synthesis of Ag (I) *N*-Heterocyclic carbenes depending on the nature of the starting material. One of the most common routes for the synthesis of Ag(I) *N*-Heterocyclic carbenes is from imidazolium salts and silver compounds such as Ag2O, Ag2CO3, Ag(OAc). 2 equiv. of dialkyl benzimidazolium salt is dissolved in a flask containing 20 mL of water and 0.046 g of Ag2O. The mixture was stirred for 2 days at room temperature until a brown suspension is formed. The suspension was then filtered through a celite to obtain a colorless solution after which the volatiles are removed in vacuum. White crystals of silverThe resulting Ag(I) NHC complex is obtained, filtered and weighed. 0.52g of the product is obtained as a camel coloured solid.8

The first step in the characterization of most products of synthesis is elemental analysis like colour examination, melting and boiling point determination among others. Further characterizations is done using 1H NMR, and 13C NMR. The formation of the resulting Ag(I) N-Heterocyclic Carbenes complex in the experimental procedure described above is monitored by the observed changes in the 1H NMR and 13C NMR spectra. The spectra of the starting material is monitored first, methylated caffeine, 1,3,7,9-tetramethylxanthinium with observed peaks at 8.93 ppm. Upon monitoring the changes in the spectra of the products, there is a disappearance in the observed resonance for the imidazolium protons and a corresponding appearance of the resulting carbene at 187.1 ppm indicating the formation of NHC silver carbene complex.3

Another synthetic route is shown in figure 3 carried out the synthesis and characterization of six new compounds using similar precursors (imidazolium salts) with different substituent’s attached.9 Of these six compounds, three were imidazolium precursors; 1-methoxyethyl-3-allylimidazolium hexafluorophosphate (1), 1-ethyl-3-allylimidazolium hexafluorophosphate (2) and 1-pentyl-3-allylimidazolium hexafluorophosphate (3). These precursors were reacted with Ag2O to obtain the corresponding silver NHCs 1-methoxylethyl-2-allylimidazolium silver (I) hexafluorophosphate (4), 1-ethyl-3-allylmidazolium silver (I) hexafluorate and 1-pentyl-3-allylimidazolium silver (1) hexafluorophosphate (6) respectively. 35 ml of a 3.24 mmol acetonitrile solution and 3.24 mmol Ag2O (0.75g) is placed in a flask in the absence of light and stirred at 50-60 oC for 12 hours. The resulting mixture is filtered using a pad of celite to obtain a colorless solution which is evaporated to dryness until a white solid is obtained. The solid is then redissolved in acetonitrile, after which the volume of acetonitrile is reduced before the subsequent addition of diethyl ether. The reprecipitated solid is then dried in a vacuum to obtain 1-methoxylethyl-2-allylimidazolium silver (I) hexafluorophosphate. For the purpose of X-ray studies, single crystals are obtained by slowly diffusing diethyl ether into the acetonitrile solution of the complex.

Figure 3: Synthesis of some silver NHC complexes (4,5,6) from imidazolium salts (1,2,3).

**Characterization**

Silver NHC complexes are the most studied member of the NHC family owing to their intriguing structural properties and numerous applications. Numerous syntheses have been reported but there is still not much known about the catalytic process. Generally, they find useful applications in the process of isomerization reactions, hydrogenation, cyclization, hydroformylation, arylaltion of carbonyl compounds, C-C bond formation, hydrosylation and much more.15,18 The foremost driving force behind the catalytic processes of NHC is their superior properties as ligands. Each of its bonding properties depending on the geometry can be adjusted by modifying the structure of the NHC precursor in use (Durmus).Its ability to act as both a lewis acid and lewis base increases its use in the coordinaton to a wide variety of metals in the periodic table. They create very highly stable metal NHC complexes as a following their strong σdonor ability. In many processes where electron transfer is required, they have gradually usurped phosphines in many of these processes. NHCs have the ability to stabilize and activate metal centers in various catalytic steps like the C-H activation, C-O, C-C and C-N bond formation.2,18 Studies have reported the use of silver (I) *N*-Heterocyclic carbenes in the preparation of enantiomerically pure complexes as in figure 4, with the introduction of chirality at various parts of the carbene molecule. Some of the catalytic reactions involving NHCs are discussed.



Figure 4: Different types of chiral NHCs

Silver (I) *N*-Heterocyclic carbenes were first employed as catalysts by Peris and co-workers in the diboration of both terminal and internal alkenes.19 They reported that the complex was chemoselective in the formation of the product. Terminal alkanes had a higher conversion rate than internal alkanes and this was attributed to the increased electron donation from the substitutions of the terminal alkenes.8,19 In another study by Waymouth and colleagues, the catalytic properties of silver NHCs was reported. Their findings revealed that certain derivatives of silver NHCs can be used to catalyze the ring-opening catalyzation of L-lactide. The thermal stability of these complexes was also studied using differential scanning calorimetry and thermogravimetric analysis. The result showed that the silver NHCs were stable but decomposed slowly at a higher temperature to release free NHCs. In an attempt to verify this speculation, Waymouth and colleagues attempted to trap the hypothesized free NHC by heating the complex in the presence of carbon disulphide as the trapping agent. NMR was used to confirm the presence of the resulting zwitterions.20

The structure of silver NHCs, as well as its role in catalysis, is determined using various techniques such as spectroscopy and elemental analysis. It is pertinent to state here that the observed spectroscopic data differs depending on the materials used in the synthesis or catalysis as the case may be. However, a general overview of characterization is presented. From FTIR studies, medium intensity bands in the range of 2960-2976 cm-1 is generally assigned to aliphatic C-H vibrations. The appearance of two sharp medium intensity bands in the range of 2100-2230 and 1380-1428 cm-1 is due to the stretching vibrations from the imidazole C=N and C-N as have been reported in some studies.15,21 During the formation of the complex, an observed shift in the band spectra from ~120 and ~25 cm-1 respectively is an indication of the formation of free C-N unit in the core of the imidazole in a process of dequarternization. This is followed by the coordination of the Ccarbene to the Ag(I).9 The essence of using various spectroscopic techniques is to provide a wide range of information that will be sufficient enough to elucidate the structure of the compound under study. FTIR cannot be used to observe metal-to-carbene carbon vibrations since they are usually observed in the far-IR region and as such, other NMR techniques are employed.

The 1H NMR data represents the acidic proton shift of imidazolium salts which is observed between δ8-10 ppm indicating the formation of the desired salts and studies have revealed that this trend is consistent with most imidazole-based NHC precursors.9 The observed triplets at δ 7.75-7.85 ppm correspond to the C4H and C5H resonances of the imidazolium. Depending on the attached substituent to the imidazolium precursor, methoxy and ethylene protons of ether resonates as a singlet and two triplets respectively at δ 3.28 and 3.68-3.47 ppm. Allyl protons appear at δ 4.90 ppm and 6.10 ppm, allylic protons (=CHcis) appear at δ 5.26-5.33 ppm while (=CHtrans) appear at δ 5.32-5.40 ppm. Alkyl resonance are found in the range of δ 0.8-4.4 ppm. The 13C-NMR downfield at δ 135.74-136.80 ppm is due to the imadole ring of the Ccarbene. δ at 10.00-49.87 ppm is due to the alkyl chain (-CH2-). In line with the information obtained from the 1H NMR, the absence of resonance for the imidazolium carbene proton is due to the shift of the N-C-N sp2 carbons which becomes the carbene center thus confirms the formation of the Ag(I)-NHC complex. Some studies have reported cases of no observed resonance in the 13C-NMR spectra and this has been attributed to the fluxional behavior of silver NHC complexes. This indicates that there is no coupling between C-107Ag and C-109Ag and such complexes are very useful as carbene transfer agents.2,3

**Conclusion**

 Several decades after the first synthesis of NHCs by Ofele and Wanzlick in 1968 and the first successful isolation of the first stable NHC transition metal complex by Arduengo in 1991, recent years have been marked by tremendous transition and evolution in the world of metal catalysis. The elasticity of their general structural design, their ability to act as stabilizers for other reactive intermediates while also retaining their primary functions as catalysts have made them a classical ligand kit for synthetic chemists. Transmetalation is a very important component of catalyzes and silver NHCs are the foundation this technique. The ease of synthesis, as well as its ability to undergo transmetalation, has made it one of the most preferred routes in the development of various NHC metal systems. Argentophilic and silver halide interactions are very important in the formation of diverse structures of NHC compounds and there is no doubt that further studies will be conducted to discover other silver motifs as well as the factors that affect the reaction mechanism.

Silver and silver compounds have been employed in the treatment of wounds for ages. Sustaining the constant release of the silver cations to the wound site has been a major challenge. Several studies have been carried out to solve this limitation and the slow decomposition of water-soluble pyridine coupled with NHC silver complexes have been demonstrated to show improvements. Silver gem-diol complex have shown lower antimicrobial activity than most other silver compounds. Its use in the production of an encapsulation mat increases the bioavailability of active silver species and its corresponding slow decomposition is an added advantage that provides a longer bacterial activity. This is a promising technique in the attainment of sustained delivery of silver ions to wounds. The potential use of silver-NHCs as effective antimicrobial agents has stirred up the hornets’ nest in a new field of research and there is no doubt that this will continue.

So far, so much have been done yet little is known about the silver NHCs. New routes of synthesis have being developed, studies are being carried out to synthesize more complexes with enhanced antimicrobial activities, various catalytic reactions are being reported and with the results from various studies so far, it is only a matter of time before this lacuna is bridged and the full applications of silver NHCs can be efficiently explored.

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